PIENAAR, ANDRé

SYNTHESIS AND CHEMISTRY OF PHOSPHONIC DERIVATIVES

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ANDRÉ PIENAAR

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SYNTHESIS AND REACTIVITY STUDIES OF PHOSPHONIC DERIVATIVES

ANDRÉ PIENAAR

Supervisor:	Professor T A Modro
Department:	Chemistry
University:	University of Pretoria
Degree:	Magister Scientiae

SUMMARY

A reliable method for the preparation of alkylphosphonyl chlorides had to be obtained to prepare precursors for the synthesis of a range of alkylphosphonates which were needed for kinetic studies. Both thionyl chloride and oxalyl chloride were studied as chlorinating agents for phosphonic esters. The use of thionyl chloride together with a catalytic amount of DMF were shown to be of general application in the efficient preparation of phosphonic mono-ester chlorides.

A wide range of esters of the formula $R_2NCH_2CH_2OPO(R')R''$, R, R' = CH_3, CH_2CH_3 and R" = OCH_3, OCH_2CH_3, $OCH(CH_3)_2$ and Cl were synthesized. These compounds were used as substrates to study the kinetics of their unimolecular decomposition. From the relative kinetic data we were able to show that two mechanisms of decomposition were followed depending on the nature of the leaving group present in the substrate molecule.

OPSOMMING

’n Betroubare metode moes gevind word vir die sintese van alkielfosfonielchloriede wat dien as uitgangstowwe vir die bereiding van ’n reeks alkielfosfonate vir kinetiese studies. Beide tionielchloried en oksalielchloried is ondersoek as chlorineermiddels vir fosfoniese esters. Die gebruik van tionielchloried tesame met ’n katalitiese hoeveelheid DMF stel ’n algemene sintese metode daar vir die bereiding van fosfoniese mono-esterchloriede.

’n Wye reeks esters met die algemene formule $R_2NCH_2CH_2OPO(R')R''$, R,R’ = CH_3, CH_2CH_3 en R" = OCH_3, OCH_2CH_3, $OCH(CH_3)_2$ en Cl is berei. ’n Kinetiese studie is uitgevoer om die monomolekulêre ontbinding van hierdie verbindings te ondersoek. Die relatiewe kinetiese data het ons in staat gestel om aan te toon dat twee meganismes gevolg word in die ontbinding van hierdie molekules afhangend van die aard van die verlatende groep teenwoordig in die uitgangstof.

TABLE OF CONTENTS

CHAPTER 1 : INTRODUCTION Page

CHAPTER 2 : RESULTS AND DISCUSSION

CHAPTER 3 : CONCLUSIONS AND FUTURE DIRECTIONS

CHAPTER 4

CHAPTER 1

INTRODUCTION

1.1 General

Phosphorus[1] was isolated for the first time in 1674 by Brand. He obtained elemental phosphorus, in the form of P_4, by distilling evaporated urine $Na(NH_4)HPO_4$. The systematic development of organophosphorus chemistry was initially undertaken by A Michaelis (1847 - 1916) and later by Arbuzov (1877 - 1968).

Schrader and Saunders discovered the insecticidal and toxic properties of certain esters containing phosphorus on the eve of World War II. This discovery led to intensive studies in the area of organophosphorus chemistry.

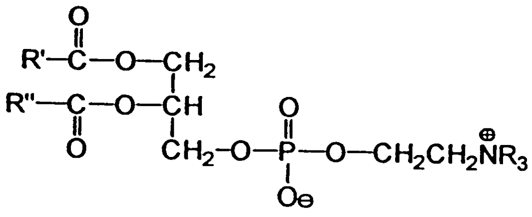
It is not surprising to find that phosphorus has such a wide range of biological functions, because this element is so abundant in the earth's crust. These functions can be divided into two different types:

(i) phosphorus in the form of inorganic, primary calcium phosphates, is the major structural material in vertebrate bone,

(ii) phosphorus in the form of organic, phosphate esters, provides linkages in biologically important systems, particularly in the DNA and RNA structures.

The major energy - storage and - transfer mechanisms in all living systems involve the synthesis and breakdown of phosphate ester and anhydride linkages.

Phospholipids (**1**) are found[2,3] in the membranes of cells and are the basic structural element in living organisms.



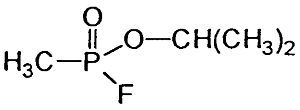
(1)

Phospholipid molecules are amphiphatic and therefore resemble soaps and detergents. The lipophilic part is the long fatty acid chain and the hydrophilic part is the dipolar ionic end. In aqueous solutions phospholipids form micelles, but under certain conditions they tend to form bilayers. In this latter form they are believed to exist in cell membranes and here they selectively control the passage of various substances e.g. nutrients, waste products, hormones etc. in and out of the cell.

1.2 Methyl-fluoro-phosphorylcholines

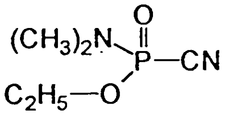
It is well established that compounds of the phosphorylating type, Sarin (**2**), Tabun (**3**), Parathion (**4**) and DFP (**5**), are potent inhibitors of cholinesterase^4. These compounds often function as nerve poisons because they deactivate the enzyme chlolinesterase irreversibly.

Isopropyl methylphosphonofluoridate



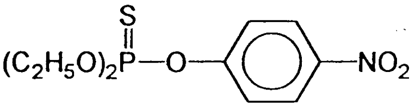
(2)

N,N-dimethylphosphoramisocyanidate



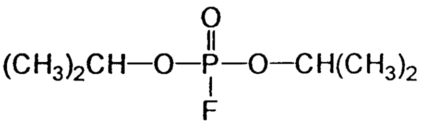
(3)

Diethyl-p-nitrophenyl monothiophosphate



(4)

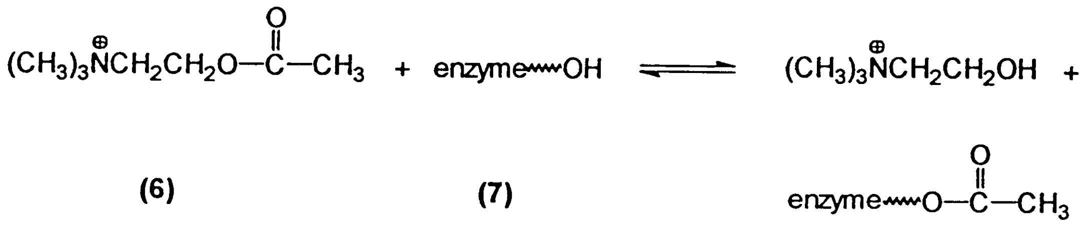
Diisopropylfluorophosphate



$(CH_3)_2CH{-}O{-}\overset{O}{\overset{\|}{\underset{F}{\underset{|}{P}}}}{-}O{-}CH(CH_3)_2$

(5)

In neurotransmission[3,5] the ester acetylcholine **(6)** is released by a nerve impulse to trigger muscle contraction. The enzyme cholinesterase **(7)** breaks the ester to the end process as shown in scheme **1**.



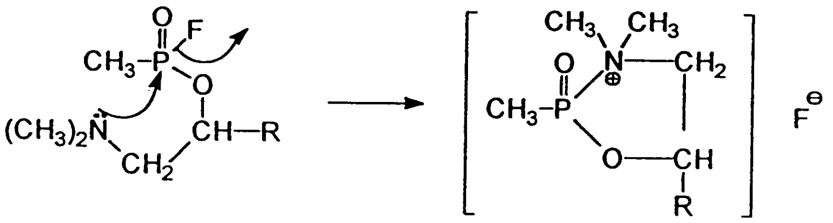
$$(CH_3)_3\overset{\oplus}{N}CH_2CH_2O-\overset{\overset{O}{\|}}{C}-CH_3 + \text{enzyme}\sim OH \rightleftharpoons (CH_3)_3\overset{\oplus}{N}CH_2CH_2OH + \text{enzyme}\sim O-\overset{\overset{O}{\|}}{C}-CH_3$$

<u>**Scheme 1**</u>

An electrophilic phosphorus compound can be the receptor for the nucleophile cholinesterase **(7)**. When the cholinesterase has reacted with the phosphorus compound, it cannot react with the acetylcholine **(6)** and therefore muscle contraction continues.

Tammelin[6] found that both N,N-dimethylaminoethyl methylphosphonofluoridate **(8)** and N,N-dimethylamino-(1-methylethyl) methylphosphonofluoridate **(9)** are subject to fast spontaneous decomposition at room temperature. Both liquids are transformed into solid compounds with the same percent composition as the initial compound. This process takes a few days for the N-ethyl derivative **(8)** and a few months for the N-methylethyl derivative **(9)**. The decomposition of these compounds complicates the investigation of their anticholinesterase properties and an understanding of the mechanism for this decomposition would be important for future studies of these classes of compounds.

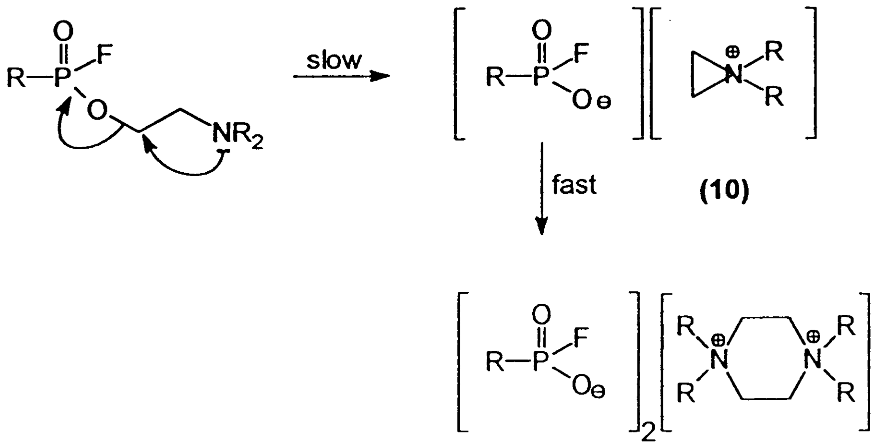
Tammelin[6] suggested the following rearrangement (scheme **2**) for compounds **(8)** and **(9)**.



(8), R = H
(9), R = Me

Scheme 2

Another possible rearrangement, analogous to that proposed by Fukuto and Stafford[7] for the thiosubstrates, and suggested by Benschop et. al.[8], is that the liquid is transformed to the ethylene-iminium salt **(10)** or to the more stable piperazinium salt **(11)** as depicted in scheme 3.



(10)

(11)

Scheme 3

Cadogan and Thomas[9] found that N,N-diethylaminoethyl diethylphosphate slowly deposited hygroscopic colourless crystals of the same elemental composition as the ester. They also showed that decomposition was facilitated by an increase in temperature, with or without methanol as solvent.

Larsson[10] studied the rearranged product of dimethylaminoethoxy-methylphosphonyl fluoride to elucidate its structure and made the following two observations in the Infra-red Spectra of the solid isomer:

(i) the strong absorption band at 11,79μ (848 cm^{-1}), assigned to the vibration of the P-F bond[11] is absent,

(ii) at 13,52μ (740 cm^{-1}) a band appears which can be attributed to the vibration of the P-N bond[11].

From these two observations Larsson concluded that the structure suggested by Tammelin[6] in scheme **2** represents that of the solid isomer.

1.3 Kinetics and mechanism of the decomposition of N,N-dimethylaminoethyl methylphosponofluoridate

Benschop et. al.[8] studied the kinetics and mechanism for the decomposition of N,N-dimethylaminoethyl methylphosphonofluoridate **(8)**, N,N-dimethylaminoethyl isopropyl methylphosphonate **(12)** and obtained the following results:

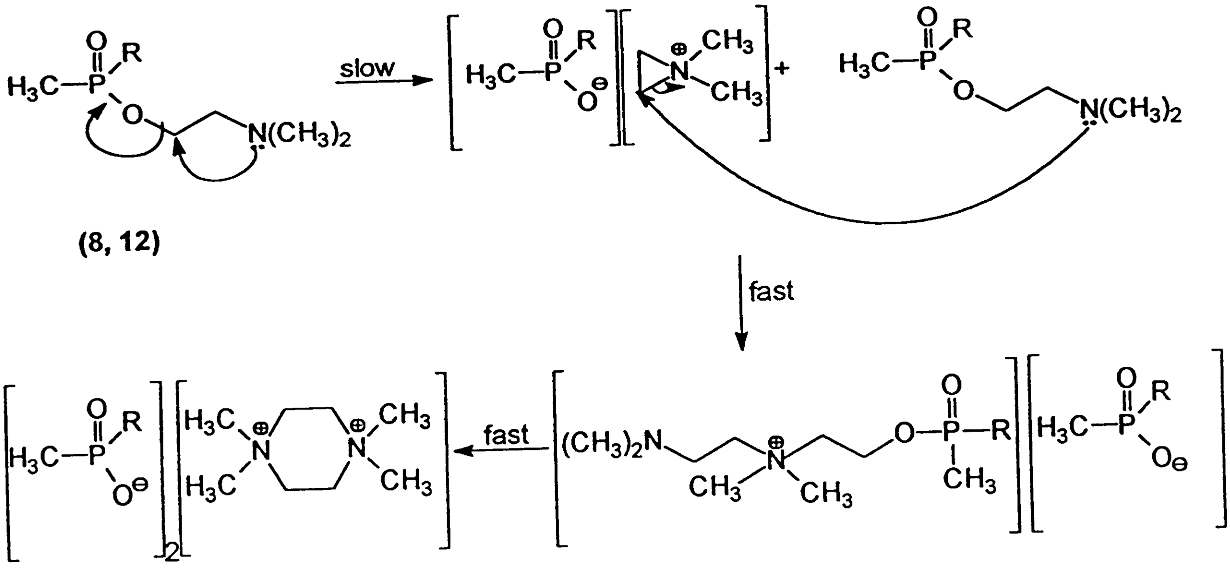
Table 1

Rates of decomposition of $(Me)_2NCH_2CH_2OPO(Me)X$ in DMSO-d_6 at (60 ± 1)°C

	X	pKa of HOPO(Me)X	conc (%v/v)	k_1 (min^{-1})
8	F	$0,85 \pm 0,05$	5	$(6,7 \pm 0,2) \times 10^{-3}$
			10	$(6,4 \pm 0,2) \times 10^{-3}$
12	$OCH(CH_3)_2$	$2,00 \pm 0,02$	5	$(8,1 \pm 0,3) \times 10^{-6}$

They used NMR spectroscopy to study the kinetics for the decomposition of the two substrates **(8, 12)** and also for the identification of the decomposition products. They employed the singlet of the NMe_2 group at δ_{1H} 2,19 of **(8, 12)** and the singlet of $\overset{+}{N}Me_2$ at δ_{1H} 3,37 of 1,1,4,4 - tetramethylpiperazinium bis(methylphosphonofluoridate) **(13)**, formed during the decomposition, for their rate measurements. Their results showed that first order kinetics were obeyed and furthermore that the dimeric product **(13)** was not formed by the intermolecular reaction of two molecules of **(8)**, due to the indifference of the reaction rates to the initial concentration of **(8)**.

Benschop proposed a possible mechanism for the decomposition of reactants **(8, 12)** shown in scheme **4**.



(8, 12)

(13)

(8), R = F
(12), R = OCH(CH$_3$)$_2$

Scheme 4

According to Benschop, the rate of the reaction in scheme **4**, is expected to increase with the acidity of the conjugate acid of the leaving group anion, and with the basicity of the nitrogen atom in the parent molecule. This seems to be the case if one compares the values of pKa of the respective acids given in Table **1**. Benschop claimed that this difference was the sole reason for the increased reactivity of **(8)** compared to **(12)**.

1.4 The project

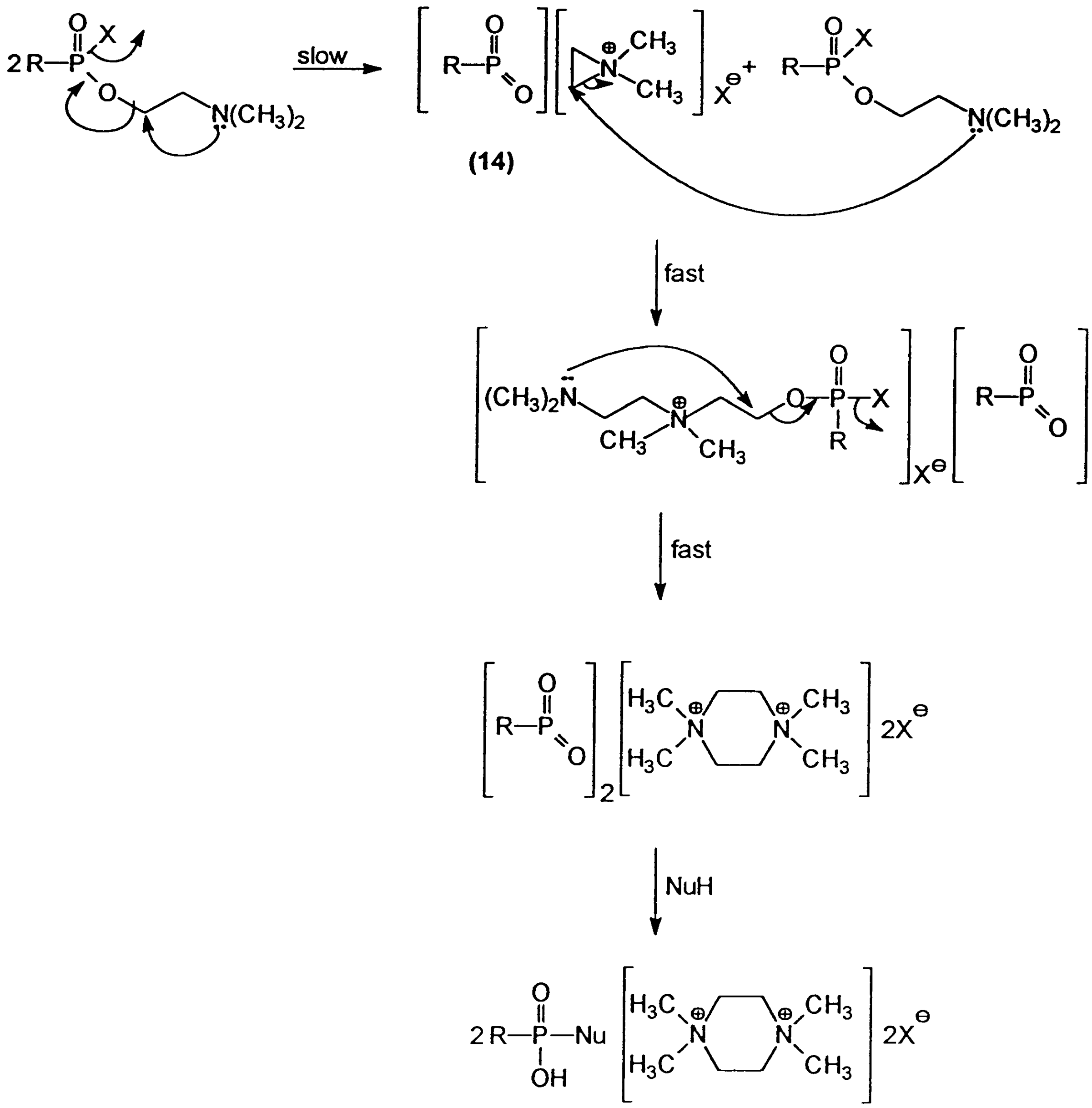
1.4.1 Kinetic and mechanistic studies

When commencing this project it was decided to study the kinetics and mechanism for the decomposition of N,N-dialkylaminoethyl alkyl alkylphosphonates.

The reason for this choice was that from the results of Benschop[8] and the mechanism proposed (scheme **4**), it seemed rather unlikely that the basicity difference of ΔpKa = 1,15 could have the effect of increasing the rate of decomposition of **8** relative to **12** of about 800. The pKa value of an acid is a measure of the extent of ionization of the acid in aqueous solution. Therefore the difference in the rates of decomposition of the two reactants **(8, 12)** were expected to be less dramatic.

The observation by Larsson[10] indicates that the P-F bond is broken during the decomposition of the liquid compound.

A different mechanism, for compounds where X is a good leaving group is proposed (scheme **5**), in which a metaphosphonate species **(14)** is formed as an intermediate.



Scheme 5

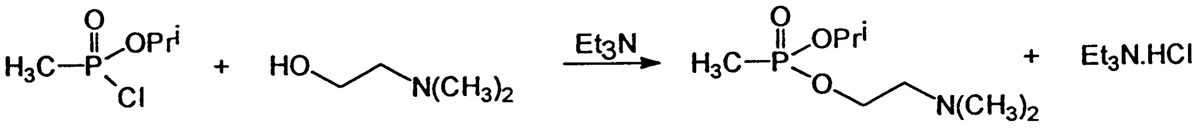
Here the leaving group X plays an important role in the slow (rate determining) step of the reaction. The nature of the leaving group would therefore greatly influence the rate of the reaction. Fluoride can act as such a leaving group and in the two examples chosen by Benschop this would explain the large difference in the rate of decomposition of the two reactants **(8, 12)**.

The initial intention was to prepare a series of compounds of a general formula $MeP(O)(X)OCH_2CH_2NR_2$ and to study the kinetics of their decomposition as a function of the pKa of XH. During the preparation of those substances some unexpected problems were encountered and some observations were made that changed, to a certain degree, the nature of this work.

1.5 Synthesis of substrates

1.5.1 N,N-dimethylaminoethyl isopropyl methylphosphonate (12)

Benschop[8] showed that simple addition of the alcohol **(15)** to the phosphonochloride **(16)** could be used for the preparation of **(12)** (scheme **6**).



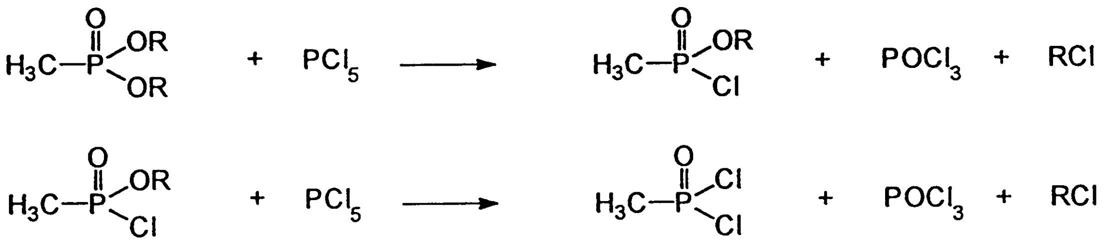
(16) **(15)** **(12)**

Scheme 6

To use the reaction shown in scheme **6**, it is essential to obtain a reliable method for the preparation of alkylphosphonylmonochlorides. Conversion of phosphonate diesters, which are made by either the Michaelis - Arbuzov or Michaelis - Becker reaction, to the monochlorides is the most evident pathway. Any one of the chlorinating agents, PCl_5[12, 13, 14], $SOCl_2$[12, 13] or $(COCl)_2$[13, 14] could be used in this conversion.

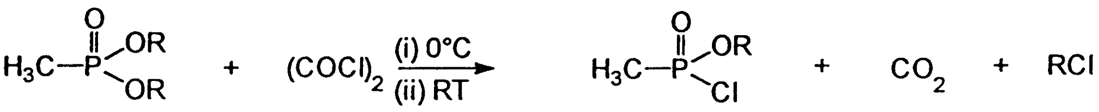
1.5.2 Alkylphosphonyl chlorides and dichlorides from phosphonic esters

The use of PCl_5 as a chlorinating agent is not favourable (scheme **7**), because often a mixture of chlorides and dichlorides is formed which is difficult to separate by fractional distillation[13]. This reaction occurs in two steps and the time required for complete conversion increases with increasing molecular weight of the alkyl group[14].



Scheme 7

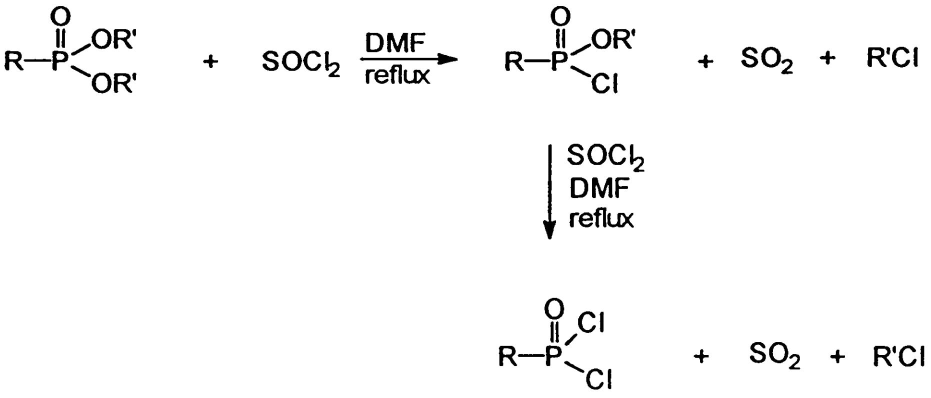
Pelchowicz[14], using $(COCl)_2$ prepared a range of alkyl methylphosphonochloridates with yields ranging from 75 - 95% (scheme **8**).



R = Me, Et, Pr^n, Pr^i, Bu^n

Scheme 8

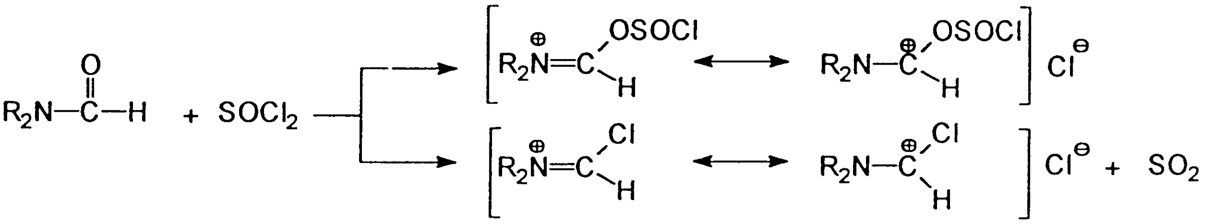
Maier[13] showed that the reaction of $SOCl_2$ with phosphonic esters can be catalyzed by N,N-disubstituted formamides. Through extensive investigation he was also able to show that the highest yield of a dichloride was obtained when the molar ratio of $SOCl_2$: phosphonate was 2,5 : 1. The amount of catalyst used was between 1 - 5 mol % per mole of phosphonate. The reaction proceeds stepwise and the half-esters are formed as first products (scheme **9**).



Scheme 9

He was also able to show that it was possible to synthesize and isolate the half-esters by changing the refluxing time of the reaction mixture. Great losses due to polymerization of the distillate were observed in these cases, although the ^{31}P NMR spectra indicated that the distillate contained nearly pure monochloride.

According to Maier, the activation of $SOCl_2$ by the catalyst, involves the formation of the following resonance stabilized ionic species (scheme **10**).



Scheme 10

Chlorination of phosphonic diesters to a monoester monochloride was an essential step in the synthesis of substrates needed for the kinetic studies. Maier's reaction[13] was however, only limited to the preparation of methylphosphonyl chloride, MeP(O)(OMe)Cl in 30% yield, since in other cases the Author observed highly advanced decomposition. That observation led to a study of the scope of this reaction.

