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THE SYNTHESIS, SPECTROSCOPY AND FUNGICIDAL ACTIVITY OF PHOSPHORIC ACID AMIDES

BY

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ABSTRACT

THE SYNTHESIS, SPECTROSCOPY AND FUNGICIDAL ACTIVITY OF PHOSPHORIC ACID AMIDES BY C.N. MAVROMMATIS 1983.

The reaction between N,N,N',N'-tetramethylphosphoric triamide (TMPT) and chloral has been shown to give chloroform, dimethylformamide, $(Me_2N)_2P(O)NHCH(CCl_3)NMe_2$ and polymeric phosphorus containing compounds. A possible mechanism for the formation of these products is given.

Compounds of the types $(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)R$ (1), $(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)CH_2R'$ (2) and $(EtO)_2P(O)NHCH(CCl_3)$-$NHC(O)R''$ (3) have been synthesised by a route which in each case involves the condensation of a phosphoramide or carboxamide with chloral, followed by chlorination of the resulting hydroxy compound, elimination of HCl to give an intermediate containing the trichloromethyl-substituted imine group, $-C(CCl_3)=N-$, and subsequent addition of a nucleophilic reagent containing acidic protons. A number of novel N-(1-hydroxy-2,2,2-trichloroethyl)- and N-(1,2,2,2-tetrachloroethyl)amide intermediates were also obtained.

N-(1,2,2,2-tetrachloroethyl) derivatives obtained from secondary amides or amines cannot give an imine and also failed to react with TMPT by direct displacement of secondary chlorine. The compounds nevertheless decomposed in the presence of triethylamine with evolution of HCl, e.g. $CCl_3CH(Cl)N(CH_3)CHO$ yielded $CCl_2=C(Cl)N(CH_3)CHO$.

Compounds of type 2 were synthesised from 2 (R'=Cl) and the appropriate sodium or potassium salt by nucleophilic displacement of the terminal chlorine. Alkoxy anions however attacked at the methine carbon with elimination of the chloroacetamido group to yield products of type $(Me_2N)_2P(O)NHCH(CCl_3)OR''$ (4). Reaction between the compound 2 (R'=H) and sodium ethanethiolate or sodium ethoxide did not yield products consistent with exclusive nucleophilic attack at the methine carbon. The results obtained are discussed and a mechanism is proposed.

The reactions of N-(1-hydroxy-2,2,2-trichloroethyl)imidazole with thionyl chloride and with N,N,N',N'-tetramethylphosphorodiamidic chloride gave products consistent with electrophilic attack at the multiply bonded nitrogen with C-N bond cleavage rather than attack at the oxygen of the hydroxy group.

The ^1H, ^{13}C, and ^{31}P NMR spectra of compounds 1,2,3,4 and of certain intermediates are reported. The proton chemical shift non-equivalence of the ethoxy groups of compounds 3 and the dimethylamido groups of compounds 1, 2, and 4 has been discussed on the basis of prochiral group interactions. General EI and FAB mass spectral fragmentations are given. An unusual rearrangement involving the apparent transfer of hydroxyl to phosphorus with the elimination of RC≡N in the EI spectra of compounds 1 and 2 is discussed.

Preliminary screening against Piricularia oryzae, Rhizoctonia solani, Botrytis cinerea, Septoria nodorum, Fusarium avenaceum and Dreschlera sativa in vitro and Dreschlera teres and Septoria nodorum in vivo showed the compounds to have low fungicidal activity against these organisms. No phytotoxicity was shown against wheat or barley.

To Bobby

and

Nicholas

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Preface

While registered as a candidate for the degree for which submission is made the author has not been registered as a candidate for another award of the CNAA or of a university.

In partial fulfilment of the requirements of the degree the author completed the M.Sc. course on Structural Methods (i.r., u.v., mass spectrometry and X-ray crystallography).

In addition the author has also attended a conference on Crop Protection at The Royal Society and The International Conference of Phosphorus Chemistry in Nice (1983).

CONTENTS

CHAPTER 1

INTRODUCTION

1.1 The need, historical development and current use of fungicides

The best available estimates of world crop damage caused by diseases, pests and weeds were made in 1967.[1] These indicate that about 18 per cent of world agricultural production was lost by disease, mainly caused by fungi. The economic loss due to diseases amounts to some £60 000 million per annum which may be compared with £700 million spent on fungicides.[2]

The commercial production of many crops such as fruits, vegetables, tobacco, potato, peanuts, cocoa, and coffee would be difficult or impossible without the use of chemicals to control the major fungal diseases. Yields of other crops such as cereals and cotton would be lower or uncertain.

The discovery of Bordeaux mixture (copper hydroxide and calcium sulphate) in the early 1880's may be considered as the first important landmark in the history of the chemical control of plant diseases. Thus chemical agents have been used against plant pathogens for about 100 years. The discovery of dithiocarbamate fungicides in 1934 and the introduction of several systemic fungicides in the late 1960s are considered to be the two other most important events in the 100-year history of chemical disease control. A fuller account of the historical development of chemical compounds for the control of diseases caused by fungi can be found in the literature.[3-6]

Fungicides in current use may be described as classical

(protective or eradicant) or systemic (which may act at sites remote from the locus of application). Until about 20 years ago practically all the established products fell into the former category and even as recently as 1974 the classical fungicides dominated world sales as indicated by table 1.1.[2]

PRODUCT GROUP	£m
Copper compounds	83
Mercurials	23
Sulphur	30
Dithiocarbamates	225
Pthalimides	187

Table 1.1 World fungicide sales by product group

The newer systemic fungicides introduced just over a decade ago have not led to the expected replacement of older materials. Recent estimates indicate that systemic fungicides accounted for approximately 20% of sales and 3-4% of the tonnage of world fungicides.[2]

1.1.1 Classical fungicides

The classical copper, sulphur and mercury based fungicides are still extensively used. Copper based fungicides, such as Bordeaux mixture, are valuable in crops such as coffee, cocoa and tea, their advantage over newer organic compounds being their exceptional stability under tropical conditions of light, heat and rainfall. However, their use for the control of potato late blight and vine downy mildew has been replaced

to some extent by newer organic compounds.

Sulphur has not been significantly superseded for the control of grape powdery mildew, but the application of lime-sulphur sprays in other fruit crops has decreased due to the introduction of more effective and less phytotoxic materials.[2]

Spraying with organomercurial fungicides has greatly declined, although arylmercurial compounds are still widely applied as cereal seed dressings to combat seed-borne fungal diseases. Due to dangers of environmental pollution, the use of organomercurial seed dressings has been severely restricted in many countries, but not in Britain, where alternative treatments have proved unsatisfactory.[7]

1.1.2 Systemic fungicides

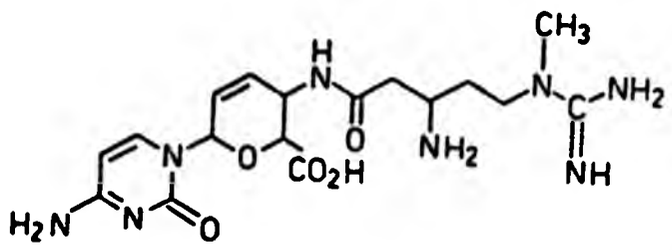
These can be divided into five major groups:[4]

i) Antibiotics such as blasticidin (1) and kasugamycin (2) both active against rice blast fungus, and polyoxin D (3) effective against rice sheath blight.

ii) Oxathiins and related carboxanilides, e.g. carboxin (4), oxycarboxin (5), fenfuram (6), pyracarbolid (7), active against rusts, smuts and bunts of cereals.

iii) Benzimidazoles and related compounds such as benomyl (8), fuberidazole (9), and thiabendazole (10), effective against a wide range of fungal diseases of fruit and vegetables.

iv) Pyrimidines like dimethirimol (11), ethirimol (12), and bupirimate are active against specific types of powdery mildews.



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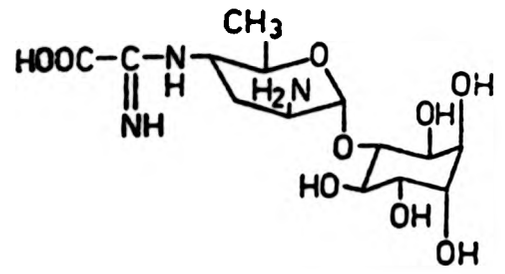

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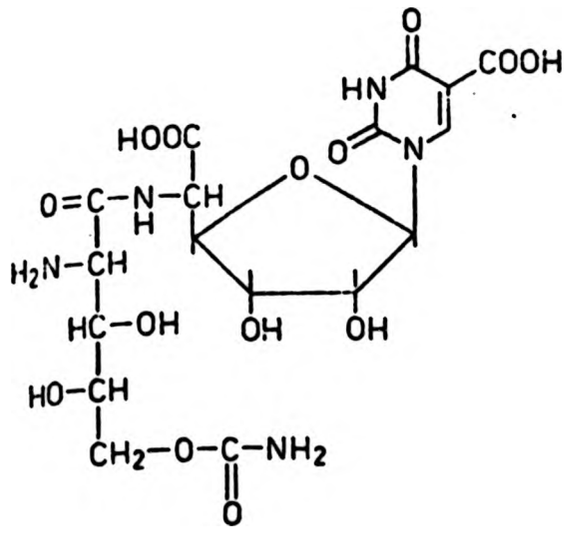

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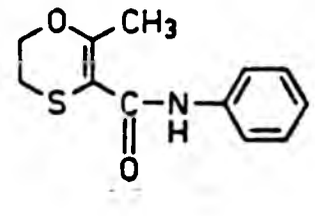

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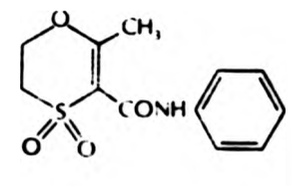

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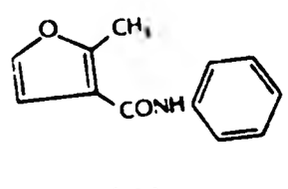

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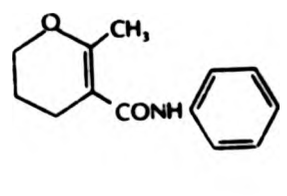

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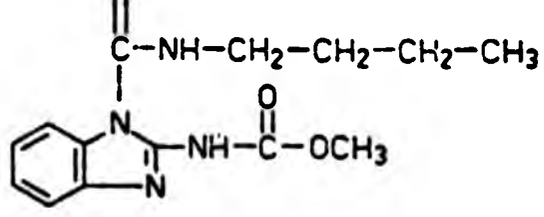

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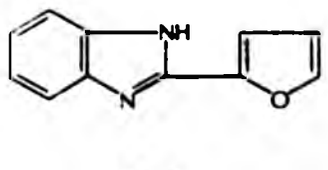

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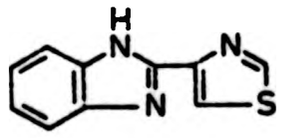

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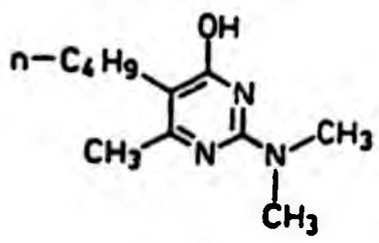

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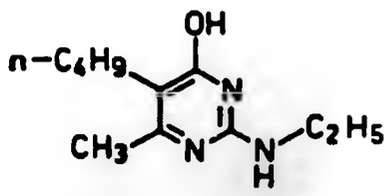

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v) Organophosphorus compounds which are treated in greater detail in the following section.

More recent developments in both surface and systemic fungicides have been reviewed.[7]

1.2 Organophosphorus Fungicides

The use of organophosphorus compounds as fungicides constitutes a relatively new and promising field of pesticide research. The first studies in which the microbiological action of organophosphorus compounds was noted were made at the beginning of the 1940's, but systematic investigations of their fungicidal and bactericidal properties began in the 1950's. By 1972, 450 publications had been devoted to organophosphorus fungicides. Some compounds have been developed commercially whilst others are in the experimental stages.

In two recent reviews,[8,9] six commercially important organophosphorus fungicides are listed (see Table 1.2). Of the six, ditalimfos is usually described as non-systemic, while the others are transported within the plant and are thus systemic. Ditalimfos, pyrazophos and triamiphos are used to control powdery mildews on a wide range of crops especially apple and cucurbits. Kitazin-P and Hinosah are used specifically against rice leaf blast (Piricularia oryzae). The former is more widely used. Kitazin-P is acropetally systemic so that the disease can be controlled by applying granules of the compound to the paddy water. Aluminium ethyl phosphite is used

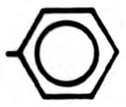
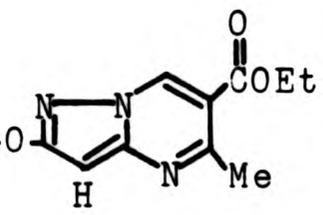
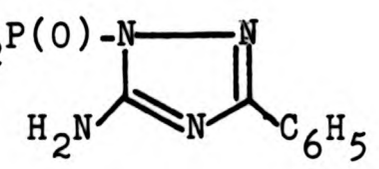
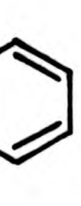
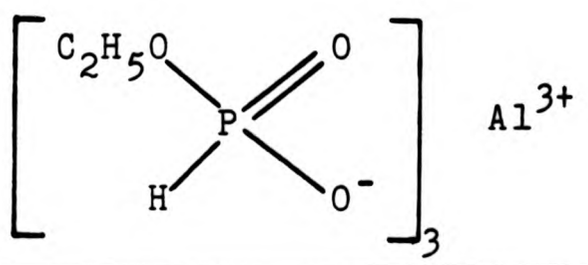
Common name	Trade name	Structure
IBP	Kitazin-P	$[(CH_3)_2CHO]_2P(O)SCH_2$ 
Edifenphos	Hinosan	$EtO\text{-}P(O)(SPh)_2$
Pyrazophos	Afugan Curamil	$(EtO)_2P(S)\text{-}O$ 
Triamiphos	Wepsyn	$(Me_2N)_2P(O)\text{-}N$ 
Ditalimfos	Plondrel	$(EtO)_2P(S)N$ 
Aluminium ethyl phosphite	Aliette	

Table 1.2 Organophosphorus fungicides of commercial importance.

to control late blight (Phytophthora infestans) on potatoes, tomatoes and pineapples.[2,7] There are indications that the chemical can move from sprayed leaves into unsprayed ones . which suggests that it is transported in the phloem, a very unusual property.[2]

Organophosphorus fungicides have been the subject of a number of reviews.[10-14] These effectively cover the literature upto 1976. Between 1977 and the end of 1982, 206 publications concerning organophosphorus fungicides were identified. Of these, fifty seven are concerned with phosphorus-nitrogen compounds [15-71] which are of special interest as the compounds synthesised in the present study fall into this group.

It can be seen from Table 1.2 that three of the fungicides are phosphorylated heterocyclic derivatives and two are phosphorothiolates. This has naturally led to a great deal of research in these areas in the search for new and improved fungicidal compounds. A few examples have been chosen to illustrate the type of synthetic work being conducted in these areas and the spectrum of fungal disease which can be successfully controlled by these compounds.

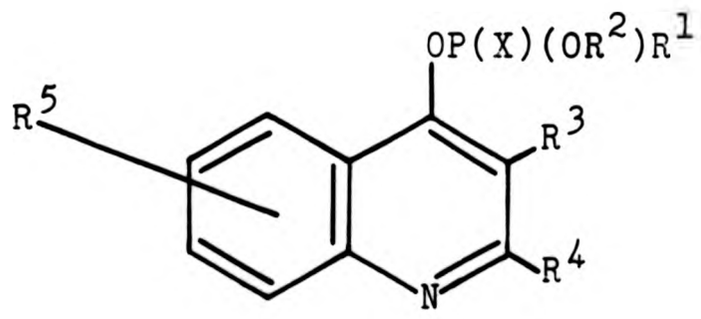
1.2.1 Phosphorylated heterocyclic derivatives.

a) Compounds containing one heteroatom.

Amongst the compounds that have been phosphorylated are the following: (substituted pyridyl-2-oxy)benzaldoximes;[72] 3-hydroxybenzothiophenes which were found to be active against

Fusarium and the fungal organisms that cause rice blast, sheath blight, and powdery mildews;[73] and 5-nitrofuran derivatives[74-75] found to be active against Botrytis cinerea, Fusarium culmorum, and Alternaria tenuis.

4- and 8- Hydroxyquinolyl derivatives have been reported as having activity against a wide range of plant pathogens.[55,63] The 8-hydroxyquinoline derivatives[55] were found to be active against Alternaria and to control mildew. Phosphorylated 4-hydroxyquinolines (13)[63] were reported to be active against Venturia inaequalis, Rhizoctonia solani, against a variety of Phycomycetes including Phytophthora infestans (causative agent of late blight), Plasmopara viticola (causative agent of downy mildew), Pythuim ultinium ("damping off" fungus) and to control mildews. They were claimed to be especially active against Piricularia oryzae and useful in the control of rusts.



(13)

Where R^3, R^4 and R^5= a wide range of substituents;
R^1= C_{1-4} alkyl, alkoxy, alkylamino, dialkylamino, alkylthio;
R^2= C_{1-4} alkyl; X= O or S.

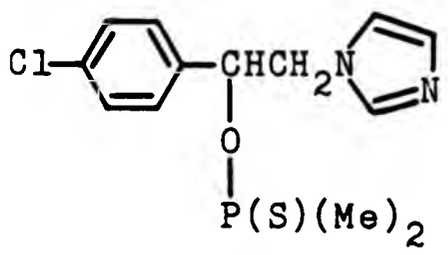
Test data from leaf spray tests are reported for Piricularia oryzae and Puccinia triticina (causative agent of brown

rust) at 1000, 500, 250 and 125 ppm. Several compounds gave complete control of these pathogens at 125 ppm. They were also shown to have systemic properties.[63]

b) Compounds containing two heteroatoms.

In this group can be included 2-aminobenzimidazoles;[21] 5-nitropyrimidines;[76] 1,2-oxazolylalkyl phosphates which completely controlled Piricularia oryzae at 1000 ppm;[77] and imidazole derivatives of the types shown (14,15).[78,36]

The imidazole derivative (14)[78] was found to give complete control of cucumber powdery mildew at 30 ppm in leaf spray test compared to only 75% control by the commercial fungicide benomyl. A series of imidazole compounds of the type 15[36] were claimed to be systemic and have a wide spectrum of



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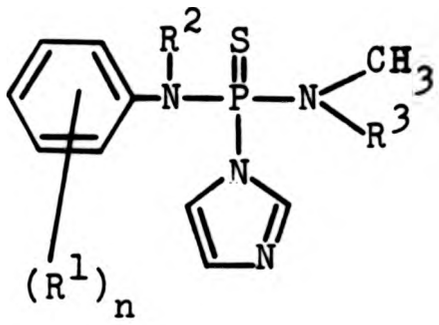
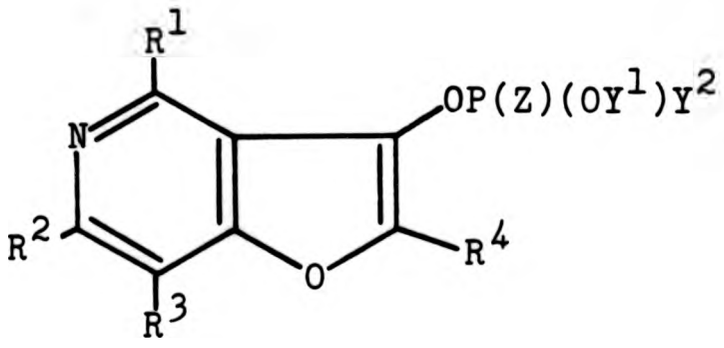


(15)

activity. The diseases claimed to be controlled by these compounds were cherry leaf spot (due to Coccomyces hiemalis), apple scab (caused by Venturia inaequalis), rice blast (due to Piricularia oryzae), powdery mildews, and late blight (caused by Phytophthora infestans). They were also active against Helminothosporium on cereals. Test results against unspecified organism(s) on barley are given and these show

90-100% control of disease at 400 ppm.

An interesting series of compounds of type 16[33] have been synthesised and claimed to be active against plant pathogens that cause rusts and others such as Pythuim ultinium, Septoria nodorum, Piricularia oryzae and Plasmopara viticola. They were reported to give exceptionally good control of powdery mildew of cucumber, cereals, apples and ornamental plants and were also claimed to control mildews resistant to benzimidazole fungicides. This latter claim has been made in other patents,[69,78] but this is the only publication where data actually appear to confirm this observation. For this reason the data reported against cucumber powdery mildew (caused by Erysiphe cichoracearum or Sphaerotheca fuligimea) in leaf spray tests are shown in Table 1.4 and 1.5, with the key to the identification of the compounds and standards shown in Table 1.3.



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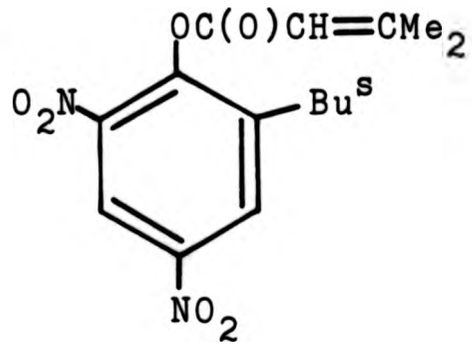


(17)

Compound	R^1	R^2	R^3	R^4	Y^1	Y^2	Z
1	CH_3	CH_3	H	CN	C_2H_5	C_2H_5O	S
2	CH_3	CH_3	H	CN	C_2H_5	CH_3	S
3	CH_3	CH_3	H	$CON(C_2H_5)_2$	C_2H_5	C_2H_5O	S
4	CH_3	CH_3	H	$CH_2CH(CH_3)_2$	C_2H_5	C_2H_5O	S
Standard A	benomyl		see pp. 5		structure (8)		
Standard B	binapacryl		see pp. 11		structure (17)		
Standard C	Hinosan		see pp. 7		Table 1.2		

Table 1.3. Compounds of type 16 and standards tested against Erysiphe cichoracearum.

Compound	Concentration (ppm)			
	500	250	120	60
1	0	0	3	5
2	0	3	5	10
3	0	3-5	10	15
A	3	5	10	15
B	5	5	15	25
C	3	10	25	100

Table 1.4. Leaf spray test results for compounds of type 16 against Erysiphe cichoracearum expressed as % control (Complete control = 0).

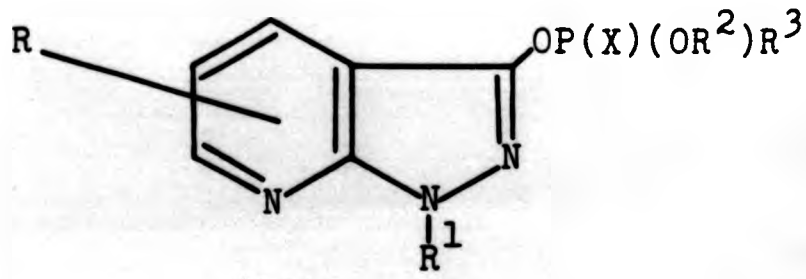
Compound	Concentration (ppm)			
	500	250	120	60
1	0	0	3	5
2	3	3	5	10
3	0	3-5	10	25
4	3-5	5	10	15
A	35	60	100	100
C	3	10	25	100

Table 1.5. Leaf spray test results for compounds of type 16 against benomyl (A) resistant Erysiphe cichoracearum expressed as % control (Complete control = 0).

c) Compounds containing 3 hetero atoms.

A number of triazole containing compounds have been reported as having useful fungicidal activity against the following plant pathogens: Helminthosporium oryzae;[75] Aspergillus flavus;[78] those causing powdery mildews[61,78,80,81] and rusts;[78] Botrytis cineiea;[78] Rhizoctonia solani;[78] Pythuim ultinium;[78] Piricularia oryzae;[71] Phytophthora infestans;[71] and Plasmopara viticola.[71] Compounds containing groups such as 1,3,4-thiadiazole,[66] 1,2,4- and 1,3,4-oxadiazole[82,83] have also been claimed as having good fungicidal properties. 1,2,4-Oxadiazoles[82] were reported to give complete control of Erysiphe cichoracearum at 250 ppm, Plasmopara viticola at 500 ppm and Piricularia oryzae at 1000 ppm in leaf spray tests. They were also reported as having activity against Botrytis cinerea and to control powdery mildews caused by Erysiphe graminis and Podosphaera leucotricha.

A series of compounds (18)[69] have been synthesised and found to have outstanding curative properties against Piricularia oryzae, various rusts, Phytophthora infestans, Plasmopara viticola, and powdery mildew on a wide variety of crops. They were claimed to be active against benzimidazole resistant mildew. However no data were given.

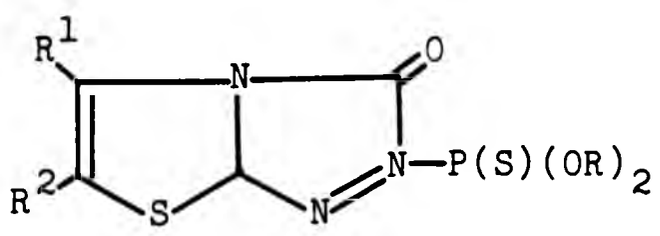


(18)

Where R = C_{1-4} alkyl, halo, NO_2, CF_3, Ph, alkoxycarbonyl; R^1 = C_{1-4} alkyl, $-CH_2CH_2CN$, $PhCH_2$, sub phenyl; R^2 = C_{1-4} alkyl; R^3 = C_{1-4} alkyl, alkoxy, alkylthio, alkylamino group.

d) Compounds containing more than 3 heteroatoms.