The use of oxalyl chloride as chlorinating agent was also investigated. Successful conversions under the conditions provided by literature[14] could not be confirmed and the reaction conditions for a smooth conversion of phosphonates were established.

CHAPTER 2

RESULTS AND DISCUSSION

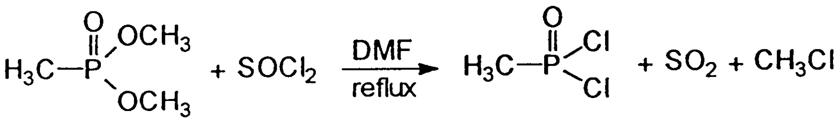
2.1 Synthesis

In view of the ambiguity in the interpretation of their results for the decomposition of N,N-dimethylaminoethyl methyl phosphonofluoridate, given by Benschop et. al.[8], and of the contradictory results obtained by Larsson[10], the first objective was to synthesize N,N-dimethylaminoethyl methylphosphonyl chloride in order to study its reactivity.

The reason for this choice results from the fact that chloride is a better leaving group than fluoride. If the proposed mechanism given in scheme **5** was followed, then the molecule containing the chloride should decompose faster than the fluoride derivative. The chloride could even be so unstable that it would decompose as soon as it was formed.

2.1.1 Attempted synthesis of N,N-dimethylaminoethyl methylphosphonyl chloride

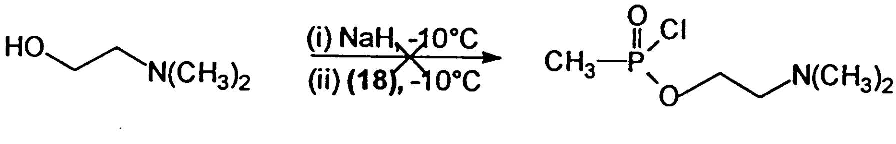
The preparation of half-esterchlorides, from the respective dichlorides and alcohols, have been used successfully in this laboratory by S Cocks[15]. The preparation of methylphosphonyl dichloride **(18)** from dimethyl methylphosphonate **(17)** was done according to the procedure published by Maier[13] and a yield of 80% of the dichloride **(18)** was obtained (scheme **11**).



(17) **(18)**

Scheme 11

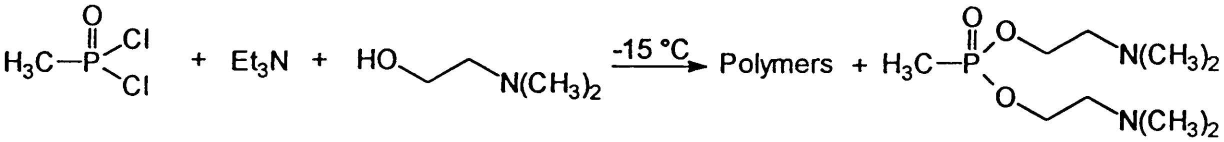
The dichloride **(18)** was then treated with one mole-equivalent of sodium 2-dimethylamino-ethanoate in the hope that the product of monosubstitution **(19)** will be formed. No expected product was, however, obtained, and the ^{31}P NMR analysis of the reaction product showed that a complex mixture of a polymeric material was produced (scheme **12**).



(19)

Scheme 12

Benschop[8] used a slightly different procedure in the preparation of the substrates that he used for the kinetic studies. The use of triethylamine as a base showed, however, that again a range of polymeric products was obtained. The ^{31}P NMR spectrum demonstrated also the formation of a single product at $\delta_{^{31}P}$ 33,73. This product was isolated and shown to be bis-N,N-dimethylaminoethyl methylphosphonate **(20)**. Its structure was identified unambiguously by ^{1}H and ^{31}P NMR spectroscopy (scheme **13**).



(18) **(20)**

Scheme 13

A theoretical yield of 50% is expected in the preparation of **(20)**, and in the preparation only a 2,2% yield of **(20)** could be obtained. This very low yield indicates two alternatives:

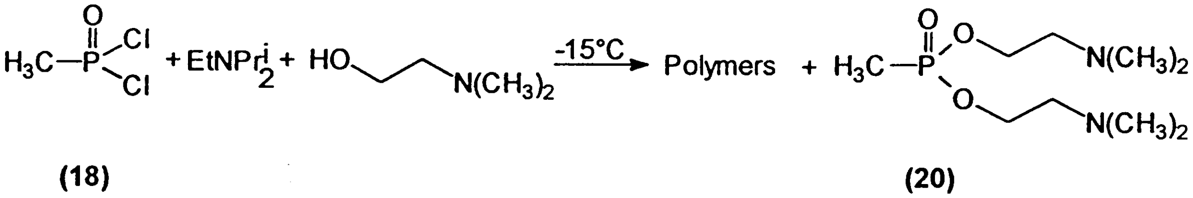
(i) The reaction conditions are not ideal for obtaining high yields of product **(20)**;

(ii) The reaction proceeds through the formation of the half-esterchloride. This intermediate can be so unstable and highly reactive that it leads to a series of side reactions giving rise to a range of phosphorus containing products observed in the ^{31}P

NMR spectra.

The chlorination of alkylphosphonates by PCl_5 , $SOCl_2$ and $(COCl)_2$[13, 14] all proceed stepwise through the formation of the half-esterchlorides. It therefore seems that if the half-esterchloride is so unstable, it could be impossible to synthesize N,N-dimethylaminoethyl methylphosphonyl chloride via this route.

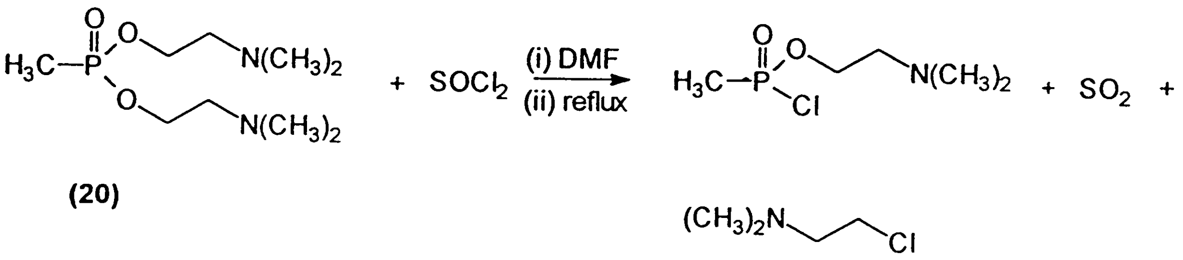
According to Lacey[16] undesired side processes occurring during the reaction of alcohols with phosphonic dichlorides can be prevented by making use of a hindered base to trap the hydrochloric acid formed in the reaction. He made use of 2,6-lutidine in his synthesis of monoester chlorides. The reaction shown in scheme **14** was therefore carried out with di-iso-propylethylamine used as base.



Scheme 14

The disubstituted product **(20)** was formed again with a yield of 10%. This reaction proved more successful than the previous one, but still the desired product could not be obtained.

Another possibility presented in scheme **15** was to first prepare **(20)** and then react it with a chlorinating agent in order to obtain the monochloride.



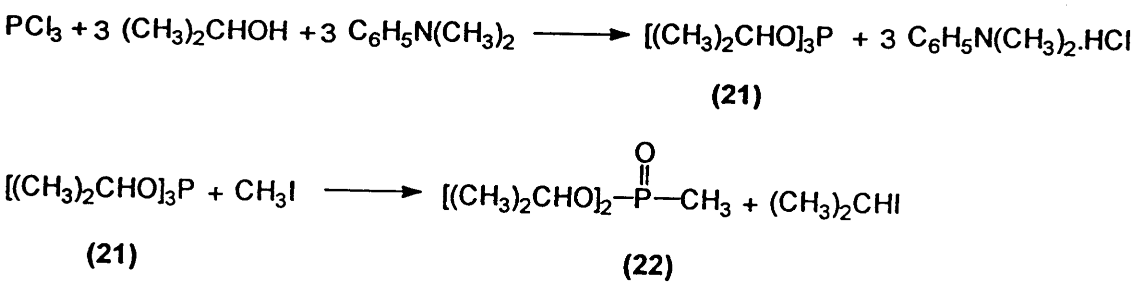
Scheme 15

2.1.2 Bis-N,N-dimethylaminoethyl methylphosphonate

The reaction shown in scheme **13** was repeated, using two mole-equivalents of the alcohol and the base. A yield of only 29% of the isolated **(20)** could be achieved. This result indicates that the mono-chloride is most probably so unstable that it would never be possible to synthesize it successfully. It was then decided to discontinue this investigation and concentrate on repeating one of Benschop's[8] reactions.

2.1.3 N,N-dimethylaminoethyl isopropyl methylphosphonate

It was decided to repeat the synthesis of **(12)**, described by Benschop, in order to learn more about the behaviour of this type of compounds. Isopropyl methylphosphonyl chloride **(16)** had to be synthesized as one of the substrates in the reaction shown in scheme **20** (see below). The procedure outlined by Ford-Moore[17, 18] was used to prepare diisopropyl methylphosphonate **(22)**. The whole sequence is shown in scheme **16**.



$$PCl_3 + 3\ (CH_3)_2CHOH + 3\ C_6H_5N(CH_3)_2 \longrightarrow [(CH_3)_2CHO]_3P + 3\ C_6H_5N(CH_3)_2.HCl$$

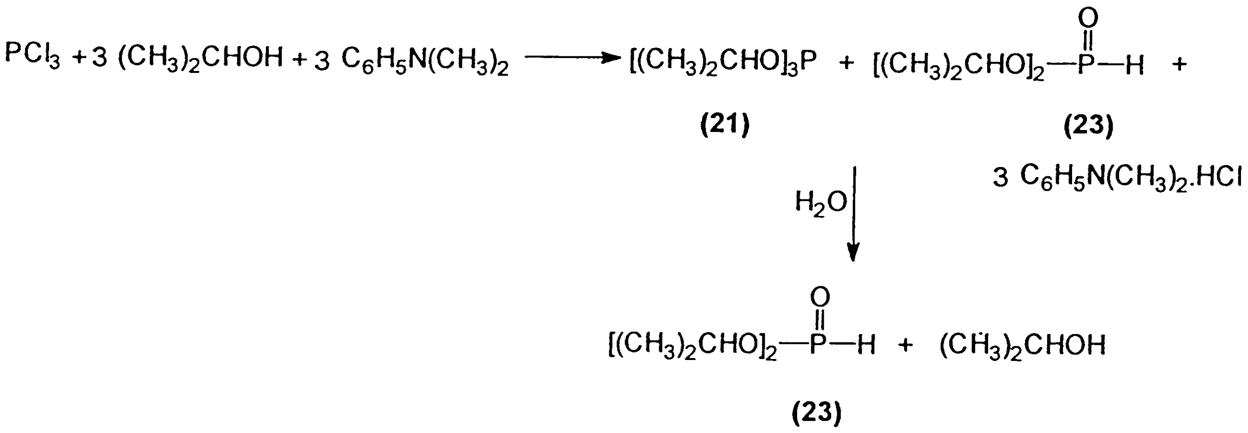
(21)

$$[(CH_3)_2CHO]_3P + CH_3I \longrightarrow [(CH_3)_2CHO]_2\overset{O}{\overset{\|}{P}}{-}CH_3 + (CH_3)_2CHI$$

(21) (22)

Scheme 16

The preparation of triisopropylphosphite **(21)** proved troublesome. In the publication[17] Ford-Moore warns that if efficient stirring is not maintained, then one of the isopropyl groups could be eliminated resulting in the appearance of dialkyl hydrogen phosphite **(23)** in the final distillate. A mechanical stirrer was not used in the preparation of **(21)** and it was found that the precipitate, formed during the reaction, was too thick for the magnetic stirrer to maintain efficient stirring. In the final distillate 40% of product **(23)** was obtained. Separation of the two compounds by fractional distillation proved very difficult, so it was decided to hydrolyse the crude product to the diisopropyl phosphite **(23)** as shown in scheme **17**.



$$PCl_3 + 3\ (CH_3)_2CHOH + 3\ C_6H_5N(CH_3)_2 \longrightarrow [(CH_3)_2CHO]_3P + [(CH_3)_2CHO]_2{-}\overset{O}{\overset{\|}{P}}{-}H + 3\ C_6H_5N(CH_3)_2.HCl$$

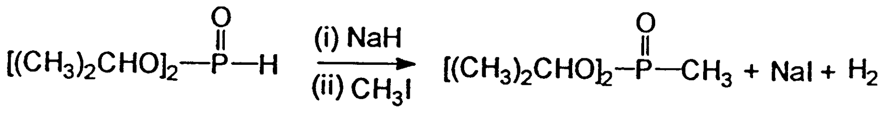
(21) (23)

$$\xrightarrow{H_2O} [(CH_3)_2CHO]_2{-}\overset{O}{\overset{\|}{P}}{-}H + (CH_3)_2CHOH$$

(23)

Scheme 17

The diisopropyl hydrogen phosphite **(23)** was then converted to diisopropyl methylphosphonate **(22)** in a Michaelis - Becker type of reaction (scheme **18**).



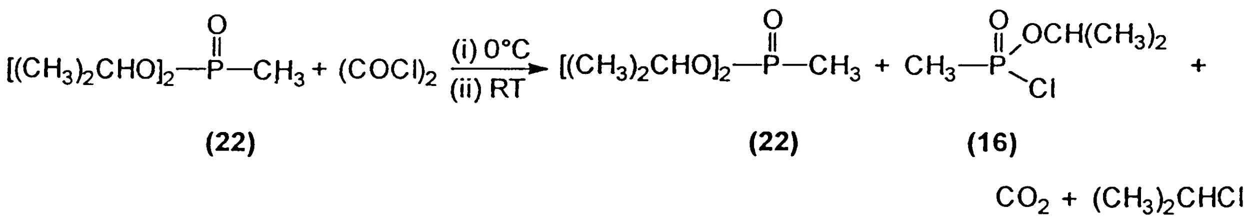
$$[(CH_3)_2CHO]_2P(=O){-}H \xrightarrow[\text{(ii) } CH_3I]{\text{(i) NaH}} [(CH_3)_2CHO]_2P(=O){-}CH_3 + NaI + H_2$$

(23) **(22)**

Scheme 18

Nevertheless on repeating the reaction depicted in scheme **16**, more solvent was used. The problem of the precipitate hindering the stirring was overcome and **(21)** was easily isolated and converted to **(22)**.

Chlorination of **(22)** was attempted next by using oxalyl chloride. Pelchowicz[14] reported a yield of 75% and Benschop[8] used this procedure to prepare isopropyl methylphosphonyl chloride **(16)**. This reaction could not be confirmed (scheme **19**), because upon distillation the distillate polymerized. When the reaction was repeated a ^{31}P NMR spectra of the crude product showed that after the reaction time of 24 hours only 20% conversion of **(22)** to **(16)** had occurred.

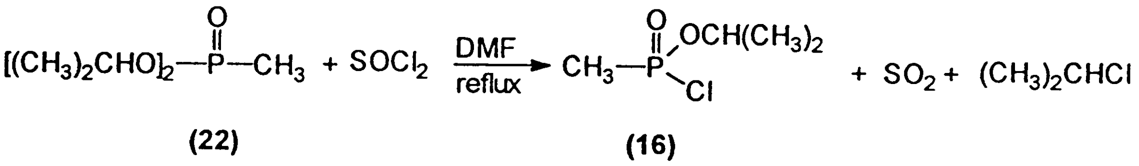


$$[(CH_3)_2CHO]_2P(=O){-}CH_3 + (COCl)_2 \xrightarrow[\text{(ii) RT}]{\text{(i) 0°C}} [(CH_3)_2CHO]_2P(=O){-}CH_3 + CH_3{-}P(=O)(OCH(CH_3)_2)Cl + CO_2 + (CH_3)_2CHCl$$

(22) **(22)** **(16)**

Scheme 19

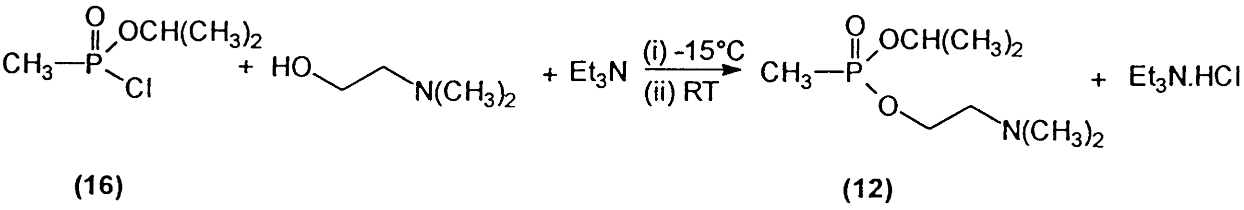
In the original publication, Maier's reaction[13] was only limited to the preparation of methyl methylphosphonyl chloride. It was decided to extend this reaction for the preparation of **(16)**. After 30 minutes of reaction, pure **(16)** was isolated by fractional distillation as a colourless oil with a yield of 62% (scheme **20**).



Scheme 20

This result suggests that the procedure introduced by Maier[13] has also value as a general route to phosphonic monoesters monochlorides.

In the final step in the synthesis of N,N-dimethylaminoethyl isopropyl methylphosphonate **(12)**, **(16)** was treated with 2-dimethylaminoethanol and triethylamine was used as base (scheme **21**).



Scheme 21

After filtration and evaporation of the ether, a white precipitate was present in the crude product. ^1H NMR spectroscopy, δ_{1H} 1,2 (t; J_{HH} 7,4 Hz; CH_3) ; 3,1 (q; J_{HH} 7,4 Hz; CH_2) confirmed that some of the triethylamine hydrochloric salt was still present in the product. From experience it is known that the presence of a chloride often leads to side reactions upon distillation and significant losses of product can be achieved. This salt had to be removed and it was decided to deprotonate it with a slightly stronger base, that is known to be insoluble in organic solvents. The crude product was therefore dissolved in chloroform and anhydrous potassium carbonate was added to the reaction mixture. This mixture was stirred overnight to ensure complete reaction and upon usual workup a clear yellow oil was obtained, with no traces of the triethylamine hydrochloride.

Later on in the project it was found that the salt could also be removed by dissolving the product in the minimum volume of chloroform and then adding five times this volume of ether. A white precipitate forms since the polarity of the solution decreases, and this salt could then be removed by filtration. ^1H NMR spectroscopy confirmed the complete removal of the ammonium salt.

The reaction shown in scheme **21** was however not as simple as written in the equation. The ^{31}P NMR showed that the additional product **(24)** was formed (Fig. **1**).

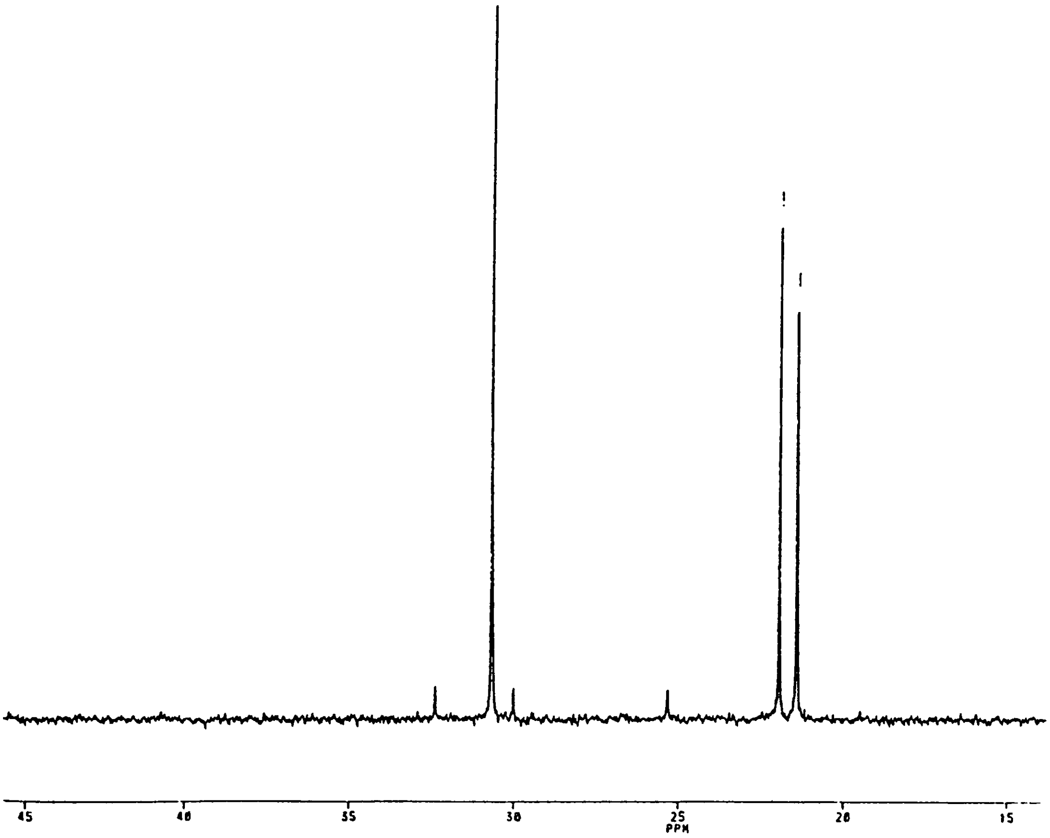
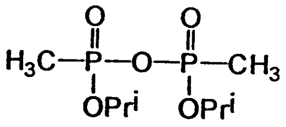


Figure 1: **^{31}P NMR spectrum of the crude product of the reaction shown in scheme 21.**

Product (12) δ_{31P} 30,6; Product (24) δ_{31P} 21,9; 21,4

Separation of the two components by bulb-to-bulb distillation proved possible, but great losses were encountered. In the first fraction pure **(12)** was obtained, but in the subsequent fractions containing **(12)** traces of **(24)** could always be found. The structure of **(12)** was confirmed by ^{1}H, ^{31}P and ^{13}C NMR spectroscopy.

Product **(24)** formed as a pair of diastereomers, was encountered is almost all condensation reactions and was identified as the symmetrical diisopropyl methylpyrophosphonate **(24)**.

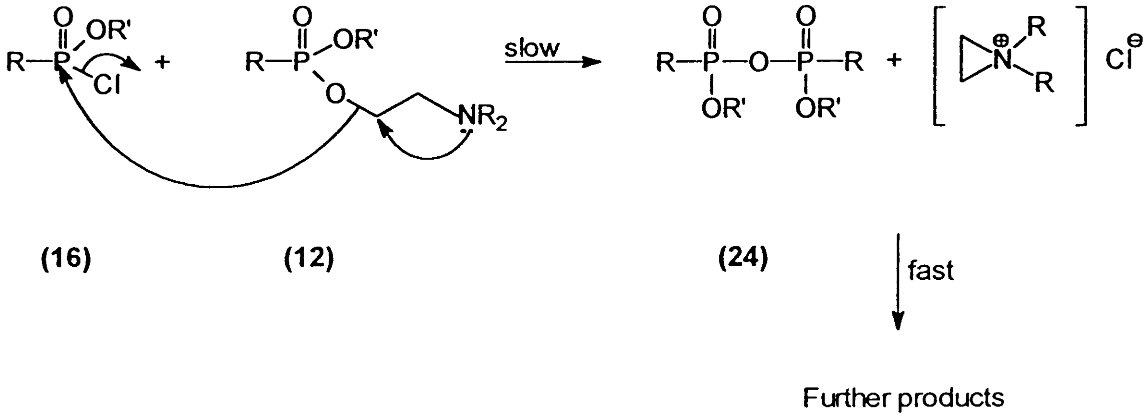


$$H_3C-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OPr^i}{|}}{P}}-O-\overset{\overset{\displaystyle O}{\|}}{\underset{\underset{\displaystyle OPr^i}{|}}{P}}-CH_3$$

(24)

At first it was thought that the appearance of **(24)** was due to the presence of moisture in the reaction medium, **[2(16) + $H_2O \rightarrow$ (24) + 2HCl]**, but careful drying of all reagents and solvent still afforded **(24)** with no appreciable change in yield.

The pyrophosphonate **(24)** could also be formed in a reaction between isopropyl methylphosphonyl chloride **(16)** and N,N-dimethylaminoethyl isopropyl methylphosphonate **(12)** produced in the reaction (scheme 22).

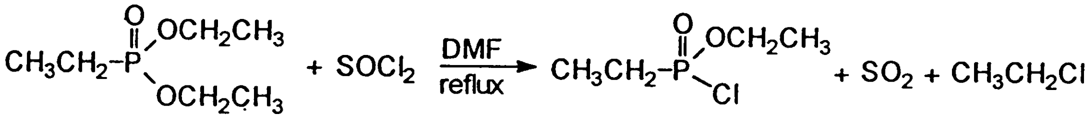


Scheme 22

The proposed mechanism shown in scheme 22, although reasonable, would be surprising because the product (12) is quite stable at room temperature and even in polar solvents the decomposition of (12) is relatively slow. In the decomposition reaction ions are formed and the polarity of the solvent will therefore play a large role. The synthesis of **(12)** was conducted in ether, which is a non-polar solvent, and would not therefore favour any decomposition. Under the conditions used the yield of the pyrophosphonate **(24)** was however quite high and no better explanation could be offered at that stage to explain the observed result than the reaction sequence shown in scheme **22**.

2.1.4 N,N-dimethylaminoethyl ethyl ethylphosphonate

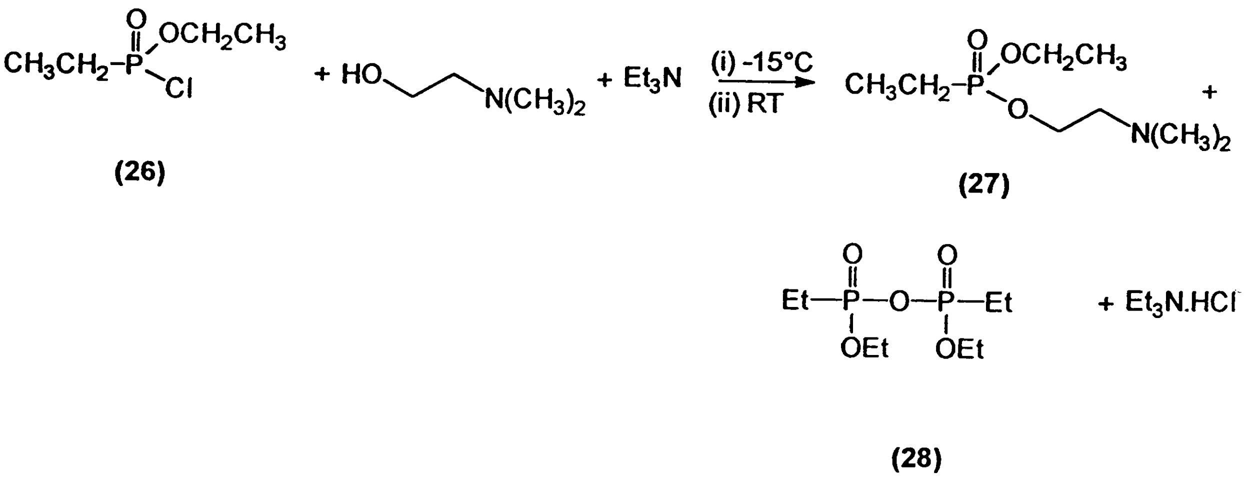
Ethyl ethylphosphonyl chloride **(26)** was synthesized (scheme **23**) according to Maier's reaction[13]. The product was isolated by fractional distillation as a colourless oil with a yield of 66%.



(25) **(26)**

Scheme 23

The reaction of the chloride **(26)** with 2-dimethylaminoethanol to produce N,N-dimethylaminoethyl ethyl ethylphosphonate **(27)** also gave diethyl ethylpyrophosphonate **(28)** as a side product (scheme **24**).



Scheme 24

The excess of triethylamine hydrochloric salt had to be removed as described in 2.1.3. The ^{31}P NMR spectra clearly indicated the formation of two phosphorus containing products (Fig. 2).

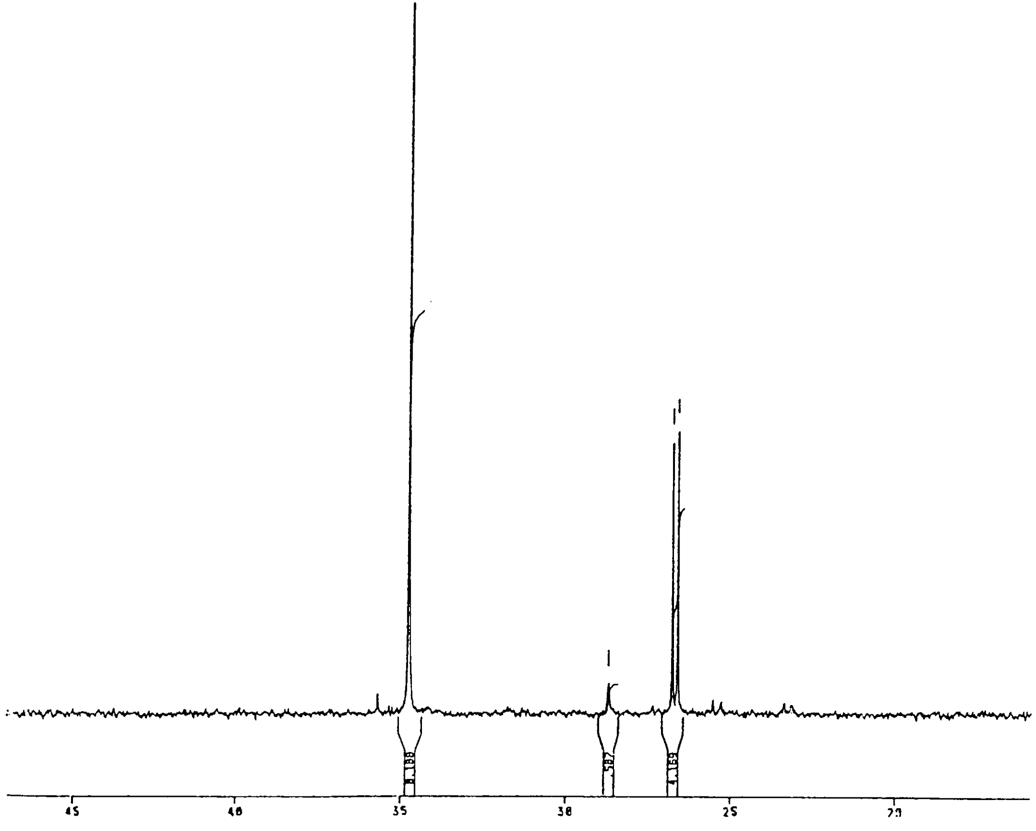
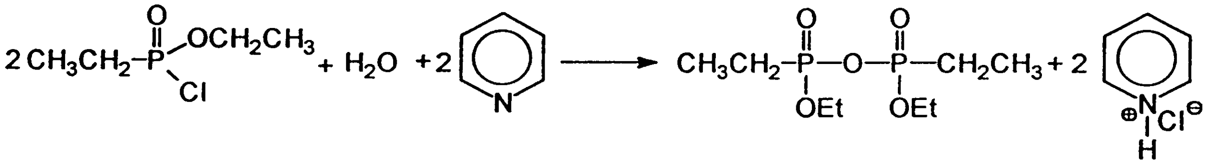


Figure 2 : ^{31}P NMR spectrum of the crude product of the reaction shown in scheme 24.

Product (27) δ_{31P} 34,8; Product (28) δ_{31P} 26,8; 26,6

It proved difficult to separate **(27)** from **(28)** by bulb-to-bulb distillation and pure **(27)** could only be obtained with a very low yield. The structure of **(27)** was confirmed by ^{1}H, ^{31}P and ^{13}C NMR spectroscopy.

The anhydride **(28)** could not be isolated by distillation, because traces of **(27)** could be found in all the fractions collected over a wide range of oven temperatures. The structure of **(28)** was confirmed by an independent synthesis[19] according to scheme **25** and comparing the ^{1}H and ^{31}P NMR spectra of the product with those of the material obtained before.



(26)

(28)

Scheme 25

The formation of the pyrophosphonate **(28)** seemed to be a general feature in the reaction reported by Benschop[8]. In scheme **22** a possible mechanism for the formation of the pyrophosphonate was presented. The formation of these compounds could be very useful, because certain derivatives of that type are used as insecticides[3]. A knowledge of the mechanism of their formation could therefore be of some importance. It was decided therefore to investigate this reaction in more detail.

2.1.4.1 Reaction of ethyl ethylphosphonyl chloride with N,N-dimethylaminoethyl ethyl ethylphosphonate

The reaction was studied in a sealed NMR tube. Equimolar amounts of both substances **(26,**

27) were mixed in deuterated chloroform. At different time intervals the ^{31}P NMR spectra of the sample was recorded and the proportion of each compound was determined.

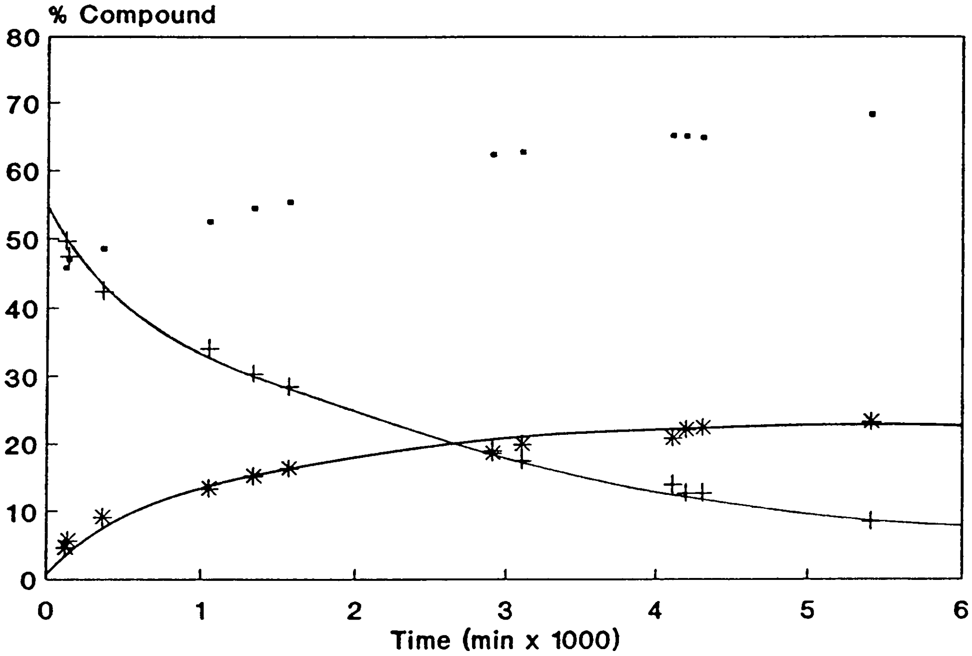
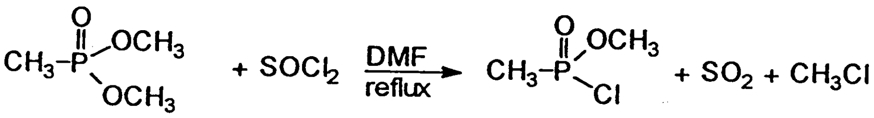


Figure 3 : Plot of the concentration (%) of 27 (■), 26 (+) and 28 (*) as a function of the reaction time in $CDCl_3$ at 60°C.

From the graph (Fig. 3) it can be clearly seen that the concentration of N,N-dimethylaminoethyl ethyl ethylphosphonate **(27)** stays constant over the whole range of time. For every two moles of the chloride **(26)** one mole of the pyrophosphonate **(28)** was produced. It was therefore concluded that the mechanism proposed in scheme **22** must be incorrect, at least for a non-polar solvent such as $CDCl_3$. No ether-d_{10} was available to carry out an analogous reaction in that solvent.

2.1.5 N,N-dimethylaminoethyl methyl methylphosphonate

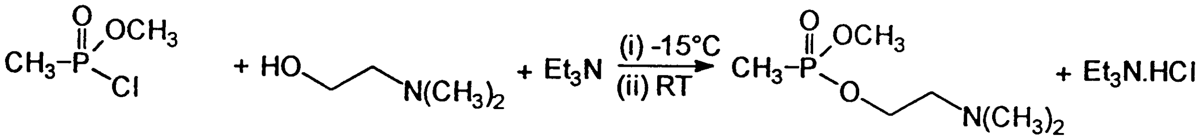
Methyl methylphosphonyl chloride **(29)** was synthesized (scheme **26**) under Maier's conditions[13]. The product was isolated by fractional distillation as a colourless oil with a yield of 65%.



(17) (29)

Scheme 26

Benschop's reaction[8] was used to obtain **(30)** (scheme 27). After the excess of triethylamine hydrochloric salt had been removed, the ^{31}P NMR spectra showed that mainly **(30)** (δ_{31P} 33,1) was formed, with only traces of other phosphorus containing compounds present. In this case the pyrophosphonate derivative was only formed in trace amounts. This time the product was easily isolated by fractional distillation. The structure of **(30)** was confirmed by ^{1}H, ^{31}P and ^{13}C NMR spectroscopy.

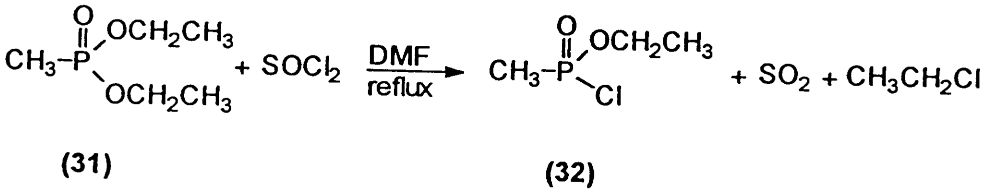


(29) (30)

Scheme 27

2.1.6 N,N-dimethylaminoethyl ethyl methylphosphonate

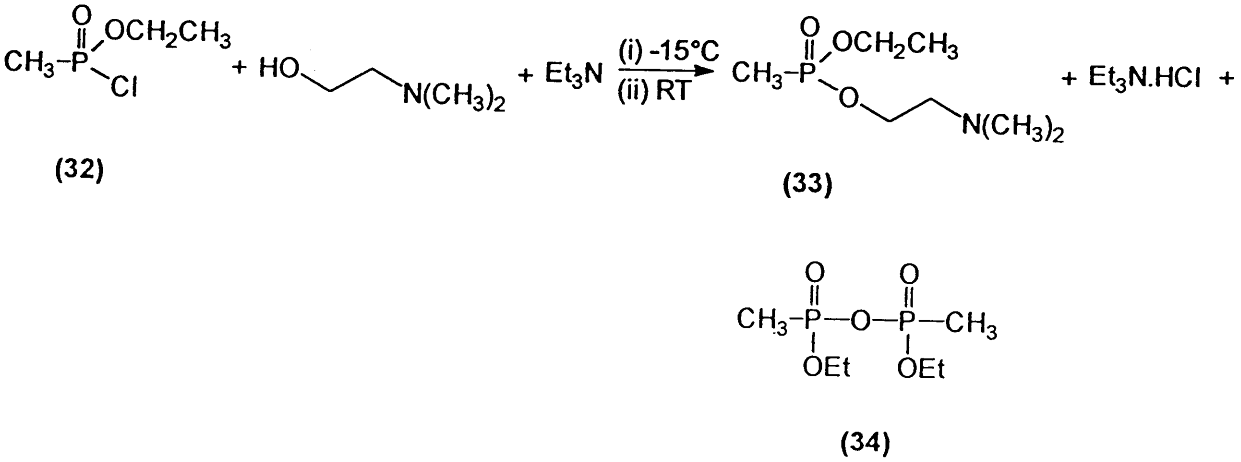
Methyl ethylphosphonyl chloride **(32)** was synthesized (scheme 28) using Maier's reaction[13]. The product was isolated as a colourless oil by fractional distillation with a yield of 60%. Its structure was confirmed by ^{1}H and ^{31}P NMR spectroscopy.



Scheme 28

During this preparation the ethyl chloride, formed as one of the products, was trapped and identified by ^{1}H NMR spectroscopy.

Benschop's reaction[8] was employed then to obtain **(33)** as shown in scheme **29.** The excess of triethylamine hydrochloric salt had to be removed. Once again, the ^{31}P NMR spectra of the crude oil showed that two products were present, **(33)** δ_{31P} 31,7 and **(34)** δ_{31P} 23,2; 22,9.

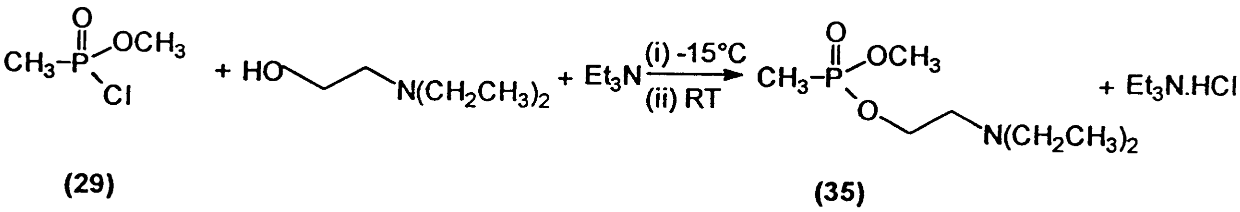


Scheme 29

Separation of **(33)** and **(34)** by distillation was not successful. Since **(33)** contains a tertiary amino function, precipitation of this product as a salt was attempted by passing dry HCl gas through the solution. Although the precipitation did not occur, extraction, followed by the neutralization of the aqueous phase and final extraction, allowed the isolation of pure **(33)** with a greatly improved yield. Further purification of **(33)** was unnecessary and its structure and purity was confirmed by ^{1}H, ^{31}P and ^{13}C NMR spectroscopy.

2.1.7 N,N-diethylaminoethyl methyl methylphosphonate

Benschop's reaction[8] was used to prepare **(35)**, as shown in scheme **30**. From the ^{31}P NMR spectra it could be seen that only one phosphorus containing product (δ_{31P} 32,8) was formed.

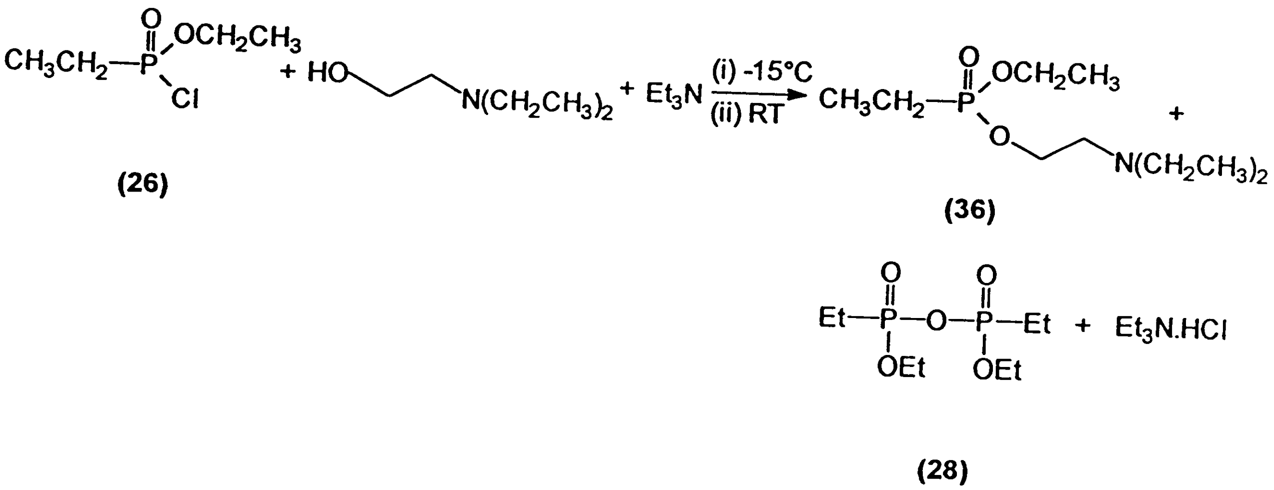


Scheme 30

After fractional distillation the structure of pure **(35)** was confirmed by ^{1}H, ^{31}P and ^{13}C NMR spectroscopy.

2.1.8 N,N-diethylaminoethyl ethyl ethylphosphonate

In this last synthesis Benschop's reaction[8] was employed again to obtain **(36)** (scheme **31**). After the excess of triethylamine hydrochloric salt was removed the ^{31}P NMR spectra showed that two phosphorus containing products had formed in the reaction, **(36)** δ_{31P} 34,6 and **(28)** δ_{31P} 26,7; 26,6.



Scheme 31

Acidification of the mixture and subsequent extraction yielded two fractions. Product **(36)** was identified by ^{1}H, ^{31}P and ^{13}C NMR spectroscopy.

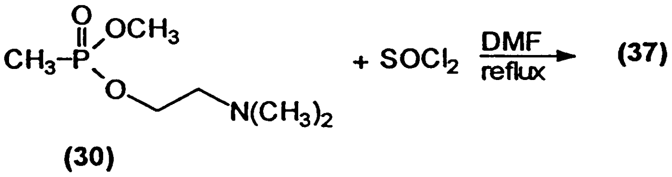
After the preparation of six mixed phosphonic diesters via the reaction between phosphonic monoesters monochlorides and 2-dimethylaminoethanol, it could be seen that the formation of pyrophosphonate as a byproduct is a random occurrence. In most cases the yield of that product was quite high, but with methyl methylphosphonyl chloride the pyrophosphonate was virtually absent. It was therefore concluded that the anhydride was formed from the chloride as a consequence of some residual moisture being present in the reaction system, with the aminoethanol acting as a basic catalyst. Benschop's reaction therefore requires extremely rigorous removal of traces of moisture from the reaction system. The mono-alkyl phosphonic monochlorides, R-P(O)(OR')Cl seem to be very susceptible to the reaction with water leading to the anhydride derivatives. When the chlorides were prepared and stored to be used in synthesis, the ^{31}P NMR spectra of each subsequent sample showed increasing amounts of the corresponding pyrophosphonates. This must have been due to slow, but inevitable (the experimental work was carried out during a particularly humid Transvaal summer) penetration of moisture in spite of all precautions taken. The ratio of the expected diester **(27)** and the pyrophosphonate **(28)** is approximately 2:1 (Fig. **2**). Simple calculation shows that such a proportion of the hydrolysis product would require approximately 0,4% (w/w) of water being present in the system. It is possible that the drying procedures, and/or handling of the reaction mixture was not efficient enough to reduce the moisture content below that level.

2.2 Reactions of thionyl chloride with phosphonic esters

Up to this stage of the project the use of thionyl chloride as chlorinating agent with N,N-dimethylformamide used as a catalyst proved to be a very successful procedure. It was decided next to investigate the reaction between N,N-dimethylaminoethyl methyl methylphosphonate **(30)** and thionyl chloride in order to see whether one of the ester groups could be replaced by chloride, as was the case in all the previous reactions of thionyl chloride. Replacement of the methoxy group by chloride seemed more likely, because the attack at this part of the molecule is sterically less hindered. If this was the case, then the target molecule, N,N-dimethylaminoethyl mehylphosphonyl chloride would be obtained, the synthesis of which was required at the beginning of the project. The initial results were puzzling at first, and gave rise to further investigation.

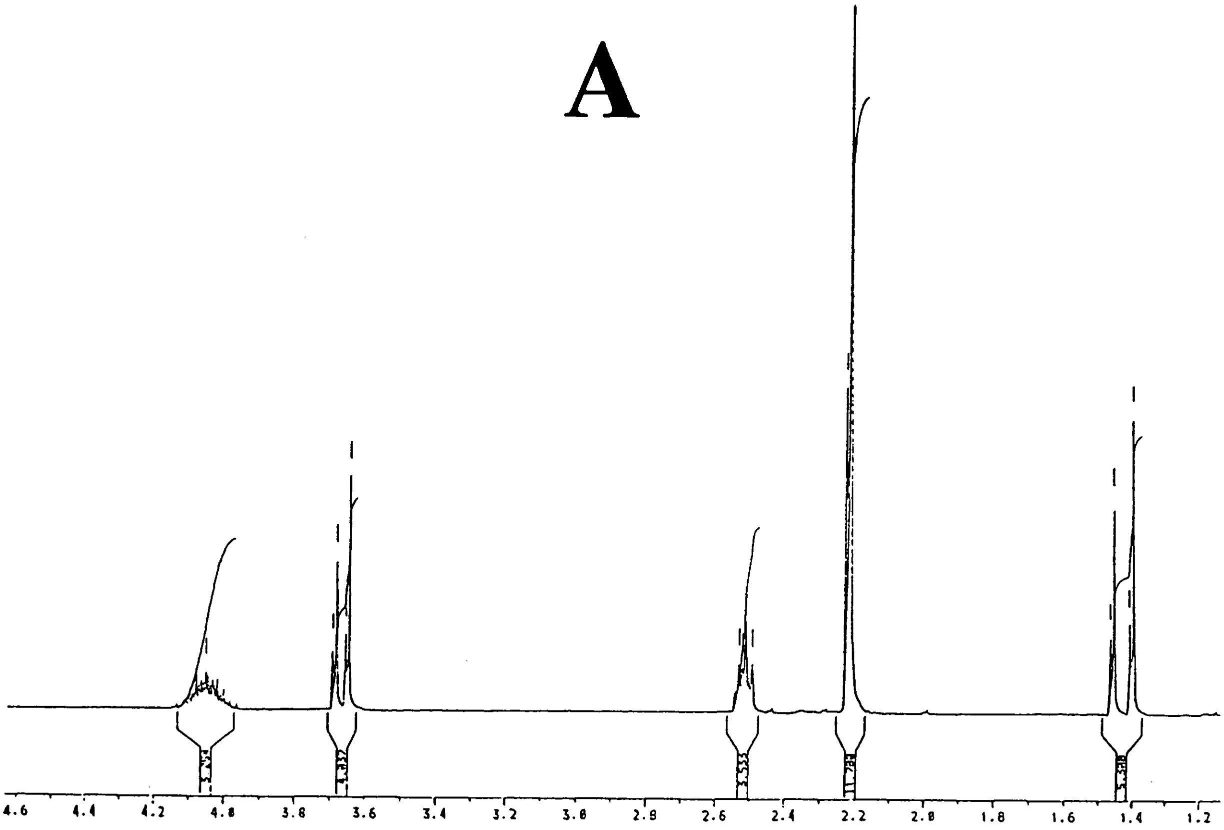
2.2.1 N,N-dimethylaminoethyl methyl methylphosphonate

The phosphonate **(30)** was reacted with thionyl chloride and DMF under Maier's conditions[13] (scheme **32**) to give a yellow precipitate, **(37)**.



Scheme 32

After recrystallization of the product in chloroform, the NMR spectra of the salt was recorded in D_2O. In the ^{31}P NMR spectrum an upfield shift from 33,1 for **(30)** to 30,6 was observed. This small shift was attributed to the different solvents used when recording the individual spectra. If chlorination had occurred, a drastic downfield shift was expected and therefore this could not have occurred. The respective ^{1}H NMR spectra of **(30)** and **(37)** are shown below (Fig. 4).



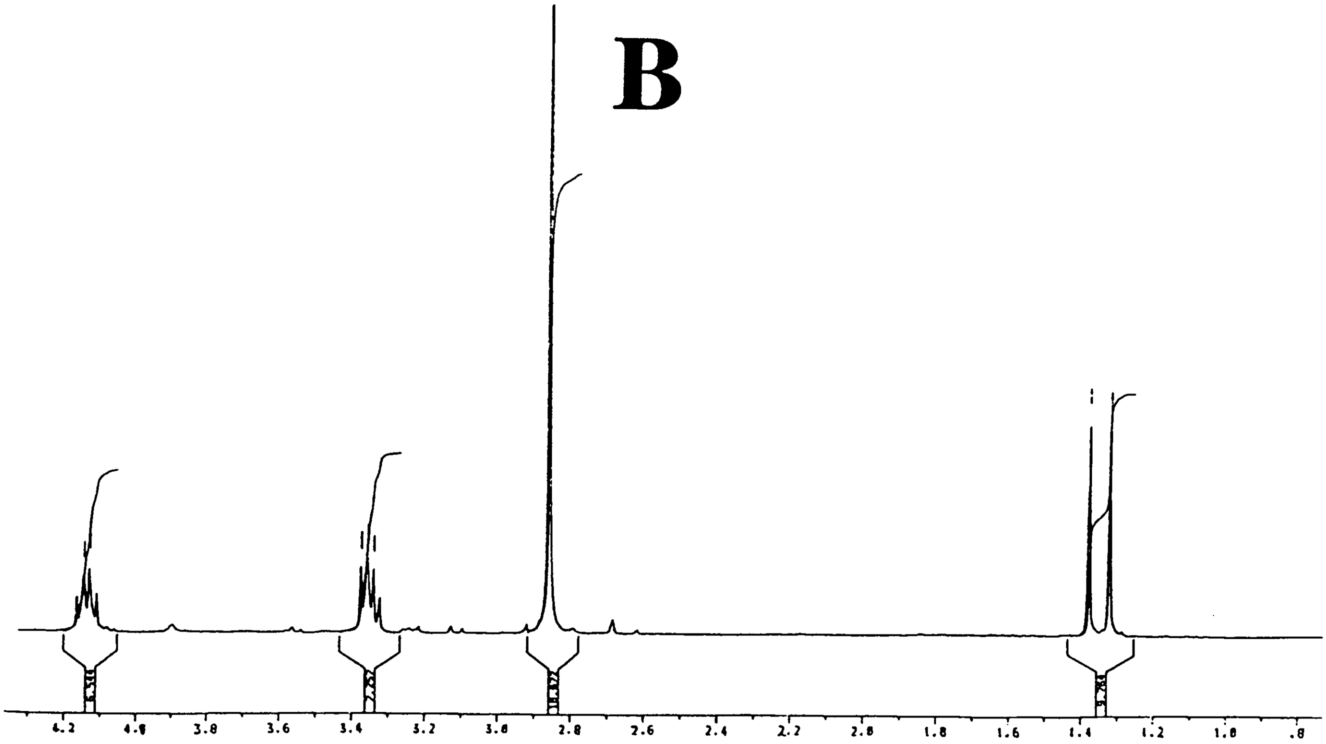
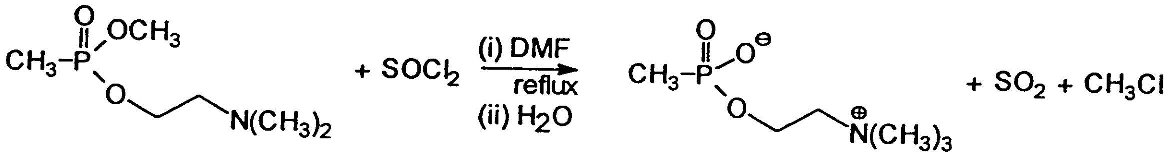


Figure 4: **A - ^{1}H NMR spectra of (30) in $CDCl_3$**

B - ^{1}H NMR spectra of (37) in D_2O

The ^{1}H NMR spectrum shows a downfield shift of all signals, plus the disappearance of the methoxy signal at δ_{1H} 3,7. The $N(CH_3)_2$ and CH_2N groups resonating at δ_{1H} 2,2 and 2,5 in **(30)** experienced the most drastic shift. This drastic downfield shift of the amino part of the molecule suggests that there should be a positive charge on the nitrogen atom.