A series of compounds (19)[58] have been synthesised from the precursor (20) and claimed to have fungicidal activity. No indication is given as to which plant pathogen they are toxic, but the precursors (20) were claimed to control rice blight.[84]



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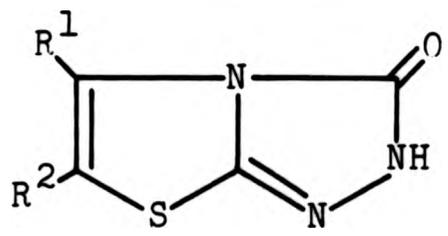


(20)

1.2.2 Phosphorothiolate derivatives

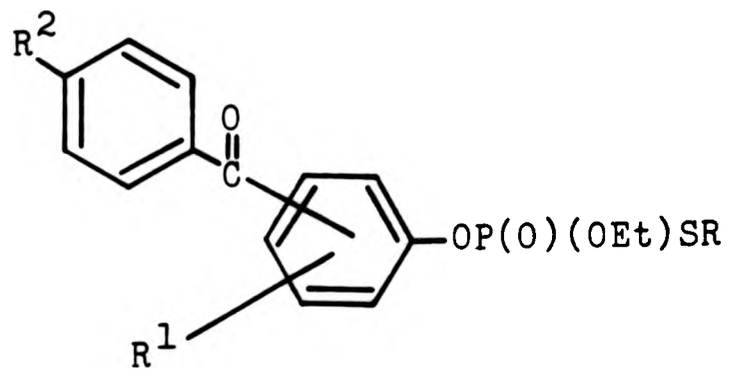
The success of Kitazin, Kitazin-P and Hinosan in controlling rice blast (caused by Piricularia oryzae) has led to a series of publications claiming phosphorothiolate compounds as rice blast fungicides.[17,38,47-49,53,59,60,77,85-87] Some compounds (21, 22) have been claimed to show better activity than Kitazin at 1000 ppm [62] and Kitazin-P.[73] Examples can be found with a much wider spectrum of activity and it is such compounds that will be highlighted in this brief review.

$R^2(R^1O)P(O)SCH_2CH_2SCN$

$R^1 = C_2H_5$; $R^2 = S\text{-}(sec\text{-}C_4H_9)$ (21)

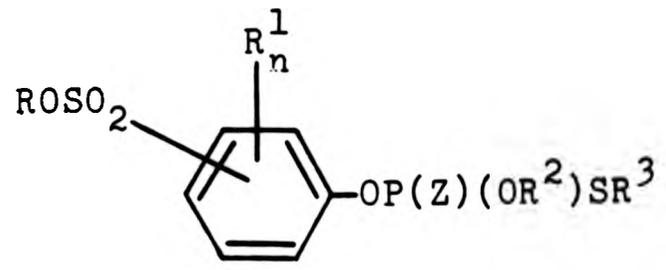
$R^1 = C_2H_5$; $R^2 = S\text{-}(i\text{-}C_3H_7)$ (22)

A number of phosphorothiolate compounds (23, 24) have been synthesised[88,89] and claimed to be effective at 300 ppm against leaf rust (caused by Puccinia recondita), bean powdery mildew (due to Erysiphe polygoni), grape downy mildew (caused by Plasmopara viticola), late blight of tomato (due to Phytophthora infestans) and rice blast (caused by Piricularia oryzae). Some data from leaf spray tests are given.[88] Another



(23)

Where R=Pr, CHMeEt; R^1=H, Me, Cl, OMe; R^2=H, Cl Me.

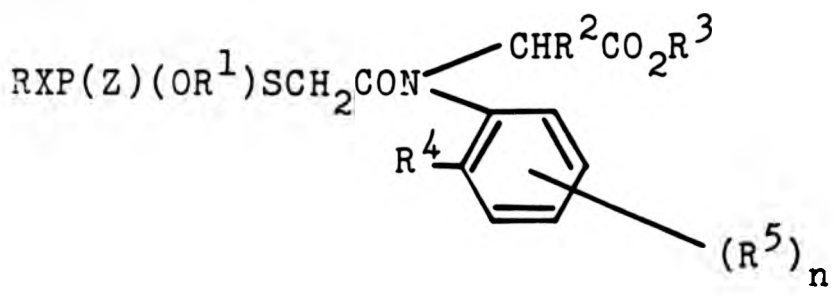


(24)

Where R=C_{1-5} alkyl optionally substituted with 1-3 halogen atoms, C_{5-6} cycloalkyl aryl; R^1=halo, C_{1-5} alkyl, C_{1-5} alkoxy; n=0-3; Z=O,S; R^2=C_{1-4} alkyl; R^3=C_{3-6} alkyl.

group of comounds (25) has been shown to have good activity against a number of Phycomycetes e.g. Phytophthora infestans causing late blight of potato and tomato; Pseudopernospora

cubensis causing downy mildew of cucumber; Plasmopara viticola causing downy mildew of grapes; and Plasmodiophora brassicae causing club root of Chinese cabbage. Data from leaf spray tests are reported against cucumber downy mildew using chlorothanalonil (2,4,5,6-tetrachloro-1,3-dicyanobenzene) as the standard. These tests showed that the compounds have curative properties and gave complete control of the disease at 500 ppm compared to the standard which gave no control in curative tests.[90]



(25)

Where R,R^1= C_{1-3} alkyl; R^2= H, Me; R^3= C_{1-4} alkyl; R^4= C_{1-3} alkyl, MeO, EtO; R^5= H, Me, Cl; n=1,2; X=O, S, NH; Z= O, S;

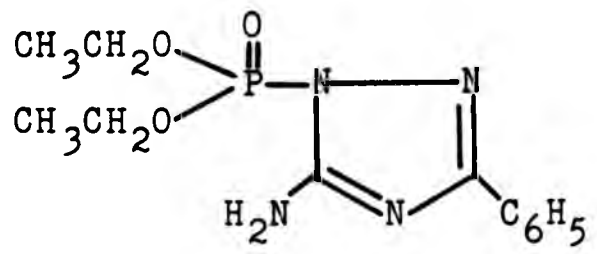
This brief review (of only two classes of organophosphorus compounds) shows that a wide variety of plant pathogens can be successfully controlled by organophosphorus compounds. Some of these compounds were shown to have systemic activity which is better than that of existing commercial fungicides. Compounds have also been developed to overcome problems of resistance to existing commercial fungicides such as benomyl and carbendazim.

1.3 The aims and background to the present work

In this thesis are presented results obtained in the quest for the synthesis of new systemic organophosphorus fungicides of the phosphoramidate type. Many phophorus-nitrogen compounds have been screened for fungicidal activity.[15-71] Those derived from phosphoric acid can be subdivided into the three main groups of monoamides, diamides and triamides of phosphoric acid.[13,14]

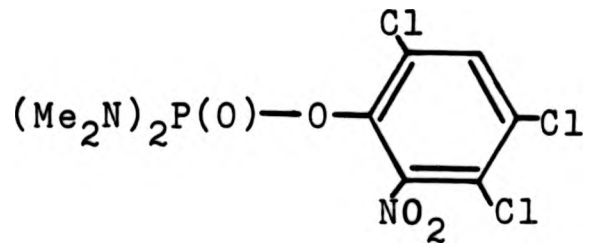
The aim of the work was to synthesise new phosphoric acid triamides containing the $(Me_2N)_2P(O)NH$ group, trichloromethyl group and other groups which have been associated with fungicidal activity in other compounds e.g. dithiocarbamate triazole, imidazole etc.

The bis(dimethylamido)phosphoryl group $(Me_2N)_2P(O)$- occurs in a number of successful fungicides, the most important of which is triamiphos (see Table 1.2). This was claimed to be the first commercial systemic fungicide. In systematic studies of the structure and biological activity of triamiphos derivatives,[91] the primary requirement for fungitoxicity was found to be the presence of the bis(dimethylamido)phosphoryl group in the 1- position. Thiophosphoryl or other phosphorus containing substituents, were found to be detrimental. In earlier studies by van den Bos *et al*. it was found that the diethoxy analogue (26) of triamiphos showed no fungitoxicity.[92] Other phosphoramidates containing the bis(dimethylamido)phosphoryl group which have been found to exhibit high fungicidal

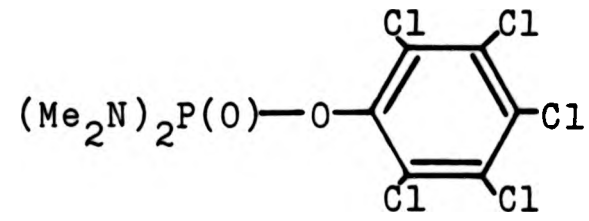


(26)

activity are O-aryl N,N,N',N'-tetramethylphosphoric acid diamides containing electronegative atoms or groups in the aryl substituent.[19,93,94] Compounds having this type of structure (27 and 28), have been tested as experimental fungicides in Czechoslovakia and Russia, respectively. These compounds were found to be effective against Erysiphe graminis on barely and Erysiphe cichoracearum on cucumber. More recently



(27)

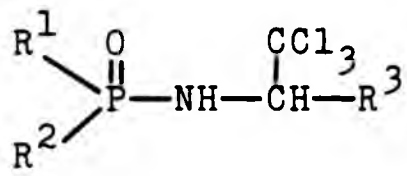


(28)

it was reported that compound 27 could not be used in practice due to its high mammalian toxicity(LD_{50} (to rats)= 12.2 mg/kg).[19]

In unpublished work carried out in these laboratories on compounds of the general formula 29 (where R^1=R^2=ethoxy or R^1=ethoxy and R^2=dimethylamido; R^3=amido,dithiocarbamato, heterocyclic groups etc.), it was found that for the compound

where R^3 = imidazole (30) greater fungitoxicity was achieved when R^1 = ethoxy and R^2 = dimethylamido group. These results confirmed observations made by other authors[52,92,95] who also found that the introduction of N-alkylamido groups increased fungitoxicity.



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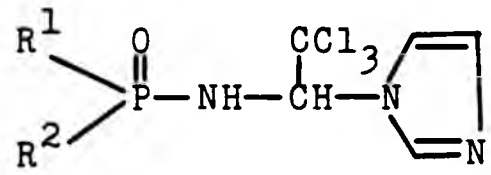
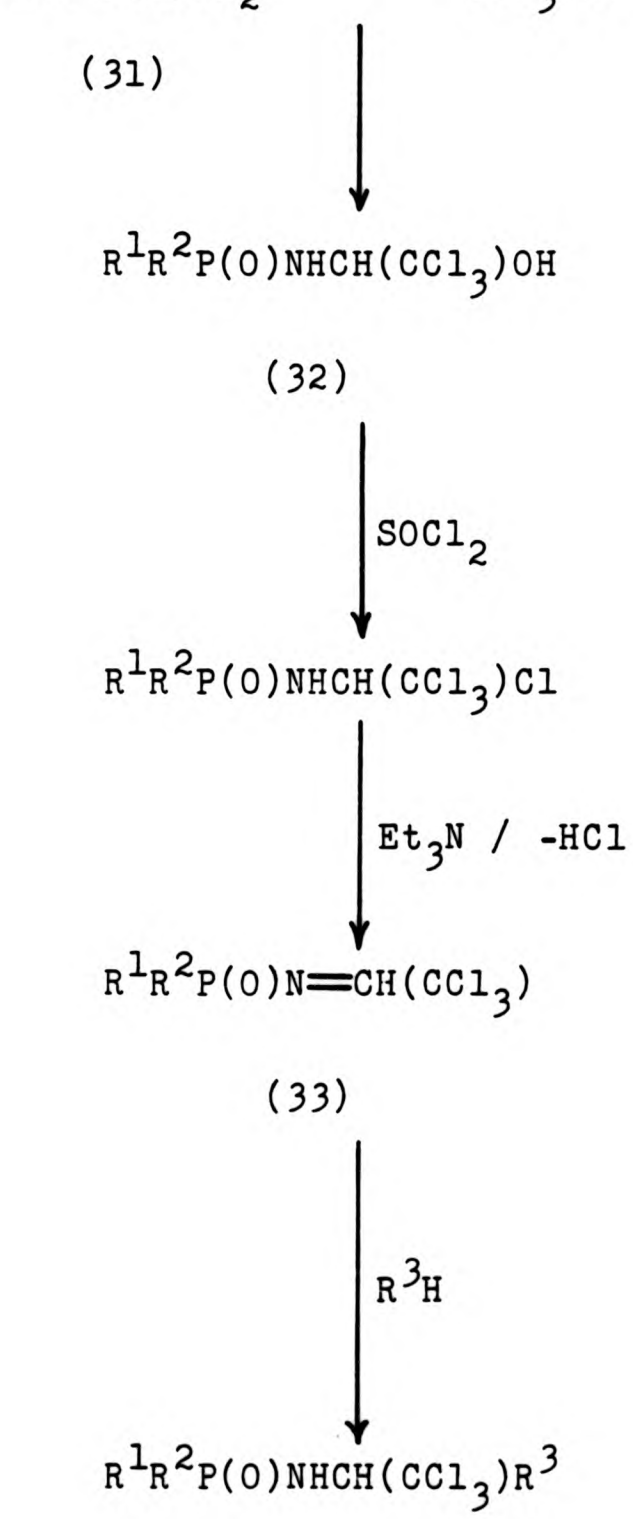


(30)

Compounds of general formula 29 were obtained by reaction of the phosphoramidate (31) with chloral, followed by chlorination of the resulting hydroxy compound (32). The chloro-compound was then condensed with an appropriate nucleophile R^3H (Scheme 1.1) via the imine (33).[96]

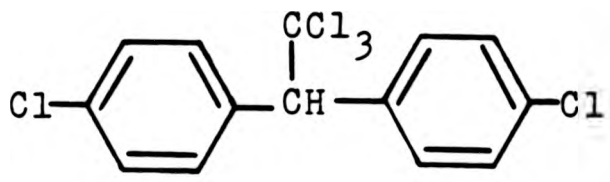
The objective of the present work was to synthesise compounds (29) in which $R^1 = R^2$ = dimethylamido group in the hope of achieving higher antifungal activity. An attempt to synthesise these phosphoric acid triamides by reaction scheme 1.1 failed because compound 35 could not be obtained from the reaction of N,N,N',N'-tetramethylphosphoric triamide (34) and chloral.[96] The synthetic routes developed to overcome these problems are discussed in Chapter 2.

(34) (35)


R1R2P(O)NH2
+
CCl3CHO
(31)
R1R2P(O)NHCH(CCl3)OH
(32)
SOCl2
R1R2P(O)NHCH(CCl3)Cl
Et3N / -HCl
R1R2P(O)N=CH(CCl3)
(33)
R3H
R1R2P(O)NHCH(CCl3)R3
(29)

Scheme 1.1

The other essential structural feature of the proposed compounds, the trichloromethyl group, is found in a wide range of successful pesticides e.g. the insecticides DDT (36) and trichlorphon (37); the herbicide sodium trichloroacetate (38); and the fungicides captan (39), triforine (40) and chloraniformethan (41).



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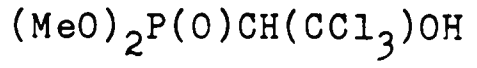
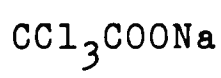
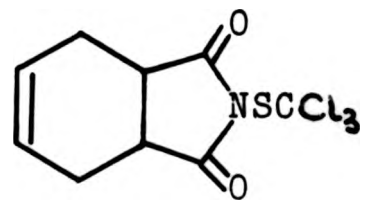


(37)



(38)



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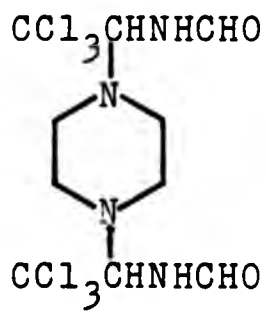

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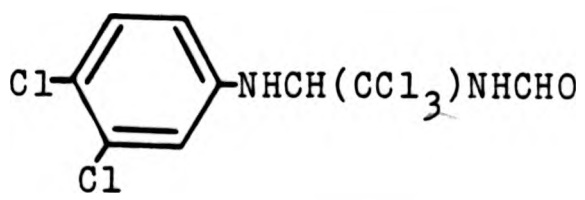


(41)

The compounds synthesised in this project are based on the reactions of chloral with amides and can be described as phosphorus-containing analogues of triforine. In addition to

triforine and its analogues other compounds based on the condensation reactions of chloral with nitrogen-containing compounds such as aliphatic amines;[97] aliphatic and aromatic amides;[98-103] and heterocyclic compounds[104-107] have been shown to be active against a number of fungi including Piricularia oryzae and those causing powdery mildews.

The role of the trichloromethyl group in contributing to the fungitoxicity of compounds is not fully understood. In a study of ethylenebisdithiocarbamate derivatives (42), Pianka et al.[98] observed that compounds of this type (42) where R was a $-CCl_3$ group showed greater activity than those without this group. These workers attributed the increase in fungi-

$$(R^1.C(O)NH.CHR.SC(S).NHCH_2)_2$$

(42)

toxicity to the greater lipid solubility of compounds with a trichloromethyl group, making it easier for the compounds to penetrate the fungal spores. Further research in this area was stimulated by the success of triforine (41) as a systemic fungicide. L.A.Summers and co-workers have synthesised and screened a large number of triforine analogues (43) in order to determine the chemical features which were necessary for systemic activity and it was proposed that the $CCl_3CHNHCHO$ group was necessary for such activity.[108,109] It was found that the chlorine atoms of compounds of this type (43) could be replaced by bromine without substantial loss of systemic

(43)

activity.[110] This observation was confirmed by Brown and Woodcock.[111] This suggests that the trichloromethyl group does not interact with a highly specific receptor, although it may contribute to activity in some less specific way, which may involve hydrophobic properties or inductive electronic effects, thus making it an attractive feature in the synthesis of new fungitoxicants.

It was also shown in the studies of Summers *et al.*[108,109,112] that systemic activity was retained in compounds of type 43 where R is O-alkyl, NH-alkyl and to some extent S-alkyl, but generally lost when R is O-aryl and S-aryl. These workers also showed that the replacement of the -CHO group by $-COOR^1$ (R^1 = alkyl) and $-COR^2$ (R^2 = alkyl or aryl) led to loss of fungitoxicity. These observations were supported by Brown and Woodcock in their study of seventy triforine analogues.[111] These latter workers also tried to synthesise compounds in which the imino hydrogen of the formamido group was replaced by a methyl group. However, they failed to synthesise N-methylformamido analogues, but did manage to synthesise compounds 44 and 46 (see Table 1.6). These compounds were shown to be less active than their straight chain analogues 45 and 47.

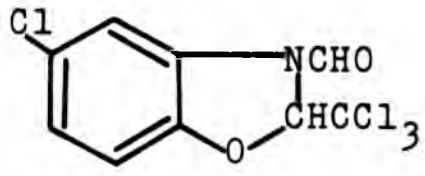
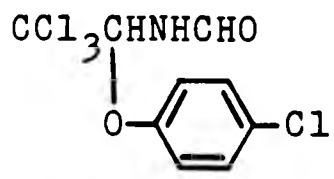
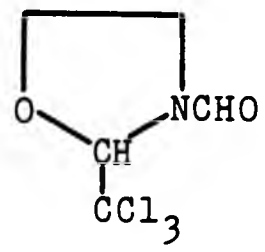
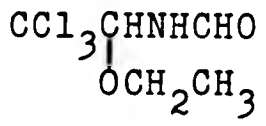
COMPOUND		10^5 ED_{50} (M)	
NUMBER	STRUCTURE	LEAF SPRAY	ROOT DRENCH
44		>400	>400
45		22	70
46		>400	>400
47		>400	35

Table 1.6. Activities against Erysiphe graminis on barley of some analogues of triforine substituted or unsubstituted at the formamido nitrogen.

This indicates that the imino proton in compounds 45 and 47 was necessary for fungitoxicity, although not for translocation as compound 44 showed phytotoxicity to barely leaf tips when applied as a root drench. However, in the N-substituted analogues steric and conformational factors could also account for the inactivity of these compounds. The importance of the imino group in the fungitoxicity of triforine analogues was confirmed in a very recent study by Grant and Summers[113] who successfully synthesised N-methyl-N -(2,2,2-trichloro-1-aryl-aminoethyl)formamides and related compounds. Tests on these compounds showed that replacement of the -NHCHO group by $-N(CH_3)CHO$ results in the loss of fungitoxicity.

An interesting result reported by Brown and Woodcock[111] was the fact that compound 48 showed no fungicidal activity although it was translocated when applied as a root drench. This indicated that another substituent linked to the methine group via a hetero atom i.e. N, O or S may be essential for

CCl_3CH_2NHCHO

(48)

activity. It was postulated that the group R in compounds of this type (43) may be involved in inhibiting the fungal organism and the trichloromethyl group or tribromomethyl group may be contributory to the fungitoxic effect by carrying the compound to the vital site of action by improving the lipophilic

character of the compound[98] or providing the required 'fit' or both.

It was interesting to note that in the work carried out by Summers *et al*. and Brown and Woodcock no triforine analogues containing phosphorus were synthesised or screened. A series of compounds of type 49 with phosphorus directly attached to the methine carbon have been synthesised and claimed to be plant protecting agents but no data were given.[114] The com-

$$(RO)_2P(O)CH(CCl_3)NR^1C(O)R^2$$

(49)

pounds synthesised as part of this research programme will contribute to the area of triforine type compounds. The initial screening results are discussed in Chapter 4.

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CHAPTER 2

CHEMICAL ASPECTS

2.1 Investigation of the reaction between N,N,N',N'-tetramethylphosphoric triamide and chloral

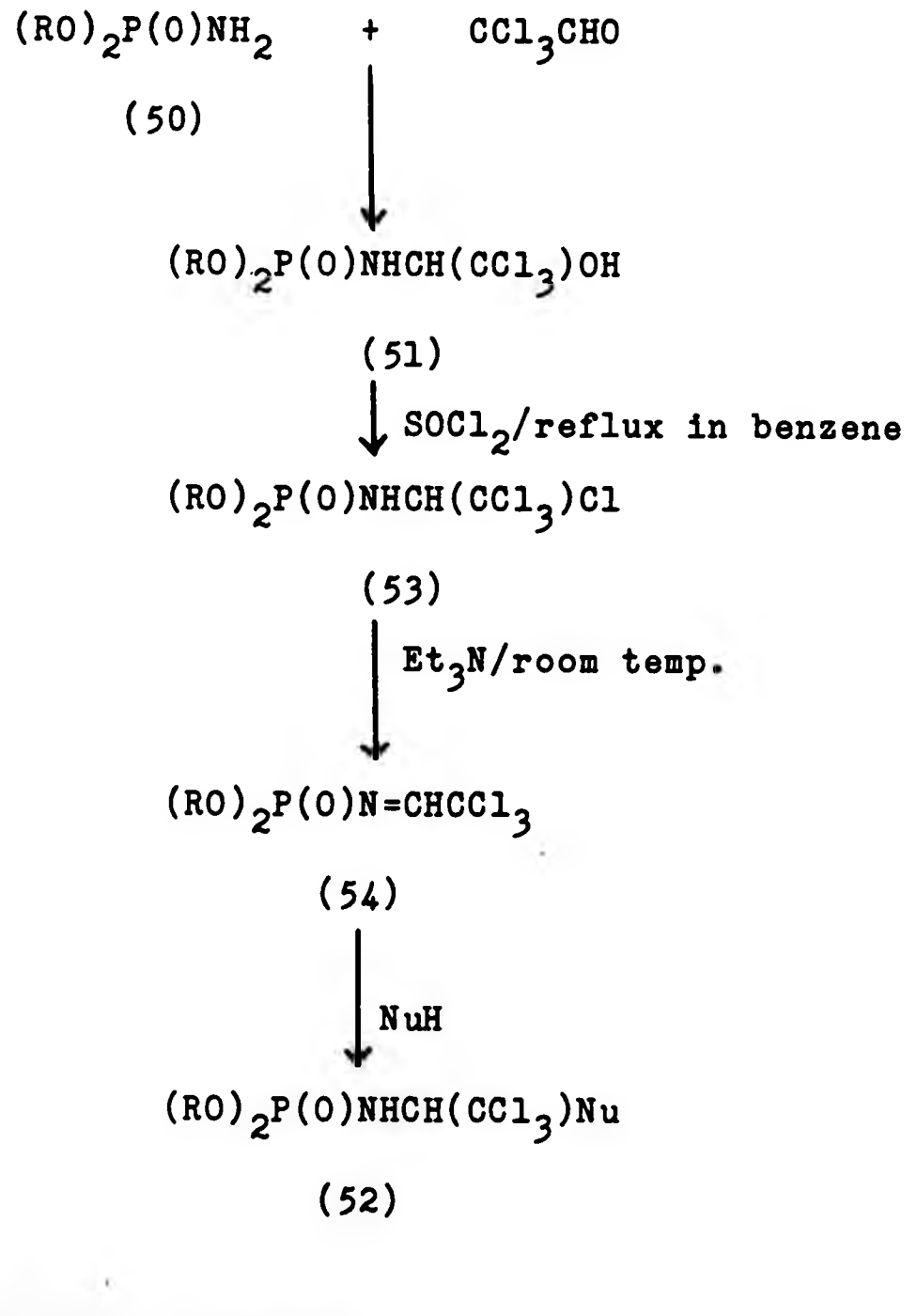
The reaction between O,O-dialkyl phosphoramidates (50) and chloral was first reported by P.I.Alimov in 1961[1] and shown to give O,O-dialkyl N-(1-hydroxy-2,2,2-trichloroethyl)-phosphoramidates (51)(Scheme 2.1). Other authors have since investigated the reaction and extended the range of derivatives.[2-4]

$$\underset{(50)}{(RO)_2P(O)NH_2} + CCl_3CHO \longrightarrow \underset{(51)}{(RO)_2P(O)NHCH(CCl_3)OH}$$

Scheme 2.1

Drach et al.[4-6] used compounds of the type 51 as intermediates in the synthesis of a series of compounds of type 52. This was achieved by chlorination of the hydroxy compounds (51) to give O,O-dialkyl N-(1,2,2,2-tetrachloroethyl)phosphoramidates (53) which were then allowed to react with nucleophiles containing reactive protons e.g. alcohols, thiols, phenols, or acids via the imines (54). The imines (54) were also isolated and characterised[4] (Scheme 2.2). A similar reaction pathway was used with a series of nucleophiles in unpublished work in these laboratories to yield a number of compounds which showed fungicidal activity.[7] In structure-activity studies O,O-diethyl N-(2,2,2-trichloro-1-imidazolylethyl)phosphoramidate (55) showed some promise and it was chosen for further study. It was found that by replacement of an ethoxy

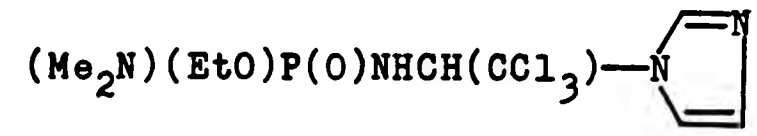
group by dimethylamido, to give O-ethyl N,N-dimethyl-N'-(2,2,2-trichloro-1-imidazolylethyl)phosporodiamidate (56), an increase in fungitoxicity occurred.