All the evidence showed that the zwitterion **(38)** had formed in the reaction as shown in scheme 33.



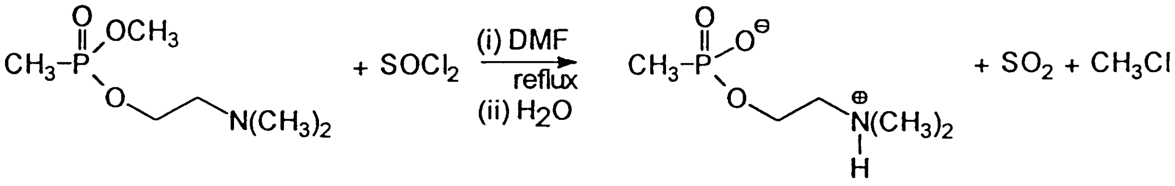
(30)

(38)

Scheme 33

The formation of zwitterions from the 2-dialkylaminoethyl esters of phosphoric and phosphonic acids are well documented in literature [20,21], but it was shown that the zwitterions are formed in a slow reaction. If the structure of **(38)** is correct, then this procedure could be very helpful in the preparation of such zwitterionic derivatives.

However, from the integration of the ^1H NMR spectra it can be seen that **(38)** was not formed. The integration data was more in agreement with only two N-Me groups present, therefore structure **(39)** was proposed (scheme **34**).

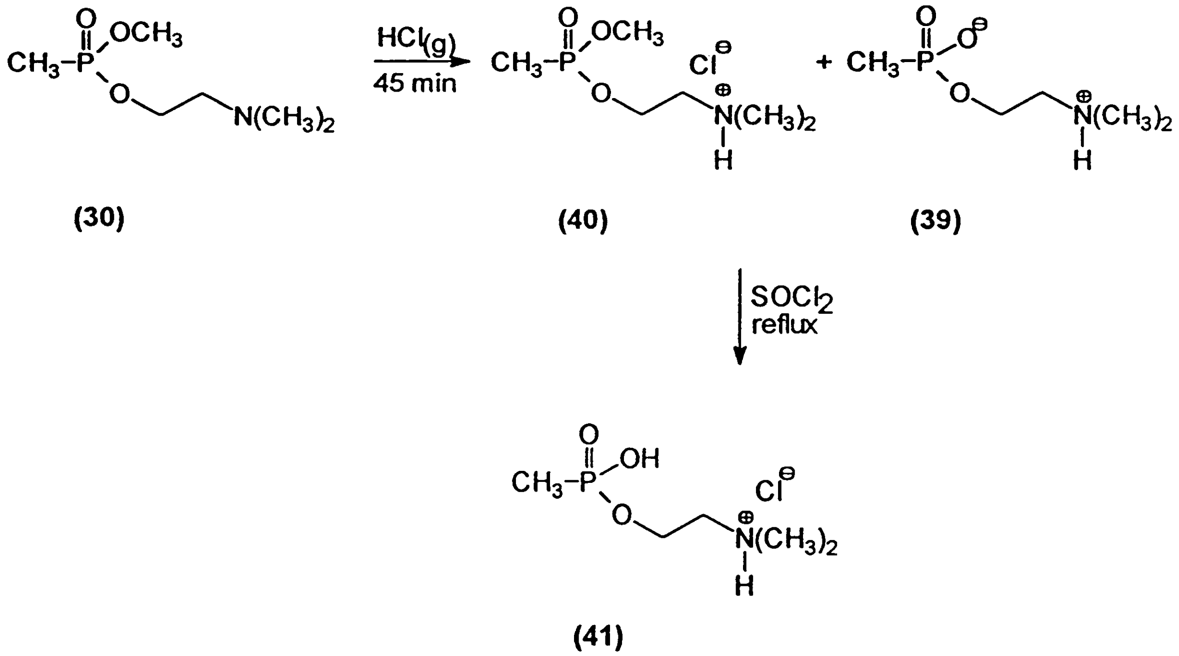


(30)

(39)

Scheme 34

To elucidate the structure of the product **(38 versus 39)**, a number of experiments were performed on substrate **(30)**. These reactions are shown in scheme **35**.



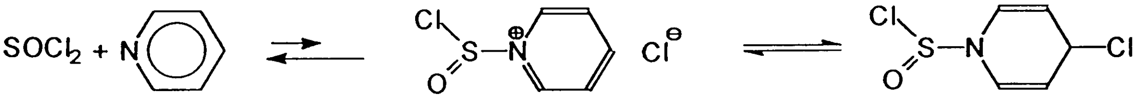
Scheme 35

Substrate **(30)** was treated with dry HCl gas at room temperature to prove that **(38/39)** are not simply formed by the reaction with HCl formed from the thionyl chloride due to the presence of moisture. Two products **(39)** δ_{31P} 30,2 and **(40)** δ_{31P} 34,0 were obtained. The structure of these products was deduced from the ^{1}H NMR spectrum of the mixture, **(40)** is a simple hydrochloric acid salt of **(30)**, while **(39)** is a zwitterion resulting from the nucleophilic demethylation of the ester function by the Cl$^-$ ion.

Warming up the mixture led to an increase of the proportion of **(39)** in the mixture, but after 12 hours at 60°C the composition of the mixture did not show further change, giving a **(39)**/**(40)** ratio of 1/3.

Treatment of the mixture of **(39)** and **(40)** with boiling thionyl chloride afforded pure **(41)**, that is the HCl salt of **(39)** δ_{31P} 32,3. Since all the NMR spectra discussed above were recorded in D_2O it was possible that this solvent was also reacting with the primary products, and that the observed spectra were in fact those of the secondary products. It was therefore decided to record the spectra of the salt **(41)** in DMSO-d_6. Interestingly enough, two phosphorus products of δ_{31P} 29,0 (Major) and 25,6 (Minor) were now observed. The difference of chemical shift of the major product relative to that of **(41)** in D_2O ($\Delta\delta_{31P}$ = -3,3 ppm) seems too large for a simple solvent effect, and it indicates that in fact two different species were recorded; the primary product in DMSO-d_6, and the product of hydrolysis in D_2O.

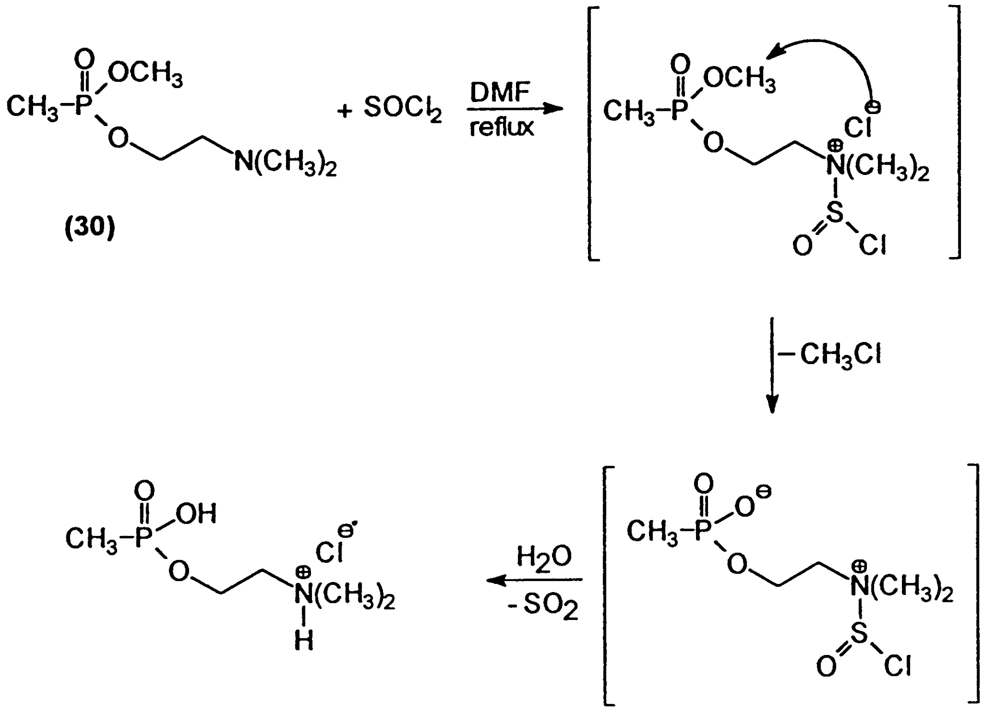
A. Maquestiau et. al.[22] reported that thionyl chlorides and N-heteroaromatic systems form an ionic product existing in equilibrium with the corresponding 1-(halosulfinyl)heteroarylium halides **(42)** as depicted in scheme **36**.



(42)

Scheme 36

It seemed therefore logical to postulate that the same type of mechanism was operating in the case of the tertiary amino group present in our substrate. In scheme **37** the formation of the primary product is shown.



(30)

(41)

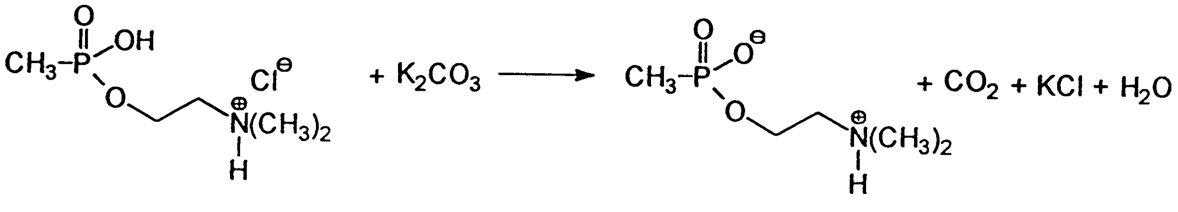
(43)

Scheme 37

The intermediate **(43)** is unstable and the presence of a trace of moisture would ensure that hydrolysis occurs. The expulsion of SO_2 gas serves as driving force for this reaction. When DMSO-d_6 was used as a solvent, only trace amounts of **(41)** were observed and **(43)** was the main product.

In principle, it is possible to confirm the presence of the S=O group by means of infrared spectroscopy. The IR spectrum of the solid product showed two absorption peaks at 1212 and 1174 cm^{-1}. They could be assigned to the P=O and S=O functions, but are too close to enable unambiguous interpretation of the spectra.

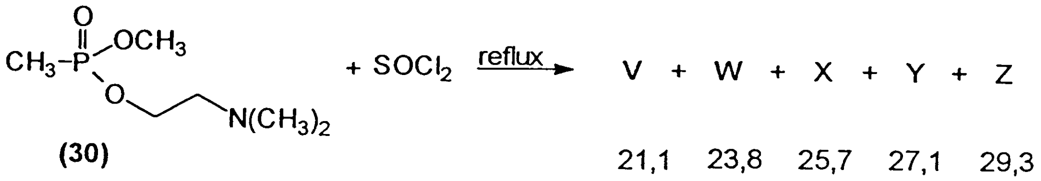
Finally to ensure that no zwitterionic product, but an HCl salt had formed, **(41)** was treated with potassium carbonate. If **(41)** was the zwitterion, then no reaction should occur, but the expulsion of carbon dioxide gas upon treatment showed that a reaction was indeed taking place (scheme **38**).



Scheme 38

The structure of **(44)** was confirmed by ^1H and ^{31}P NMR spectroscopy.

As shown in scheme **35**, salt **(41)** could be obtained by reacting the hydrochloric salt of the diester **(40)** with thionyl chloride in the absence of any catalyst. The omission of the catalyst in the "normal" Maier's reaction[13] lead to the formation of five phosphorus containing products as shown by ^{31}P NMR spectroscopy (scheme **39**).



Scheme 39

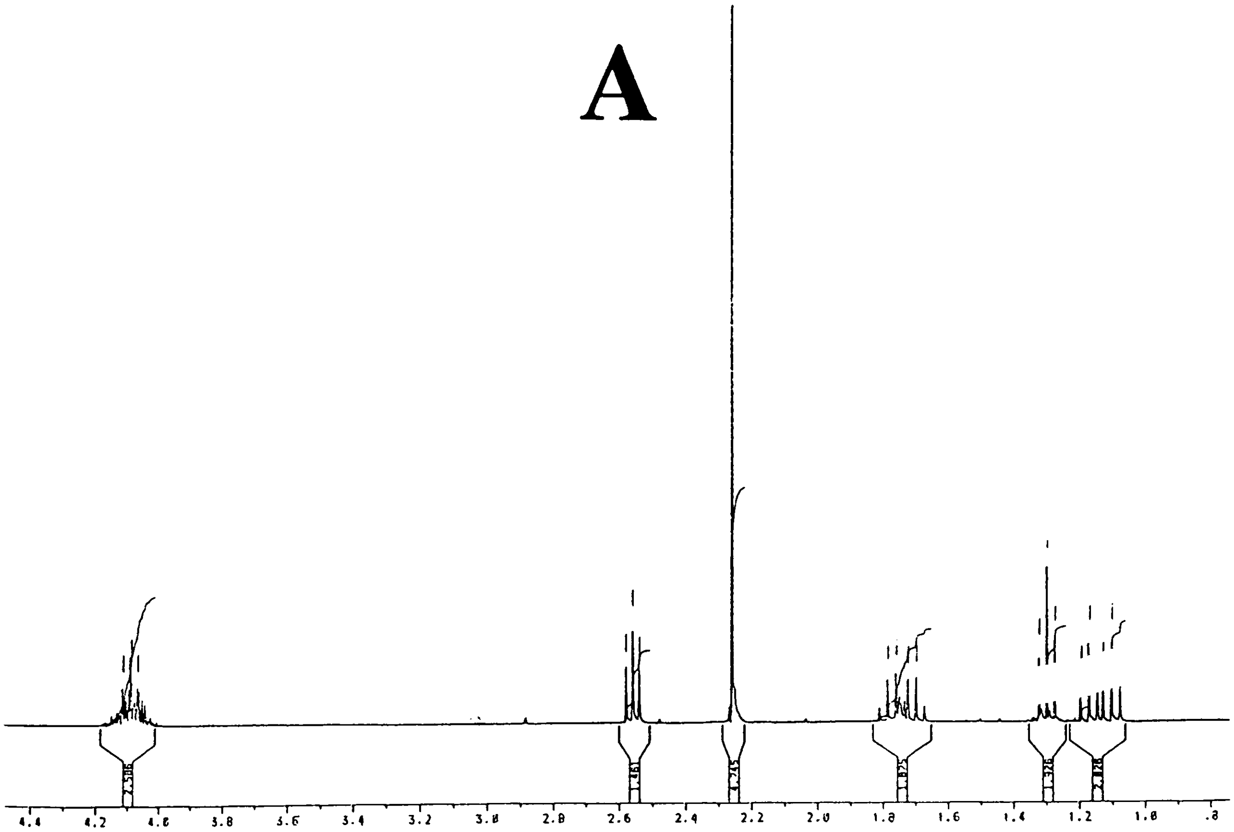
The reactions discussed above showed that the "normal" Maier's reaction[13] did not work in a usual way if a tertiary amino group was present in the substrate's molecule. It was decided therefore to investigate a system in which the tertiary amine was not present in the substrate, but was added externally as a reagent in the form of triethylamine.

2.2.2 Dimethyl methylphosphonate

The reaction between dimethyl methylphosphonate and thionyl chloride, in the presence of N,N-dimethylformamide, was shown in scheme **26** and a yield of 65% of the half-ester chloride was obtained. When the reaction was repeated at low temperature with an equimolar amount of triethylamine present, only a wide range of polymeric products was obtained.

2.2.3 N,N-dimethylaminoethyl ethyl ethylphosphonate

Upon reacting N,N-dimethylaminoethyl ethyl ethylphosphonate with thionyl chloride, in the presence of DMF, under Maier's conditions[13], a yellow oil was obtained. The ^{31}P NMR spectra recorded in $CDCl_3$ showed that two phosphorus containing products (δ_{31P} 36,5 and 50,1) had formed. The ^{1}H NMR spectrum showed (Fig. **5**) the same features as those described in 2.2.1.



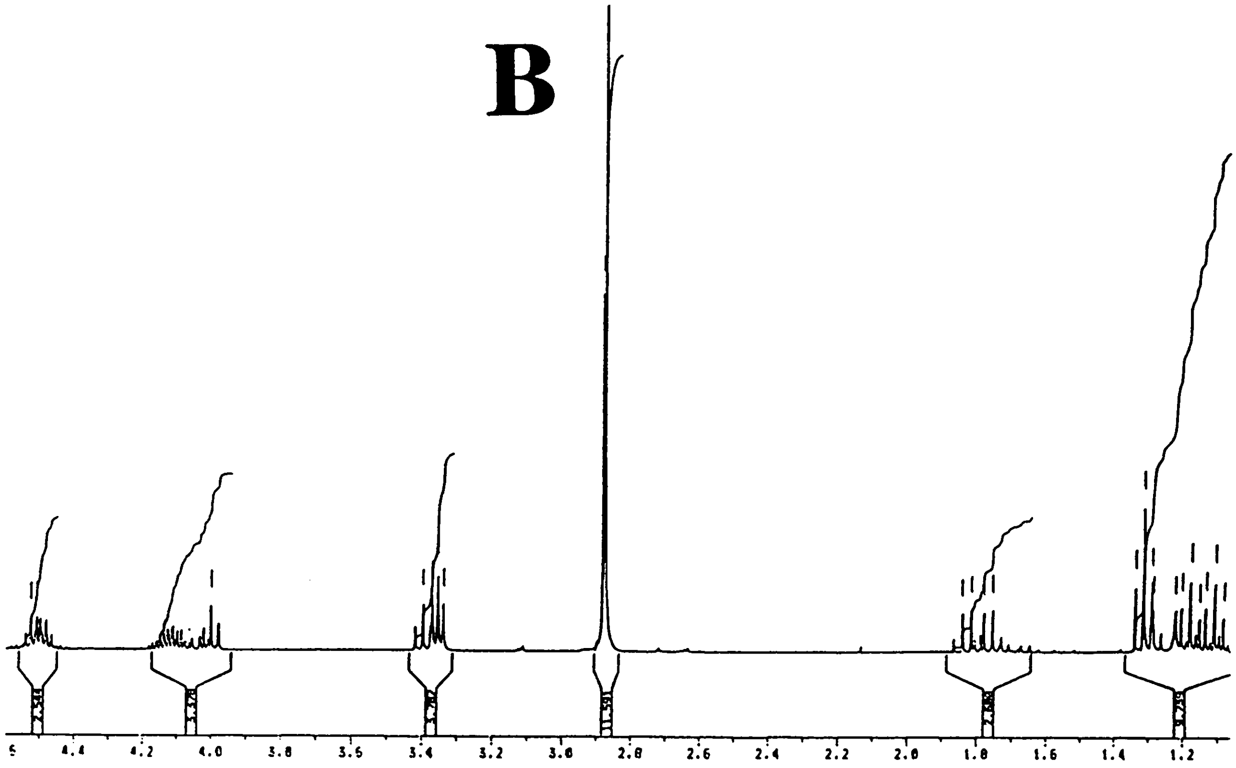
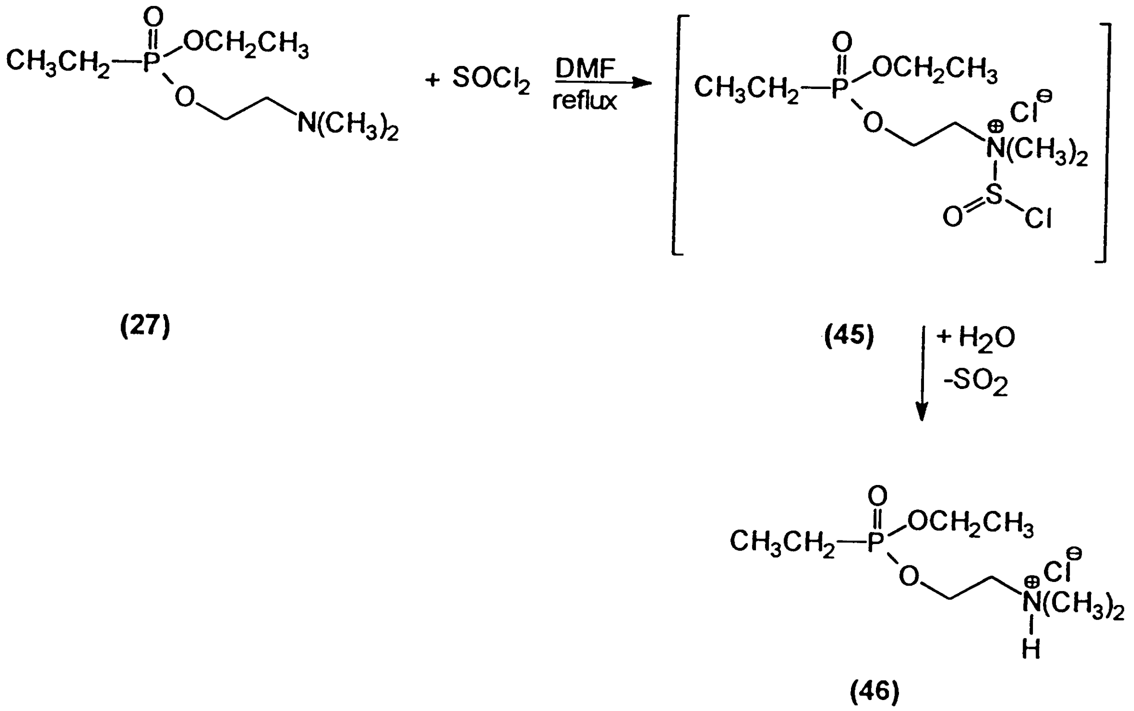


Figure 5: A - ^{1}H NMR spectra of (27) in $CDCl_3$

B - ^{1}H NMR spectra of (46) in $CDCl_3$

The large downfield shift of the NMe_2 , CH_2N and OCH_2 signals shows that deshielding effects are concentrated at this part of the molecule. The other peaks were also effected, but the effect was not as drastic. Removal of the ethoxy ester group had not occurred in this case as was expected, due to the known lower reactivity of ethyl esters in dealkylation. The shift in the ^{31}P spectrum was also very small (δ_{31P} 34,8 shifting to 36,5).

It is therefore suggested that **(45)** was formed in the reaction, as an unstable intermediate, and reacted with traces of moisture to yield **(46)**, as shown in scheme **40**.



Scheme 40

Again, the presence of the tertiary amino group in the substrate had changed the course of Maier's reaction. To investigate the displacement of an ester group by a chloride ion, in the presence of a tertiary amino group, it was decided to carry out the reaction between diethyl ethylphosphonate and thionyl chloride in the presence of an equimolar amount of triethylamine.

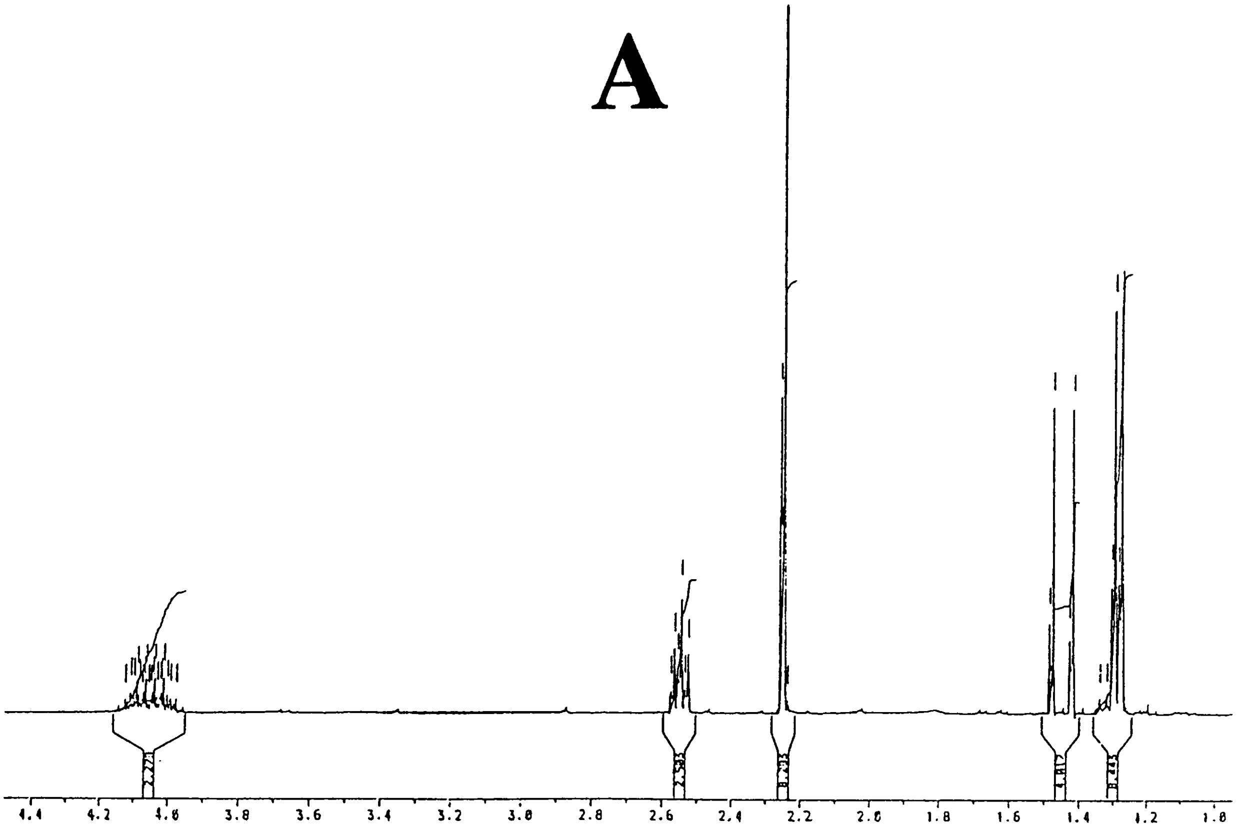
2.2.4 Diethyl ethylphosphonate

The reaction between diethyl ethylphosphonate and thionyl chloride in the presence of a catalytic amount of DMF was presented in scheme **23** and gave a yield of 66% of the half-ester chloride. When the reaction was repeated using an equimolar amount of triethylamine in place of DMF, the exothermic reaction yielded a dark-brown precipitate with no evidence of the conversion of the ester to the chloro ester.

The presence of the tertiary amino group therefore catalyses the reaction between the diester and thionyl chloride, but inhibits the chlorination if the concentration of the tertiary amino group becomes too large. This result is in agreement with Maier's observation[13] that the best yields of dichlorides from a diester were obtained when the amount of the catalyst was between 1 and 5 mol % of the diester.

2.2.5 N,N-dimethylaminoethyl isopropyl methylphosphonate

In the reaction between N,N-dimethylaminoethyl isopropyl methylphosphonate and thionyl chloride with DMF a yellow crystalline material was obtained. This product was purified by recrystallization from chloroform. Again the change in the ^{31}P NMR spectrum was small (δ_{31P} 30,6 changed to 31,4), but the ^{1}H NMR spectra (Fig. 6) again showed the drastic downfield shift for all the protons in the vicinity of the nitrogen atom.



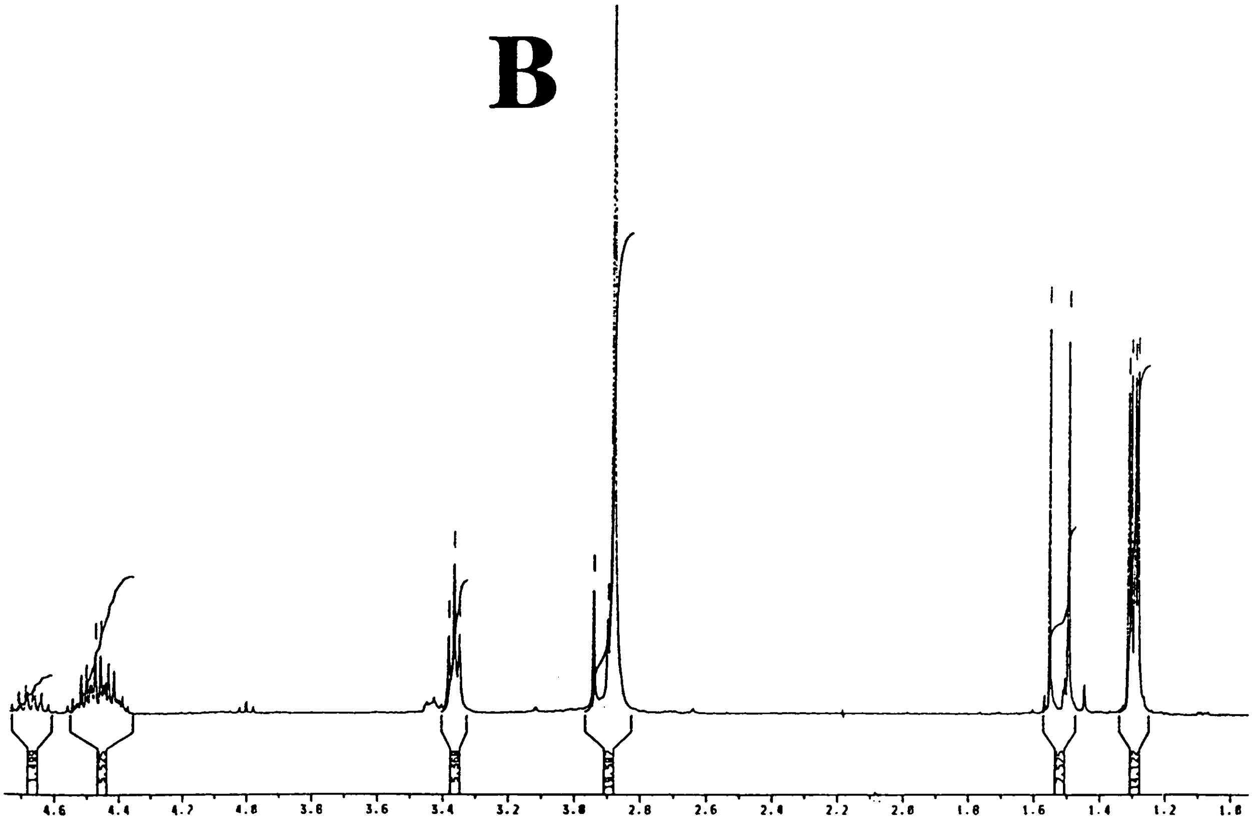
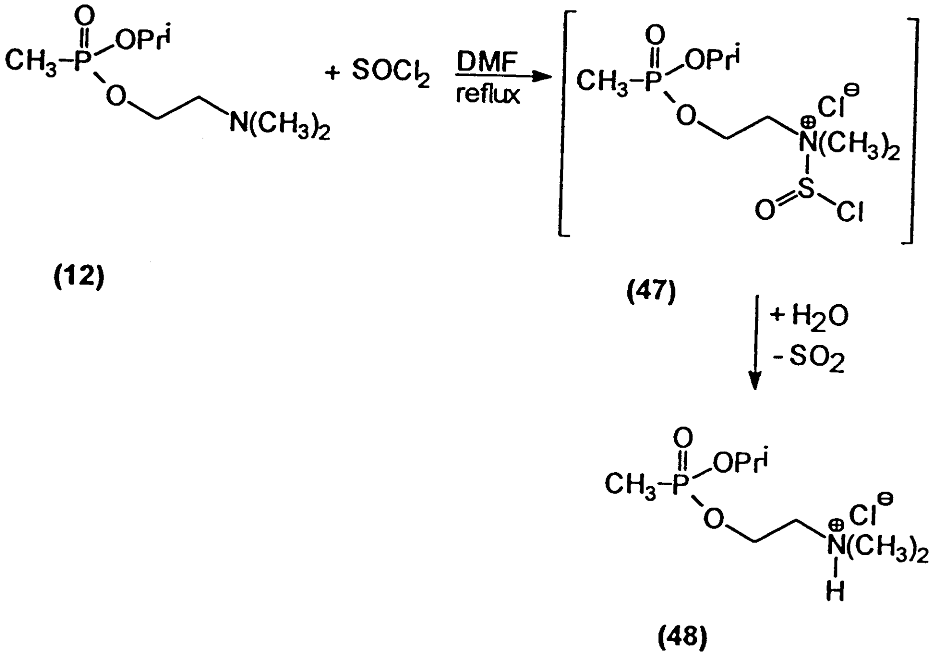


Figure 6: A - ^{1}H NMR spectra of (12) in CDCl$_3$

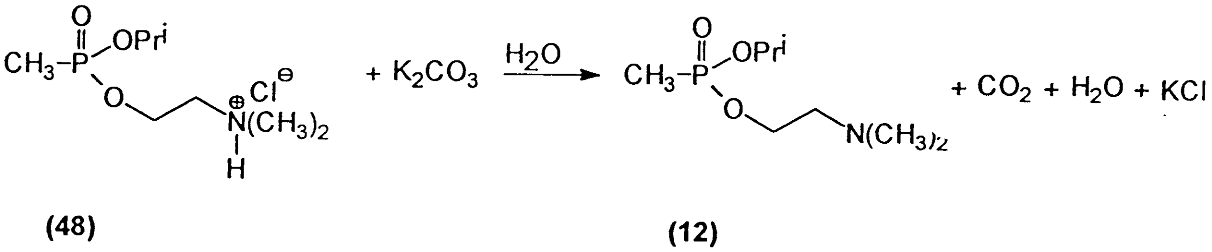
B - ^{1}H NMR spectra of (48) in CDCl$_3$

This downfield shift was again attributed to the effect of a positive charge forming on the nitrogen atom. The signal of the isopropoxy group remained unchanged (δ_{1H} 1,3 and 4,5 for the CH$_3$ and CH groups, respectively). Chlorination of the ester group was therefore also inhibited by the presence of the tertiary amino group in the molecule. The unstable intermediate **(47)** was therefore probably formed (scheme **42**) and decomposed fast to the more stable salt **(48)**.



Scheme 42

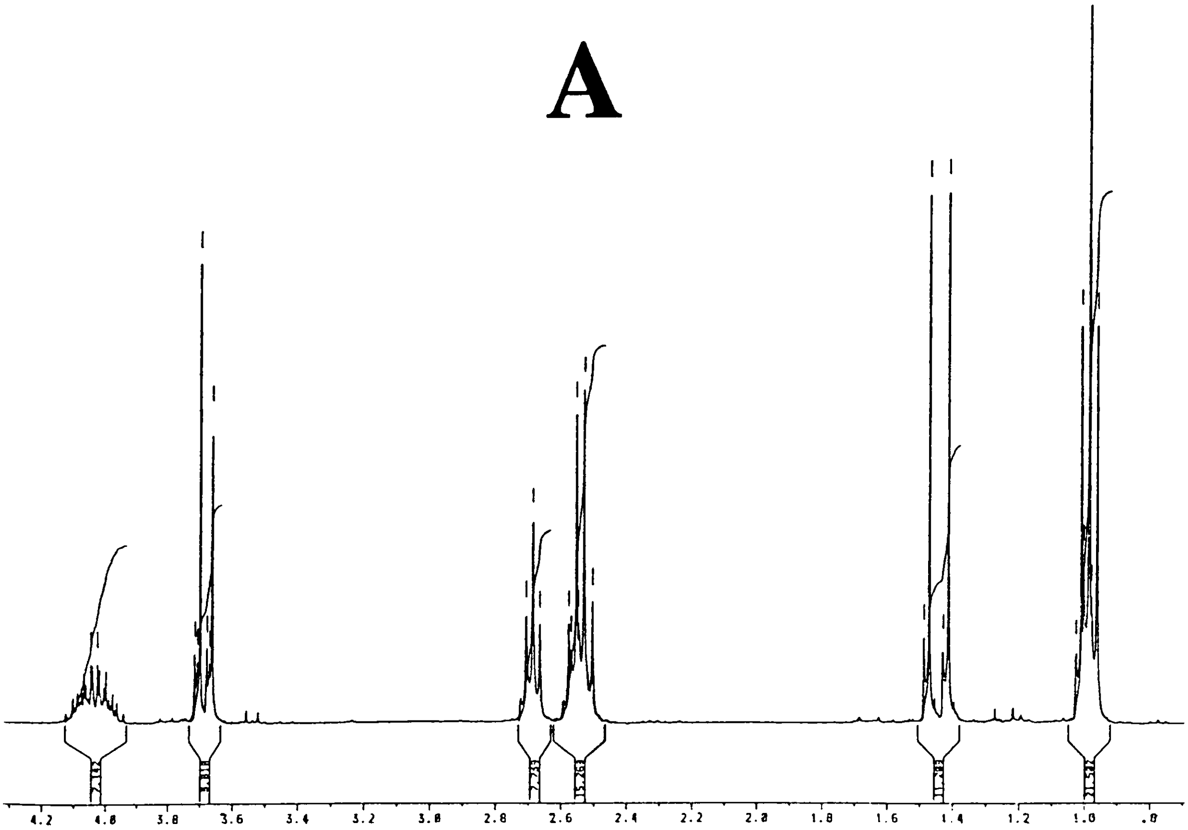
To identify the hydrochloric salt **(48)**, the same salt was synthesized by treating the substrate **(12)** with dry HCl gas. The ^1H and ^{31}P NMR spectra obtained were identical to those of product **(48)**. When the salt **(48)** was dissolved in water and potassium carbonate was added, carbon dioxide gas was released and the original ester was recovered (scheme **43**), as shown by ^1H and ^{31}P NMR spectroscopy.



Scheme 43

2.2.6 N,N-diethylaminoethyl methyl methylphosphonate

When N,N-diethylaminoethyl methyl methylphosphonate was treated with thionyl chloride and DMF under Maier's conditions[13] a brown oil, containing two phosphorus products was obtained. In contrast to the previous reactions of 2-dialkylaminoethyl phosphonates with thionyl chloride, the shift of the ^{31}P signal for the product was far downfield i.e. ($\delta_{^{31}P}$ 32,8 to 43,3). This in itself suggested that chlorination had occurred and that the half-ester chloride had formed. The minor phosphorus peak was attributed to the decomposition product of this ester chloride and later in the kinetic studies it was shown to be indeed the case. The ^1H NMR spectra of the substrate **(35)** and product **(49)** are given below (Fig. 7).



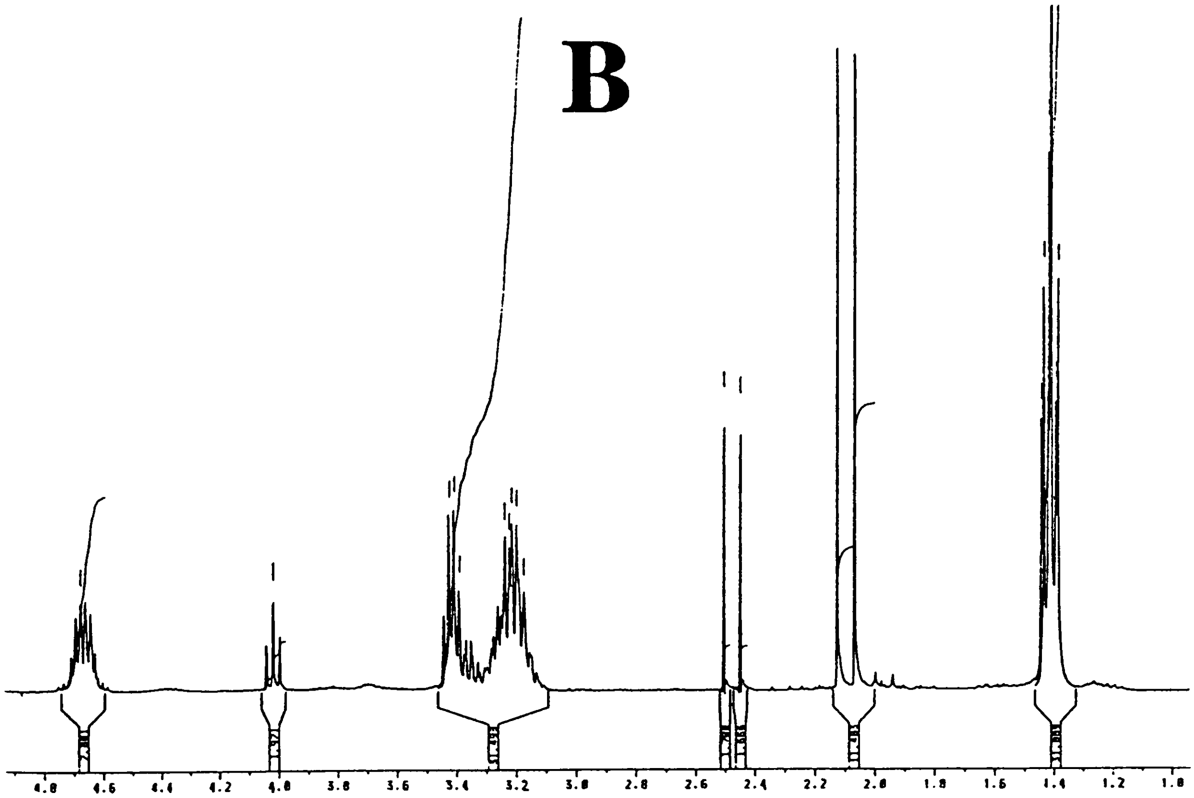
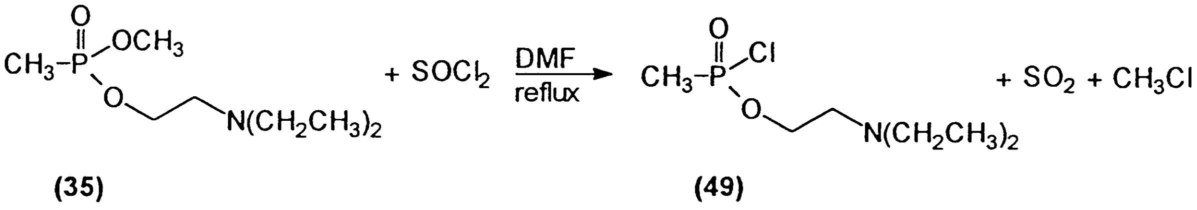


Figure 7: A - ^{1}H NMR spectra of (35) in $CDCl_3$

B - ^{1}H NMR spectra of (49) in $CDCl_3$

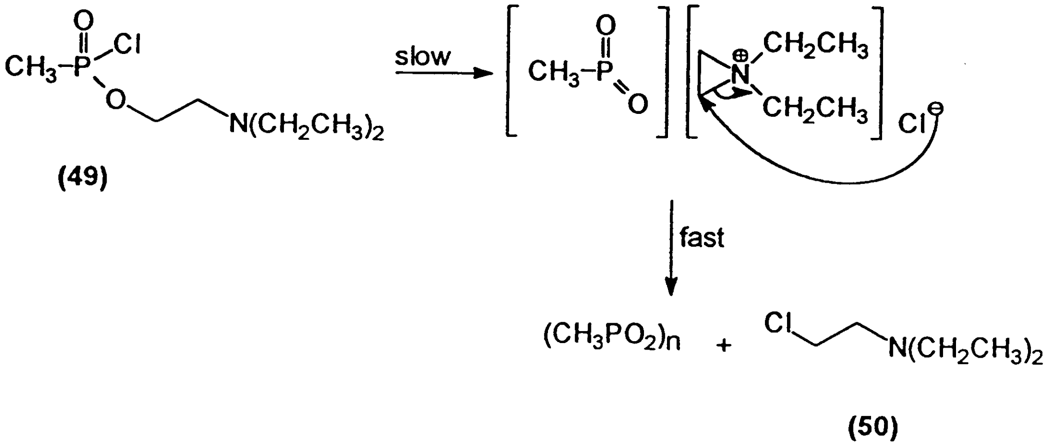
The disappearance of the methoxy group (δ_{1H} 3,7 in **(35)**) could be seen as well as the downfield shift of the signals, due to the effect of the electronegative chloride atom present in the molecule. Distillation of the chloride was not attempted due to its high reactivity.



Scheme 44

The reaction in scheme **44** indicates that the mechanism of chlorination of the diesters is also effected by the nature of the alkyl groups on the nitrogen atom.

The appearance to the triplet at δ_{1H} 4,0 (Fig. **7 B**) could not initially be explained. It was, however realized that such a signal is to be expected if a spontaneous fragmentation of **(49)**, following the mechanism shown in scheme **45**, was taking place. The fragmentation should lead to the molecule diethyl-(2-chloroethyl)amine **(50)** as a final product, and the observed triplet at δ_{1H} 4,0 corresponds to the CH_2Cl group of that product. The mechanism of the postulated fragmentation of **(49)** is shown in scheme **45**.



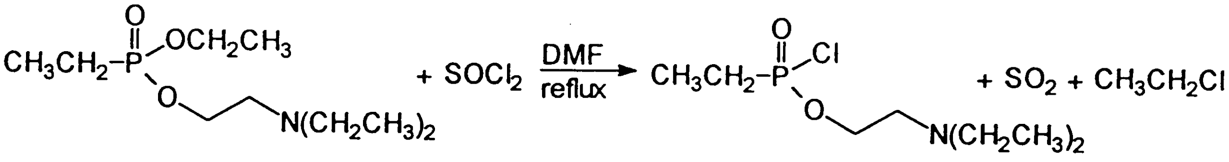
Scheme 45

In the fragmentation of phosphonic 2-dialkylaminoethyl esters monofluorides, Benschop[8] observed the formation of the N,N,N',N'-tetrasubstituted piperazinium ion as final product. Since the chloride ion is a better nucleophile than fluoride, we explain the absence of the piperazinium salt by the nucleophilic ring opening of the aziridinium intermediate by the chloride ion.

2.2.7 N,N-diethylaminoethyl ethyl ethylphosphonate

N,N-diethylaminoethyl ethyl ethylphosphonate reacted with thionyl chloride and DMF under

Maier's conditions[13] to give more than one phosphorus containing product as shown by the ^{31}P NMR spectra. The shift in δ_{31P} value for the major product was far downfield i.e.(from δ_{31P} 34,6 to 49,7). This shift together with the disappearance of the ethoxy ester group (δ_{1H} 1,3 and 4,1) indicated that the half-ester chloride **(51)** had formed (scheme **46**). Distillation of this chloride was not attempted.



(36) **(51)**

Scheme 46

The appearance of the triplet at δ_{1H} 4,0 could once again be observed, but the other triplet at δ_{1H} 3,4 was obscured by the CH_2 signal of the chloride **(51)**. The decomposition of **(51)** most likely follows the same pathway as that shown in scheme **45**.

2.3 Kinetic studies of the decomposition of 2-dialkylaminoethyl esters of phosphonic acids

Benschop et. al.[8] studied the kinetics and mechanism for the decomposition of N,N-dimethylaminoethyl methylphosphonofluoridate **(8)** and N,N-dimethylaminoethyl isopropyl methylphosphonate **(12)** and obtained the results shown in Table 1 (pp 6).

They were able to show that first order kinetics were obeyed and that the decomposition was an intramolecular process. Their kinetic studies were followed by NMR spectroscopy and the samples were incubated at 60 °C in DMSO-d_6 as a solvent.

It was decided to employ the same reaction conditions for a larger number of phosphonic derivatives in order to come to more general conclusions about the reaction mechanism. It was however found that the singlet of the $\overset{+}{N}Me_2$ group of the reaction product (δ_{1H} 3,4) was not as undisturbed as reported by Benschop to be easily used for rate measurements. In some cases more than one decomposition product was observed, so all of these product signals were taken into account in the determination of the rate of the reaction.

A typical example of a plot of ln (percentage unreacted substrate) against time is given in Fig. 8. All the graphs gave straight lines confirming that first order kinetics were obeyed and their respective slopes were used to determine the rate constants.

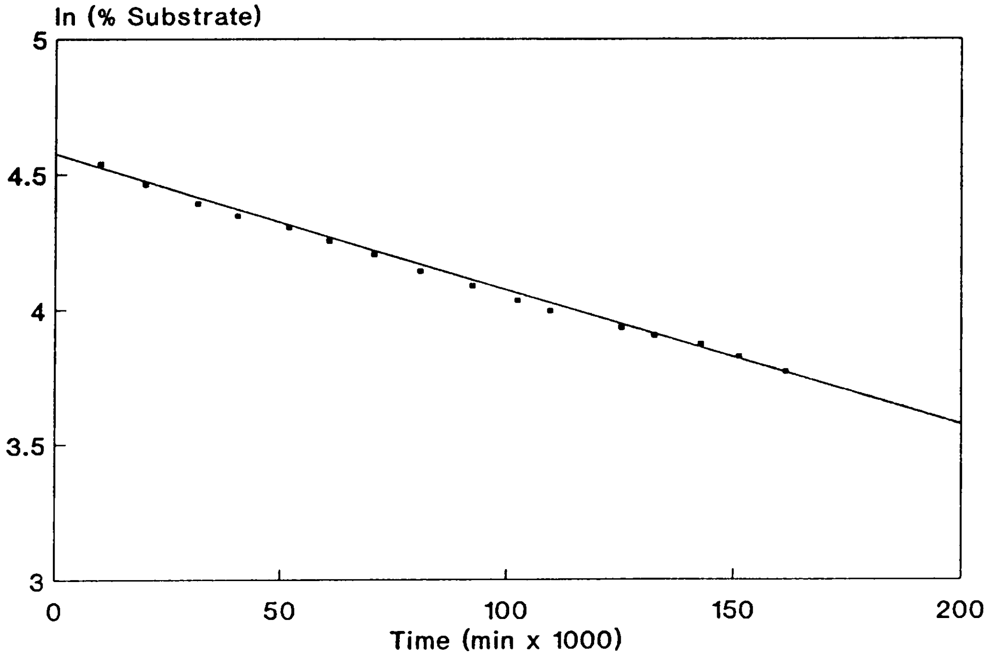


Figure 8: **Graph of ln (% Substrate) versus time for the decomposition of N,N-dimethylaminoethyl isopropyl methylphosphonate at 60°C in DMSO-d_6.**

The results obtained are summarized in Table 2 below.

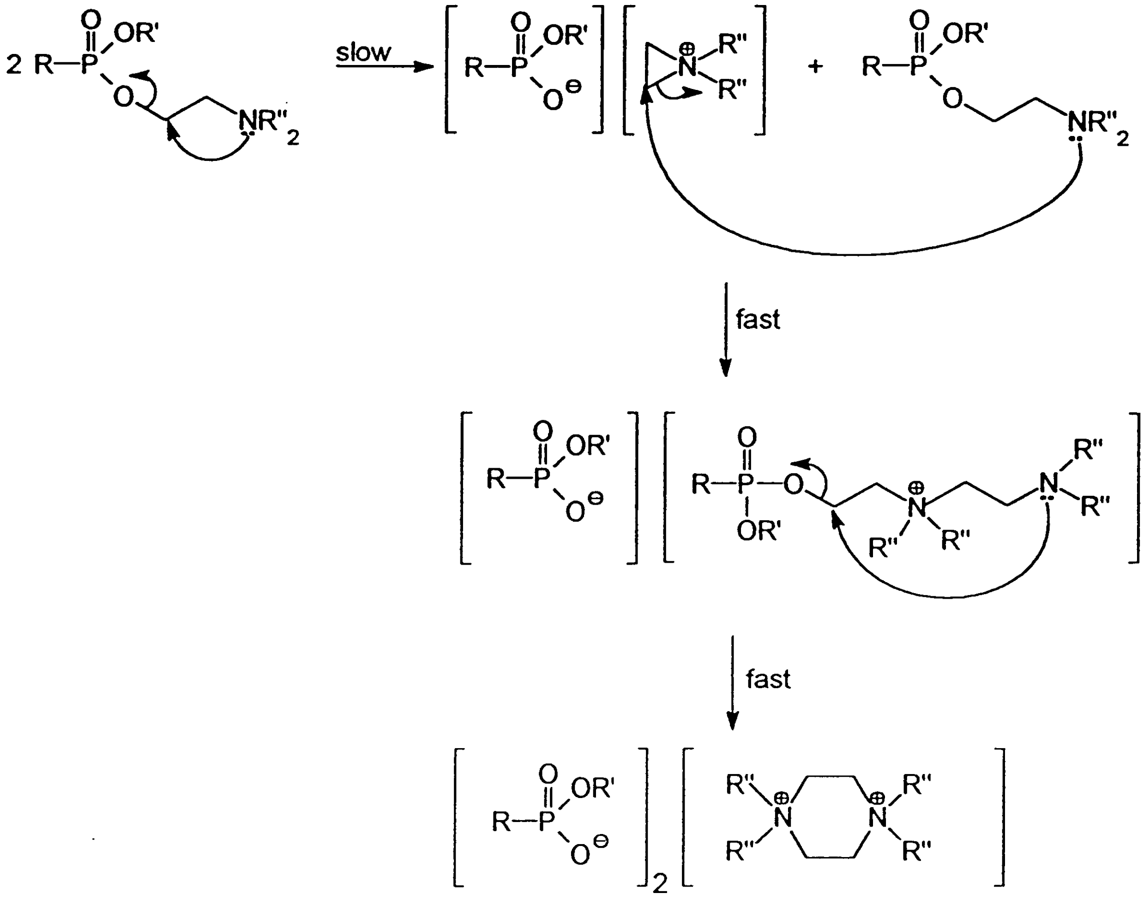
Table 2

Rate of decomposition of $R_2NCH_2CH_2OPO(R')R''$ at 60 °C.