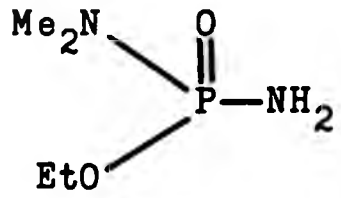
Scheme 2.2

Compound 56 was obtained by reaction of O-ethyl N,N-dimethyl-phosphorodiamidate (57) with chloral to give the corresponding hydroxy compound (58), followed by a modified procedure analogous to that of Scheme 2.2. However, the yield of O-ethyl-

(55)



(56)



(57)

$(Me_2N)(EtO)P(O)NHCH(CCl_3)OH$

(58)

N,N-dimethyl-N'-(1-hydroxy-2,2,2-trichloroethyl)phosphorodiamidate (58) was much lower than had been obtained for the dialkyl phosphoramidate. An attempt to synthesise N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-imidazolylethyl)phosphoric triamide failed because N,N,N',N'-tetramethyl-N"-(1-hydroxy-2,2,2-trichloroethyl)phosphoric triamide (60) could not be obtained from the reaction of N,N,N',N'-tetramethylphosphoric triamide (59) with chloral.[7]

$(Me_2N)_2P(O)NH_2$ + CCl_3CHO ⟶ $(Me_2N)_2P(O)NHCH(CCl_3)OH$

(59) (60)

The reaction between compound 59 and chloral was reinvestigated in the present work by mixing equimolar amounts of the reagents in dry AnalaR benzene and allowing the mixture to stir at room temperature for from 3 hours to four days, with the exclusion of moisture. The solvent and other volatiles were then removed under reduced pressure and the residue

examined by ^{1}H, ^{13}C and ^{31}P N.M.R. Initial results from short term experiments indicated that condensation was taking place but that the reaction was complex. ^{31}P chemical shifts for various related phosphorus species are shown in Table 2.1 for comparison and indicate that substitution of the free amido group in N,N,N',N'-tetramethylphosphoric triamide (i, Table 2.1) moves the ^{31}P chemical shift slightly upfield i.e. to a more negative value, an important observation in the study of this system. It can be seen from Table 2.1 that successive

	Compound	Chemical shift
i	$(Me_2N)_2P(O)NH_2$	22.6[a]
ii	$(Me_2N)_2P(O)NHCH(CCl_3)NHCHO$	20.1[a]
iii	$(EtO)_2P(O)NHCH(CCl_3)NHCHO$	6.1[a]
iv	$(Me_2N)_2P(O)NHCH_2CH_2OH$	23.6[b]
v	$(Me_2N)_2P(O)OCH_2CH_2NH_2$	19.0[b]
vi	$(Me_2N)(EtO)P(O)NHCH_2CH_2OH$	18.8[b]
vii	$(Me_2N)(EtO)P(O)OCH_2CH_2NH_2$	11.1[b]

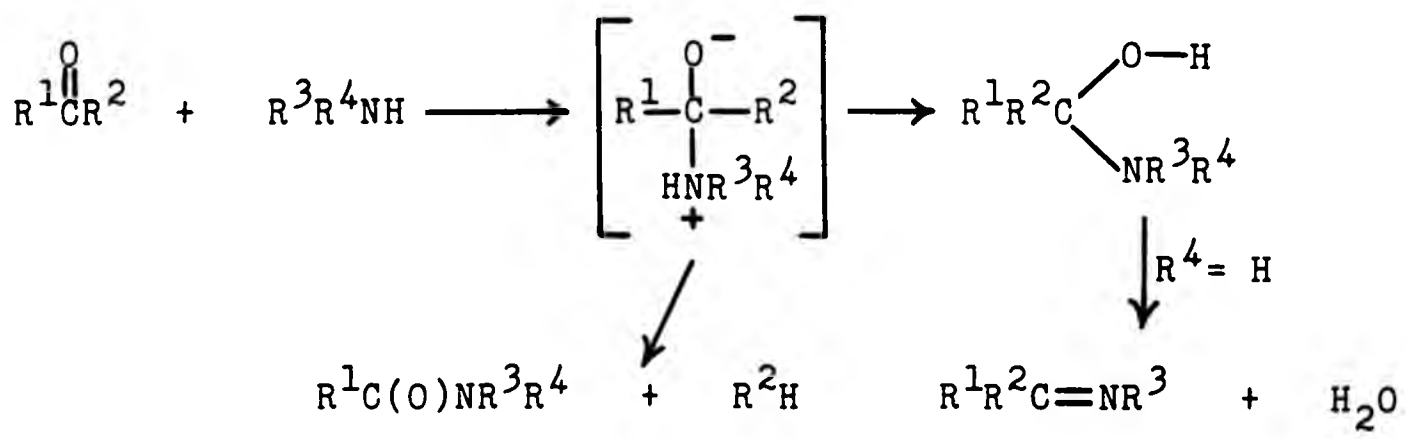
a) See experimental section for details; b) see ref. 8

Table 2.1 ^{31}P chemical shifts of some related phosphorus-nitrogen compounds to show the effect of replacing P-N bonds by P-O bonds.

replacement of P-N bonds by P-O bonds again moves the ^{31}P

chemical shift to more negative values i.e. comparison of compounds (ii) and (iii); compounds (iv) and (vi); compounds (v) and (vii) etc. Figure 2.1 shows the ^{31}P spectrum obtained from a 3-hour reaction, after which much of the N,N,N',N'-tetramethylphoshoric triamide was unreacted (peak at δ + 23.1) but it appeared that a product of condensation was also present (δ + 20.5). Products resulting from P-N bond fission are also indicated (δ + 11.7, + 5.8, - 6.8, -9.3).

The complexity of the reaction was believed to be due to the presence of two nucleophilic centres in the phosphoric triamide viz. the dimethylamido group and the free amido group. As previously discussed, reaction at the free amido group leads to 1:1 adducts. The reaction of dimethylamine and of amines in general with chloral has been studied[9-11] and can be rationalised by Scheme 2.3.[12] The pathway depends on the ease



$R^2 = CCl_3$; R^1 = H (chloral).

Scheme 2.3

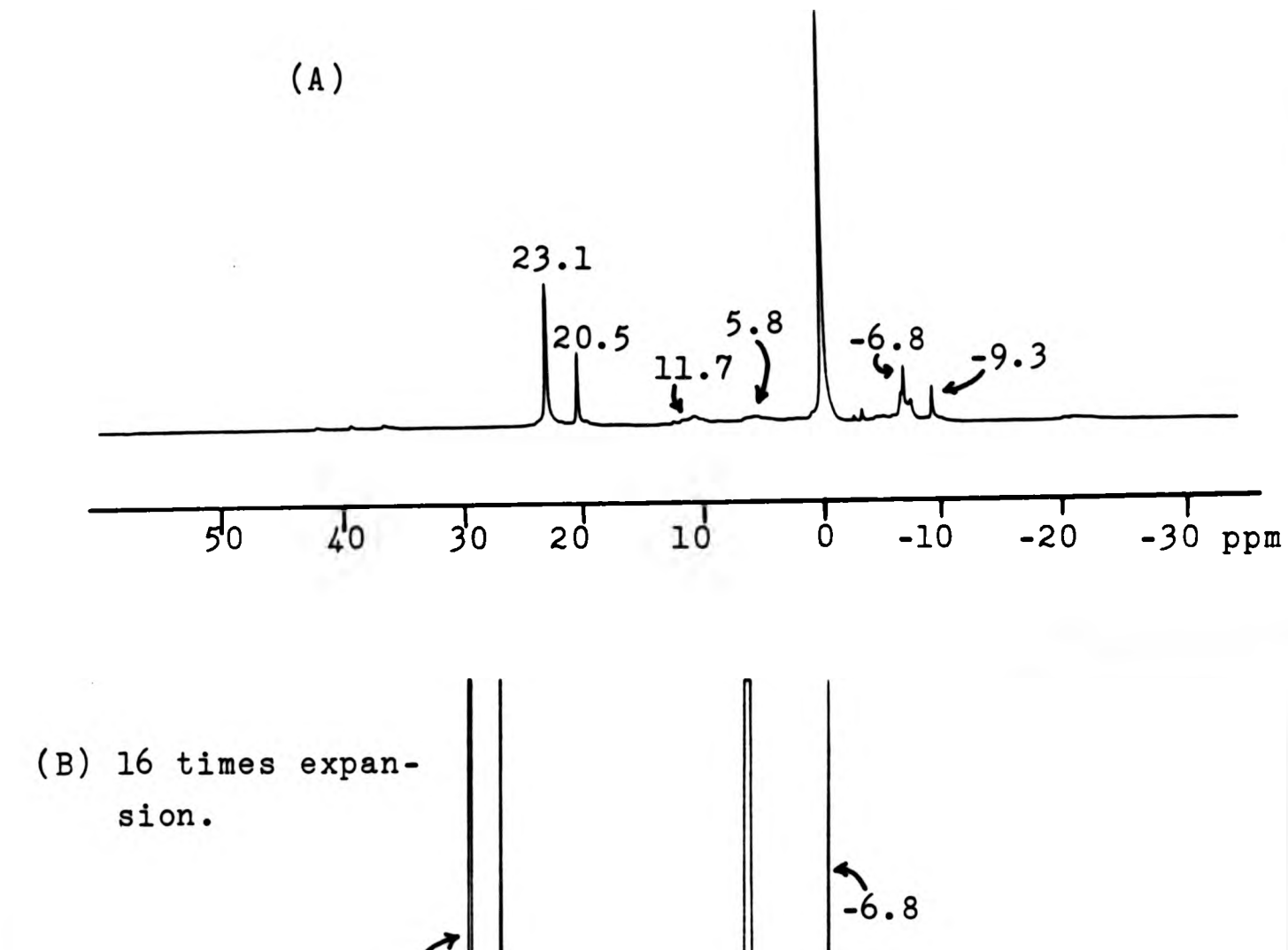


Figure 2.1 ^{31}P spectrum of a 3 hour residue (A), including a 16 times expansion (B) to show the complexity of this system.

with which the leaving group R^2 or OH^- splits off. Strong electron-withdrawing groups in R^2 e.g. Cl would facilitate the formation of the amide and this is generally observed with chloral (i.e. $R^2 = CCl_3$) for which N-formylation occurs with the production of chloroform. However, Schiff's bases derived from the reactions of amines with chloral can be obtained by the use of mild dehydrating conditions and removing the water formed in a Dean and Stark apparatus.[13-15] Thus it was found that the reaction between dialkylamines and chloral yielded dialkylformamides and chloroform.[16,17] In view of this, it was anticipated that attack at the dimethylamido group of the tetramethylphosphoric triamide would yield dimethylformamide (DMF) and chloroform, these also being possible products from the decomposition of the expected N,N,N',N'-tetramethyl-N"-(1-hydroxy-2,2,2-trichloroethyl)-phosphoric triamide. An indication that DMF and chloroform were present was first obtained from the ^1H N.M.R. spectrum of 3-hour experiment residues. The reaction time was then extended to 4 days and g.l.c. was used to detect and to quantitatively monitor any DMF and/or chloroform formed. From the results shown in Tables 2.1 and 2.2, it can be seen that approximately 20% of the theoretical amount of DMF was obtained and although 46% of the expected chloroform was present after 1 day, this decreased to only 18% over the period of the reaction, indicating that it might have undergone further reaction. During the course of 3- and 4-day reactions a resinous material also separated. Both this and the residue obtained from the benzene (solvent) were studied by ^1H, ^{13}C and ^{31}P N.M.R..

Time days	% $CHCl_3$ of theoretical
1	46
2	36
4	18

Table 2.1 Quantitative determination of chloroform during a 4-day reaction time between N,N,N',N'-tetramethylphosphoric triamide and chloral.

Time days	% DMF of theoretical
1	20
2	26
4	20

Table 2.2 Quantitative determination of DMF during a 4-day reaction time between N,N,N',N'-tetramethylphosphoric triamide and chloral.

The ^{31}P spectrum of a typical residue obtained from a benzene layer (Figure 2.2) indicates that some of the starting material remained (δ +22.9) and two similar condensation products were present (δ +20.4 and +20.2). The conclusions were confirmed by ^{13}C N.M.R. which showed characteristic doublets for the $[(CH_3)_2N]_2P(O)$- and $-CH(CCl_3)$ groups. The ^{13}C results are shown in Table 2.3 and are compared to shifts and coupling constants obtained from known condensation products synthesised during the course of this research. Recrystallisation of the residue obtained from the benzene

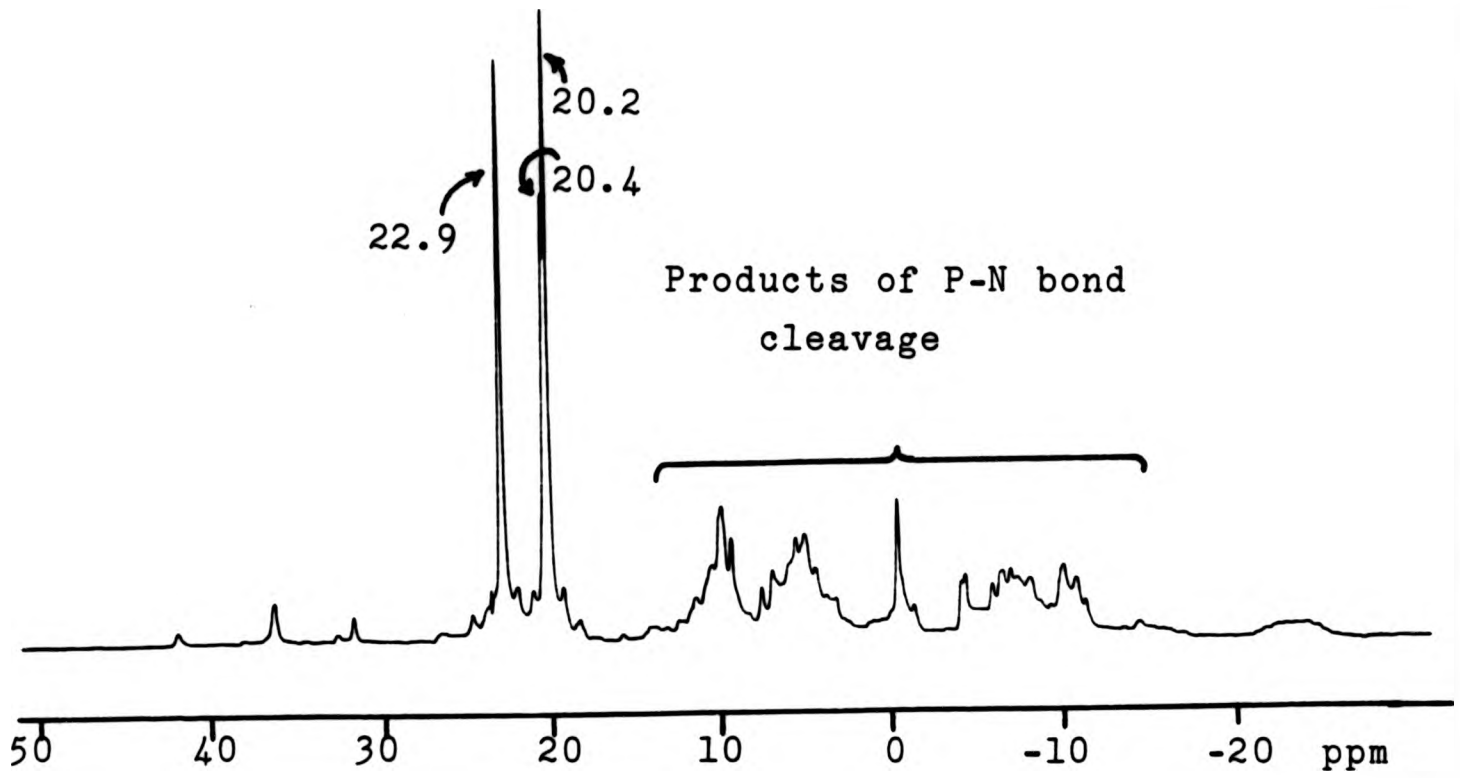


Figure 2.2 ^{31}P spectrum of a benzene fraction isolated from a 3 day reaction.

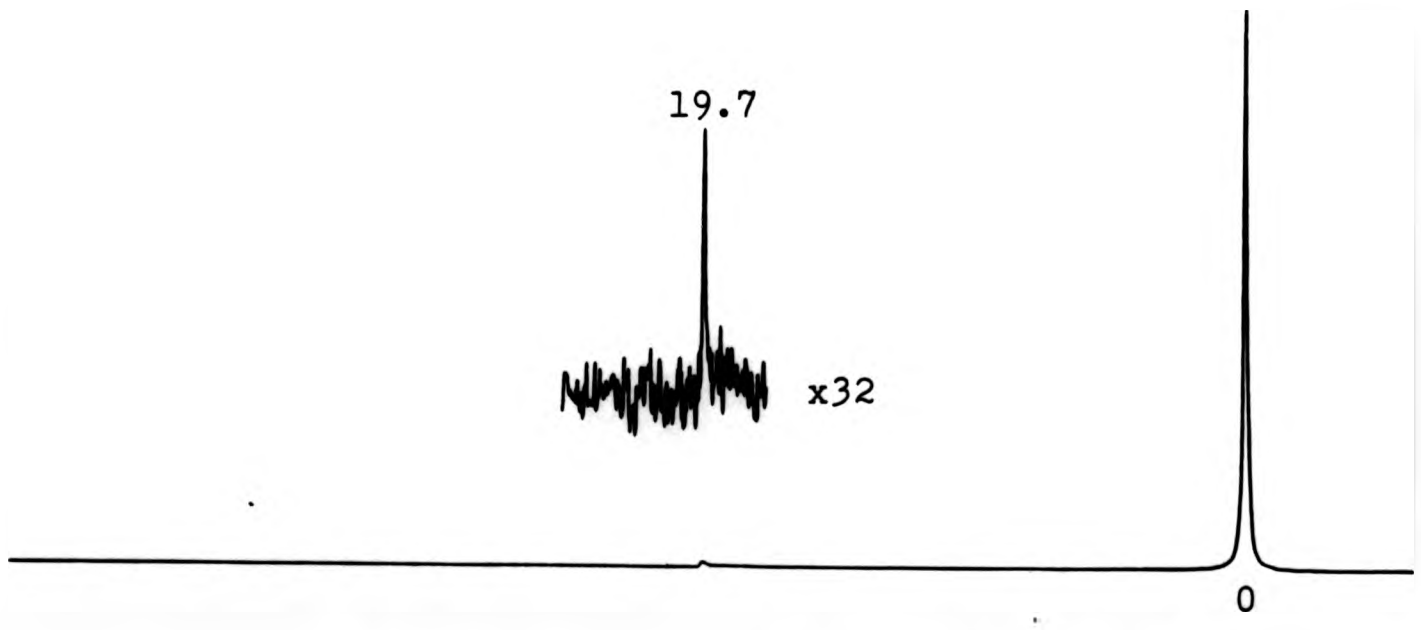


Figure 2.3 ^{31}P spectrum of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-dimethylaminoethyl)phosphoric triamide.

Table 2.3 Comparison of ^{13}C chemical shifts and coupling constants obtained from known condensation products with those obtained from unknown reaction products of a reaction mixture derived from the reaction of N,N,N',N'-tetramethylphosphoric triamide and chloral.

Group	Shifts and coupling constants (J Hz) observed for condensation products	Shifts and coupling constants (J Hz) observed for unknown reaction products (1 and 2)	
		1	2
$(Me_2N)_2P(O)NH$-	36.2 $^2J_{PNC}$ 3	36.7 J 3	36.7 J 3
-$\underline{CH}(CCl_3)$-O-	91-92 $^2J_{PNC}$ 6	83.2 J 4	85.2 J 5
-$\underline{CH}(CCl_3)$-NH-	69.5 $^2J_{PNC}$ 5		
-CH($\underline{CCl_3}$)-O-	102.0 $^3J_{PNCC}$ 10	101.4 J 10	102.4 J9
-CH($\underline{CCl_3}$)-NH-	103.2 $^3J_{PNCC}$ 10		

layer by removing the solvent under reduced pressure, yielded a small quantity of crystals which were identified by ^{31}P, ^{1}H N.M.R. (see Figures 2.3 and 2.4) and X-ray crystallography (see Figure 2.5 and Appendix 1 for data) as N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-dimethylaminoethyl)phosphoric triamide. Its presence in the original residue was indicated by a large singlet in the ^{13}C spectrum at δ 34.7 assigned to the isolated $-N(CH_3)_2$ group, thus eliminating any possibility that it may have been formed due to a rearrangement during the work-up procedure.

The ^{31}P spectrum of the resinous material which separated showed this to be a very complex mixture. The major feature of the spectrum which consisted of more than 80 peaks and is shown in Figure 2.6, was that it showed little evidence for the presence of phosphoric triamide species (i.e. peaks at δ +23.9 and +20.7). The other peaks indicate compounds containing P-O bonds and several peaks appear at δ~0 indicating phosphoric acid derivatives. P-N bond cleavage was also indicated by the ^{13}C spectrum which showed that the doublet at δ 36.2 corresponding to the $(Me_2N)_2P(O)NH-$ group, was very small. Attempted fractional crystallisation of this residue from a number of solvents failed to yield any compounds which could be identified. Due to the complex nature of this material no further attempts were made to separate the components.

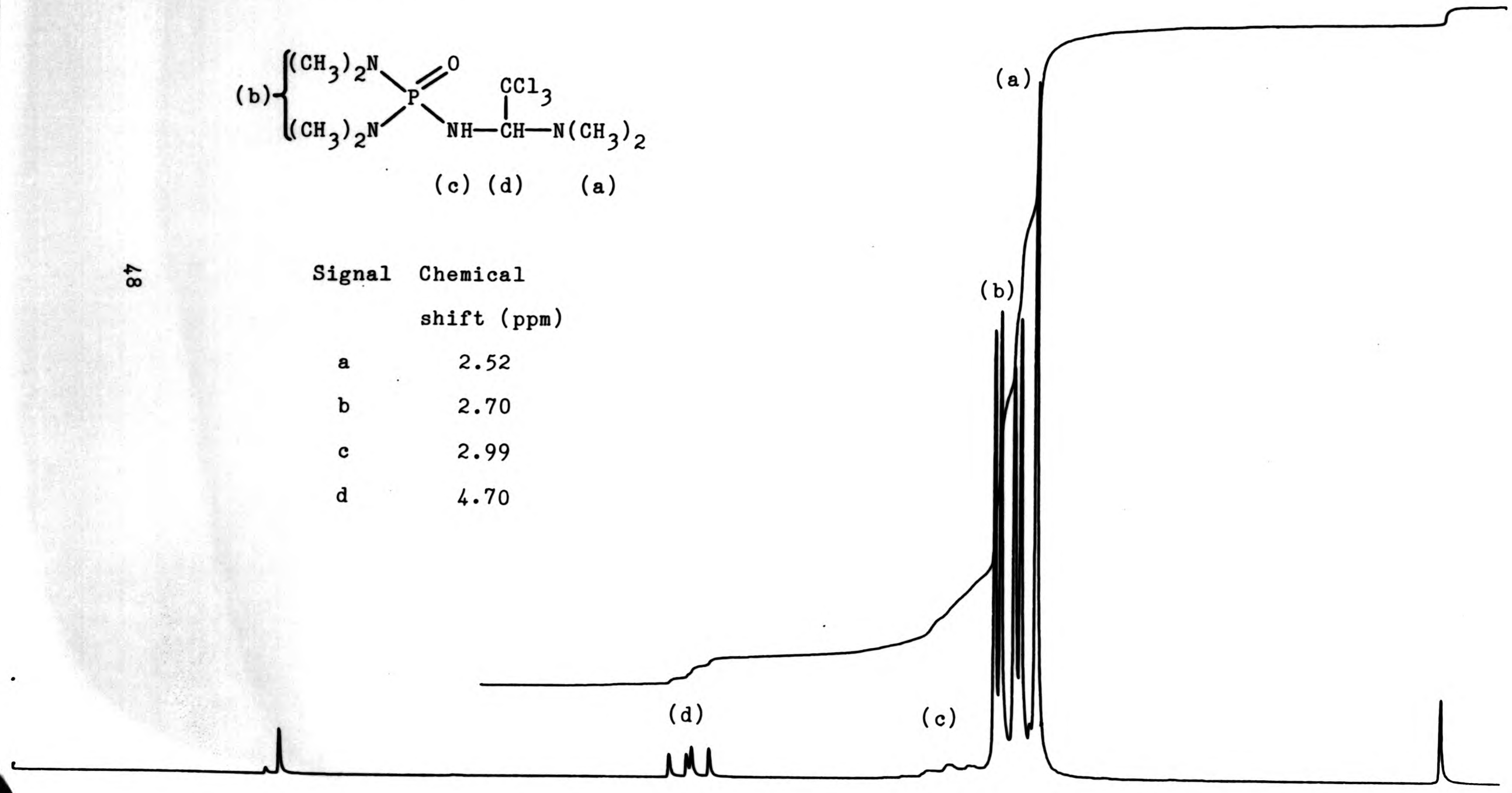
The reaction between hexamethylphosphoric triamide (HMPT) and chloral was studied in order to determine whether a similar cleavage of the P-N bond occurred in this case and

Figure 2.4 ^1H spectrum of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-dimethylamidoethyl)-phosphoric triamide

(b) $\left\{\begin{matrix}(CH_3)_2N \\ (CH_3)_2N\end{matrix}\right.$ P(=O)–NH–CH(CCl_3)–$N(CH_3)_2$

(c) (d) (a)

Signal	Chemical shift (ppm)
a	2.52
b	2.70
c	2.99
d	4.70



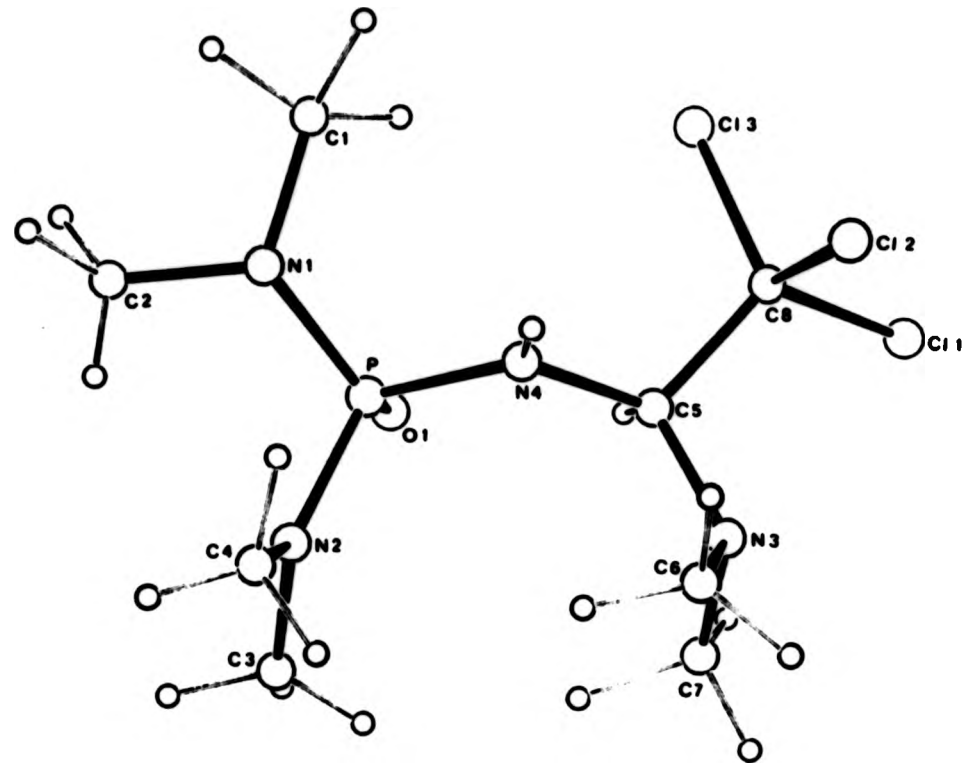


Figure 2.5 X-ray crystal structure of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-dimethylaminoethyl)phosphoric triamide.