	R	R'	R"	Solvent	Conc (M)	$k_1(min^{-1})$	Rel. rate
12	CH_3	CH_3	$OCH(CH_3)_2$	DMSO-d_6	0.29	4.9×10^{-6} Lit.[8] 8.1×10^{-6}	1
27	CH_3	CH_3CH_2	OCH_2CH_3	DMSO-d_6	0.28	6.1×10^{-6}	1.2
30	CH_3	CH_3	OCH_3	DMSO-d_6	0.28	4.1×10^{-5}	8.4
				$CDCl_3$	0.32	6.2×10^{-6}	1.3
33	CH_3	CH_3	OCH_2CH_3	DMSO-d_6	0.23	1.2×10^{-5}	2.4
35	CH_3CH_2	CH_3	OCH_3	DMSO-d_6	0.19	3.1×10^{-5}	6.3
36	CH_3CH_2	CH_3CH_2	OCH_2CH_3	DMSO-d_6	0.24	5.0×10^{-5}	10.2
49	CH_3CH_2	CH_3	Cl	$CDCl_3$	0.23	1.9×10^{-4}	38.8
						3.7×10^{-4} *	75.5
				CD_3CN	0.23	4.2×10^{-4}	85.7
						1.2×10^{-4} *	24.5
51	CH_3CH_2	CH_3CH_2	Cl	$CDCl_3$	0.24	3.3×10^{-4}	67.3

* Rate of appearance of diethyl-(2-chloroethyl)amine.

From the relative rates (last column in Table 2) it could be seen that compounds **(12)**, **(27)**, **(30)**, **(33)** and **(36)** are of comparable reactivity in the decomposition reactions. The R" groups is these substrates are the alkoxy groups, therefore known as poor leaving groups in nucleophilic substitution. It was therefore concluded that in those cases the mechanism of fragmentation, shown in scheme **47**, involves the departure of the alkyl alkylphosphonate ion as a much better leaving group. The appearance of the signals at δ_{1H} 3,4 and 3,9 serve as evidence that the piperazinium ion was formed as final product in the decomposition.

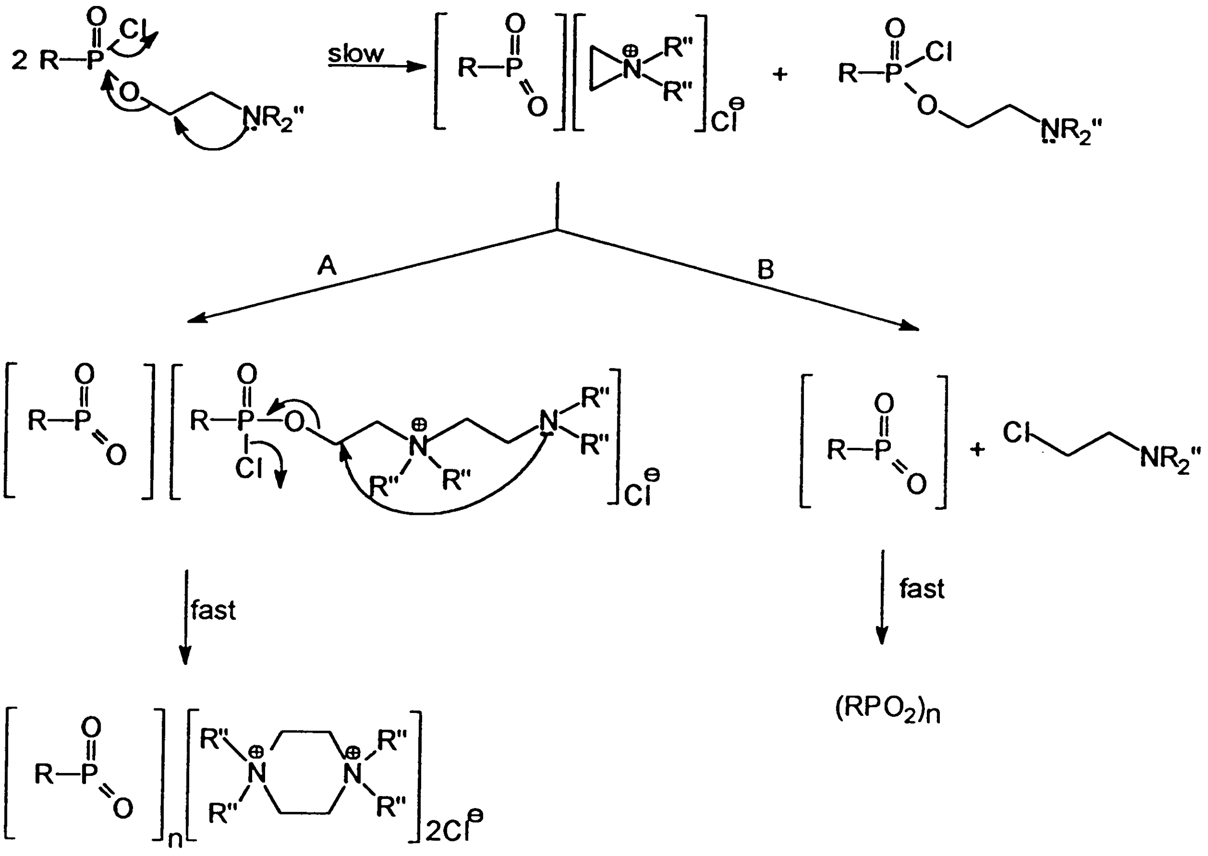


Scheme 47

The first six substrates listed in Table **2** can be arranged in groups of close analogues, in which only one structural function (R, R' or R") is varied. The effect of that single variable is reflected on the relative reactivity of substrates within each group. Compounds **(36)** and **(27)** differ only in the nature of the N-substituents (Et versus Me), and their relative rates is k(**36**)/k(**27**) = 8.5. Higher nucleophilicity of the NEt_2 versus NMe_2 group[23] increases the rate of the intramolecular attack of the 2-dialkylamino nucleophile at the α-carbon of the substituted ethyl group. In the **(27)** and **(33)** pair, the only difference is the P-alkyl group (Et versus Me), and **(33)** is twice as reactive as **(27)**. The result indicates that in DMSO methylphosphonic acid is a stronger acid than its ethyl analogue, so the conjugate base is a better leaving group in the fragmentation step. In the three-substrate series, **(12)**, **(33)**, **(30)**, the ester group is changed from i-Pr to Et to Me, and the relative reactivity increases in the order 1 : 2.4 : 8.4, respectively. Again, the decreasing basicities of the corresponding anions (pKa values for propyl- hyl-, and methylphosphoric acids are 1.88, 1.60 and 1.54 respectively[24]) is responsible for the activation of the substrates to the nucleophilic displacement.

The rate-determining step of the fragmentation (scheme **47**) involves the formation of two ions from a neutral precursor. As a consequence of that, the reaction rate should be strongly solvent-dependent, and indeed, it was found that incubation of **(30)** in $CDCl_3$ at 60 °C gave an indication of a 11 % change after a period of one week. Considering the accuracy of the NMR spectroscopy, this gives an upper limit of the reactivity of **(30)** in $CDCl_3$ as $k_1 \approx 6,2\text{x}10^{-6}\ \text{min}^{-1}$.

The behaviour of the phosphonic ester chlorides, **(49)** and **(51)**, was very different from that of the diesters. Interestingly enough, both substrates proved to be stable in DMSO-d_6 (no change in the NMR spectrum after 56 h at 60 °C). That stabilizing effect, due no doubt to some specific solvent-substrate interaction, is currently studied in this laboratory. As can be seen in Table **2**, however, substrates **(49)** and **(51)**, when dissolved in $CDCl_3$ (or CD_3CN), underwent much faster fragmentation than did the diesters **(12)** - **(36)** in a more polar solvent (DMSO). When reactivities in $CDCl_3$ are compared, **(49)** and **(51)** were found to be more reactive than **(30)** by a factor of more than 60! In addition, the non-phosphorus product from the fragmentation was in those two cases different from the previously observed: the formation of diethyl-(2-chloroethyl)amine was demonstrated in the ^1H NMR spectrum and confirmed by comparison with authentic compound. As expected for an ion-producing reaction, fragmentation of **(49)** in acetonitrile was about twice as fast as in chloroform (Table **2**). Substrates **(49)** and **(51)** differ from the previous compounds in that a good leaving group - chlorine atom is present at the phosphoryl centre. For those substrates a different mechanism is proposed for the decomposition - a more complete fragmentation involving expulsion of the Cl^- ion, aziridinium ion, and a metaphosphonate species, $R\text{-}PO_2$ (scheme **48**). Fragmentation of various organophosphorus substrates accompanied by loss of a metaphosphate intermediate, $X\text{-}PO_2$, was often reported in the literature and observed in this laboratory[25, 26]. The proposed ability of esters **(49)** and **(51)** to release as a leaving group a conjugate base of a strong acid (Cl^-) should explain the much higher reactivity observed for those substrates.

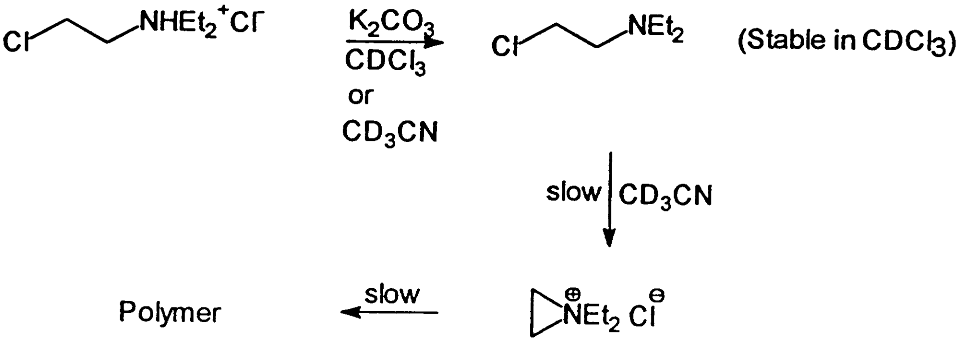


Scheme 48

After the aziridinium ion was formed in the first step (scheme **48**) either pathway A or B could be followed. The nucleophilicity of all species present would determine which pathway is followed. For substrates **(49)** and **(51)** no evidence was found for the formation of the piperazinium ion, but the two triplets of diethyl-(2-chloroethyl)amine could be clearly observed in the ^{1}H NMR spectrum. The presence of the chloride also proved that the chloride acts as leaving group in the first step of the reaction, for it to act as a nucleophile in the second step.

In Table **2** it can also be seen that the decomposition product, diethyl-(2-chloroethyl)amine was formed from **(49)** faster in the relatively non-polar solvent $CDCl_3$ than in CD_3CN. It

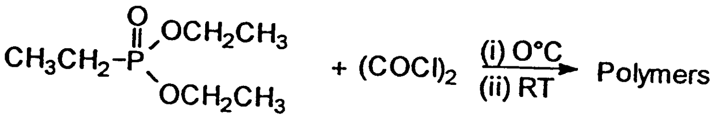
was decided to investigate the behaviour of this product in more detail by preparing , in each solvent, 0,30 M solutions of the hydrochloric salt of the chloride. The salt was then slowly deprotonated with solid anhydrous potassium carbonate and the ^1H NMR spectra were recorded at different time intervals. The free base proved to be stable in chloroform, but in acetonitrile the formation of a singlet at δ_{1H} 2,2 ppm showed that the aziridinium ion was formed. This peak grows in intensity to reach a maximum after four days and then slowly disappears. The formation of ranges of peaks in the ^1H NMR spectra indicate that the ion decomposes to polymeric material. The whole reaction is shown in scheme 49.



Scheme 49

2.4 Reaction conditions for the use of oxalyl chloride as chlorinating agent in the preparation of phosphonic mono-ester chlorides.

The results obtained by Pelchowicz[14] looked very encouraging as a route to compounds RP(O)(OR')Cl. He was able to isolate the half-ester chlorides with yields up to 90%. When the reaction in scheme **50** was repeated, under the conditions specified in the report, only a range of polymers were obtained on attempts of distillation.



(23)

Scheme 50

The reaction was repeated and the percentage conversion of the ester **(23)** was monitored by ^{31}P NMR spectroscopy. After 24 hours it could be seen that only a 20% conversion to the half-ester chloride was obtained.

It was decided then to monitor the effect of temperature on the reaction. The reaction was repeated but this time at refluxing temperature. The ^{31}P NMR spectra showed that even after 2½ hours no conversion had occurred. After 24 hours a 53% conversion could be observed. It was therefore clear that the reaction rate was more than doubled by a slight increase in the temperature of the reaction mixture.

It was decided to monitor the extent of the reaction in the absence of any solvent present. After addition of substrates at room temperature, the reaction mixture was refluxed. The ^{31}P NMR spectra showed that just after 30 minutes 100% conversion was obtained. It was also shown that no dichloride derivative was formed even if the refluxing time was extended.

In the last experiment the reaction was repeated at room temperature in the absence of any solvent. The reaction still proceeded cleanly to give 100% conversion after 3 hours. In conclusion, some modifications of the reported procedure resulted in a simple and efficient method for the preparation of phosphonic monoester monochlorides.

CHAPTER 3

Conclusions and future directions

3.1 Synthesis

The use of thionyl chloride, as chlorinating agent in the preparation of half-ester chlorides from phosphonic diesters, under Maier's conditions[13] have been extended to a wider range of compounds. All the chlorides were obtained in a good yield and it was shown that the reaction provides a fast, clean and effective synthetic method for the preparation of phosphonic monoester monochlorides. The project was however only limited to the preparation of aliphatic ester chlorides and the preparation of aromatic ester chlorides should also be investigated.

The reaction reported by Benschop for the preparation of N,N-dimethylaminoethyl isopropyl methylphosphonate[8] were also shown to be of value as a general procedure in the preparation of N,N-dialkylaminoethyl alkylphosphonates. Modification of the workup procedure resulted in more effective methods for the isolation and purification of these compounds.

It was also shown that mono-alkylphosphonic monochlorides RP(O)(OR')Cl are very susceptable to the reaction with traces of water leading to the formation of pyrophosphonates. Benschop's reaction therefore requires extremely anhydrous conditions.

3.2 Reactions of thionyl chloride with phosphonic esters

It was shown that the presence of a tertiary amino-group in the molecule of the substrate changed the outcome of the reaction with thionyl chloride. When the substrates of the type $R_2NCH_2CH_2OPO(R')R''$ were treated with thionyl chloride, the expected product, in which the ester group was displaced by chloride, was not always obtained.

For R = Me the formation of the N-sulfinyl-N,N-dimethylaminoethyl derivative as a chloride salt was shown, and this intermediate reacted with trace amounts of water to afford the more stable hydrochloric salt of the substrate. In consequence, all these compounds with the exception of the methyl esters did not exchange any of the substituents at phosphorus by means of $SOCl_2$ or $HCl_{(g)}$. Both these reagents afforded a stable hydrochloric salt of the starting ester. With methyl esters, extensive de-O-methylation took place.

For R = Et, normal nucleophilic attack and substitution of the ester group by chlorine was observed.

3.3 Kinetic studies

The stability of the compounds of the type $R_2NCH_2CH_2OPO(R')R''$ was studied for R,R' = CH_3, CH_2CH_3, and R" = OCH_3, OCH_2CH_3, $OCH(CH_3)_2$ and Cl. From the kinetic data obtained it can be clearly seen that the mechanism of decomposition is greatly influenced by the nature of the leaving group anion in nucleophilic substitution. For compounds where R" = alkoxy groups, the mechanism of fragmentation involves the departure of the alkyl alkylphosphonate ion. In these cases the rate of the reaction is increased by an increase in the acidity of the leaving group anion. Compounds in which R" = Cl proved very different from that of the diesters. The formation of the piperazinium ion could be detected in the decomposition product of all the diesters but not in that of the phosphonic ester chlorides. However in the latter case the formation of diethyl-(2-chloroethyl)amine could be observed in the ^1H NMR spectrum. The isolation of diethyl-(2-chloroethyl)amine gave evidence of two facts:

(i) The azidinium ion was formed as an intermediate in the reaction even though it could not be observed by ^1H NMR spectroscopy.

(ii) The chloride-phosphorus bond must be broken in the first step of the decomposition, allowing the chloride ion to act as a nucleophile and attack and open the aziridinium ring.

Therefore a different mechanism for the decomposition is proposed involving the expulsion of the chloride ion, aziridinium ion and the metaphosphonate species, $R\text{-}PO_2$.

The nature of the group R on the nitrogen atom was also shown to influence the rate of decomposition. The more electron donating ethyl groups increased the basicity of the nitrogen atom and increased the rate of decomposition of these compounds. This trend needs to be investigated more extensively to enable to come to more definite conclusions.

3.4 Reaction conditions for the use of oxalyl chloride as chlorinating agent in the preparation of phosphonic mono-ester chlorides

The reaction reported by Pelchowicz[14] could not be confirmed. Modification of the reported procedure resulted in a simple and efficient method for the preparation of ethyl ethylphosphonyl chloride. The conditions have however only been tested on this single compound and have to be tested on a wider range of diesters.

CHAPTER 4

4.1 Experimental

Solvents and commercially available substrates were purified by conventional methods immediately before use. Mass spectra were recorded on a Varian MAT-212 double-focusing direct-inlet spectrometer at an ionization potential of 70 eV. NMR spectra were recorded on a Bruker AC 300 spectrometer (and, in some cases, on a Bruker AMX 500 spectrometer). The chemical shift values are given in δ (ppm) relative to $SiMe_4$(^1H, ^{13}C) as an internal standard, and 85% H_3PO_4 (^{31}P) as an external standard. Melting points were determined on a Gallenkamp melting point apparatus no. MFB595010M and are uncorrected. The infrared spectra were recorded on a Bomem Michelson 100 spectrophotometer. Micro distillations were done using a Buchi GKR-50 glass tube oven. Water pump distillations were done on a Buchi B169 Vacuum-System no. 1286260. The solvents used for the analysis of NMR spectra were chloroform-d_1 (Uvasol, Merck), dimethylsulfoxide-d_6 (Uvasol, Merck) and deuterium oxide-d_2 (Uvasol, Merck), acetonitrile-d_3 (Uvasol, Merck). Kinetic studies were preformed in a water bath at 60 °C fitted with a Gallenkamp Thermostirrer BKL-200 no. 870090. Elemental analysis (C, H, N) were performed at the Department of Chemistry at the University of Cape Town.

4.2 Synthesis

4.2.1 Methylphosphonyl dichloride

According to a standard procedure[13] a mixture of dimethyl methylphosphonate 16,979g (0,136 mol) and N,N-dimethylformamide 0,110g ($1,5x10^{-3}$ mol) reacted with thionyl chloride 40,297g (0,339 mol) to give methylphosphonyl dichloride 14,509g (80%) after fractional distillation, b.p. 63°C/25 mmHg (lit[27] b.p. 55°C/17 mmHg) m.p. 33,0 °C (lit[27] m.p. 33 °C).

δ_{1H} 2,48 (3H; d; J_{HP} 16,4 Hz; CH_3)

δ_{31P} 44,23

4.2.2 Attempted synthesis of N,N-dimethylaminoethyl methylphosphonyl chloride

(I) Sodium hydride 0,216g (9,00x10^{-3} mol) was placed in a three-necked round bottom flask which was protected from moisture at all times. N,N-dimethylaminoethanol 0,378g (4,25x10^{-3} mol) was dissolved in 4 cm^3 toluene and added dropwise to the sodium hydride with stirring. After addition the mixture was stirred for 2 hours while hydrogen gas evolved.

A second round bottom flask was fitted with a dropping funnel, low temperature thermometer and drying tube. Methylphosphonyl dichloride 0,603g (4,50x10^{-3} mol) in 4 cm^3 dry ether was placed in the flask. The sodium salt was filtered from the slight excess of sodium hydroxide, used in its preparation, which was washed with 2 x 5 cm^3 aliquots of toluene. The combined solution was added dropwise to the solution of methylphosphonyl dichloride cooled to -10°C. After addition the reaction mixture was stirred for 3 hours at room temperature. The sodium chloride salt was removed by filtration and the solvents under reduced pressure to yield 1,105g of the crude product.

δ_{31P} Range of polymers.

(II) Methylphosphonyl dichloride 2,440g (1,82x10^{-2} mol) in 10 cm^3 ether reacted with a mixture of N,N-dimethyl-aminoethanol 1,625g (1,83x10^{-2} mol) and triethylamine 1,856g (1,84x10^{-2} mol) in 5 cm^3 ether according to a standard procedure[8] to give a salt precipitate after filtration and evaporation of the solvent. The salt was dissolved in chloroform and filtered through glass wool to give 1,262g of a yellow oil after evaporation of the solvent. After about 70 hours a white precipitate was observed in the oil. It was removed by filtration and the NMR in D_2O of the salt was recorded. The oil was distilled under reduced pressure to yield a clear oil. {Vacuum pump not functioning correctly and therefore no b.p. given.}

SALT:

δ_{1H} 1,72 (3H; d; J_{HP} 17,9 Hz; CH_3 of MePO)
2,92 (12H; s; 4 x CH_3 on N)
3,49 (4H; t; J_{HH} 5,0 Hz; 2 x CH_2 vic to N)
4,42 (4H; m; 2 x CH_2 vic to O)

δ_{31P} 37,11

OIL:

δ_{1H} Mixture of compounds observed.

δ_{31P} 31,22 (Major)
32,28 (Range of phosphorus compounds)

(III) Methylphosphonyl dichloride 1,400g ($1,04x10^{-2}$ mol) was dissolved in 10 cm^3 ether. To this solution, cooled at -10 °C, was added dropwise with stirring, a solution of N,N-dimethylaminoethanol 0,898g ($1,01x10^{-2}$ mol) and di-isopropylethylamine 1,313g ($1,00x10^{-2}$ mol) in 10 cm^3 ether in the course of 1 hour. The reaction mixture was filtered to give 3,9g of an oil. An NMR spectra of the salt precipitate, yield 0,232g (10%) was run in D_2O.

SALT:

δ_{1H} 1,72 (3H; d; J_{HP} 17,6 Hz; CH_3 of MePO)
2,92 (12H; s; 4 x CH_3 on N)
3,49 (4h; t; J_{HH} 5,0 Hz; 2 x CH_2 vic to N)
4,41 (4H; m; 2 x CH_2 vic to O)

δ_{31P} 37,13

OIL:

No assignment could be made to the ^{1}H NMR signals. The shifts for of the major peaks are only given.

δ_{1H} 1,35 (q)
1,42 (q)
2,86 (m)
3,01 (m)
3,56 (m)

4.2.3 Bis-N,N-dimethylaminoethyl methylphosphonate

A solution of N,N-dimethylaminoethanol 2,665 g ($2{,}99 \times 10^{-2}$ mol) and triethylamine 3,031g ($3{,}00 \times 10^{-2}$ mol) in 20 cm^3 ether was added dropwise with stirring, in the course of one hour, to a solution of methylphosphonyl dichloride 2,067g ($1{,}56 \times 10^{-2}$ mol) in 20 cm^3 ether. The temperature of the reaction mixture was kept at -10°C for an additional hour and then allowed to rise to room temperature. The salt was removed by filtration and the solvent removed under reduced pressure to yield a crystalline material. The product was recrystallized from chloroform to yield 1,027g (29%) of a semi-solid material.

δ_{1H} 1,44 (3H; d; J_{HP} 17,7 Hz; CH_3 of MePO)
2,20 (12H; s; 4 x CH_3 on N)
2,50 (4H; m; 2 x CH_2 vic to N)
4,01 (2H; m; CH_2 vic to O)
4,05 (2H; m; CH_2 vic to O)

δ_{31P} 32,34

δ_{13C} 11,17 (d of q; J_{CP} 145,1 Hz; J_{CH} 128,6 Hz; CH_3 of MePO)

45,56 (q; J_{CH} 133,2 Hz; 4 x CH_3 on N)

59,20 (d of t; J_{CP} 6,4 Hz; J_{CH} 134,9 Hz; 2 x CH_2 vic to N)

62,99 (d of t; J_{CP} 6,4 Hz; J_{CH} 150,1 Hz; 2 x CH_2 vic to O)

MS m/e 239 ($M^+ < 1$) 168 (90%) 72 (88%) 57 (33%)

42 (98%) 30 (47%)

4.2.4 Triisopropyl phosphite

A mixture of isopropanol 18,025g (0,300 mol) and dimethylaniline 36,358g (0,300 mol) reacted with phosphorus trichloride 8,0cm^3 (9,8x10^{-2} mol) according to a standard procedure[17] to give 20,467g (99%) triisopropyl phosphite, b.p. 40°C/0.9 mmHg. A small amount of the hydrolysed product was detected in the NMR spectra.

δ_{1H} 1,23 (18H; d; J_{HP} 6,2 Hz; 6 x CH_3)

4,37 (3H; m; 3 x CH)

δ_{31} 60,75

4.2.5 Diisopropyl methylphosphonate

(I) Methyl iodide 3,0 cm^3 (4,8x10^{-2} mol) reacted with triisopropyl phosphite 10,120g (4,86x10^{-2} mol) according to a standard procedure[18] to give after distillation 7,040g (81%) of diisopropyl methylphosphonate, b.p. 44 - 45 °C/0,8 mmHg.

δ_{1H} 1,27 (12H; d; J_{HP} 6,2 Hz; 4 x CH_3 of $POPr^i$)

1,38 (3H; d; J_{HP} 17,5 Hz; CH_3 of MePO)

4,63 (2H; m; CH of $POPr^i$)

δ_{31P} 28,91

(II) Sodium hydride 0,606g ($2,53 \times 10^{-2}$ mol) was placed in 10 cm^3 hexane and diisopropyl hydrogen phosphite 4,000g ($2,41 \times 10^{-2}$ mol) in 10 cm^3 hexane was added dropwise to this solution. The reaction mixture was stirred at room temperature for 90 minutes. Methyl iodide 7,5 cm^3 (0,12 mol) was then added dropwise to this solution. After addition the reaction mixture was stirred for 90 minutes at room temperature and then kept for 3 hours at reflux temperature. A little water was added to the mixture, dried over $MgSO_4$, filtered and the solvent removed under reduced pressure. Distillation yielded 1,563g (35%) diisopropyl methylphosphonate, b.p. 47 °C/1 mmHg.

δ_{1H} 1,27 (12H; d; J_{HP} 6,2 Hz; 4 x CH_3 of $POPr^i$)
1,38 (3H; d; J_{HP} 17,5 Hz; CH_3 of MePO)
4,63 (2H; m; CH of $POPr^i$)

δ_{31P} 28,91

4.2.6 Isopropyl methylphosphonyl chloride

(I) Diisopropyl methylphosphonate 5,002g ($2,76 \times 10^{-2}$ mol) in 40 cm^3 of ether reacted with oxalyl chloride 4,455g ($3,51 \times 10^{-2}$ mol) dissolved in 3 cm^3 of ether according to a standard procedure[14] to give a black polymeric substance upon distillation.

(II) A mixture of diisopropyl methylphosphonate 5,142g ($2,86 \times 10^{-2}$ mol) and N,N-dimethylformamide 0,036g ($4,9 \times 10^{-4}$ mol) reacted with thionyl chloride 8,631g ($7,25 \times 10^{-2}$ mol) according to a standard procedure[13] to give after distillation 2,720 g (62%) of a colourless oil, b.p. 36 °C/0,8 mmHg.

δ_{1H} 1,38 (6H; d of q; J_{HP} 4,0 Hz; J_{HH} 6,2 Hz; 2 x CH_3 of $POPr^i$)
1,92 (3H; d; J_{HP} 17,6 Hz; CH_3 of MePO)
4,94 (1H; m; CH of $POPr^i$)

δ_{31P} 39,19

4.2.7 N,N-dimethylaminoethyl isopropyl methylphosphonate

A mixture of N,N-dimethylaminoethanol 0,507g (5,70x10^{-3} mol) and triethylamine 0,633g (6,26x10^{-3} mol) in 2 cm^3 ether reacted with isopropyl methylphosphonyl chloride 0,896g (5,73x10^{-3} mol), dissolved in 10 cm^3 ether, according to a standard procedure[8] to yield 1,283g of a salt precipitate. The precipitate was dissolved in 20 cm^3 chloroform and anhydrous potassium carbonate 0,905g (6,55x10^{-3} mol) was added to the mixture. The mixture was stirred overnight. Filtration, evaporation and subsequent bulb-to-bulb distillation (oven temperature 70 °C/0,3 mmHg) yielded 0,428 g (36%) of pure N,N-dimethylaminoethyl isopropyl methylphosphonate.

δ_{1H} 1,28 (6H; d; J_{HP} 6,2 Hz; 2 x CH_3 of $POPr^i$)
1,44 (3H; d; J_{HP} 17,5 Hz; CH_3 of MePO)
2,24 (6H; s; 2 x CH_3 on N)
2,54 (2H; t; J_{HP} 5,9 Hz; CH_2 vic to N);
4,05 (2H; m; CH_2 vic to O)
4,66 (1H; m; CH of $POPr^i$)

δ_{31P} 30,64

δ_{13C} 11,88 (d of q; J_{CP} 144,9 Hz; J_{CH} 128,1 Hz; CH_3 of MePO)
23,89 (d of q; J_{CP} 4,1 Hz; J_{CH} 126,7 Hz; 2 x CH_3 of $POPr^i$)
45,63 (q; J_{CH} 133,2 Hz; 2 x CH_3 on N)
59,23 (d of t; J_{CP} 6,4 Hz; J_{CH} 131,3 Hz; CH_2 vic to N)
62,78 (d of t; J_{CP} 6,3 Hz; J_{CH} 146,1 Hz; CH_2 vic to O)
70,15 (d of d; J_{CP} 6,3 Hz; J_{CH} 146,3 Hz; CH of $POPr^i$)

Table 3

Correlation obtained from heteronuclear two dimensional (^{13}C, ^{1}H) NMR spectrum:

δ_{1H}	δ_{13C}
1.28	23.89
1.44	11.88
2.24	45.63
2.54	59.23
4.05	62.78
4.66	70.15

The racemic product gave the following NMR signals:

δ_{1H} 1,30 (12H; d; J_{HP} 6,2 Hz; 4 x CH_3 of $POPr^i$)

1,64 (6H; d; J_{HP} 13,3 Hz; 2 x CH_3 of MePO)

4,84 (2H; m; 2 x CH of $POPr^i$)

δ_{31P} 21,41

21,94

4.2.8 Ethyl ethylphosphonyl chloride

A mixture of diethyl ethylphosphonate 3,005g ($1,81x10^{-2}$ mol) and N,N-dimethylformamide 0,015g ($1,8x10^{-4}$ mol) reacted with thionyl chloride 3,3 cm^3 ($4,5x10^{-2}$ mol) according to a standard procedure[13] to give 1,863 g (66%) after distillation, b.p. 37 °C/0,6 mmHg.

δ_{1H} 1,25 (3H; d of t; J_{HP} 24,7 Hz; J_{HH} 7,7 Hz; CH_3 of EtPO)
1,36 (3H; t; J_{HH} 7,0 Hz; CH_3 of POEt)
2,11 (2H; d of q; J_{HP} 17,4 Hz; J_{HH} 7,6 Hz; CH_2 of EtPO)
4,24 (2H; m; CH_2 of POEt)

δ_{31P} 47,29

4.2.9 N,N-dimethylaminoethyl ethyl ethylphosphonate

A mixture of triethylamine 1,216g (0,120 mol) and N,N-dimethylaminoethanol 1,075g ($1,21\times10^{-2}$ mol) in 5 cm^3 ether reacted with ethyl ethylphosphonyl chloride 1,750g ($1,12\times10^{-2}$ mol) dissolved in 10 cm^3 ether, according to a standard procedure[8] to give a white salt. This salt was dissolved in 20 ml chloroform and anhydrous potassium carbonate 1,796g (0,130 mol) was added. This mixture was stirred overnight, filtered and the solvent removed at water pump pressure. Subsequent bulb-to-bulb distillation (oven temperature 75 °C/ 0,3 mmHg) yielded 0,502 g (22%) of pure N,N-dimethylaminoethyl ethyl ethylphosphonate.

δ_{1H} 1,12 (3H; d of t; J_{HP} 20,0 Hz; J_{HH} 7,7 Hz; CH_3 of EtPO)
1,29 (3H; t; J_{HH} 7,0 Hz; CH_3 of POEt)
1,73 (2H; d of q; J_{HP} 18,3 Hz; J_{HH} 7,7 Hz; CH_2 of EtPO)
2,24 (6H; s; 2 x CH_3 on N)
2,55 (2H; t; J_{HH} 5,9 Hz; CH_2 vic to N)
4,07 (4H; m; 2 x CH_2 vic to O)

δ_{31P} 34,77

δ_{13C} 6,53 (d of q; J_{CP} 6,4 Hz; J_{CH} 129,3 Hz; CH_3 of EtPO)

16,43 (d of q; J_{CP} 6,4 Hz; J_{CH} 127,1 Hz; CH_3 of POEt)

18,82 (d of t; J_{CP} 143,1 Hz; J_{CH} 126,7 Hz; CH_2 of EtPO)

45,73 (q; J_{CH} 133,2 Hz; 2 x CH_3 on N)

59,40 (d of t; J_{CP} 6,4 Hz; J_{CH} 132,8Hz; CH_2 vic to N)

61,57 (d of t; J_{CP} 6,4 Hz; J_{CH} 146,6 Hz; CH_2 of POEt) *

63,12 (d of t; J_{CP} 6,4 Hz; J_{CH} 146,3 Hz; CH_2 vic to O) *

* The values of these two peaks were assigned on the basis of the shielding/ deshielding the surrounding groups provide.

Table 4

Correlation obtained from heteronuclear two dimensional (^{13}C, ^{1}H) NMR spectrum:

δ_{1H}	δ_{13C}
1,12	6,53
1,29	16,43
1,73	18,82
2,24	45,73
2,55	59,40
4,07	61,57 63,12

The racemic product gave the following NMR signals:

δ_{31P} 26,63

26,79

^{1}H NMR signals were too complex to interpret.

4.2.10 Diethyl ethylpyrophosphonate

A mixture of water 0,030g (1,7x10^{-3} mol) and pyridine 0,132g (1,67x10^{-3} mol) reacted with a solution of ethyl ethylphosphonyl chloride 0,488g (3,12x10^{-3} mol) and pyridine 0,126g (1,59x10^{-3} mol) in 50 cm^{3} of benzene according to a standard procedure[19] to give after bulb-to-bulb distillation 0,098g (12%) of diethyl ethylpyrophosphonate (oven temperature 90°C / 0,6 mmHg).

δ_{1H} 1,19 (6H; d of t; J_{HP} 21,6 Hz; J_{HH} 7,7 Hz; 2 x CH_3 of EtPO)
1,33 (6H; t; J_{HH} 7,1 Hz; 2 x CH_3 of EtOP)
1,92 (4H; d of q; J_{HP} 18,3 Hz; J_{HH} 7,7 Hz; 2 x CH_2 of EtPO)
4,24 (4H; m; 2 x CH_2 of EtOP)

δ_{31P} 26,77
26,61

δ_{13C} 6,20 (q; J_{CH} 129,6 Hz; 2 x CH_3 of EtPO)
16,08 (q; J_{CH} 127,4 Hz; 2 x CH_3 of EtOP)
19,10 (d of t; J_{CP} 5,3 Hz; J_{CH} 128,0 Hz; 2 x CH_2 of EtPO)
21,09 (d of t; J_{CP} 5,7 Hz; J_{CH} 128,0 Hz; 2 x CH_2 of EtOP)

4.2.10.1 Reaction between ethylphosphonyl chloride and N,N-dimethylaminoethyl ethyl ethylphosphonate

A 1,3 M solution of N,N-dimethylaminoethyl ethyl ethylphosphonate was prepared by dissolving 0,3959g (1,89x10^{-3} mol) of the substrate in 1,5 cm^{3} deuterated chloroform. A 1,3 M solution of ethyl ethylphosphonyl chloride was prepared by dissolving 0,3816g (2,42x10^{-3} mol) of this substrate in 1,9 cm^{3} deuterated chloroform. 40μl of each solution was placed in an NMR tube and 0,5 cm^3 of deuterated chloroform added. ^{31}P NMR spectra were used to monitor the extent of the reaction at room temperature (22 °C).

(I) N,N-dimethylaminoethyl ethyl ethylphosphonate ^{31}P 34,96

(II) Ethyl ethylphosphonyl chloride ^{31}P 47,08

(III) Diethyl ethylpyrophosphonate ^{31}P 26,58; 26,74

Table 5

Percentage of I, II and III as a function of time

% (I)	%(II)	%(III)	Time (min)
45.7	49.7	4.6	120
52.5	34.1	13.4	1050
54.5	30.3	15.2	1340
55.3	28.4	16.3	1570
65.2	13.9	20.9	4110
64.9	12.7	22.4	4310
68.3	8.5	23.2	5410
46.9	47.4	5.7	135
48.5	42.4	9.1	360
62.4	19.0	18.6	2905
62.7	17.4	19.9	3105
65.1	12.7	22.1	4200

4.2.11 Methyl methylphosphonyl chloride

A mixture of dimethyl methylphosphonate 4,458g ($3{,}59\mathrm{x}10^{-2}$ mol) and N,N-dimethylformamide 0,025g ($3{,}6\mathrm{x}10^{-4}$ mol) reacted with thionyl chloride 6,5 cm^3 ($8{,}9\mathrm{x}10^{-2}$ mol) according to a standard procedure[13] to give 3,152g (68%) of a clear oil after distillation, b.p. 27-28 °C/0,7 mmHg.

δ_{1H}	1,95	(3H; d; J_{HP} 17,6 Hz; CH_3 of MePO)
	3,84	(3H; d; J_{HP} 13,5 Hz; CH_3 of POMe)
δ_{31P}	42,76	

4.2.12 N,N-dimethylaminoethyl methyl methylphosphonate

A mixture of N,N-dimethylaminoethanol 2,106g ($2,37x10^{-2}$ mol) and triethylamine 2,625g ($2,60x10^{-2}$ mol) in 5 cm^3 ether reacted with methyl methylphosphonyl chloride 3,060g ($2,38x10^{-2}$ mol) , dissolved in 10 cm^3 ether, according to a standard procedure[8] to give a salt precipitate after filtration and evaporation of the solvent. The precipitate was dissolved in 20 cm^3 of chloroform, anhydrous potassium carbonate 3,894g ($2,82x10^{-2}$ mol) was added and the mixture stirred overnight. Subsequent filtration and evaporation of the solvent yielded a yellow oil which was purified by bulb-to-bulb distillation (oven temperature 60°C/ 0,5mmHg) yielding 1,426g (33%) of a colourless oil.

δ_{1H}	1,46	(3H; d; J_{HP} 17,4 Hz; CH_3 of MePO)
	2,24	(6H; s; 2 x CH_3 on N)
	2,54	(2H; t; J_{HH} 5,7 Hz; CH_2 vic to N)
	3,69	(3H; d; J_{HP} 11,3Hz; CH_3 of POMe)
	4,08	(2H; m; CH_2 vic to O)
δ_{31P}	33,14	
δ_{13C}	10,49	(d of q; J_{CP} 144,8 Hz; J_{CH} 128,4 Hz; CH_3 of MePO)
	45,58	(q; J_{CH} 133,1 Hz; 2 x CH_3 on N)
	51,95	(d of q; J_{CP} 6,3 Hz; J_{CH} 147,3 Hz; CH_3 of POMe)
	59,25	(d of t; J_{CP} 5,8 Hz; J_{CH} 131,7 Hz; CH_2 vic to N)
	63,10	(d of t; J_{CP} 15,5 Hz; J_{CH} 147,4 Hz; CH_2 vic to O)

Table 6

Correlation obtained from heteronuclear two dimensional (^{13}C, ^{1}H) NMR spectrum:

δ_{1H}	δ_{13C}
1.46	10.49
2.24	45.58
2.54	51.95
3.69	59.25
4.08	63.10

4.2.13 Methyl ethylphosphonyl chloride

A mixture of methyl diethylphosphonate 2,006g ($1,32x10^{-2}$ mol) and N,N-dimethylformamide 0,0098g ($1,3x10^{-4}$ mol) reacted with thionyl chloride 3,924g ($3,30x10^{-2}$ mol) according to a standard procedure[13] to give after distillation, b.p. 41 °C/ 1 mmHg, 1,120g (60%) of a colourless oil.

δ_{1H} 1,37 (3H; t; J_{HH} 7,1 Hz; CH_3 of POEt)
1,94 (3H; d; J_{HP} 17,5 Hz; CH_3 of MePO)
4,24 (2H; m; CH_2 of POEt)

δ_{31P} 40,67

During the reaction the gas that evolved was trapped in $CDCl_3$ kept at -30 °C. An NMR spectra was run on this dissolved gas confirming the formation of ethyl chloride.

δ_{1H} 1,46 (3H; t; J_{HH} 7,2 Hz; CH_3)
3,54 (2H; q; J_{HH} 7,3 Hz; CH_2)

4.2.14 N,N-dimethylaminoethyl methyl ethylphosphonate

A mixture of N,N-dimethylaminoethanol 0,701g ($7,88\times10^{-3}$ mol) and triethylamine 0,800g ($7,92\times10^{-3}$ mol) in 3 cm^3 ether was added dropwise to a solution of methyl ethylphosphonyl chloride 1,120g ($7,86\times10^{-3}$ mol) in 10 cm^3 ether according to a standard procedure[8] to give a white crystalline material. After filtration the salt was dissolved in the minimum amount of chloroform and five times the volume of ether added to this solution. The white precipitate of triethylamine hydrochloric salt was removed by filtration to yield a yellow oil.

The oil was dissolved in dry ether and dry $HCl_{(g)}$ was bubbled through the solution. A white precipitate formed which later disappeared as the acidity of the ether increased. The ether and excess $HCl_{(g)}$ was removed at water pump pressure. The oil was dissolved in chloroform and extracted with 3 x 20 cm^3 of water. The pH of the water layer was raised to 11 by adding sufficient potassium carbonate. This water mixture was stirred for 1 hour and then extracted with 3 x 20 cm^3 of chloroform, dried over $MgSO_4$, and the solvent removed under water pump pressure to yield 1,098g (72%) of N,N-dimethylaminoethyl methyl ethylphosphonate.

δ_{1H}	1,29	(3H; t; J_{HH} 7,1 Hz; CH_3 of POEt);
	1,46	(3H; d; J_{HP} 17,6 Hz; CH_3 of MePO)
	2,24	(6H; s; 2 x CH_3 on N)
	2,54	(2H; t; J_{HH} 5,9 Hz; CH_2 vic to N)
	4,07	(4H; m; 2 x CH_2 vic to O)
δ_{31P}	31,71	

δ_{13C} 10,75 (d of q; J_{CP} 144,8 Hz; J_{CH} 128,4 Hz; CH_3 of MePO)

15,90 (d of q; J_{CP} 5,7 Hz; J_{CH} 126,5 Hz; CH_3 of POEt)

45,23 (q; J_{CH} 133,0 Hz; 2 x CH_3 on N)

58,89 (d of t; J_{CP} 6,0 Hz; J_{CH} 133,7 Hz; CH_2 vic to N)

61,01 (d of t, J_{CP} 6,0 Hz; J_{CH} 147,0 Hz; CH_2 of POEt) *

62,60 (d of t; J_{CP} 6,1 Hz; J_{CH} 145,1 Hz; CH_2 vic to O) *

* The values of these two peaks were assigned on the basis of the shielding/deshielding the surrounding groups provide.

Table 7

Correlation obtained from heteronuclear two dimensional (^{13} C, ^{1}H) NMR spectrum:

δ_{1H}	δ_{13C}
1.29	15.90
1.46	10.75
2.24	45.23
2.54	58.89
4.07	61.01 62.60

4.2.15 N,N-diethylaminoethyl methyl methylphosphonate

A mixture of N,N-diethylaminoethanol 1.817g (1,55x10^{-2} mol) and triethylamine 1,606g (1,59x10^{-2} mol) in 10 cm^3 ether reacted with methyl methylphosphonyl chloride 2,000g (1,56x10^{-2} mol) in 15 cm^3 ether according to a standard procedure[8] to give a white salt after filtration and evaporation of the solvent. This salt was dissolved in the minimum of chloroform and five times the volume ether added to produce a white salt that was removed by filtration. Removal of the solvent gave 0,185g (5,5%) of a colourless oil after distillation, b.p. 87 °C/ 0,9mmHg.

δ_{1H}	0,99	(6H; t; J_{HH} 7,2 Hz; 2 x CH_3 of NEt_2)
	1,44	(3H; d; J_{HP} 17,5 Hz; CH_3 of MePO)
	2,54	(4H; q; J_{HH} 7,1 Hz; 2 x CH_2 of NEt_2)
	2,68	(2H; t; J_{HH} 6,3 Hz; CH_2 vic to N)
	3,68	(3H; d; J_{HP} 11,1 Hz; CH_3 of POMe)
	4,03	(2H; m; CH_2 vic to O)
δ_{31P}	32,84	
δ_{13C}	10,47	(d of q; J_{CP} 144,6 Hz; J_{CH} 128,5 Hz; CH_3 of MePO)
	11,62	(q; J_{CH} 125,4 Hz; 2 x CH_3 of NEt_2)
	47,54	(t; J_{CH} 132,6 Hz; 2 x CH_2 of NEt_2)
	52,01	(d of q; J_{CP} 6,3 Hz; J_{CH} 144,2 Hz; CH_3 of POMe)
	52,78	(d of t; J_{CP} 6,2 Hz; J_{CH} 134,6 Hz; CH_2 vic to N)
	63,59	(d of t; J_{CP} 6,4 Hz; J_{CH} 147,2 Hz; CH_2 vic to O)

Table 8

Correlation obtained from heteronuclear two dimensional (^{13}C, ^{1}H) NMR spectrum:

δ_{1H}	δ_{13C}
0.99	11.62
1.44	10.47
2.54	47.54
2.68	52.78
3.68	52.01
4.03	63.59

4.2.16 N,N-diethylaminoethyl ethyl ethylphosphonate

A mixture of N,N-diethylaminoethanol 0,463 g ($3{,}96\times10^{-3}$ mol) and triethylamine 0,396g ($3{,}92\times10^{-3}$ mol) in 2 cm^3 ether reacted with ethyl ethylphosphonyl chloride 0,617 g ($3{,}92\times10^{-3}$ mol) according to a standard procedure[8] to give a white salt after filtration and removal of the solvent. This salt was dissolved in the minimum amount of chloroform and five times the volume of ether added. The mixture was filtered and the solvent removed to give a yellow oil. The oil was dissolved in 50 cm^3 dry ether and dry $HCl_{(g)}$ was bubbled through the mixture. A white precipitate formed which disappeared as the acidity of the ether increased. The ether and excess $HCl_{(g)}$ was removed at water pump pressure. The oil was dissolved in chloroform and extracted with 3 x 20 cm^3 water. The pH of the water fraction was increased to 11 by adding potassium carbonate. This mixture was stirred for 1 hour and then extracted with 3 x 20 cm^3 chloroform, dried over $MgSO_4$, and the solvent removed at water pump pressure to give 0,369g (39%) of a colourless oil.

δ_{1H}	1,00	(6H; t; J_{HH} 7,1 Hz; 2 x CH_3 of NEt_2)
	1,12	(3H; d of t; J_{HP} 20,0 Hz; J_{HH} 7,7 Hz; CH_3 of EtPO)
	1,28	(3H; t; J_{HH} 7,1 Hz; CH_3 of POEt)
	1,73	(2H; d of q; J_{HP} 18,3 Hz; J_{HH} 7,7 Hz; CH_2 of EtPO)
	2,56	(4H; q; J_{HH} 7,1 Hz; 2 x CH_2 on N)
	2,70	(2H; t; J_{HH} 6,4 Hz; CH_2 vic to N)
	4,07	(4H; m; 2 x CH_2 vic to O)
δ_{31P}	34,55	
δ_{13C}	6,31	(q; J_{CH} 130,0 Hz; CH_3 of EtPO)
	11,59	(q; J_{CH} 125,4 Hz; 2 x CH_3 of NEt_2)
	16,24	(d of q; J_{CP} 5,9 Hz; J_{CH} 126,9 Hz; CH_3 of EtPO)
	18,55	(d of t; J_{CP} 142,7 Hz; J_{CH} 126,8 Hz; CH_2 of EtPO)
	47,44	(t; J_{CH} 132,8 Hz; 2 x CH_2 of NEt_2)
	52,69	(d of t; J_{CP} 6,3 Hz; J_{CH} 133,0 Hz; CH_2 vic to N)
	61,27	(d of t; J_{CP} 6,4 Hz; J_{CH} 148,5 Hz; CH_2 of POEt) *
	63,25	(d of t; J_{CP} 6,5 Hz; J_{CH} 149,7 Hz; CH_2 vic to O) *

* The values of these two peaks were assigned on the basis of the shielding/deshielding the surrounding groups provide.

Table 9

Correlation obtained from heteronuclear two dimensional (^{13}C, ^{1}H) NMR spectra:

δ_{1H}	δ_{13C}
1.00	11.59
1.12	6.31
1.28	16.24
1.73	18.55
2.56	47.44
2.70	52.69
4.07	61.27 63.25

4.3 Reactions of thionyl chloride with phosphonic esters

4.3.1 N,N-dimethylaminoethyl methyl methylphosphonate

(I) A mixture of N,N-dimethylaminoethyl methyl methylphosphonate 0,512g ($2,83x10^{-3}$ mol) and N,N-dimethylformamide 0,0327g ($4,48x10^{-4}$ mol) reacted with thionyl chloride 0,886g ($7,45x10^{-3}$ mol) according to a standard procedure[13] to give a yellow precipitate. This precipitate was dissolved in the minimum of chloroform and five time the volume of ether added to give 0,334g (58%) of a white salt. The melting point of the salt could not be determined because it was too hygroscopic. NMR spectra were run in D_2O.

δ_{1H} 1,35 (3H; d; J_{HP} 16,9 Hz; CH_3 of MePO)

2,86 (6H; s; 2 x CH_3 on N)

3,35 (2H; t; J_{HH} 5,0 Hz; CH_2 vic to N)

4,13 (2H; m; CH_2 vic to O)

δ_{31P} 30,57

δ_{13C} 13,28 (d of q; J_{CP} 137,3 Hz; J_{CH} 127,6 Hz; CH_3 of MePO)

45,46 (q; J_{CH} 143,9 Hz; 2 x CH_3 on N)

59,95 (d of t; J_{CP} 7,6 Hz; J_{CH} 143,2 Hz; CH_2 vic to N)

60,80 (d of t; J_{CP} 4,6 Hz; J_{CH} 148,9 Hz; CH_2 vic to O)

(II) A second sample of N,N-dimethylaminoethyl methyl methylphosphonate 0,211g ($1,17 \times 10^{-3}$ mol) was dissolved in 50 cm^3 ether and dry $HCl_{(g)}$ was bubbled through the solution for 45 minutes. A milky precipitate formed which disappeared as the acidity of the ether increased. The ether and excess $HCl_{(g)}$ was removed at water pump pressure to give a colourless oil containing two products. NMR spectra were run in D_2O.

Product A: (Major)

δ_{1H} 1,52 (3H; d; J_{HP} 17,6 Hz; CH_3 of MePO)

2,88 (6H; d of d; J_{HP} 2,3 Hz; J_{HH} 4,9 Hz; 2 x CH_3 on N)

3,38 (2H; q; J_{HH} 5,0 Hz ; CH_2 vic to N)

3,70 (3H; d; J_{HP} 11,2 Hz; CH_3 of POMe)

4,44 (2H; m; CH_2 vic to O)

δ_{31P} 34,00

Product B: (Minor)

δ_{1H} 1,49 (3H; d; J_{HP} 17,8 Hz; CH_3 of MePO)

2,91 (6H; d; J_{HP} 4,8 Hz; 2 x CH_3 on N)

3,46 (2H; m; CH_2 vic to N)

4,44 (2H; m; CH_2 vic to O)

δ_{31P} 31,75

The NMR spectra of the same oil were run in DMSO-d_6. This spectra confirm the spectra run in D_2O.

(III) The oil was dissolved in 50 cm^3 ether and $HCl_{(g)}$ was bubbled through the solution for a further 45 minutes. ^1H and ^{31}P NMR spectra showed that no change had occurred.

(IV) 0,025 g of the oil was dissolved in 0,5 cm^3 deuterated chloroform in an NMR tube. The tube was sealed and placed in a water bath at 60°C. ^1H NMR showed the appearance of a new singlet peak at δ_{1H} 1,17. This peak grew in intensity and the doublet at δ_{1H} 3,70 became smaller. After 12 hours no changes in the intensity of these two peaks were observed.

(V) The hydrochloric salt 0,186g ($8,55x10^{-4}$ mol) was added to boiling thionyl chloride 0,505g ($4,24x10^{-3}$ mol) and refluxed for 30 minutes. A white precipitate 0,138g (79%) was obtained after the excess thionyl chloride was removed, m.p. 119°C. The NMR spectra were run in D_2O.

δ_{1H}	1,37	(3H; d; J_{HP} 17,4 Hz; CH_3 of MePO)
	2,80	(6H; s; 2 x CH_3 on N)
	3,32	(2H; t; J_{HH} 5,0 Hz; CH_2 vic to N)
	4,13	(2H; t; J_{HH} 4,2 Hz; CH_2 vic to O)
δ_{31P}	32,33	
δ_{13C}	13,28	(d of q; J_{CP} 137,3 Hz; J_{CH} 127,6 Hz; CH_3 of MePO)
	45,46	(q; J_{CH} 143,9 Hz; 2 x CH_3 on N)
	59,95	(d of t; J_{CP} 7,6 Hz; J_{CH} 143,2 Hz; CH_2 vic to N)
	60,80	(d of t; J_{CP} 4,6 Hz; J_{CH} 148,9 Hz; CH_2 vic to O)
IR	1212	P=O
	1174	S=O

Calc. for $[C_5H_{15}NO_3PCl]$ (203,6)	: C 29,5;	N 6,9;	H 7,4
Found:	: C 27,96	N 6,78	H 7,78

The NMR spectra of the same salt were run in DMSO-d_6. This spectra confirm the spectra run in D_2O but the presence of a minor product could also be observed.