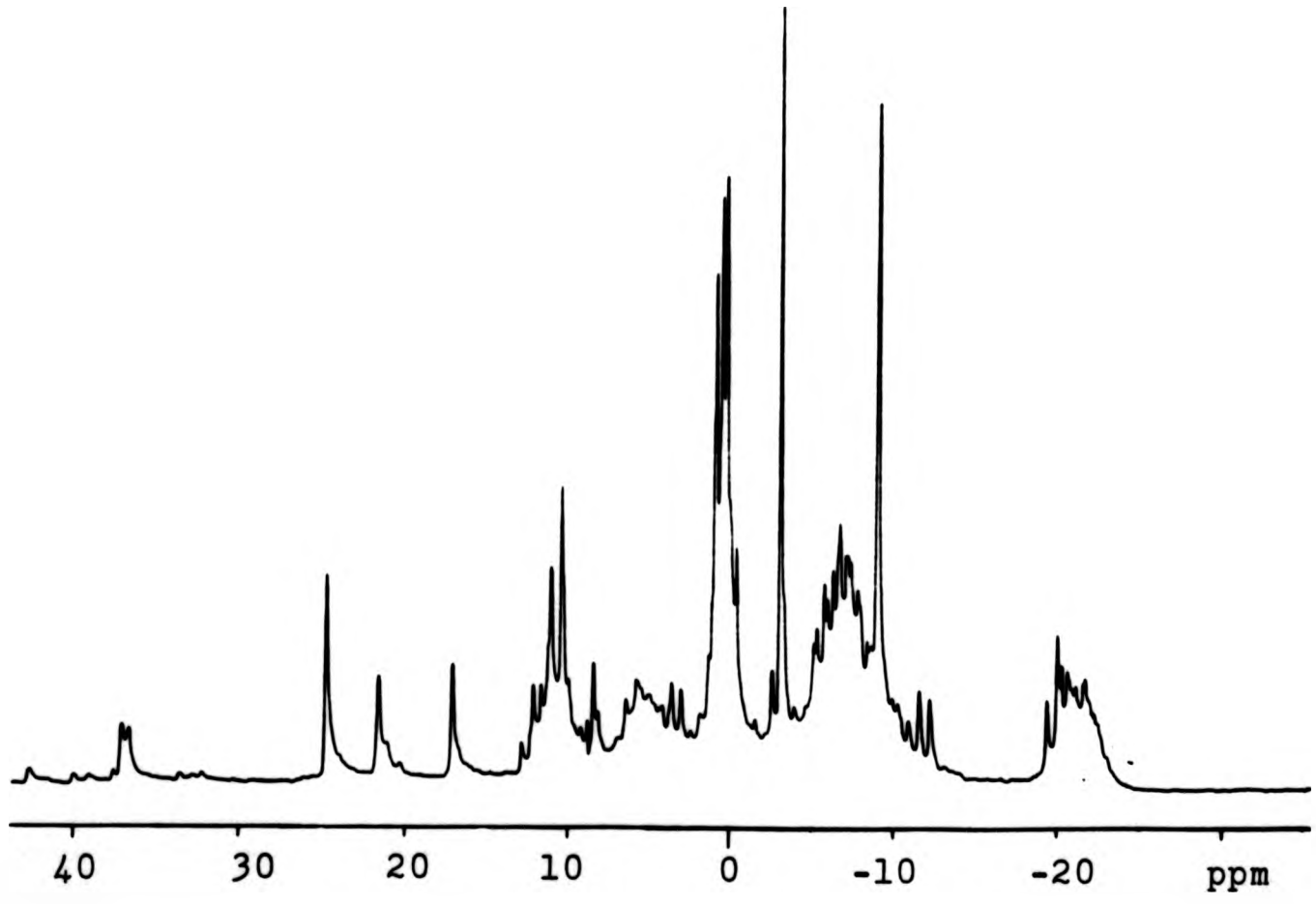


Figure 2.6 ^{31}P spectrum of the resinous material isolated. (The H_3PO_4 standard is not displayed).

hence to provide further information on the possible site of reaction in N,N,N',N'-tetramethylphosphoric triamide. The reaction was carried out under the same conditions as for the N,N,N',N'-tetramethylphosphoric triamide but over a 4-day period no DMF or chloroform could be detected by g.l.c. Removal of the solvent and investigation of the residue by ^{31}P after 16 days also showed that no reaction had taken place (Figures 2.7 and 2.8). These results indicate that no attack occurs at the dimethylamido group.

A possible mechanism which accounts for the reaction products obtained from the tetramethyl compound is shown in Schemes 2.4 and 2.5. This is based on the initial formation of N,N,N',N'-tetramethyl-N"-(1-hydroxy-2,2,2-trichloroethyl)-phosphoric triamide (61), although this was not isolated. However, its formation could be inferred from the isolation of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-dimethylamino-ethyl)phosphoric triamide (63) and spectroscopic evidence of another related product (see Figure 2.2). The hypothetical intermediate (62) can account for the existence of all the identified products. The route by which bonds a and d are broken is clearly that of catalytic decomposition of compound 61 and a similar process could account for the low yield of O-ethyl N,N-dimethyl-N'-(1-hydroxy-2,2,2-trichloroethyl)-phosphorodiamidate (58) isolated from the reaction of the corresponding phosphorodiamidate (57) and chloral in earlier work.[7] Catalytic decomposition of N-(1-hydroxy-2,2,2-trichloro-ethyl) compounds in the presence of triethylamine to yield N-formyl derivatives and chloroform has been observed by

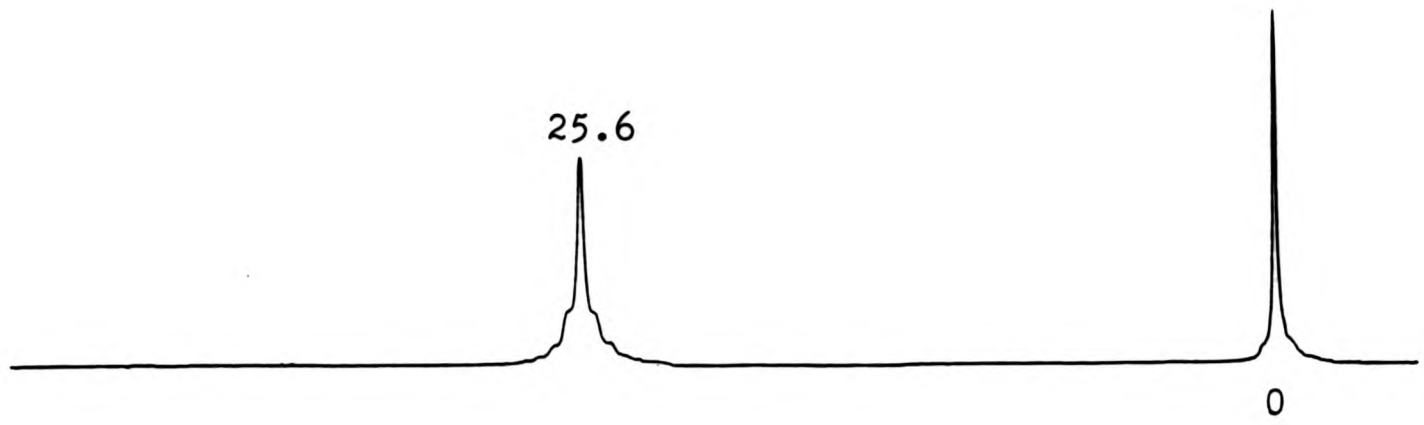


Figure 2.7 ^{31}P spectrum of HMPT used in the reaction with chloral.

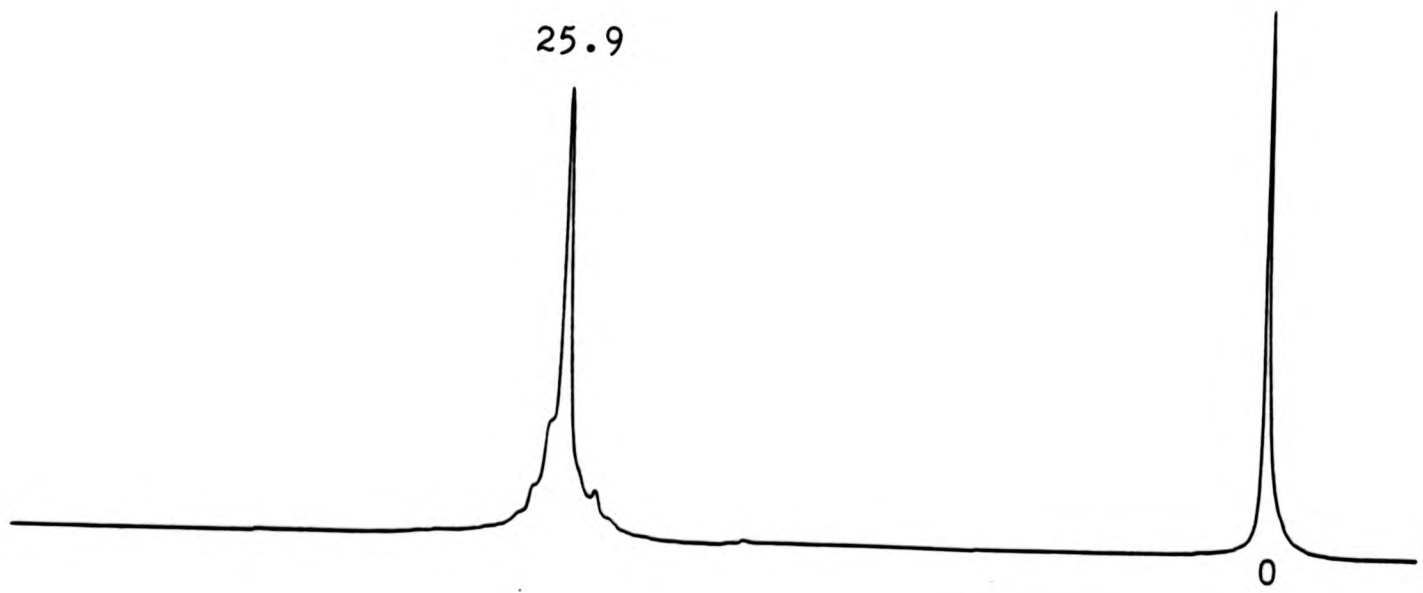
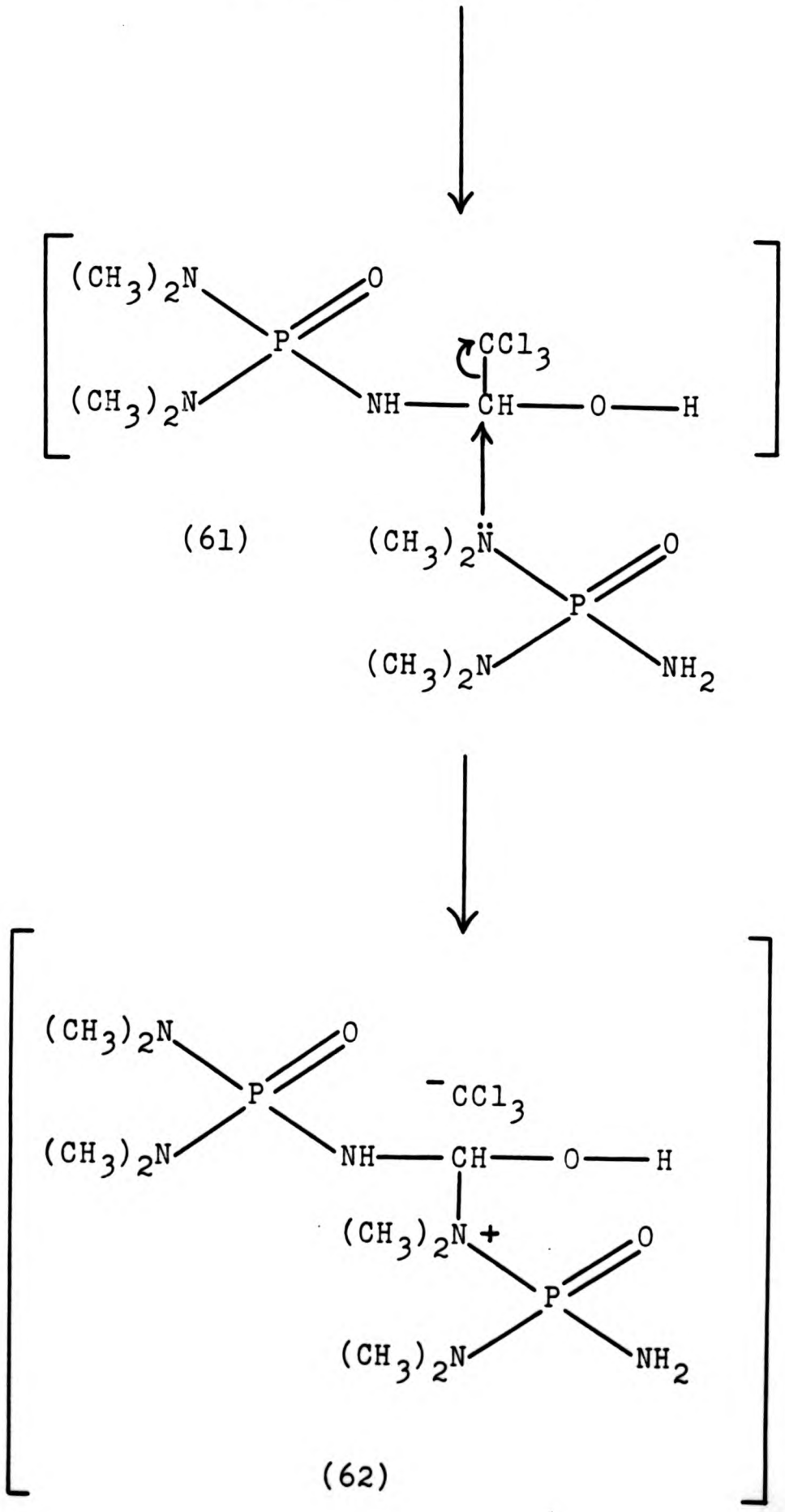


Figure 2.8 ^{31}P spectrum of HMPT and chloral reaction mixture after 16 days.

Scheme 2.4


(Me2N)2P(O)NH2 + CCl3CHO
(CH3)2N
O
P
(CH3)2N
CCl3
NH
CH
O
H
(61)
(CH3)2N
O
P
(CH3)2N
NH2
-CCl3
(62)

Scheme 2.5

OTHER PHOSPHORUS COMPOUNDS

↑

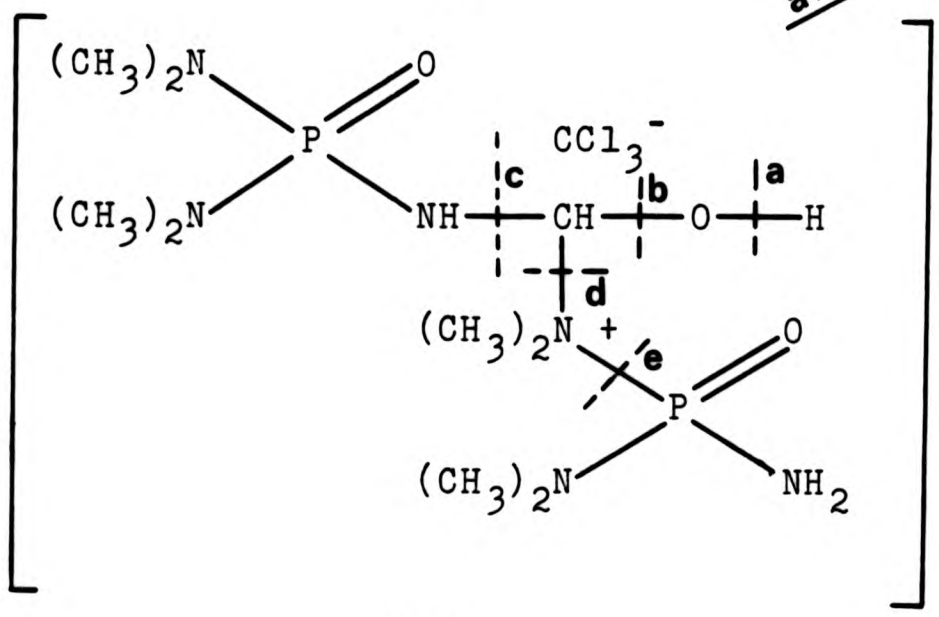
$(Me_2N)_2P(O)NH_2$ + $(Me_2N)_2P(O)NHCHO$ + $CHCl_3$

a,d

$CHCl_3$ + Me_2NCHO +

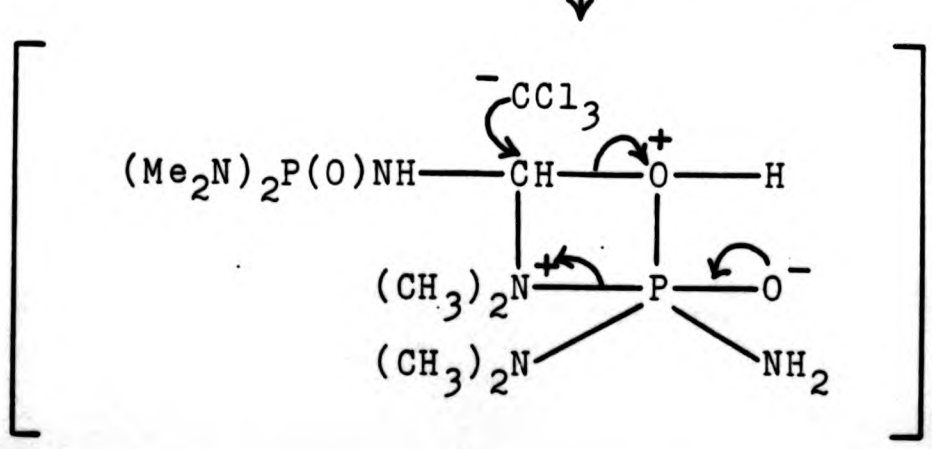
PHOSPHORUS COMPOUNDS

a,c,e



(62)

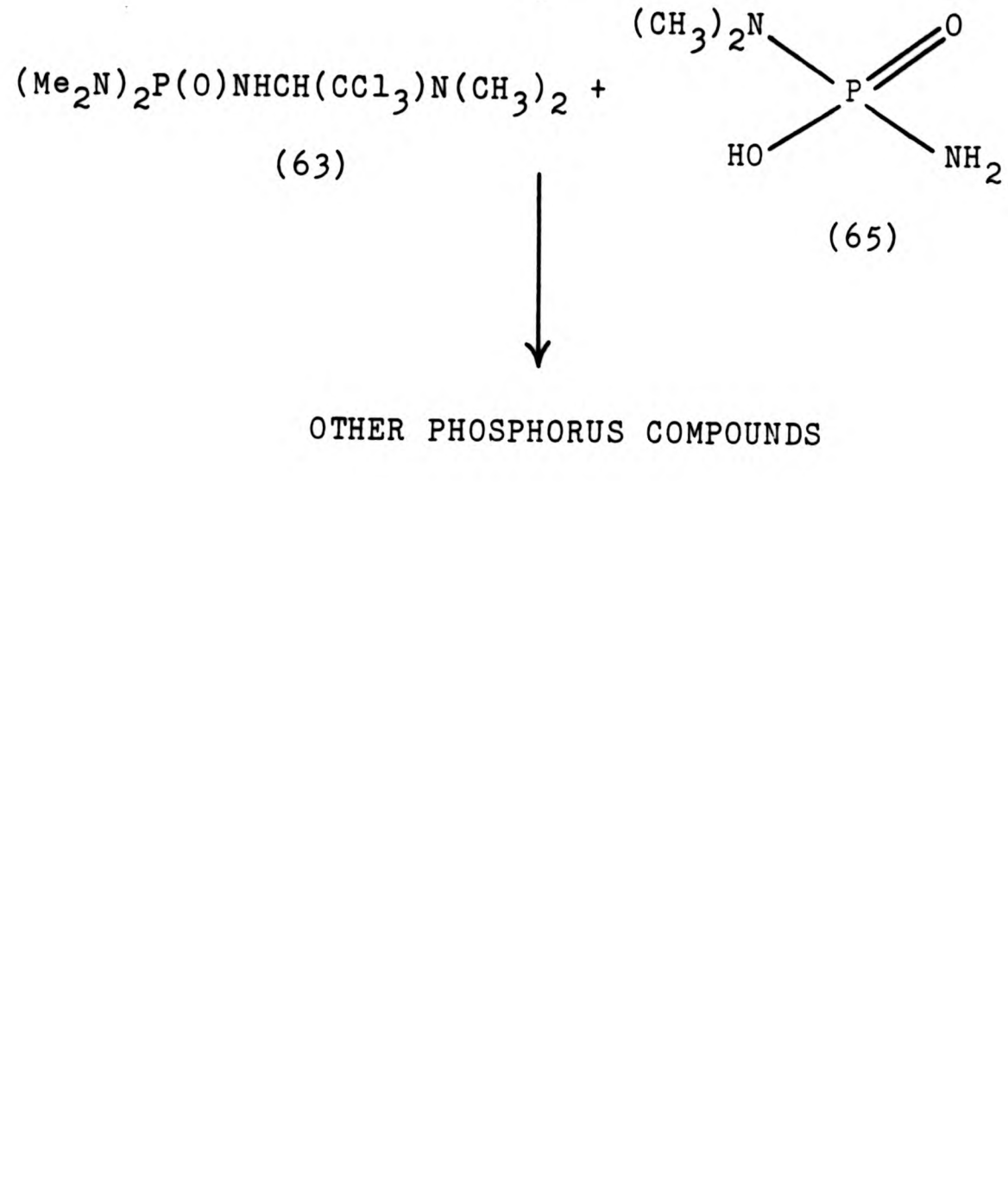
b
-OH transfer



(64)

Continued on next page.

Scheme 2.5 continued.



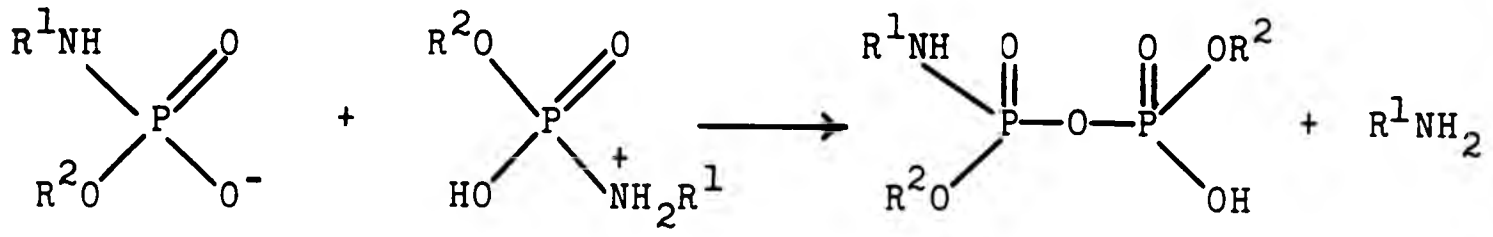
other authors.[2,18] Nikonorov *et al.* studied the decomposition of *O*,*O*-dialkyl *N*-alkyl-*N*-(1-hydroxy-2,2,2-trichloroethyl)-phosphoramidates in the presence of triethylamine as shown below and isolated the *N*-formyl derivatives from their reactions.[2]

$$(RO)_2P(O)NR^1H + CCl_3CHO \longrightarrow (RO)_2P(O)NR^1CH(CCl_3)OH \xrightarrow{Et_3N} (RO)_2P(O)NR^1CHO + CHCl_3$$

Migration of oxygen to phosphorus *via* 4-membered cyclic transition states is a known feature of phosphorus chemistry, e.g. the Wittig reaction etc.[19,20] and a similar process could give rise to the intermediate structure 64 and thus to compound 63.

The complexity of the phosphorus-containing components of this reaction system could be partly accounted for by further reaction of the free amido and hydroxy groups of phosphoramide 65. It has been shown that a number of phosphoric acid amides act as donors of the phosphate group to give pyrophosphates,[21,22] which can then undergo further reaction to give triphosphates etc. Kinetic studies of such systems have shown that pyrophosphates are formed as a result of attack by the phosphoramidate anion on the protonated molecule with the elimination of one mole of base.[23,24] By analogy, the compound 65 could undergo protonation at either the amido group or the dimethylamido group, thus leading to a whole

series of diphosphates and triphosphates *via* the hydroxy group (see Scheme 2.6). In addition, any compound containing the dimethylamido group could act in the same way as the *N*,*N*,*N*',*N*'-tetramethylphosphoric triamide in forming intermediates of type 62, thus adding to the complexity of the system. The ^{31}P



Scheme 2.6

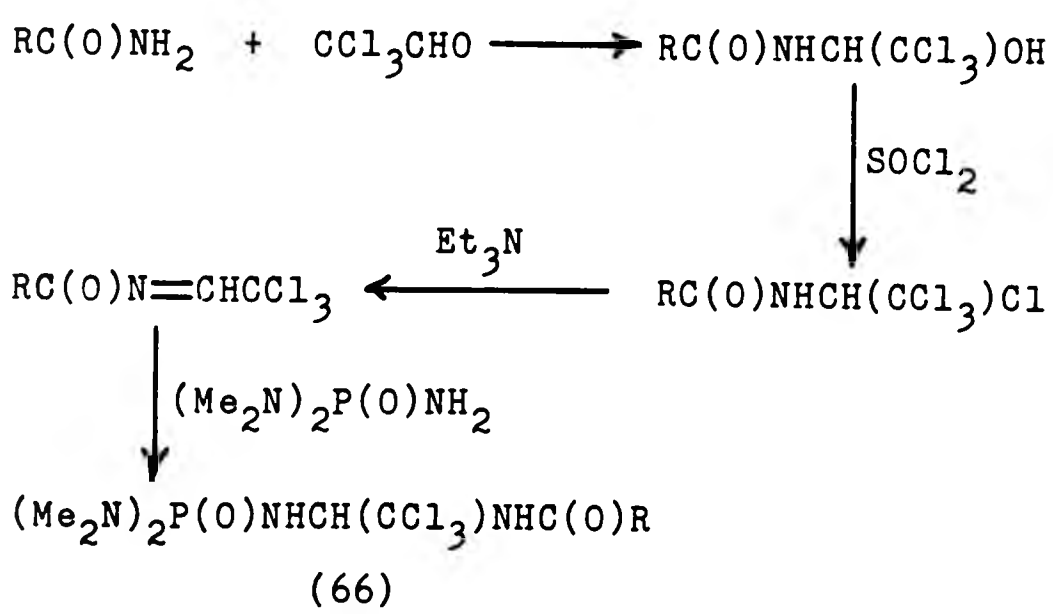
chemical shifts of a series of diphosphates and a triphosphate are shown in Table 2.4.[25] When these are compared to the shifts observed for the resinous material isolated from our reaction system (see Figure 2.6) it is reasonable to suppose that this material may contain similar polymeric phosphorus species.

Structure	Shift/ppm
$(NaO)_2P(O)OP(O)(ONa)_2$	-6.0
$(NaO)_2P(O)NH(O)(ONa)_2$	+2.7
$(EtO)_2P(O)OP(O)(OEt)_2$	-13.4
$(EtO)_2P(O)NHP(O)(OEt)_2$	+2.5
$(Me_2N)_2P(O)NHP(O)(NMe_2)_2$	+11.5*
$(NaO)_2P_\alpha(O)OP_\beta(O)(ONa)OP_\alpha(O)(ONa)_2$	-4 (P_α)
	-18 (P_β)

Table 2.4 ^{31}P chemical shifts of diphosphates and a triphosphate[25] (* see ref. 26)

2.2 Synthesis of compounds containing bis(dimethylamido)-phosphoryl and trichloromethyl groups.

Since compounds of this type could not be synthesised by the same route used to obtain diethoxy and ethoxydimethylamido analogues (Scheme 2.2) a different approach was sought and is shown in Scheme 2.7. In this method, which involves a reverse sequence, chloral is first condensed with the relevant amide and the resulting hydroxy compound chlorinated. The chloro-compound is then treated with a tertiary base e.g. triethylamine, to give the imine and the reaction is completed by the addition of N,N,N',N'-tetramethylphosphoric triamide to give the desired product (66). The generation of imines in this way and their further reaction with nucleophiles has been reported by Drach *et al*.[27]

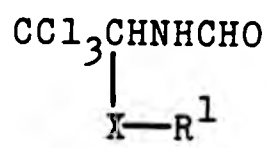


(66)

Scheme 2.7

Scheme 2.7 was found satisfactory for primary amides. The

reaction was carried out under anhydrous conditions using benzene as the solvent and allowing the mixture to stand at room temperature for between 1 and 3 days. The compounds which have been synthesised by this method are shown in Table 2.5, the starting amides in this series having been chosen carefully from compounds which have been shown to have fungicidal activity. This represents an important point in the light of results obtained by Brown and Woodcock on triforine derivatives.[28] These workers found that the biologically active centre of their triforine analogues of the type 67 may have been contained in the group X-R^1; thus the nature of R in the compounds synthesised of type 66 could also be very important. Another factor in the choice of



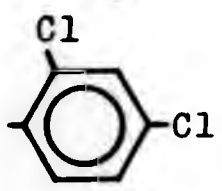
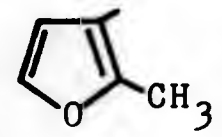
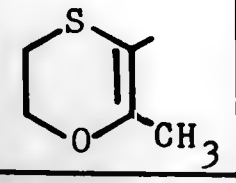
(67)

Where X = N, O, S and R^1 = alkyl, aryl, heterocycle, etc.

amides has been the desire to cover various types of chemical structure i.e. alkyl, chloroalkyl, aryl, substituted aryl, and heterocyclic group.

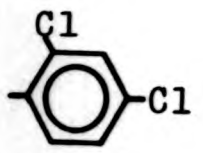
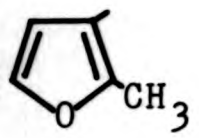
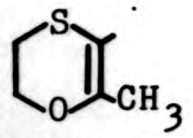
All the N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-amidoethyl)phosphoric triamides (66) synthesised were white crystalline solids with high melting points and all decomposed on melting. They were insoluble in water and their solubilities in organic solvents depended to some extent on the nature of the amide residue. Generally they were only

Table 2.5 N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-amidoethyl)phosphoric triamides $(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)R$

Comp. No.	R	m.p.* (°C)	Found C	H	N	Cl	P	Molecular formula	Requires C	H	N	Cl	P	Molecular weight[A] Found	Requires
I	H	190[B]	26.1	4.9	17.4	32.9	9.4	$C_7H_{16}Cl_3N_4O_2P$	25.8	4.9	17.2	32.7	9.5	324.0061	324.0076
II	CH_3	200[B]	28.3	5.3	16.2	30.9	9.3	$C_8H_{18}Cl_3N_4O_2P$	28.3	5.4	16.5	31.3	9.1	338.0243	338.0233
III	CH_2Cl	187[B]	25.4	4.4	15.0	38.3	8.1	$C_8H_{17}Cl_4N_4O_2P$	25.7	4.5	15.0	38.0	8.3	371.9836	371.9842
IV	CCl_3	180[B]	21.7	3.4	12.4	-	7.2	$C_8H_{15}Cl_6N_4O_2P$	21.7	3.4	12.6	-	7.0	440.9[C]	440.9[C]
V		205[D]	33.3	4.0	11.9	38.1	6.5	$C_{13}H_{18}Cl_5N_4O_2P$	33.2	3.8	11.9	37.7	6.6	469.0[C]	469.0[C]
VI		185[E]	35.2	4.9	13.7	26.3	7.5	$C_{12}H_{20}Cl_3N_4O_3P$	35.5	4.9	13.8	26.3	7.6	404.0332	404.0338
VII		197[D]	32.8	5.0	12.6	-	6.8	$C_{12}H_{22}Cl_3N_4O_2P$	32.8	5.0	12.7	-	7.0	438.0205	438.0215

* All the compounds decompose on melting; A m/z; B From chloroform/petrol (b.p. 60-80 °C); C M+1 from FAB mass spectrometry; D From aqueous ethanol; E Hot filtered from acetone.

Table 2.6 Solubility data for the compounds synthesised.

Comp. No.*	R	Solubility †																	
		Petrol		Toluene		Et_2O		$CHCl_3$		CCl_4		Acetone		H_2O		MeOH		EtOH		THF		DMSO	
		C	H	C	H	C	H	C	H	C	H	C	H	C	H	C	H	C	H	C	H	C	H
I^A	H	IS	IS	IS	IS	IS	IS	SP	S	SP	SS	SP	SS	SP	S	S	-	S	-	IS	SP	SS	S
II^A	CH_3	IS	IS	IS	IS	IS	IS	SP	S	SP	S	SP	SS	SS	S	S	-	S	-	SS	S	S	-
III^A	CH_2Cl	IS	IS	IS	IS	IS	IS	SS	S	IS	SP	IS	SP	IS	IS	S	-	SS	S	SP	S	S	-
IV^A	CCl_3	IS	IS	SP	S	IS	IS	SP	S	IS	SP	SS	S	IS	IS	S	-	S	-	SS	S	S	-
V^A		IS	IS	IS	IS	IS	IS	SP	S	SP	SS	SP	SS	IS	SP	S	-	SS	S	SP	SS	SS	S
VI^A		IS	IS	IS	IS	IS	IS	SS	S	IS	SP	IS	SP	IS	IS	S	-	SP	S	IS	IS	SS	S
VII^A		IS	IS	IS	IS	IS	IS	SP	S	SP	SS	IS	SS	IS	IS	S	-	SS	S	IS	SP	SS	S

(See the end of the table for key, p. 62)

Cont.

Table 2.6 cont.

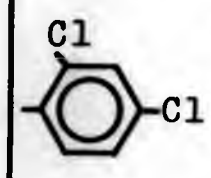
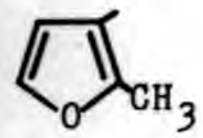
Comp. No.*	R	Solubility †																	
		Petrol		Toluene		Et_2O		$CHCl_3$		CCl_4		Acetone		H_2O		MeOH		EtOH		THF		DMSO	
		C	H	C	H	C	H	C	H	C	H	C	H	C	H	C	H	C	H	C	H	C	H
VIII[B]	H	IS	IS	SP	S	IS	SP	S	-	SS	S	S	-	SP	S	S	-	S	-	S	-	S	-
IX[B]	CH_2Cl	IS	IS	SP	S	IS	IS	S	-	SP	SS	S	-	IS	IS	S	-	S	-	S	-	S	-
X[B]	CCl_3	IS	IS	SP	S	IS	IS	S	-	SP	SS	S	-	IS	IS	S	-	S	-	S	-	S	-
XI[B]		IS	IS	SP	S	IS	IS	S	-	SP	S	S	-	IS	SP	S	-	S	-	S	-	S	-
XII[B]		IS	IS	SP	S	IS	IS	S	-	SP	S	SS	S	IS	SP	S	-	S	-	S	-	S	-
XIII[C]	SC(S)OEt	IS	IS	IS	IS	IS	IS	S	-	IS	SP	SP	S	IS	IS	S	-	SS	S	SS	S	S	-
XIV[C]	$SC(S)NMe_2$	IS	IS	IS	SP	IS	IS	S	-	IS	SP	SP	S	IS	IS	S	-	S	-	SP	S	S	-
XV[C]	$SC(S)NEt_2$	IS	IS	SP	S	IS	SP	S	-	SP	SS	SS	S	IS	IS	S	-	SS	S	SP	S	S	-
XVII[C]		IS	IS	IS	IS	IS	IS	SP	S	SP	SS	SP	S	SS	S	S	-	S	-	IS	SP	SS	S
XVIII[C]	$SP(S)(OEt)_2$	IS	IS	SP	S	IS	SP	S	-	SP	SS	SP	S	IS	IS	S	-	SP	S	SS	S	SS	S

Table 2.6 Cont.

Key to Table 2.6

* Compound numbers correspond to the structures shown in Tables 2.5, 2.9 and 2.12

† The solubility data are reported as follows: C = Cold; H = Hot; IS = Insoluble; SP = Sparingly soluble; SS = Slightly soluble; and S = Soluble; - = Not tested

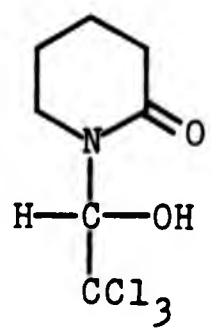
A General structure $(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)R$

B General structure $(EtO)_2P(O)NHCH(CCl_3)NHC(O)R$

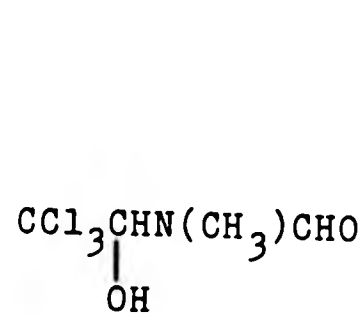
C General structure $(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)CH_2R$

soluble in polar organic solvents e.g. methanol and DMSO. Solubility data, together with those for other compounds listed later in Tables 2.9 and 2.12, are given in Table 2.6. The spectroscopic data and biological tests are discussed in Chapters 3 and 4 respectively.

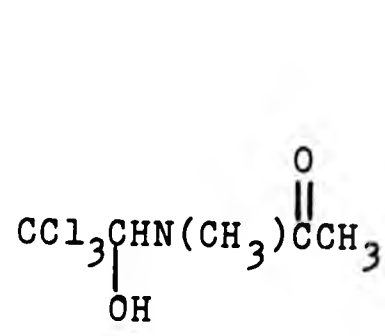
Scheme 2.7 was found to be unsatisfactory for secondary amides. Various secondary amides e.g. 2-piperidone, N-methylformamide and N-methylacetamide were allowed to react with chloral in order to obtain the N-(1-hydroxy-2,2,2-trichloroethyl)amides, compounds 68, 69 and 70 respectively. Data for the 2-piperidone and N-methylacetamide derivatives and for other unreported N-(1-hydroxy-2,2,2-trichloroethyl)- and N-(1,2,2,2-tetrachloroethyl)amides that were synthesised during the course of this programme are shown in Table 2.7. The 2-piperidone and N-methylformamide hydroxy compounds (68 and 69) were chlorinated. Attempted reaction of these chloro compounds with N,N,N',N'-tetramethylphosphoric triamide in the



(68)



(69)



(70)

presence of triethylamine failed, the triamide being recovered unreacted, along with triethylamine hydrochloride. The latter indicated that the compounds were decomposing with the evolution

Table 2.7 Novel N-(1-hydroxy-2,2,2-trichloroethyl)- and N-(1,2,2,2-tetrachloroethyl) derivatives synthesised.

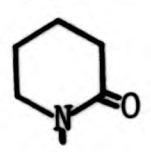
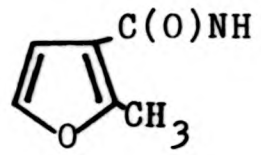
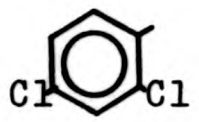
Comp. type	m.p. (°C)	R	Found C	Found H	Found N	Required C	Required H	Required N	Other evidence for structure
A[1]	97		34.3	4.0	5.6	34.1	4.1	5.7	Found: Cl, 42.9 Requ.: Cl, 43.2
A[2]	92		28.0	2.5	13.3	27.9	2.3	13.0	^{1}H NMR
A	122		35.5	3.2	4.8	35.2	2.9	5.1	^{1}H NMR
B	124		31.8	1.7	4.2	30.3	1.4	3.9	Fully characterised phosphoramide deriv.
B	97	CCl_3	14.4	0.86	4.7	14.4	0.61	4.3	^{1}H NMR. Found: Cl, 76.4. Requ.: Cl, 75.6
A[3]	94	$N(CH_3)C(O)CH_3$	26.8	3.6	6.1	27.2	3.6	6.1	^{1}H NMR
A[4]	127	$NHC(O)CCl_3$	15.5	0.98	4.3	15.5	0.97	6.1	^{1}H NMR
A	52	$NHC(O)CH_2OC_4H_9$	34.7	5.0	5.0	34.5	5.0	5.0	^{1}H and ^{13}C NMR
A	-	$NHC(O)CH_2OC_{12}H_{25}$	-	-	-	-	-	-	^{1}H and ^{13}C NMR

Table 2.7 cont.

Key to Table 2.7

A Basic structure $CCl_3CH(OH)R$

B Basic structure $CCl_3CH(Cl)NHC(O)R$

1, 2, 3 and 4 These compounds are reported in the literature but are included here as inadequate data was available in these sources. For literature references see experimental section.

of HCl, although imines cannot be formed, and it was also clear that nucleophilic displacement of chlorine by the phosphoramide did not occur in these compounds. Decomposition of trichloromethyl compounds in the presence of base to give HCl and/or chloroform has been observed by other authors.[2,29,30]

The elimination of HCl from N-methyl-N-(1,2,2,2-tetrachloroethyl)formamide (i.e. chlorinated 69) did not occur with pyridine in benzene, but triethylamine in hot toluene gave triethylamine hydrochloride and a colourless oil which discoloured rapidly in light. This oil was shown by FAB mass spectrometry to have a molecular weight of 187 (found M+1 188) which together with its ^{1}H and ^{13}C N.M.R. spectra showed the compound to be N-(1,2,2-trichloroethenyl)-N-methylformamide (71)(Scheme 2.8). Elimination of HCl in this fashion has been postulated by Atavin et al.[31] in order to account for some of the reaction products isolated from their attempts to synthesise $CCl_2{=}CClOC_4H_9$ from $CCl_3CHClOC_4H_9$ using concentrated alkali at 135-140 °C, although the desired product appeared to have reacted further and thus could not be isolated.

$$CCl_3CH(Cl)N(CH_3)CHO \xrightarrow[Et_3N]{\text{Refluxing toluene}} CCl_2{=}C(Cl)N(CH_3)CHO \ (71) \ + \ Et_3N^+HCl^-$$

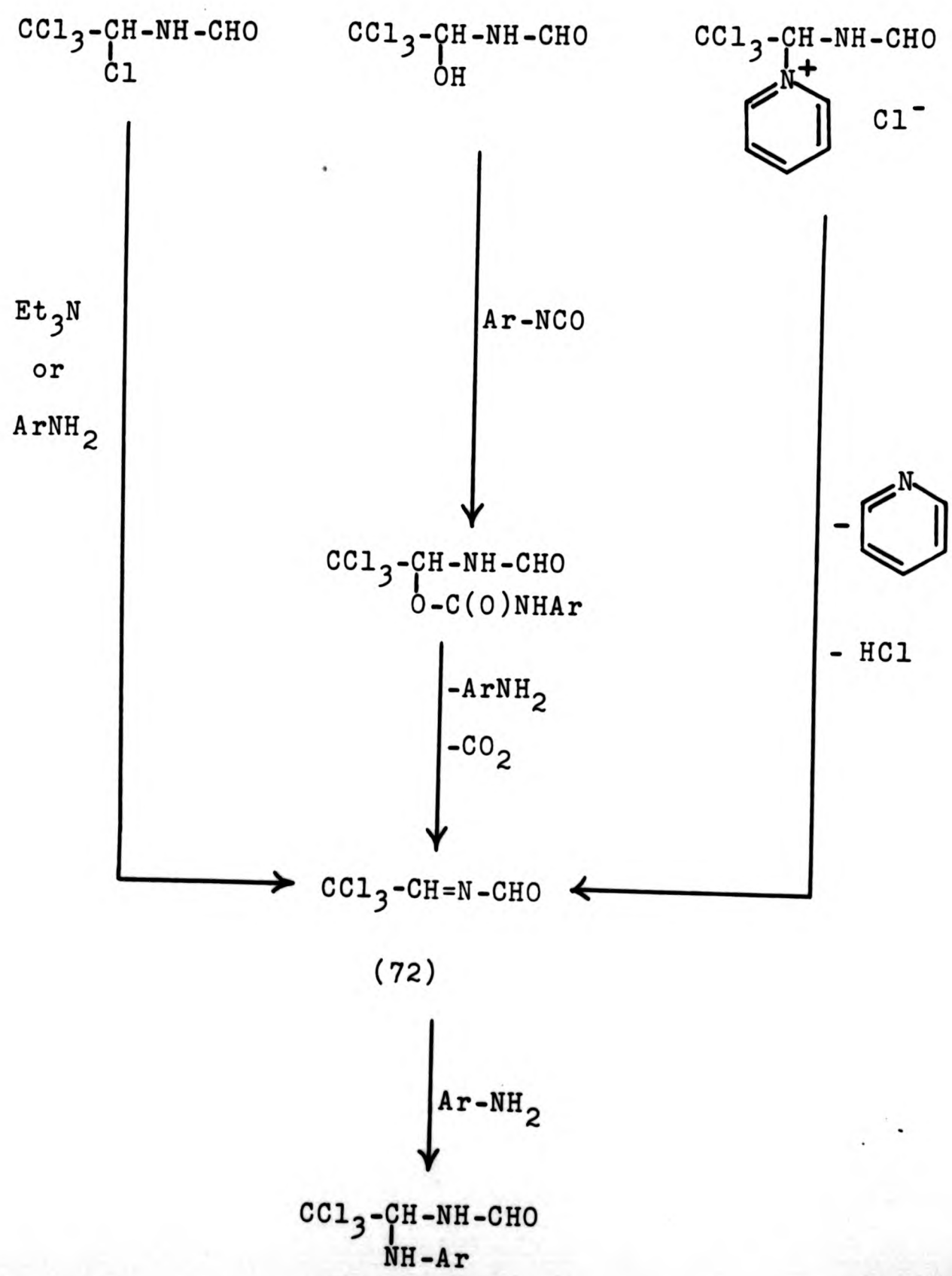
Scheme 2.8

N-(1,2,2-trichloroethenyl)-N-methylformamide is similar to compounds of the type $X_2C{=}CXCH_2YR$ (where X = halo-

gen, R is a variety of groups including -CHO and Y = O or NH) which have been claimed in a series of patents to show fungicidal activity against a wide range of plant pathogens including Piricularia oryzae, Aspergillus niger and Fusarium moniliforme.[32-38]

It is clear that the active C═N group of an imine, formed as an intermediate from a primary amide (Scheme 2.7), is a prerequisite for the condensation with phosphoric triamide. The formation of a formylimine as a reactive intermediate has been postulated by Loeffler et al.[39] in their studies of N-(1-substituted-2,2,2-trichloroethyl)formamides. These workers reviewed the methods used to synthesise such compounds and proposed Scheme 2.9, which consists of three general routes, all of which depend on the formylimine 72. In view of this it was anticipated that in the absence of a tertiary base the phosphoric triamide might also react with N-(1,2,2,2-tetrachloroethyl)amides in a stepwise elimination-addition type reaction. No such reaction between N-(1,2,2,2-tetrachloroethyl)acetamide and N,N,N',N'-tetramethylphosphoric triamide could however be detected by ^{1}H N.M.R. The results showed that elimination of HCl did not occur at 35 °C or at 50 °C, and although the ^{1}H N.M.R. spectrum changed considerably when the mixture was allowed to stand for five days at room temperature (Table 2.8), the exact nature of the reactions taking place in this system are not known. The most significant change was the collapse of the doublet at δ 2.6 corresponding to the $(Me_2N)_2P(O)$- group to a badly resolved

Scheme 2.9


Route A
Route B
Route C
CCl3-CH(Cl)-NH-CHO
CCl3-CH(OH)-NH-CHO
CCl3-CH(N+C5H5 Cl-)-NH-CHO
Et3N or ArNH2
Ar-NCO
- C5H5N
- HCl
CCl3-CH(O-C(O)NHAr)-NH-CHO
-ArNH2
-CO2
CCl3-CH=N-CHO
(72)
Ar-NH2
CCl3-CH(NH-Ar)-NH-CHO

multiplet at δ 2.7. Much of the N-(1,2,2,2-tetrachloroethyl)-acetamide was still present. The results demonstrate the importance of the imine as a reactive intermediate which allows the reaction to proceed smoothly at room temperature and of the need for a suitable base for its formation.

Compound	Chemical shifts/ppm †
$(Me_2N)_2P(O)NH_2$	2.6 (d)
$CCl_3CH(Cl)NHC(O)CH_3$	2.1 (s), 6.5 (d), 7.0 (bs).
$CCl_3CH{=}NHC(O)CH_3$	2.3 (s), 7.9 (s).
$(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)CH_3$	1.9 (s)*, 2.5 (dd), 4.7 (m), 5.7 (m), 8.4 (d).
Initial reaction mixture	2.2 (s), 2.6 (d), 6.6 (d), 8.8 (bs).
5-day reaction mixture	2.0 (s), 2.2 (s), 2.3 (s), 2.7 (m), 5.6 (d), 6.6 (d), 7.8 (bs), 9.3 (bs).

† Solvent was $CDCl_3$ unless otherwise stated.

* DMSO-d_6

Table 2.8 Chemical shifts of compounds of interest when studying the N-(1,2,2,2-tetrachloroethyl)acetamide/ N,N,N',N'-tetramethylphosphoric triamide system.

2.3 Kinetics and mechanism of nucleophilic addition to imines

Drach et al.[40] studied the kinetics of the reaction

between N-(2,2,2-trichloroethylidene)amides and ethanethiol (Scheme 2.10) using an iodometric technique. These workers showed the reaction to be second order and the rate to depend on the electronegativity of the acyl group. The lower the electronegativity of the acyl group the higher the electron density on the azomethine carbon atom and the more slowly ethanethiol adds. Their method is not general,however, as appropriate techniques of analysis must be found for each different type of nucleophile. Our own studies of the spectroscopic properties of N-(1,2,2,2-terachloroethyl)acetamide and N-(2,2,2-trichloroethylidene)acetamide showed that the UV and ^{1}H N.M.R. spectra of the latter contained peaks whose decay might be used for kinetic measurements. The peak at λ_{max} 252 nm,

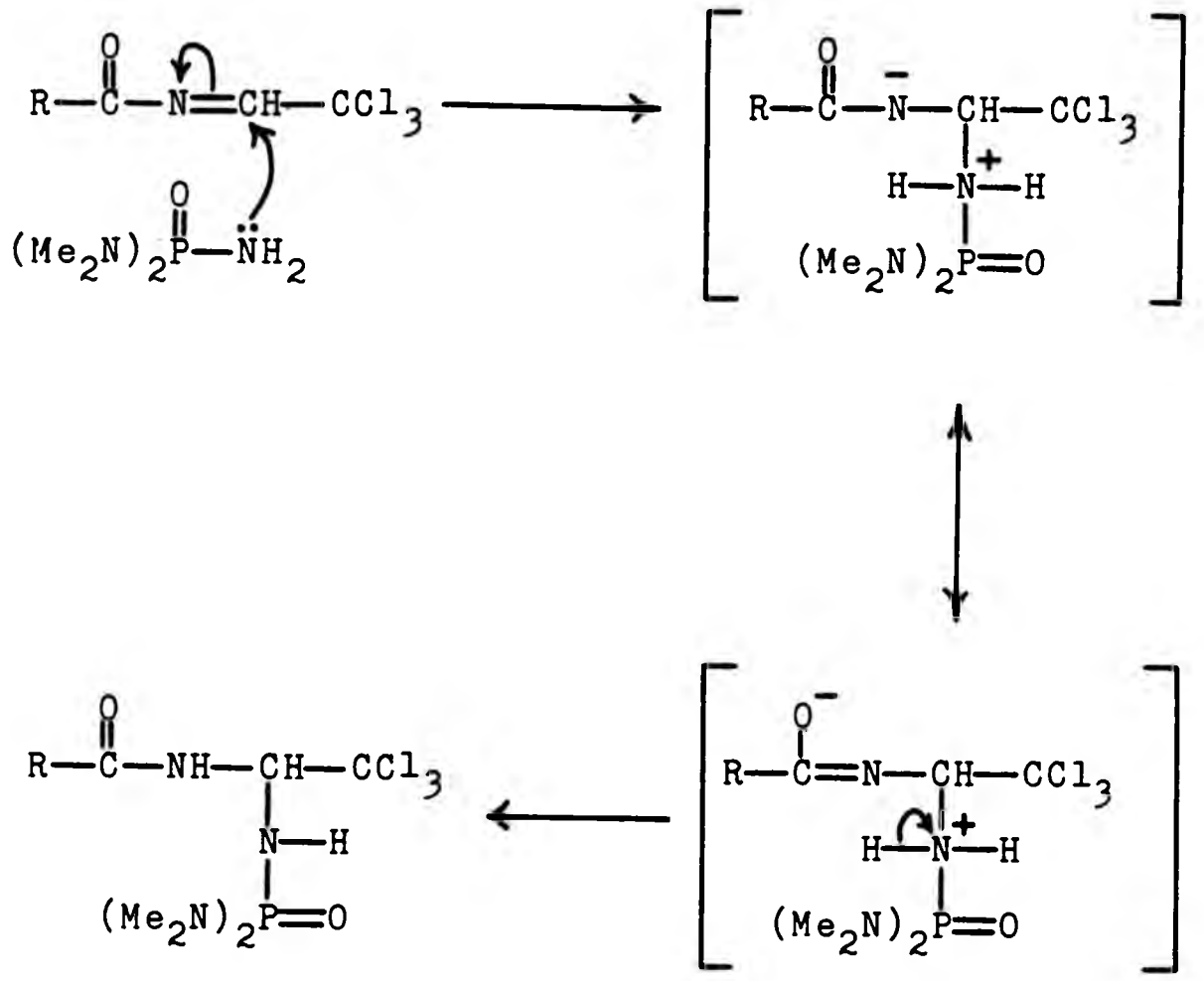
$$CCl_3CH{=}NC(O)CH_3 \quad + \quad EtSH \longrightarrow CCl_3CH(SEt)NHC(O)CH_3$$

Scheme 2.10

shown by the freshly prepared imine, appears particularly promising although further development of the procedures is necessary. Water and other nucleophilic species, e.g. ethanol used as the stabaliser in chloroform, must be rigorously excluded. Ethyl acetate showed some promise as a suitable solvent.