δ_{31P} 25,60 (Minor)
29,01 (Major)

(VI) The NMR tube containing the salt in D_2O was treated with anhydrous potassium carbonate. The pH of this solution was raised to ± 11,5. The NMR spectra of this mixture gave the following results (Only the values of the major peaks are given):

δ_{1H} 1,42 (3H; d; J_{HP} 16,3 Hz; CH_3 of MePO)
2,57 (6H; s; 2 x CH_3 on N);
2,96 (2H; t: J_{HH} 5,0 Hz; CH_2 vic to N)
4,11 (2H; t; J_{HH} 5,0 Hz; CH_2 vic to O)

δ_{31P} 20,95 (Minor)
27,60 (Major)

(VII) N,N-dimethylaminoethyl methyl methylphosphonate 0,203g ($1,12 \times 10^{-3}$ mol) was added to boiling thionyl chloride 0,395g ($3,32 \times 10^{-3}$ mol) and kept at refluxing temperature for 30 minutes. After the excess thionyl chloride was removed 0,574g of a yellow crystalline material was obtained. The NMR spectra in DMSO-d_6 shows the following five products:

δ_{31P} 21,14; 23,76; 25,67; 27,09; 29,27

4.3.2 Dimethyl methylphosphonate

A mixture of dimethyl methylphosphonate 0,603g ($4,82 \times 10^{-3}$ mol), N,N-dimethylformamide 0,0068g ($9,3 \times 10^{-5}$ mol) and triethylamine 0,476g ($4,71 \times 10^{-3}$ mol) was added to thionyl chloride 1,397g ($1,17 \times 10^{-2}$ mol) at 0°C. After addition the reaction mixture was refluxed for 30 minutes, cooled to room temperature and the excess thionyl chloride removed at water pump pressure. An NMR spectra were run on the black precipitate in $CDCl_3$. The ^{31}P NMR spectra showed various peaks typical for the formation of polymeric material.

4.3.3 N,N-dimethylaminoethyl ethyl ethylphosphonate

A mixture of N,N-dimethylaminoethyl ethyl ethylphosphonate 0,0646g ($2,73x10^{-4}$ mol) and N,N-dimethylformamide 0,0015g ($2,1x10^{-5}$ mol) reacted with thionyl chloride 1,0 cm^3 ($1,4x10^{-2}$ mol) according to a standard procedure[13] to give 0,051g of a yellow oil.

δ_{1H}	1,16	(3H; d of t; J_{HP} 20,7 Hz; J_{HH} 7,7 Hz; CH_3 of EtPO)
	1,33	(3H; t; J_{HH} 7,0 Hz; CH_3 of POEt)
	1,83	(2H; d of q; J_{HP} 18,2 Hz; J_{HH} 7,7 Hz; CH_2 of EtPO)
	2,91	(6H; s; 2 x CH_3 on N)
	3,39	(2H; m; CH_2 of EtOP)
	4,14	(2H; m; CH_2 vic to N)
	4,51	(2H; m; CH_2 vic to O)
δ_{31P}	36,45	(Major)
δ_{13C}	6,10	(d of q; J_{CP} 6,6 Hz; J_{CH} 129,5 Hz; CH_3 of EtPO)
	16,19	(d of q; J_{CP} 5,4 Hz; J_{CH} 128,7 Hz; CH_3 of POEt)
	18,24	(d of t; J_{CP} 141,1 Hz; J_{CH} 129,0 Hz; CH_2 of EtPO)
	43,28	(q; J_{CH} 140,9 Hz; 2 x CH_3 on N)
	56,90	(d of t; J_{CP} 6,4 Hz; J_{CH} 143,1 Hz; CH_2 vic to N)
	59,13	(d of t; J_{CP} 6,1 Hz; J_{CH} 148,7 Hz; CH_2 of POEt)
	62,39	(d of t; J_{CP} 6,5 Hz; J_{CH} 147,8 Hz; CH_2 vic to O)

4.3.4 Diethyl ethylphosphonate

A mixture of diethyl ethylphosphonate 2,016g (1,21x10^{-2} mol), N,N-dimethylformamide 0,012g (1,6x10^{-4} mol) and triethylamine 1,212g (1,20x10^{-2} mol) reacted with thionyl chloride 3,583g (3,01x10^{-2} mol) according to a standard procedure[13] to give 3,462g of a black precipitate.

δ_{1H} 1,12 (3H; d of t; J_{HP} 19,9 Hz; J_{HH} 7,7 Hz; CH_3 of EtPO)
1,28 (3H; t; J_{HH} 7,1 Hz; CH_3 of EtOP)
1,70 (3H; d of q;
4,06 (4H; m; 2 x CH_2 of EtOP)

δ_{31P} 34,25

4.3.5 N,N-dimethylaminoethyl isopropyl methylphosphonate

(I) A mixture of N,N-dimethylaminoethyl isopropyl methylphosphonate 0,100g (4,76x10^{-4} mol) and N,N-dimethylformamide 0,0004g (5x10^{-6} mol) reacted with thionyl chloride 1,666g (1,40x10^{-2} mol) according to a standard procedure[13] to give 0,051g of a yellow crystalline material. The salt was dissolved in the minimum of chloroform and five time the volume of ether was added. A white salt precipitated out and was removed by filtration yielding 0,041g. Obtaining the melting point proved impossible, because the salt was too hygroscopic.

δ_{1H} 1,30 (6H; d of d; J_{HP} 2,5 Hz; J_{HH} 6,2 Hz; 2 x CH_3 of POPr^i)
1,52 (3H; d; J_{HP} 17,5 Hz; CH_3 of MePO)
2,88 (6H; s; 2 x CH_3 on N)
3,36 (2H; t; J_{HH} 4,9 Hz; CH_2 vic to N)
4,46 (2H; m; CH_2 vic to O)
4,67 (1H; m; CH of POPr^i)

δ_{31P} 31,42

δ_{13C} 13,86 (d of q; J_{CP} 138,9 Hz; J_{CH} 48,5 Hz; CH_3 of MePO)
13,21 (d of q; J_{CP} 137,4 Hz; J_{CH} 48,5 Hz; CH_3 of MePO)
25,85 (d of q; J_{CP} 4,0 Hz; J_{CH} 126,8 Hz; 2 x CH_3 of POPr^{i})
40,43 (t; J_{CH} 153,9 Hz; CH_2 vic to N)
45,34 (q; J_{CH} 144,3 Hz; 2 x CH_3 on N)
60,77 (t; J_{CH} 146,3 Hz; CH_2 vic to O)
74,22 (d of d; J_{CP} 5,9 Hz; J_{CH} 142,0 Hz; CH of POPr^{i})

(II) The salt was dissolved in water and potassium carbonate was added to this mixture until a pH of ± 11 was obtained. The NMR spectra run on this sample confirmed that the origonal substrate was recovered.

δ_{1H} 1,30 (6H; d; J_{HP} 6,2 Hz; 2 x CH_3 of POPr^{i})
1,46 (3H; d; J_{HP} 17,7 Hz; CH_3 of MePO)
2,27 (6H; s; 2 x CH_3 on N)
2,57 (2H; t; J_{HH} 5,9 Hz; CH_2 vic to N)
4,06 (2H; m; CH_2 vic to O)
4,67 (1H; m; CH of POPr^{i})

δ_{31P} 30,67

(III) N,N-dimethylaminoethyl isopropyl methylphosphonate 0,223g ($1{,}07\times10^{-3}$ mol) was dissolved in 100 cm^3 dry ether. Dry $HCl_{(g)}$ was bubbled through this solution. At first a white precipitate formed which later disappeared. The ether and excess $HCl_{(g)}$ was removed at water pump pressure to give a white salt, m.p. 106,3 -106,8 °C.

δ_{1H} 1,26 (6H; d of d; J_{HP} 2,6 Hz; J_{HH} 6,2 Hz; 2 x CH_3 of $POPr^i$)

1,49 (3H; d; J_{HP} 17,5 Hz; CH_3 of MePO)

2,86 (6H; s; 2 x CH_3 on N)

3,35 (2H; m; CH_2 vic to N)

4,42 (2H; m; CH_2 vic to O)

4,65 (1H; m; CH of $POPr^i$)

δ_{31P} 31,22

4.3.6 N,N-diethylaminoethyl methyl methylphosphonate

A mixture of N,N-diethylaminoethyl methyl methylphosphonate 0,161g ($1,11\times10^{-4}$ mol) and N,N-dimethylformamide 0,00063 cm^3 ($7,7\times10^{-6}$ mol) reacted with thionyl chloride 0,304g ($2,55\times10^{-3}$ mol) according to a standard procedure[13] to give 0,143g (87%) of a brown oil containing two products:

Major:

δ_{1H} 1,41 (6H; t; J_{HH} 7,3 Hz; 2 x CH_3 of NEt_2)

2,10 (3H; d; J_{HP} 17,5 Hz; CH_3 of MePO)

3,21 (4H; m; 2 x CH_2 of NEt_2)

3,41 (2H; m; CH_2 vic to N)

4,67 (2H; m; CH_2 vic to O)

δ_{31P} 43,30

Minor:

δ_{1H} 1,42 (6H; t; J_{HH} 7,3 Hz; 2 x CH_3 of NEt_2)

2,48 (3H; d; J_{HP} 16,4 Hz; CH_3 of MePO)

3,34 (2H; m; CH_2 of $ClCH_2\underline{CH_2}NEt_2$)

4,02 (t; J_{HH} 6,8 Hz; CH_2 of $Cl\underline{CH_2}CH_2NEt_2$)

δ_{31P} 44,07

4.3 7 N,N-diethylaminoethyl ethyl ethylphosphonate

A mixture of N,N-diethylaminoethyl ethyl ethylphosphonate 0,1164g ($4{,}91 \times 10^{-4}$ mol) and N,N-dimethylformamide 0,0005g (7×10^{-6} mol) reacted with thionyl chloride 0,156g ($1{,}31 \times 10^{-3}$ mol) according to a standard procedure[13] to give 0,096g (86%) of a brown oil containing two products.

Major:

δ_{1H} 1,27 (3H; d of t; J_{HP} 25,4 Hz; J_{HH} 7,7 Hz; CH_3 of EtPO)
1,40 (6H; t; J_{HH} 7,3 Hz; 2 x CH_3 of NEt_2)
2,25 (2H;d of q; J_{HP} 17,2 Hz; J_{HH} 7,6 Hz; CH_2 of EtPO)
3,21 (4H; m; 2 x CH_2 of NEt_2)
3,41 (2H; m; CH_2 vic to N)
4,66 (2H; m; CH_2 vic to O)
δ_{31P} 49,69

Minor:

δ_{31P} 36,18

4.4 Kinetic studies of the decomposition of 2-dialkylaminoethyl esters of phosphonic acids

4.4.1 N,N-dimethylaminoethyl isopropyl methylphosphonate

N,N-dimethylaminoethyl isopropyl methylphosphonate 30mg was dissolved in 0,5 cm^3 DMSO-d_6 in an NMR tube and incubated in a thermoregulated water bath at 60 °C. It was found that the peaks used by Benschop[8] i.e. δ_{1H} 3,37 and 3,95 for the rate measurements were not undisturbed. The doublets at δ_{1H} 1,08 and 1,22 were however undisturbed and used in the calculation of the reaction rates. Each doublet corresponds to three hydrogen atoms.

Table 10

Percentage decomposition of substrate as a function of time in DMSO-d_6 at 60°C

% SUBSTRATE	% PRODUCT	TIME (min)
93.4	6.6	9900
86.7	13.3	19800
80.7	19.3	31560
77.1	22.9	40275
73.9	26.1	51670
70.4	29.6	60545
66.9	33.1	70550
63.0	37.0	80850
59.6	40.4	92220
56.5	43.5	102240
54.3	45.7	109440
51.1	48.9	125220
49.7	50.3	132540
48.0	52.0	142740
45.9	54.1	151110
43.4	56.5	161340

4.4.2 N,N-dimethylaminoethyl ethyl ethylphosphonate

N,N-dimethylaminoethyl ethyl ethylphosphonate 29mg was dissolved in 0,5 cm^3 DMSO-d$_6$ in an NMR tube and placed in a water bath at 60 °C. It was observed that a quartet equivalent to two hydrogens started to form at δ_{1H} 3,65. This peak together, with the singlet at δ_{1H} 2,17, equivalent to six hydrogens were used to determine the rate of the reaction.

Table 11

Percentage decomposition of substrate as a function of time in DMSO-d$_6$ at 60 °C

% SUBSTRATE	% PRODUCT	TIME (min)
85.4	14.6	19800
84.3	15.7	31740
78.7	21.3	40280
74.4	25.6	51680
72.8	27.2	56280
70.3	29.7	60550
64.3	35.4	70665
60.8	39.2	80850
53.8	46.2	96180
53.8	46.2	102180
51.8	48.2	109440
42.7	57.3	125220

42.1	57.9	142740
41.0	59.0	151110
38.3	61.7	161340

4.4.3 N,N-dimethylaminoethyl methyl methylphosphonate

N,N-dimethylaminoethyl methyl methylphosphonate 25mg was dissolved in 0,5 cm^3 DMSO-d$_6$ in an NMR tube and left in a water bath at 60 °C. The NMR spectra of this mixture was recorded as a function of time. Signals at δ_{1H} 0,91; 0,93; 1,43; 1,54 were used to calculate the percentage of the substrate left in the reaction mixture. All peaks are equivalent to three hydrogen atoms.

Table 12

Percentage decomposition of substrate as a function of time in DMSO-d$_6$ at 60 °C

% SUBSTRATE	% PRODUCT	TIME (min)
71.2	28.8	8400
34.1	65.9	14400
22.9	77.1	21660
12.3	87.7	37560
8.7	91.3	44760
6.9	93.1	54960
4.6	95.4	63330
4.4	95.6	73560

N,N-dimethylaminoethyl methyl methylphosphonate 29 mg was dissolved in 0,5 cm^3 $CDCl_3$-d_1 in an NMR tube and placed in a water bath at 60 °C. The ^1H NMR spectra were run on this mixture at different time intervals. The doublets at δ_{1H} 1,43 and 1,22 correspond to three hydrogen atoms each and were used to determine the percentage of the substrate left in the mixture.

Table 13

Percentage decomposition of substrate as a function of time in $CDCl_3$-d_1 at 60°C

% SUBSTRATE	% PRODUCT	TIME (min)
93.3	6.7	3840
89.1	10.9	11160
84.6	15.4	19740

4.4.4 N,N-dimethylaminoethyl methyl ethylphosphonate

N,N-dimethylaminoethyl methyl ethylphosphonate 22mg was dissolved in 0,5 cm^3 DMSO-d_6 in an NMR tube and incubated in a water bath at 60 °C. The triplet at δ_{1H} 1,21 of the substrate and at δ_{1H}1,07 of the product were used to determine the rate of the reaction. Each peak corresponds to three hydrogen atoms.

Table 14

Percentage decomposition of substrate as a function of time in DMSO-d_6 at 60 °C

% SUBSTRATE	% PRODUCT	TIME (min)
90.3	9.7	10380
77.8	22.2	20520
67.3	32.7	30600
61.0	39.0	40500
54.1	45.9	50760
48.7	51.3	60480

4.4.5 N,N-diethylaminoethyl methyl methylphosphonate

N,N-diethylaminoethyl methyl methylphosphonate 20mg was dissolved in 0,5 cm^3 DMSO-d_6 and placed in an NMR tube. This tube was placed in a water bath kept at 60 °C and the ^1H spectra were recorded at different time intervals. The singlet at δ_{1H} 3,82 and quartet at δ_{1H} 2,56, corresponding to 8 and 4 protons respectively, were used.

Table 15

Percentage decomposition of substrate as a function of time in DMSO-d_6 at 60 °C

% SUBSTRATE	% PRODUCT	TIME (min)
78.3	21.7	10320
63.7	36.3	20460
49.1	50.9	30540
35.9	64.1	40440
21.6	78.4	50700

4.4.6 N,N-diethylaminoethyl ethyl ethylphosphonate

N,N-diethylaminoethyl ethyl ethylphosphonate 29mg was dissolved in 0,5 cm^3 DMSO-d_6 and placed in an NMR tube. This mixture was incubated in a water bath at 60 °C and the spectra were recorded as a function of time. The two doublet of quartet signals at δ_{1H} 1,71 and 1,38 were used to calculate the rate of the reaction. Both signals correspond to three protons.

Table 16

Percentage decomposition of substrate as a function of time in DMSO-d_6 at 60 °C

% SUBSTRATE	% PRODUCT	TIME (min)
64.9	35.1	10320
42.8	57.2	20460
27.3	72.7	30540
14.8	85.2	40440
8.7	91.3	50700

4.4.7 N,N-diethylaminoethyl methylphosphonyl chloride

N,N-diethylaminoethyl methylphosphonyl chloride 25mg was dissolved in 0,5 cm^3 $CDCl_3$-d_1 in an NMR tube and left in a water bath at 60 °C. The ^1H NMR spectra were recorded at different time intervals to monitor the extent of decomposition. The doublets at δ_{1H} 2,09 and 2,48 were used to determine the rate constant for the disappearance of the substrate while the triplet at δ_{1H} 3,99 and multiplet at 4,50 were used to calculate the rate of formation of diethyl-(2-chloroethyl)amine. The first two peaks correspond to three protons and the last two correspond to two protons each.

Table 17

Percentage decomposition of substrate as a function of time in $CDCl_3$-d_1 at 60 °C

% SUBSTRATE	% PRODUCT	TIME (min)
77.3	20.2	0
59.3	43.8	1200
42.4	63.3	2520
29.8	81.5	3390
28.8	89.2	5640

N,N-diethylaminoethyl methylphosphonyl chloride 25 mg was dissolved in 0,5 cm^3 CD_3CN-d_3 in an NMR tube and placed in a water bath at 60 °C. The ^1H NMR spectra were recorded at different time intervals to monitor the extent of decomposition. The doublets at δ_{1H} 2,10 and 1,78, corresponding to three hydrogen atoms each were used to calculate the percentage of the substrate that remained, while the triplet at δ_{1H} 3,95 and the multiplet at 4,50, corresponding to two hydrogens each, were used to calculate the percentage of diethyl-(2-chloroethyl)amine that had formed.

Table 18

Percentage decomposition of substrate as a function of time in CD_3CN-d_3 at 60°C

% SUBSTRATE	% PRODUCT	TIME (min)
62.4	6.6	0
52.4	6.2	150
45.2	9.3	390
26.1	18.1	1500
23.2	20.6	1860
17.9	27.9	2790
9.5	37.4	4260
-	44.9	5670
-	71.9	10080

4.4.8 N,N-diethylaminoethyl ethylphosphonyl chloride

N,N-diethylaminoethyl ethylphosphonyl chloride 27mg was dissolved in 0,5 cm^3 $CDCl_3$-d_1 in an NMR tube and incubated in a water bath at 60 °C. The ^1H signals at δ_{1H} 4,02 (triplet) and 4,68 (multiplet) were used to monitor the extent of the decomposition. Both signals correspond to two protons each.

Table 19

Percentage decomposition of substrate as a function of time in $CDCl_3$-d_1 at 60 °C

% SUBSTRATE	% PRODUCT	TIME (min)
19.5	80.5	0
79.2	20.8	4080

4.4.9 Stability of diethyl-(2-chloroethyl)amine in chloroform and acetonitrile

Two 0,295 M solutions of diethyl-(2-chloroethyl)ammonium chloride were prepared by dissolving 0,101g ($5.91x10^{-4}$ mol) of the salt in 2 cm^3 $CDCl_3$-d_1 and CD_3CN-d_3 respectively. After recording the ^1H NMR spectra of each sample solid anhydrous potassium carbonate 0,082g ($5,93x10^{-4}$ mol) was added to each solution. These mixtures were stirred and the ^1H spectra recorded at different time intervals.

The free base proved to be stable for up to 6 days in $CDCl_3$ and only gave rise to the following ^1H signals:

δ_{1H} 1,34 (6H; t; J_{HH} 7,2 Hz; 2 x $CH_3$of Et)
3,10 (4H; q; J_{HH} 7,3 Hz; 2 x CH_2 of Et)
3,28 (2H; t; J_{HH} 6,9 Hz; CH_2 vic to N)
3,91 (2H; t; J_{HH} 6,9 Hz; CH_2 vic to Cl)

The following ^1H NMR spectra were recorded of the free base in CD_3CN:

δ_{1H} 1,19 (6H; t; J_{HH} 7,3 Hz; 2 x CH_3 of Et)
2,92 (4H; q; J_{HH} 7,2 Hz; 2 x CH_2 of Et)
3,13 (2H; t; J_{HH} 7,2 Hz; CH_2 vic to N)
3,86 (2H; t; J_{HH} 7,1 Hz; CH_2 vic to Cl)

After 1 day a singlet at δ_{1H} 2,20 started to appear together with ranges of peaks at δ_{1H} 3,4 and 1,2. These peaks grew in intensity to reach a maximum after 4 days. On day 5 the ^1H NMR spectra showed that the peak at δ_{1H}2,20 had disappeared and the spectrum stayed constant from then on.

4.5 Reaction conditions for the use of oxalyl chloride as chlorinating agent in the preparation of phosphonic mono-ester chlorides

In a paper by Pelchowicz[14] various reactions are presented for the preparation of half-ester phosphates where oxalyl chloride is used as chlorinating agent. Only polymeric material was obtained when the reaction was repeated. At this stage it was decided to investigate this reaction and determine suitable conditions for chlorination of alkylphosphonates.

(I) Diethyl ethylphosphonate 0,205g ($1,23 \times 10^{-3}$ mol) in 10 cm^3 ether reacted with oxalyl chloride 0,302g ($2,38 \times 10^{-3}$ mol) in 2 cm^3 ether according to a standard procedure[14]. After 24 hours the solvent was removed at water pump pressure and an NMR spectra run on the product. Two phosphorus peaks were observed i.e. δ_{31P} 34,64 (80%) assigned to the substrate and 47,09 (20%) due to the product. From this it can be seen that only a small conversion is obtained under these conditions. It was decided to repeat the reaction at refluxing temperature.

(II) Diethyl ethylphosphonate 0,205g ($1,23 \times 10^{-3}$ mol) dissolved in 10 cm^3 ether was added to oxalyl chloride 0,307g ($2,41 \times 10^{-3}$ mol) dissolved in 2 cm^3 ether. After addition the reaction mixture was refluxed and samples were taken at time intervals to determine the extent of the reaction.

Table 20

Percentage conversion to the monochloride as a function of time

% PRODUCT	% REACTANT	TIME (Hours)
0	100	0.5
0	100	2.5
52.6	47.4	23.8

From the table it can be clearly seen that the reaction is temperature dependent. It was now decided to investigate the effect concentration had on the reaction rate.

(III) Diethyl ethylphosphonate 0,561g (3,36x10^{-3} mol) was added dropwise to oxalyl chloride 0,850g (6,69x10^{-3} mol). After addition the mixture was kept at refluxing temperature. Samples were drawn and NMR spectroscopy used to determine the extent of the reaction. After 30 minutes full conversion was obtained.

δ_{1H} 1,24 (3H; d of t; J_{HP} 24,6 Hz; J_{HH} 7,7 Hz; CH_3 of EtPO)
1,35 (3H; t; J_{HH} 7,1 Hz; CH_3 of POEt)
2,10 (2H; d of q; J_{HP} 17,4 Hz; J_{HH} 7,7 Hz; CH_2 of EtPO)
4,23 (2H; m; CH_2 of POEt)

δ_{31P} 47,10

After 1 hour another sample was drawn from the reaction mixture. The ^{31}P and ^{1}H NMR spectra were exactly the same as that of the first sample. Therefore no dichloride had started to form up to this stage.

(IV) Diethyl ethylphosphonate 0,607g (3,63x10^{-3} mol) was added to oxalyl chloride 0,848g (6,68x10^{-3} mol) at room temperature. The mixture was stirred at room temperature, samples were extracted and the extent of the reaction determined by NMR spectroscopy.

Table 21

Percentage conversion to the monochloride as a function of time

% PRODUCT	% REACTANT	TIME (Hours)
55.4	44.6	0.5
89.0	11.0	2
100	0	3

CHAPTER 5

References

1 H Goldwhite, "*Introduction to phosphorus chemistry*", Cambride University Press, Cambridge (1981) Chapt. 1.

2 R T Morrison and R N Boyd, "*Organic Chemistry*", Fourth ed., Allyn and Bacon Inc., Boston (1983) Chapt. 27.

3 W C Browman and M J Rand, "*Textbook of pharmocology*", Second ed., Blackwell Scientific publications, Oxford (1980) Chapt. 10.

4 J Emsley and D Hall, "*The Chemistry of Phosphorus*", Harper and Row, London (1976) Chapt. 12.2.

5 S H Pine, "*Organic chemistry*", Fifth ed., McGraw-Hill Book Company, New York (1987) 307, 865.

6 L E Tammelin, *Acta. Chem. Scand.*, **11** (1957) 859.

7 T R Fukuto and E M Stafford, *J. Am. Chem. Soc.*, **79** (1957) 6083.

8 H P Benschop, G R van den Berg and G W Kraay, *Organophosphorus Compounds*, **89** (1970) 1025.

9 J I G Cadogan and L C Thomas, *J. Chem. Soc.*, (1960) 2248.

10 L Larsson, *Acta. Chem. Scand.*, **12** (1958) 587.

11 L Larsson, *Acta. Chem. Scand.*, **6** (1952) 1470.

12 M Fild, R Schmutzler and S C Peake, *Organic Phosphorus Compounds*, ed. G M Kosolapoff and L Maier, J Wiley and Sons, **4** (1972) 155.

13 L Maier, *Phosphorus, Sulfur and Silicon*, (1990) 465.

14 Z Pelchowicz, *J. Chem. Soc.*, (1961) 238.

15 S Cocks, *The electrophilicity and chemistry of phosphate esters*, Ph.D. Thesis, University of Cape Town, (1986).

16 C J Lacey and L M Loew, *J. Org. Chem.*, **48** (1983) 5214.

17 A H Ford-Moore and B J Perry, *Org. Synthesis*, **31** (1951) 111.

18 A H Ford-Moore and B J Perry, *Org. Synthesis*, **31** (1951) 33.

19 D G Coe, B J Perry and P K Brown, *J. Chem. Soc.*, (1957) 3604.

20 T A Modro and C M Moorhoff, *J. Phys. Org. Chem.*, **2** (1989) 263.

21 C J Lacey and L M Loew, *Tetrahedron Lett.*, **21** (1980) 2017.

22 A Maquestiau, E Anders, A Mayence and J Vanden Eynde, *Chem. Ber.*, **124** (1991) 2013.

23 R T Morrison and R N Boyd, "*Organic Chemistry*", Fourth ed., Allyn and Bacon Inc., Boston (1983) 889.

24 D E C Corbridge, "*Phosphorus*", Fourth ed., Elsevier, Amsterdam (1990) 502.

25 D Quin and S Jankowski, *J. Org. Chem.*, **59** (1991) 4402.

26 S Cocks and T A Modro, *Tetrahedron Lett.*, **26** (1985) 945.

27 R S Edmundson, Dictionary of Organophosphorous Compounds, ed. Chapmann and Hall (1988).