By analogy with the results of Drach et al.[40] it is, however, reasonable to suppose that the addition of N,N,N',N'-tetramethylphosphoric triamide to N-(2,2,2-trichloroethylidene)amides proceeds via a mechanism such as

that shown in Scheme 2.11.



Scheme 2.11

2.4 Synthesis of compounds containing the bis(dimethylamido)-phosphoryl, trichloromethyl and other groups associated with fungicidal activity

The aim of synthesising compounds containing the bis(dimethylamido)phosphoryl group, the trichloromethyl group and other groups associated with fungicidal activity, such as imidazole, triazole, dithiocarbamate, xanthate etc., led to

the preparation and use of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)phosphoric triamide (73) as an intermediate. The compound (73) was synthesised by the

$$(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)CH_2Cl$$

(73)

normal procedure (see Scheme 2.2 p. 38) using chloroacetamide. The replacement of the chlorine of the chloroacetamido moiety has been achieved by condensation with potassium or sodium salts of various compounds of interest as shown in Scheme 2.12.

$$(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)CH_2Cl \xrightarrow{NaX \text{ or } KX} (Me_2N)_2P(O)NHCH(CCl_3)NHC(O)CH_2X$$

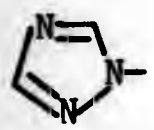
Scheme 2.12

The compounds synthesised by this method are shown in Table 2.9.

These compounds were white or off-white crystalline solids which decomposed on melting. Their melting points and solubilities depended on the substituent, R, and the solubilities are shown in Table 2.6. The spectroscopic and fungicidal data are discussed in Chapters 3 and 4 respectively.

Attempts to synthesise derivatives 74 and 75 by

Table 2.9 Compounds of the type $(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)CH_2R$

Comp. No.	R	m.p.* (°C)	Found					Molecular formula	Requires					Molecular weight[A]	
			C	H	N	Cl	P		C	H	N	Cl	P	Found	Requires
XIII	$SC(S)OEt$	184[B]	28.8	4.7	12.3	—	6.8	$C_{11}H_{22}Cl_3N_4O_3PS_2$	28.7	4.8	12.2	—	6.7	457.9933	457.9936
XIV	$SC(S)NMe_2$	191[C]	28.6	4.8	15.4	—	6.9	$C_{11}H_{23}Cl_3N_5O_2PS_2$	28.8	5.0	15.3	—	6.8	457.0092	457.0096
XV	$SC(S)N(Et)_2$	171[D]	31.9	5.6	14.4	—	6.3	$C_{13}H_{27}Cl_3N_5O_2PS_2$	32.1	5.5	14.4	—	6.4	485.0397	485.0409
XVI	$SC_{12}H_{25}$	108[E]	44.6	7.6	10.5	19.6	5.8	$C_{20}H_{42}Cl_3N_4O_2PS$	44.5	7.8	10.4	19.7	5.7	539.1[F]	539.2
XVII[H]		182[D]	28.2	4.7	24.3	26.6	7.6	$C_{10}H_{19}Cl_3N_7O_2P$	29.5	4.7	24.1	26.2	7.6	405.0406	405.0402
XVIII	$SP(S)(OEt)_2$	125[D]	27.5	5.3	10.7	—	11.9	$C_{12}H_{27}Cl_3N_4O_4P_2S_2$	27.5	5.2	10.7	—	11.8	522.0012	522.0014
XIX	OC_4H_9	137[G]	34.2	6.3	13.1	—	—	$C_{12}H_{26}Cl_3N_4O_3P$	35.0	6.3	13.6	—	—	411.0[F]	411.1

* All the compounds decompose on melting; A m/z; B From aqueous ethanol; C From $CHCl_3$/petrol (b.p. 40-60 °C); D From $CHCl_3/Et_2O$; E From Et_2O; F M+1 from FAB mass spectrometry; G From benzene/petrol (b.p. 60-80 °C); H Mixture of 1- and 4-isomers.

Scheme 2.12 failed. In the reaction of sodium or potassium

$$(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)CH_2R$$

where R = $OC_{12}H_{25}$ (74)

R = imidazolyl (75)

dodecanoxide with compound 73, only small quantities of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-dodecanoxyethyl)-phosphoric triamide (76) were isolated. This was a totally

$$(Me_2N)_2P(O)NHCH(CCl_3)OC_{12}H_{25}$$

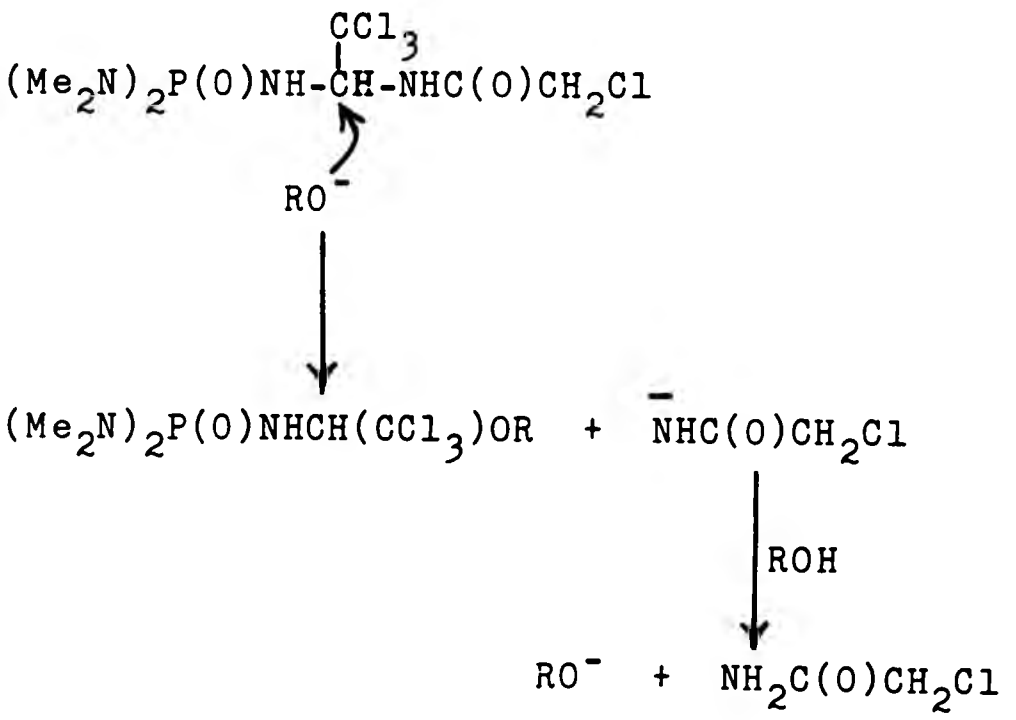
(76)

unexpected product indicating that nucleophilic attack on the carbon carrying the trichloromethyl group had occurred. In view of certain difficulties in the use of dodecanol (difficult generation of dodecanoxide anion and its high boiling point which led to decomposition of reaction products on trying to remove it even under reduced pressure) it was decided to use butanol as a model in order to study the reaction further. The reaction between sodium butoxide and compound 73, carried out in butanol, yielded N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-butoxyethyl)phosphoric triamide (77) as the only isolated product (28%, recrystallised), together with chloroacetamide which was identified by ^1H N.M.R. No products consistent with nucleophilic attack at

$(Me_2N)_2P(O)NHCH(CCl_3)OC_4H_9$

(77)

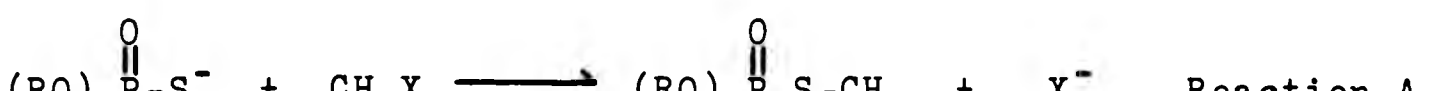
the chloromethyl group could be detected. A mechanism for this reaction is proposed in Scheme 2.13 in order to account for these observations. The exact reasons for the



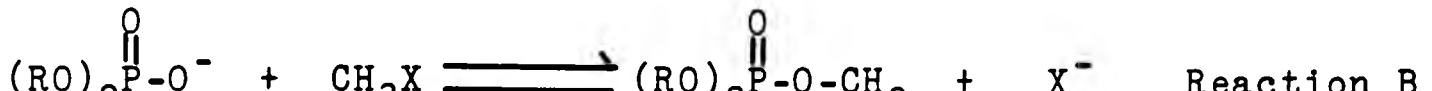
Scheme 2.13

difference between alkoxy anions and anions of sulphur or nitrogen in their reaction with compound 73 are not known, although it is suspected that steric factors may have a significant influence on the mode of reaction since the carbon carrying the trichloromethyl group is in a sterically hindered environment. It is known that the covalent radii of oxygen, sulphur, and nitrogen increase in the order $O < N << S$,[41] although this is a simplistic argument as the overall "shapes"

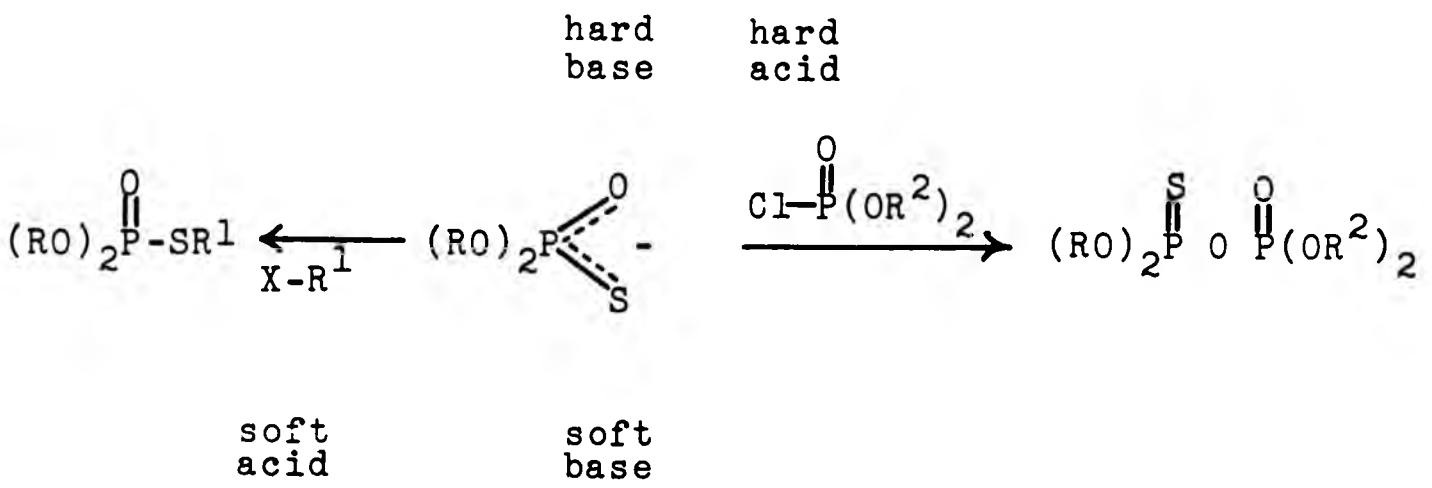
of the anions used during these experiments will be more important than the sizes of the heteroatoms in determining their steric properties. The steric aspects of these reactions will need further investigation. Reactions using alkoxides derived from secondary and tertiary alcohols would be worth studying in order to determine whether attack at the chloromethyl group can be induced in preference to attack at the methine carbon atom. The differences in the behaviour of $C_{12}H_{25}O^-$ and $C_{12}H_{25}S^-$ can be considered in the light of the "soft" and "hard" acids and bases principle proposed by Pearson.[42] This type of approach has been used by other authors to explain the position of nucleophilic or electrophilic attack in compounds with more than one reactive centre.[19,43,44] The examples highlighted by Eto[43] are worth noting here. O,O-Dialkyl phosphorothioate ion has two nucleophilic centres, the soft S^- and the hard O^-, as shown in Scheme 2.14. When this compound is allowed to react with alkyl halides which have soft acid centres, the softer nucleophile S^- is found to be the more reactive, in preference to the harder O^-. It was predicted that the equilibrium constant for reaction A would be at least 10^4 times larger than that of reaction B. On changing the electrophile to a hard acid such as $Cl\text{-}P(O)(OR^1)_2$ only the oxygen of the ion is phosphorylated, to give monothionopyrophosphates. In the case of N,N,N',N'-tetramethyl-N''-(2,2,2-trichloro-1-chloroacetamidoethyl)phosphoric triamide (73) three hard acid centres (i.e. $(Me_2N)_2\underline{P}(O)NH$-, -NH$\underline{C}$(O)-, and -NH-$\underline{C}$H($CCl_3$)-NH-) and one soft acid centre (-$\underline{C}H_2Cl$) are present. The present experimental findings



Reaction A



Reaction B



Scheme 2.14

indicate that the soft base $C_{12}H_{25}S^-$ attacks the soft acid $-CH_2Cl$ group preferentially, whereas the hard base $C_{12}H_{25}O^-$ attacks the hard acid centre -NH-CH(CCl_3)-NH-. Products resulting from alkoxide ion attack at the other hard acid centres have not been detected but such alternative reactions may account for the low yields of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-alkoxyethyl)phosphoric triamides (76 and 77) isolated from these reactions.

Derivatives containing alkoxy groups on the terminal methyl group such as compound 74 were synthesised using Scheme 2.15. Sodium or potassium alkoxide was first condensed

with chloroacetamide, followed by reaction with chloral to give the N-(1-hydroxy-2,2,2-trichloroethyl)-alkoxyacetamides (78). These intermediates were isolated and characterised by elemental analysis, ^{1}H and ^{13}C N.M.R. so that later steps of the reaction could be followed with some degree of confidence. Compounds of this type (78) where R = Bu or $C_{12}H_{25}$ were synthesised and are included in Table 2.7 as novel adducts of chloral. The hydroxy compounds (78) were then chlorinated using

$ClCH_2C(O)NH_2 + RO^- Na^+ (K^+)$

$\downarrow$

$ROCH_2C(O)NH_2$

$\downarrow CCl_3CHO$

$ROCH_2C(O)NHCH(OH)CCl_3$

(78)

$\downarrow SOCl_2$

$ROCH_2C(O)NHCH(Cl)CCl_3$

(79)

$\downarrow Et_3N/-HCl$

$ROCH_2C(O)N{=}CHCCl_3$

(80)

$\downarrow (Me_2N)_2P(O)NH_2$

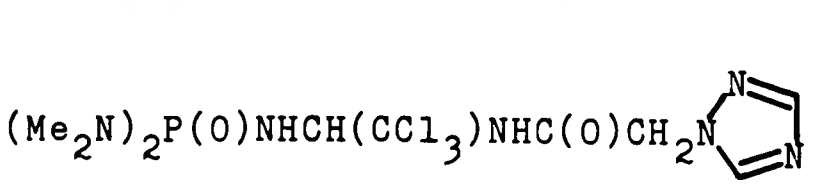
$(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)CH_2OR$

(81)

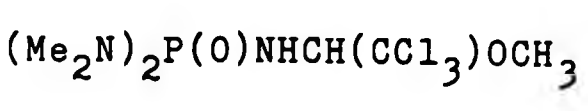
Scheme 2.15

thionyl chloride to give the corresponding N-(1,2,2,2-tetrachloroethyl)-alkoxyacetamides (79), which were then used *in situ* for conversion to the imines (80) and further reaction with N,N,N',N'-tetramethylphosphoric triamide to give the desired compounds (81). In the case of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-butoxyacetamidoethyl)phosphoric triamide (81, R = $n\text{-}C_4H_9$) an analytically pure sample was obtained which was fully characterised by ^1H, ^{13}C and ^{31}P N.M.R., and mass spectrometry. However, the dodecanol derivative (81, R = $n\text{-}C_{12}H_{25}$ was obtained as an oily residue which failed to crystallise from a number of solvents. It was however shown by ^1H, ^{13}C and ^{31}P N.M.R. to be mainly the required compound (74), together with unreacted phosphoric triamide. No further attempts were made to purify this material.

In an attempt to synthesise compound 75 the commercially available sodium salt of imidazole was used for the condensation, with methanol as the reaction medium. A similar reaction using the sodium salt of 1,2,4-triazole yielded the expected compound, N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-triazolylacetamidoethyl)phosphoric triamide (82). However,



(82)

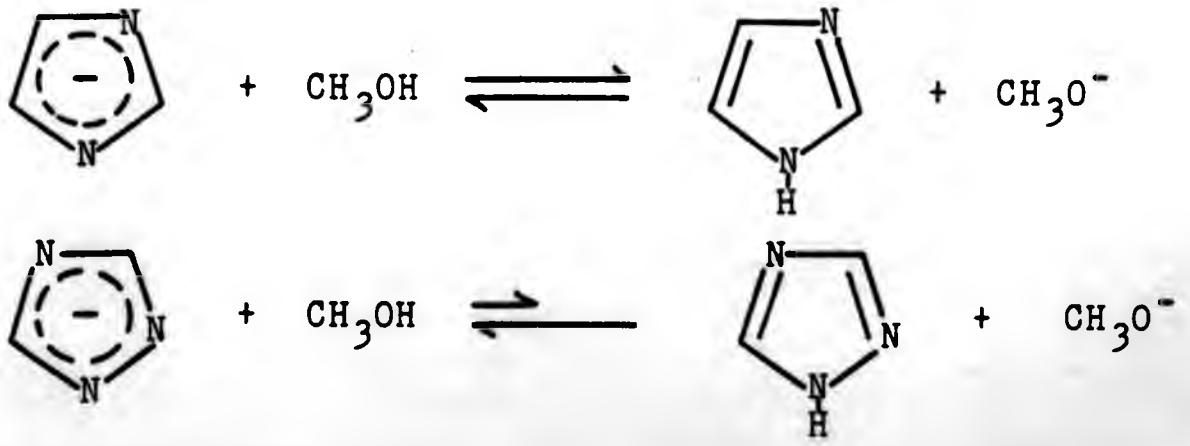


(83)

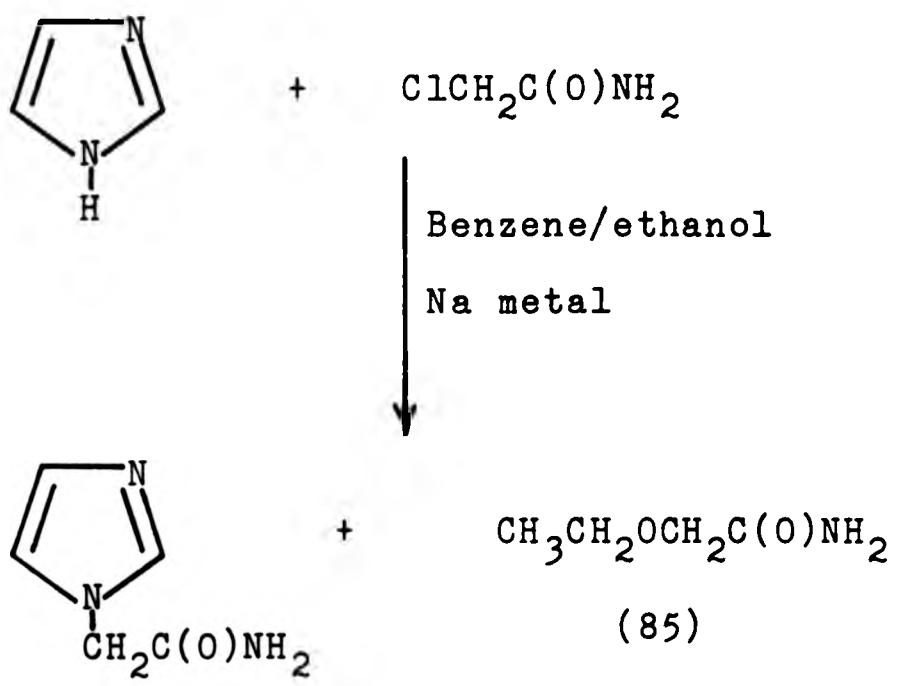
in the reaction with imidazole sodium salt in methanol only N,N,N',N'-tetramethyl-N''-(2,2,2-trichloro-1-methoxyethyl)-phosphoric triamide (83) could be isolated, indicating attack by methoxide ion as previously discussed (see Scheme 2.13, p. 75). The difference in the types of product derived from the reactions of the sodium salts of 1,2,4-triazoles and of imidazole is probably due to the difference in the pK_a values of these heterocycles which are shown together with those of certain alcohols in Table 2.10. The values indicate that the equilibrium concentration of methoxide in the following equilibria will be much higher in the case of the imidazole system and that this may account for the results obtained.

Compound	pK_a
1,2,4-Triazole	10
Imidazole	14.52
Methanol	15.09
Ethanol	15.93
Tert. butyl alcohol	>19

Table 2.10 pK_a values of compounds of interest



The reaction between the sodium salt of imidazole in ethanol and chloroacetamide was shown to give 1-(acetamido)imidazole (84) as the main product (63% yield after recrystallisation) together with some ethoxyacetamide (85, 6% yield from work-up of filtrates)(Scheme 2.16). This indicated that ethanol may be a more favourable solvent and that the reaction of compound 73 with the sodium salt of imidazole in ethanol might yield the required compound (75). The reaction however failed;



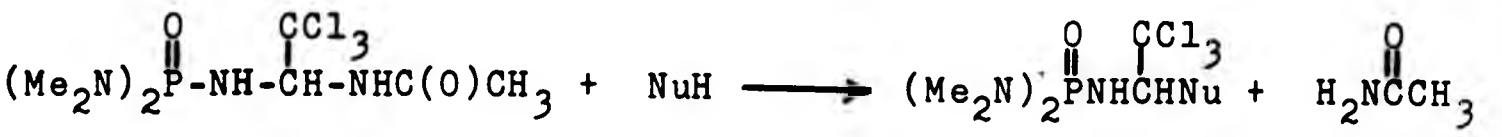
Scheme 2.16

only the ethoxy derivative (88) could be isolated. Further investigation of this reaction by using non-hydroxylic solvents e.g. DMSO or alcohols with higher pK_a values (including sterically hindered alcohols) as reaction media must be carried out before firm conclusions can be drawn.

It can be seen from the previous discussion that a series

of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-alkoxyethyl)-phosphoric triamide derivatives have been synthesised during the course of this programme, by the unexpected reactions of alkoxides with N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)phosphoric triamide (Scheme 2.13). The compounds are shown in Table 2.11. All were white or off-white crystalline solids, which decomposed on melting. Their characteristic spectroscopic properties are discussed in Chapter 3.

Bis (dimethylamido)phosphoryl compounds containing the trichloromethyl group and other groups of interest e.g.imidazole, triazole, etc. directly on the methine carbon (29, $R^1 = R^2 = Me_2N$, p.19) have proved difficult to synthesise because of the failure of N,N,N',N'-tetramethylphosphoric triamide (59) to condense with chloral (see p. 39). The fortuitous synthesis of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-alkoxyethyl)phosphoric triamides (Table 2.11) by the method referred to above (Scheme 2.13) led to the investigation of the reaction between N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-acetamidoethyl)phosphoric triamide (86) and model nucleophiles in the expectation that an analogous displacement of the acetamide group might occur (Scheme 2.17).



(86)

Scheme 2.17

Table 2.11 N,N,N',N''-tetramethyl-N''-(2,2,2-trichloro-1-alkoxyethyl)phosphoric triamides $(Me_2N)_2P(O)NHCH(CCl_3)OR$

R	m.p.* (°C)	Found C	Found H	Found N	Molecular formula	Requires C	Requires H	Requires N	Molecular weight[A] Found	Molecular weight[A] Requires
CH_3	157[B]	26.3	5.5	13.8	$C_7H_{17}Cl_3N_3O_2P$	26.9	5.4	13.4	312.0	312.0
CH_2CH_3	152[B]	29.4	5.9	13.0	$C_8H_{19}Cl_3N_3O_2P$	29.4	5.8	12.7	325.9	326.0
$CH_2(CH_2)_2CH_3$	115[B]	33.4	6.5	11.8	$C_{10}H_{23}Cl_3N_3O_2P$	33.9	6.5	11.8	354.0	354.1
$CH_2(CH_2)_{10}CH_3$	-	44.2	8.1	9.3	$C_{18}H_{39}Cl_3N_3O_2P$	46.3	8.4	9.0	466.0	466.2

* All the compounds decompose on melting; A m/z, M+1 from FAB mass spectrometry;

B From diethyl ether.

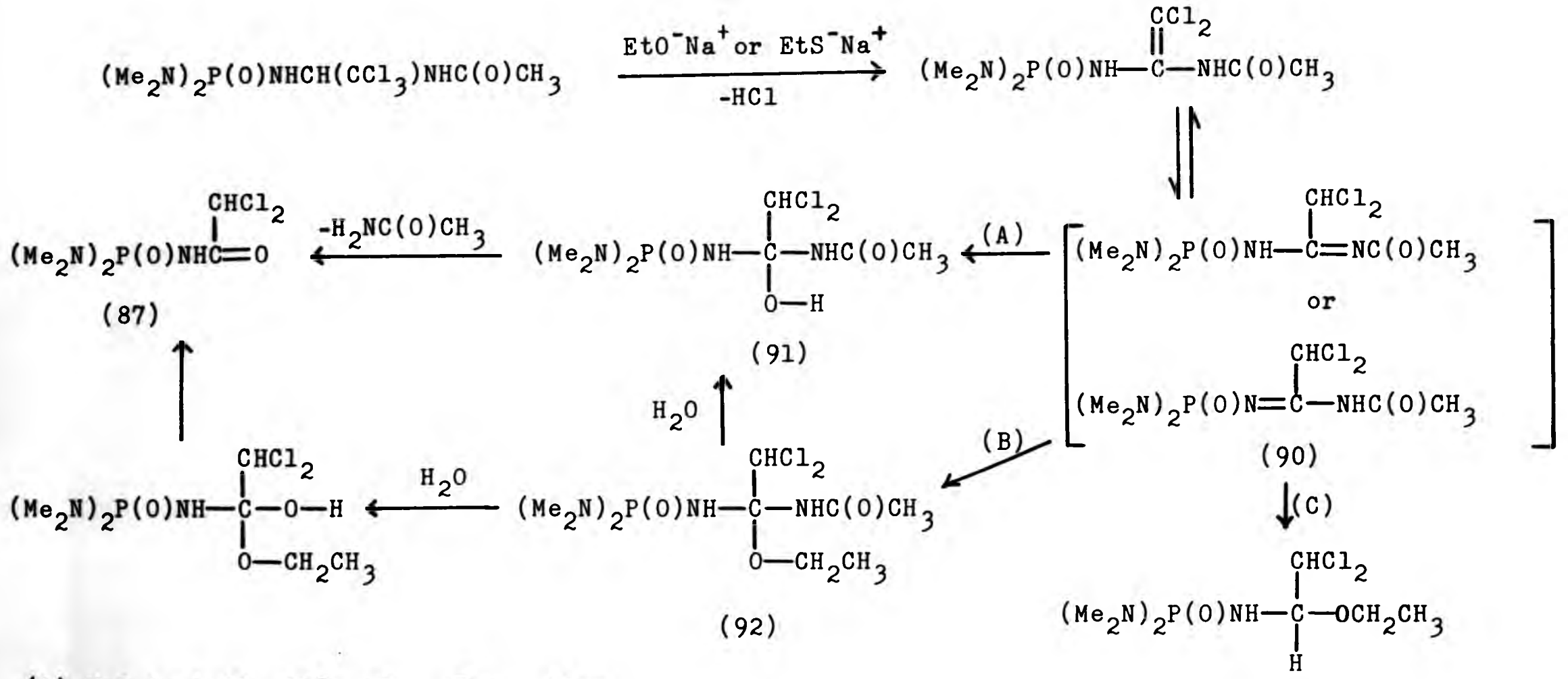
The model nucleophiles used were sodium ethoxide and sodium ethanethiolate and it was hoped that the absence of a chloromethyl group in this case would allow nucleophiles previously shown to react with this centre, to attack the methine carbon. The results obtained were unexpected in that with both sodium ethoxide and sodium ethanethiolate a white precipitate of sodium chloride was formed after 5-10 minutes of heating under reflux. In addition, three products were isolated and identified by ^{1}H, ^{13}C, ^{31}P and mass spectrometry, viz. N,N,N',N'-tetramethyl-N"-dichloroacetylphosphoric triamide (87), which was isolated from both reactions, the expected compound N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-ethoxyethyl)phosphoric triamide (88) which was only isolated from the reaction with sodium ethoxide, and N,N,N',N'-tetramethyl-N"-(2,2-dichloro-1-ethoxyethyl)phosphoric triamide (89) which was

$$(Me_2N)_2P(O)NHCH(CCl_3)OCH_2CH_3$$

(88)

isolated from the reaction with sodium ethanethiolate. The yields of compounds 87, 88 and 89 isolated from these reactions were relatively small. The formation of compound 88 has been discussed previously (see p. 75). The formation of compounds 87 and 89 can be explained by the proposed Scheme 2.18, in which nucleophilic addition to the highly reactive azomethine group of tautomeric structure 90 occurs. In the case of compound 87 the nucleophiles are water (introduced during

Scheme 2.14



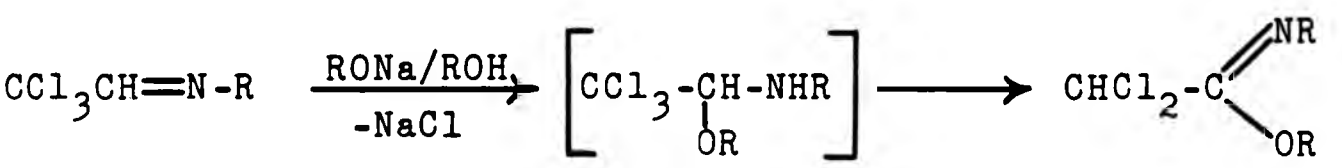
(A) H_2O in both EtO^- and EtS^- reactions

(B) EtOH in both EtO^- and EtS^- reactions

(C) Isolated only from EtS^- reaction

the work-up procedure) and ethanol which was present as the solvent. The hypothetical intermediates 91 and 92 both contain a carbon carrying two nitrogens and an oxygen and would be expected to be intrinsically unstable because of the large number of electron withdrawing groups attached to this carbon atom. The exact nature and reason for the decomposition of the proposed intermediates 91 and 92 is unknown. The formation of compound 89 from structure 90 is unclear, but the presence of the dichloromethyl group in this compound suggests that it is derived from this intermediate (90).

Loss of HCl, followed by tautomerism to give an azomethine such as that shown for intermediate 90 has also been observed by Borrmann and Wegler[15] in the reactions of N-(2,2,2-trichloroethylidene)alkylamines with sodium alkoxide and alcohol. These workers proposed the reaction scheme shown below:-



Compounds of the type $CHCl_2C(OR):NR$ were isolated and fully characterised.[15]

In the reaction with sodium ethanethiolate most of the starting material was recovered unreacted. No compounds consistent with attack on the methine carbon of N,N,N',N'-tetramethyl-N''-(2,2,2-trichloro-1-acetamidoethyl)phosphoric triamide (86) by ethanethiolate anion could be detected or isolated. These observations indicate that the reaction between compound(86) and nucleophiles (Scheme 2.17) cannot be used as

a general procedure for the preparation of compounds of the required type (29, $R^1 = R^2 = NMe_2$, p. 19).

2.5 Synthesis of O,O-diethyl N-(2,2,2-trichloro-1-amidoethyl)phosphoramidates

The need to obtain a correlation between structure and activity led to the synthesis of this series of diethoxy analogues of N,N,N',N'-tetramethyl-N''-(2,2,2-trichloro-1-amidoethyl)phosphoric triamides already discussed.

These novel compounds were obtained by reaction of the appropriate amide with O,O-diethyl N-(2,2,2-trichloroethylidene)phosphoramidate (93) as shown in Scheme 2.19. The reaction was carried out under anhydrous conditions, using benzene as the solvent and heating under reflux for 3-8 hours.

The O,O-diethy N-(2,2,2-trichloro-1-amidoethyl)phosphoramidates (94) obtained in this way are shown in Table 2.12.

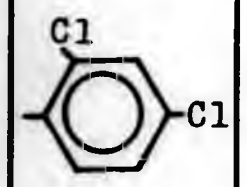
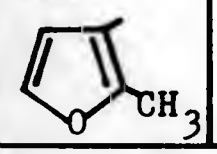
$$(EtO)_2P(O)NHCH(CCl_3)Cl \xrightarrow[\text{benzene/ room temp.}]{Et_3N} (EtO)_2P(O)N{=}CHCCl_3 \quad (93)$$

$$\xrightarrow[\text{reflux}]{RC(O)NH_2} (EtO)_2P(O)NHCH(CCl_3)NHC(O)R \quad (94)$$

Scheme 2.19

Table 2.12 O,O-Diethyl N-(2,2,2-trichloro-1-amidoethyl)phosphoramidates

$(EtO)_2P(O)NHCH(CCl_3)NHC(O)R$

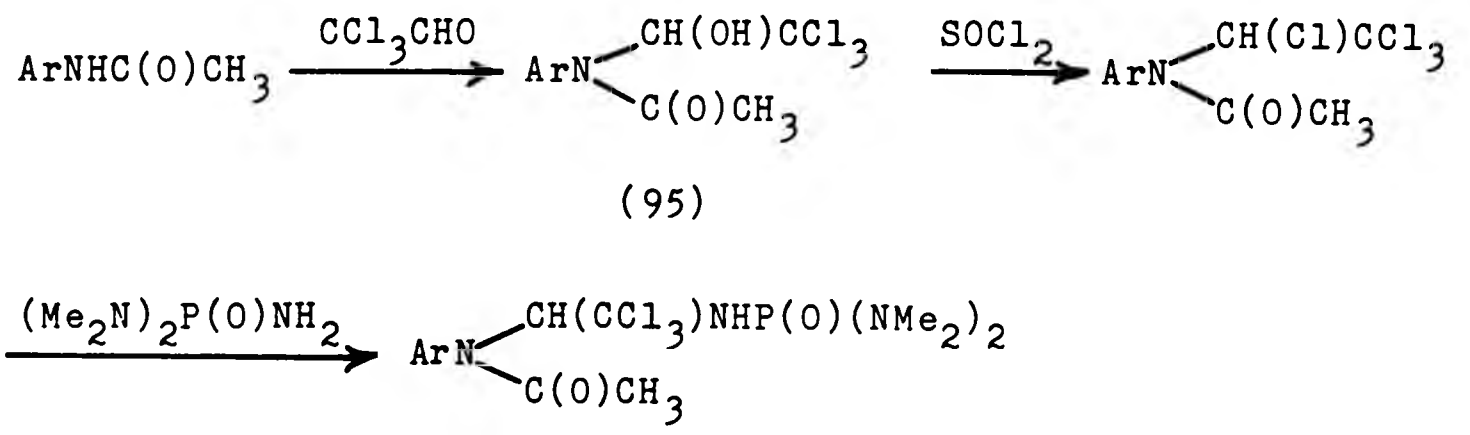
Comp. No.	R	m.p. (°C)	Found C	H	N	Cl	P	Molecular formula	Requires C	H	N	Cl	P	Molecular weight[A] Found	Requires
VIII	H	146[B]	26.5	4.4	8.3	33.0	9.2	$C_7H_{14}Cl_3N_2O_4P$	25.6	4.3	8.5	32.5	9.5	327.0	327.0
IX	CH_2Cl	183[C]	25.5	4.2	7.6	37.9	8.2	$C_8H_{15}Cl_4N_2O_4P$	25.5	4.0	7.5	37.8	8.2	375.0	375.0
X	CCl_3	183[C]	21.3	3.1	6.3	47.9	7.1	$C_8H_{13}Cl_6N_2O_4P$	21.6	2.9	6.3	47.9	7.0	442.8	442.9
XI		203[D]	33.3	3.4	5.9	37.8	6.5	$C_{13}H_{16}Cl_5N_2O_4P$	33.0	3.4	5.9	37.6	6.6	470.8	470.9
XII		169[C]	36.5	4.8	6.9	26.1	7.7	$C_{12}H_{18}Cl_3N_2O_5P$	35.3	4.4	6.9	26.1	7.6	406.0006	406.0018[E]

A m/z, M+1 from FAB mass spectrometry; B Not recrystallised; C From benzene; D From aqueous ethanol; E M^+, EI.

All were high melting white crystalline solids, which were more soluble in organic solvents than their bis(dimethylamido) analogues, but which were again generally insoluble in water (Table 2.6, p. 61). Their spectroscopic and fungicidal properties are discussed in Chapters 3 and 4 respectively.

2.6 A study of the reaction between chloral and acetanilide under neutral conditions

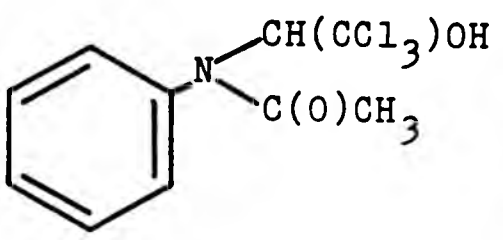
The reaction between acetanilide and chloral under neutral conditions was investigated in the hope that reactions of this type could be used as a general route for the synthesis of carboxanilide-chloral adducts and that these could be converted to phosphoric triamide derivatives (Scheme 2.20).



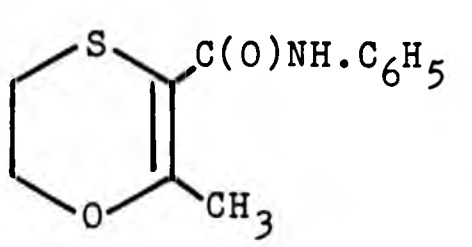
Scheme 2.20

Similar reactions with the commercial fungicides carboxin (96) and fenfuran (97) were also envisaged, although it was subsequently found (see p. 63) that secondary amide-chloral adducts do not react with phosphoramides. N-Phenyl-N-(1-hydroxy-2,2,2-

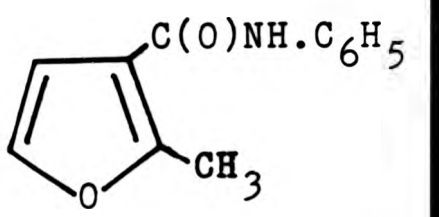
trichloroethyl)acetamide (95) has been reported in a patent[45] but no reference was made to the reaction conditions used or to any physical data for this compound.



(95)

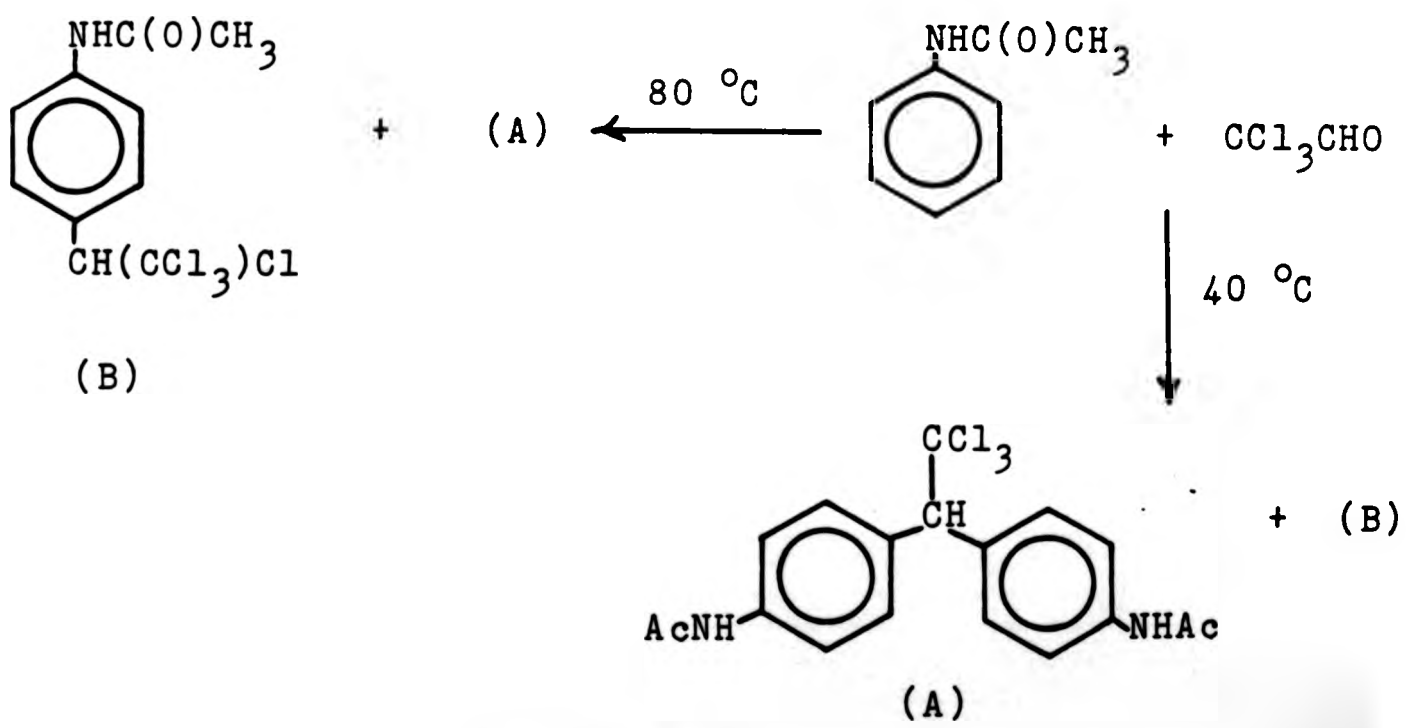


(96)



(97)

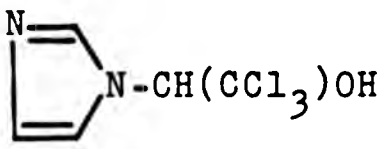
In the present investigation no reaction occurred between acetanilide and chloral under neutral conditions even after 48 hours heating, presumably because of the low nucleophilicity of the nitrogen atom in the anilide. Under acid conditions reaction occurs in the para position (Scheme 2.21).[46]



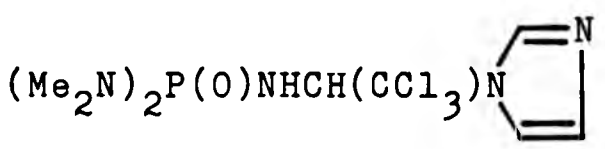
Scheme 2.21

2.7 The reaction between imidazole and chloral and its potential use as an intermediate in the synthesis of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-imidazolylethyl)phosphoric triamide

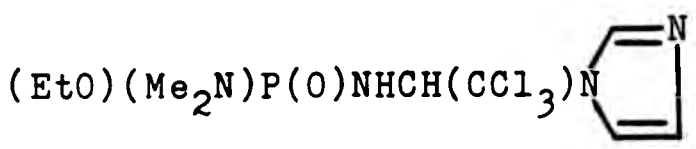
Heterocyclic compounds containing a reactive proton, have been shown to react with chloral to give N-(1-hydroxy-2,2,2-trichloroethyl) derivatives.[47-51] The N-(1-hydroxy-2,2,2-trichloroethyl)imidazole (98) was of particular interest as a potential intermediate for the preparation of compound 99 by Scheme 2.22. This compound was an important derivative in the structure-activity relationship studies which we are



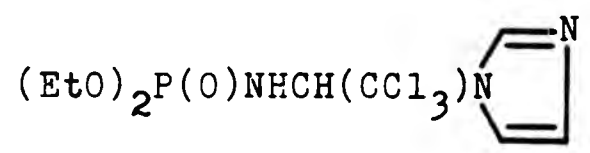
(98)



(99)



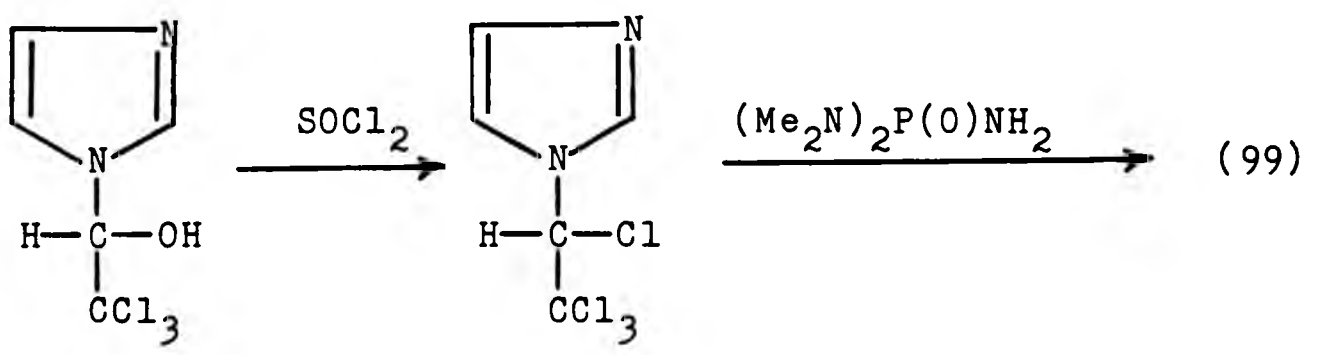
(100)



(101)

conducting, as compound 100 had already been shown to have higher fungicidal activity than compound 101.[7] Attempts to chlorinate compound 98 failed however due to cleavage of the N-C bond. This was indicated by the isolation of imidazole hydrochloride. However, in the presence of pyridine as the

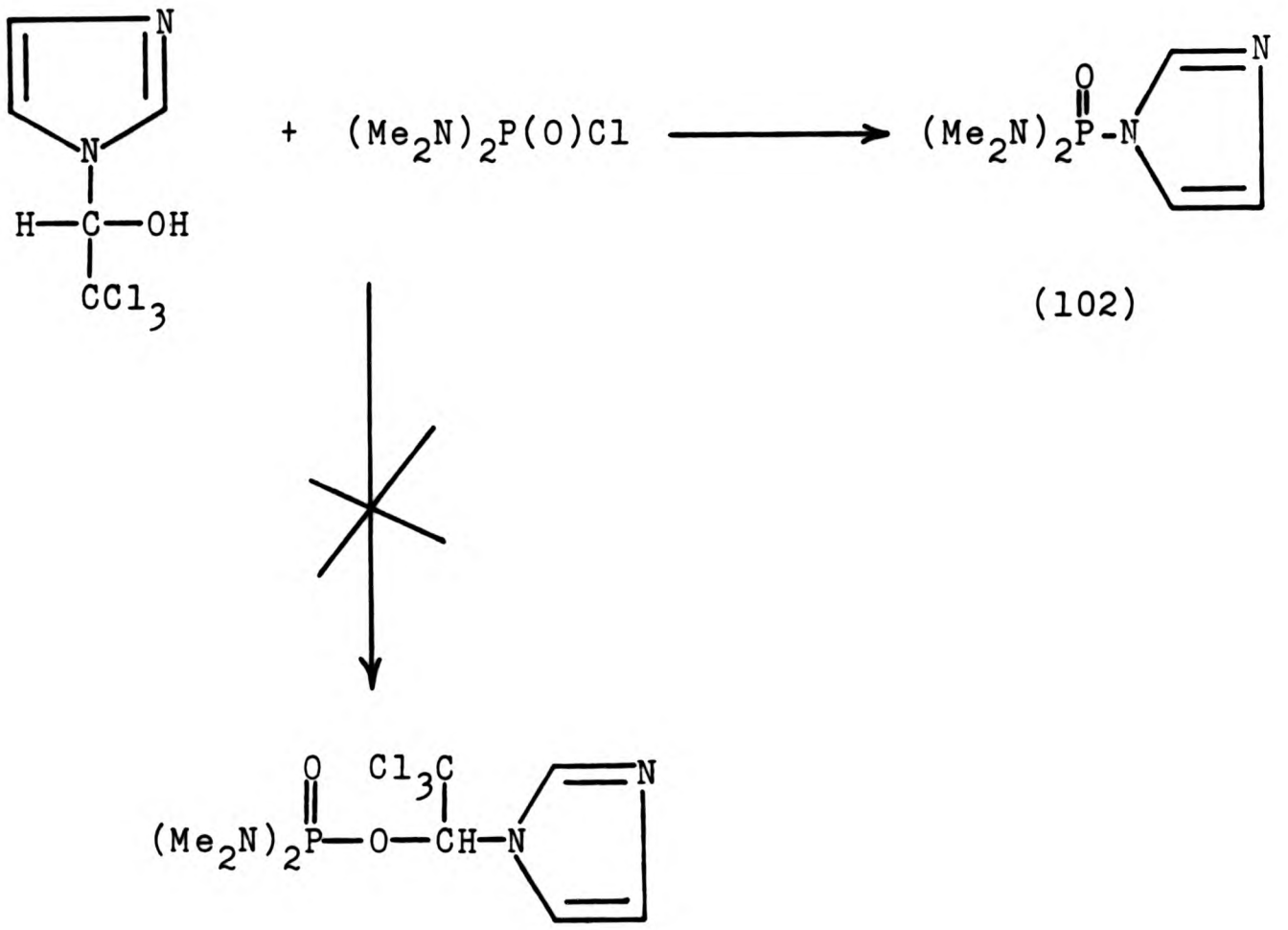
HCl acceptor a compound was detected by ^1H N.M.R. that had the characteristics of the desired compound (chlorinated 98) although it could not be isolated. Attempted reaction of compound 98 with N,N,N',N'-tetramethylphosphorodiamidic chloride $[(Me_2N)_2P(O)Cl]$ also resulted in the cleavage of the C-N bond to give compound 102 instead of the expected compound (103) (Scheme 2.23). It has been reported that electrophilic attack of imidazoles having a free NH occurs at the tertiary nitrogen, as shown in Figure 2.10.[52] The ease by which electrophilic substitution takes place depends on the nature of ring substituents as these affect the electron density at the tertiary nitrogen. The results obtained on attempting to chlorinate



(98)

Scheme 2.22

the adduct 98 or on allowing it to react with $(Me_2N)_2P(O)Cl$ can thus be rationalised by Schemes 2.24 and 2.26 respectively. In the case of the reaction with thionyl chloride two possible electrophiles exist viz. the thionyl chloride itself (Scheme 2.25) and the proton of the HCl (Scheme 2.24). The proposed



(102)

(103)

Scheme 2.23

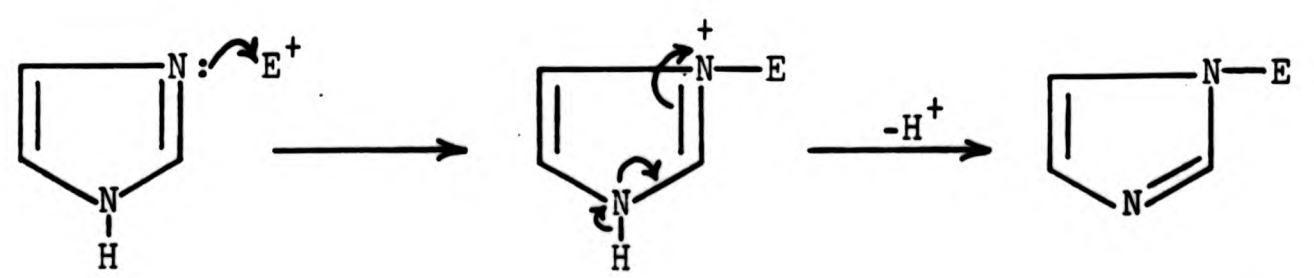
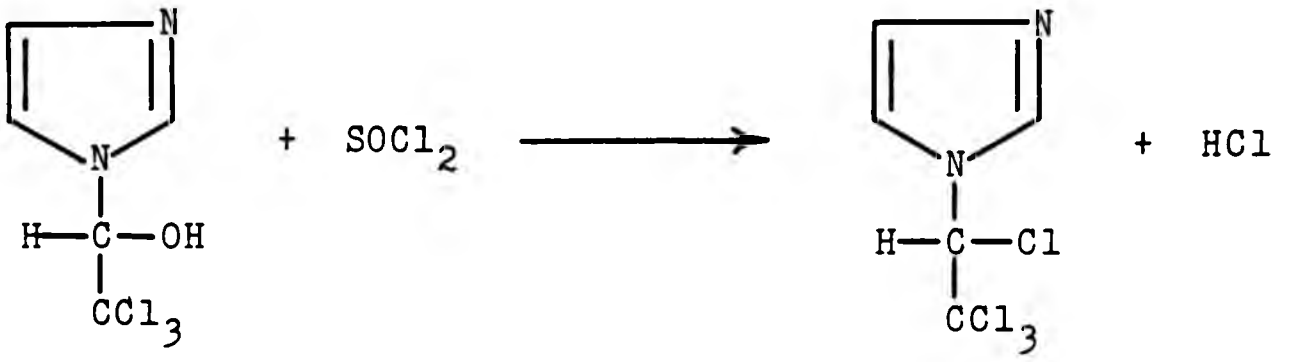
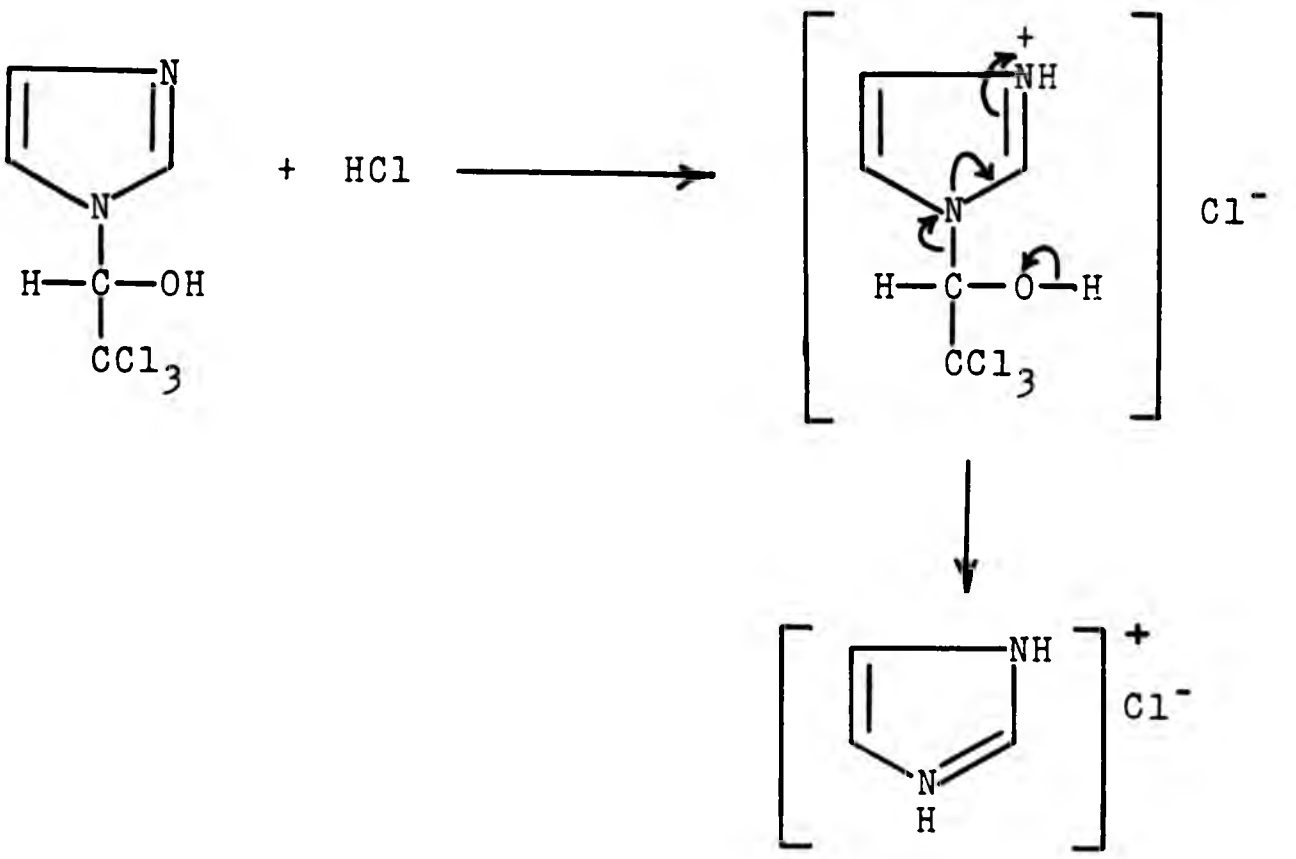


Figure 2.10 Electrophilic substitution of imidazoles.



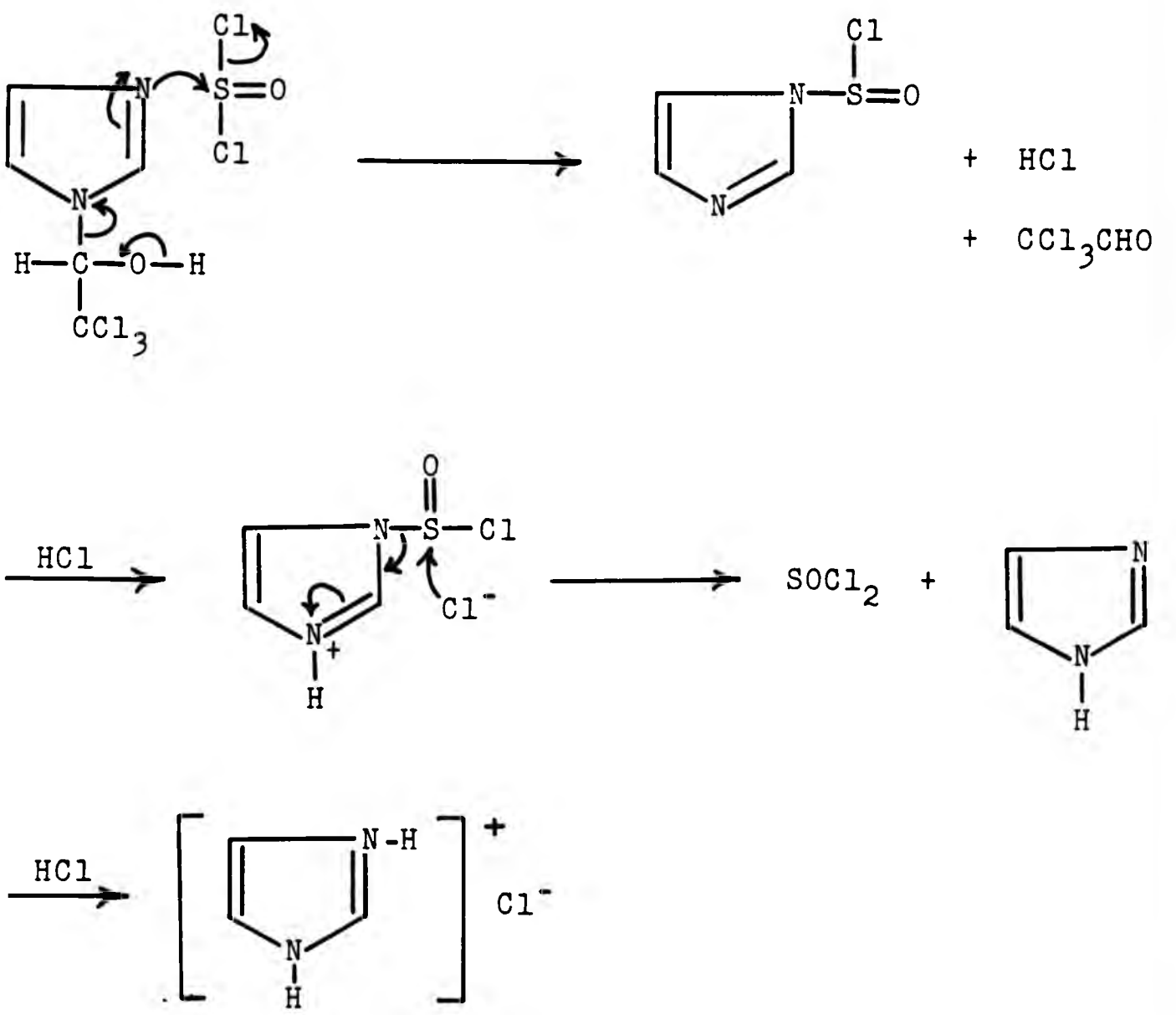
(104)



Scheme 2.24

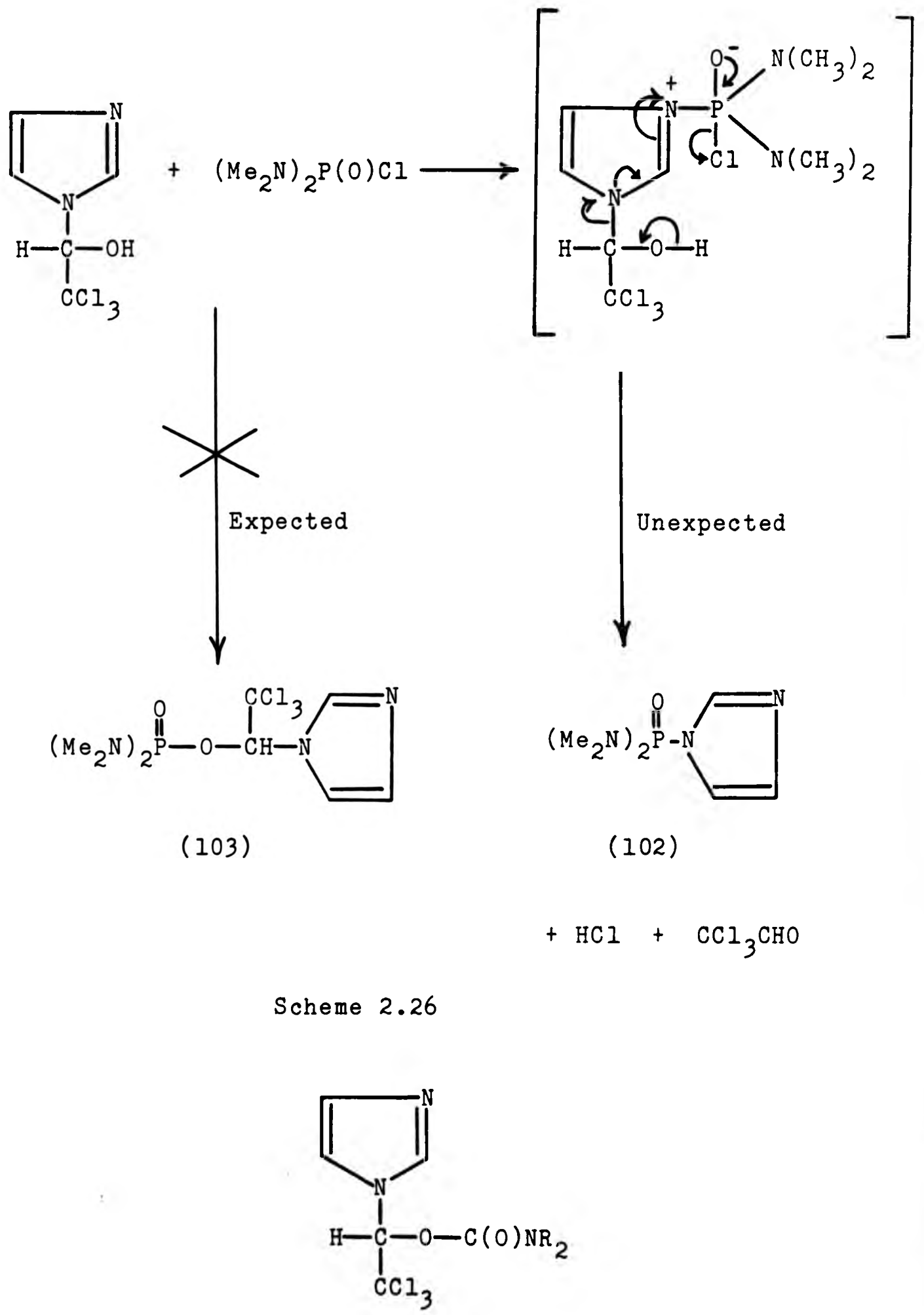
N-(1,2,2,2-tetrachloroethyl)imidazole (104) may also decompose in the presence of HCl and thionyl chloride. In the case of N,N,N',N'-tetramethylphosphorodiamidic chloride the electrophilic centre is the phosphorus (Scheme 2.26) and the results in this case show clearly that the multiply bonded nitrogen

of the imidazole ring is the nucleophile rather than the oxygen of the hydroxy group. This result contrasts with that reported in a Ciba-Geigy patent,[47] which claimed that several compounds of the type 105 were synthesised by treating N-(1-hydroxy-2,2,2-trichloroethyl)imidazole (98) with carbamoyl chlorides $R_2NC(O)Cl$, although no analytical data or yields



Scheme 2.25

were reported. Several attempts by us to repeat the preparation using N,N-dimethylcarbamoyl chloride failed to yield the required



Scheme 2.26

(105)

product (compound type 105, R = Me). In the light of our observations this was to be expected, although no products from the reaction mixture could be isolated in support of electrophilic attack at the multiply bonded nitrogen. ^{1}H N.M.R. studies of the residues did however indicate C-N bond cleavage as the proton of the $-CH(CCl_3)$ group at δ 6.7 could not be detected.

The direct reaction between N-(1-hydroxy-2,2,2-trichloroethyl)imidazole and N,N,N',N'-tetramethylphosphoric triamide was also attempted using Dean and Stark conditions in the hope that the elimination of water would give the desired product, but no detectable reaction occurred.

References

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CHAPTER 3

SPECTROSCOPY

3.1 Infra-red spectroscopy

The infra-red (i.r.) spectra of the following compounds were recorded as KBr discs:

$(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)R$ .....Type A.
$(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)CH_2R^1$ .....Type B.
$(EtO)_2P(O)NHCH(CCl_3)NHC(O)R^2$ .....Type C.

An example illustrating each group of compounds is shown in Figures 3.1, 3.2 and 3.3 respectively. The large number of bands present in these spectra reflect the complexity of these compounds. The only bands which could be assigned with any certainty were those associated with the C=O and P=O groups. These frequencies are shown in Table 3.1.

The variation in the frequency associated with the carbonyl group of compounds of Type A and C reflects the nature of the groups R and R^2 respectively. When R and R^2 have a double bond capable of conjugating with the carbonyl group e.g. 2,4-$Cl_2C_6H_3$, 2-Me-furan-3-yl, 5,6-dihydro-2-methyl-1,4-oxathiin-3-yl amide compounds, a small shift to lower frequencies of 10-15 cm^{-1} was observed. This was the expected effect, but in view of other factors such as crystal form and the possibility of hydrogen bonding, such results cannot be used to draw firm deductions as to the nature of the amide environment. These effects are considered more fully by Bellamy.[1] The introduction of other groups α to the carbonyl group appeared to have little effect on the carbonyl frequency as

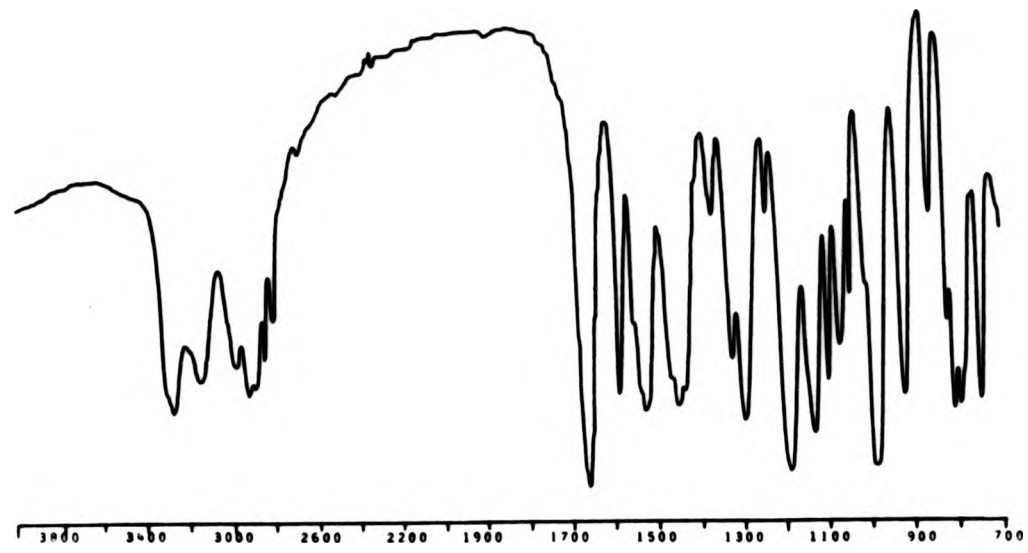


Figure 3.1 IR spectrum of compound A, R= 2,4-$Cl_2C_6H_3$.

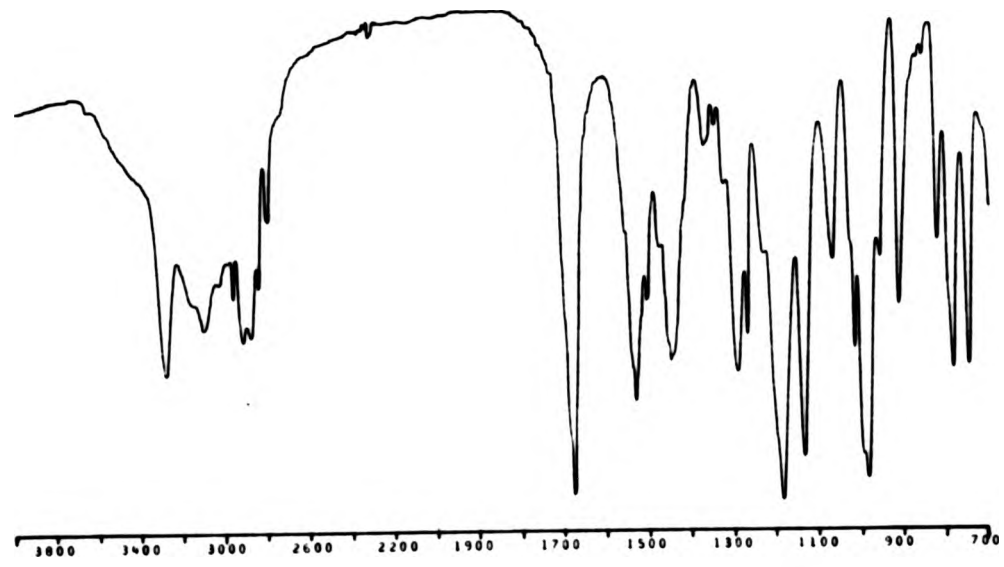


Figure 3.2 IR spectrum of compound B, R^1= triazolyl.

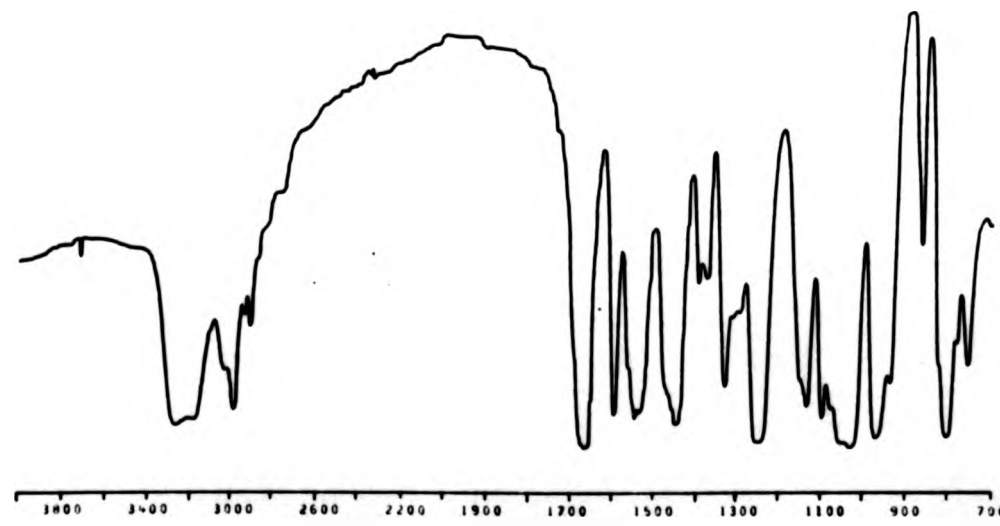


Figure 3.3 IR spectrum of compound C, R^2= 2,4-$Cl_2C_6H_3$.

Compound Type	Frequency cm^{-1}	
	C=O str	P=O str
A	1665 - 1710	1168 - 1200
B	1660 - 1675	1175 - 1190
C	1645 - 1700	1230 - 1245

Table 3.1. Characteristic frequencies of the C=O and P=O groups of compounds of Types A, B and C.

indicated in compounds of Type B. This was the case with a single α - chlorine, but on introduction of the trichloromethyl group a significant shift of 30 cm^{-1} to higher frequency was observed. These latter results are summarised in Table 3.2 and are in accordance with observations of other workers on α-chloro-carbonyl compounds.[33]

Compound Type	R(R_2)	ν cm^{-1} C=O
A	CH_3	1685
A	CH_2Cl	1680
A	CCl_3	1710
C	CH_2Cl	1670
C	CCl_3	1700

Table 3.2. The effect of α -chlorine on the stretching frequency of the carbonyl band in compounds of the Types A and C.

The observed P=O stretching frequencies for the $(Me_2N)_2$-P(O)-NH- group of 1168-1200 cm^{-1} and the $(EtO)_2P(O)$-NH- group of 1230-1245 cm^{-1} are in accordance with results obtained by

other workers.[1,4-6] These workers also showed that by increasing the electronegativity of substituents on phosphorus an increase in the P=O stretching frequency occurred. This would account for the observed difference in the P=O stretching frequency of compounds containing the $(Me_2N)_2P(O)$-NH- and $(EtO)_2P(O)$-NH- groups, the higher frequency of the latter being due to the more electronegative ethoxy groups.

3.2 Ultra-violet spectroscopy

The ultra-violet (UV) spectra of N,N,N',N'-tetramethylphosphoric triamide (I, $(Me_2N)_2P(O)NH_2$), N,N,N',N'-tetramethyl-N''-(2,2,2-trichloro-1-acetamidoethyl)phosphoric triamide (II, $(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)CH_3$), N-(1,2,2,2-tetrachloroethyl)-acetamide (III, $CCl_3CH(Cl)NHC(O)CH_3$) and N-(2,2,2-trichloroethylidene)acetamide (IV, $CCl_3CH{=}NC(O)CH_3$) were recorded during the course of this project. The data are summarised in Table 3.3.

Compound	Wavelength λ_{max}/nm	Intensity ε_{max}/m^2 mol^{-1}	Assignment
I	242	1.99	$n \rightarrow \pi^*$ P=O
II	242	2.80	$n \rightarrow \pi^*$ P=O & C=O
III	242	2.56	$n \rightarrow \pi^*$ C=O
IV	252	21.31	—
	268	16.49	—

Table 3.3. Ultra-violet spectral data obtained for compounds I-IV (see this page).

The low intensity band at λ_{max} 242 nm observed for compounds

I, II and III has been assigned to the $n \longrightarrow \pi^*$ transition of the carbonyl group and/or the phosphoryl group. The UV spectrum of N-(2,2,2-trichloroethylidene)acetamide shows two bands at λ_{max} 252 and 268 nm the latter being in the form of a shoulder. The low intensity of these bands indicates that they are either due to $n \longrightarrow \pi^*$ or $n \longrightarrow \sigma^*$ transitions, of the azomethine (C=N) and carbonyl groups. The higher ε values of IV would seem to indicate $n \longrightarrow \sigma^*$ transitions. However little appears to be known about the electronic spectra of carbonyl compounds conjugated with an azomethine group and such systems will need further investigation before firm conclusions can be drawn as to which transitions are responsible for the observed bands. The electronic spectra of azomethine compounds have been reviewed[7] but no mention is made of conjugation to a carbonyl group.

3.3 ^{1}H, ^{13}C and ^{31}P Nuclear magnetic resonance spectroscopy

The ^{1}H, ^{13}C and ^{31}P nuclear magnetic resonance (NMR) spectra of the following phosphoric acid amides are reported:

$(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)R$ .....Type D.
$(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)CH_2R^1$ .....Type E.
$(Me_2N)_2P(O)NHCH(CCl_3)OR^2$ .....Type F.
$(EtO)_2P(O)NHCH(CCl_3)NHC(O)R^3$ .....Type G.

Only the general features of the ^{1}H and ^{13}C NMR spectra of these compounds will be discussed. The signals originating from the groups R, R^1, R^2 and R^3 will be discussed only if

they are of special interest. The assignment of the signals originating from these groups can be found in the experimental section of this thesis (Chapter 5). The ^{1}H, ^{13}C and ^{31}P NMR spectra of certain intermediates have also been recorded and interpreted. These will not be considered here. The reader is referred to Appendix 2 (p.A14) for a list of such intermediates and a reference to the section in which their spectral data can be found.

3.3.1 ^{1}H NMR spectroscopy

The general ^{1}H NMR chemical shifts and coupling constants observed for compounds of Types D, E, F and G are summarised in Tables 3.4, 3.5, 3.6 and 3.7 respectively. A typical spectrum for each type of compound is shown in Figures 3.4, 3.5, 3.6 and 3.7 respectively.

In the diethoxy phosphoryl compounds of Type G the signal due to the methylene protons of the ethoxy group (CH_3-$\underline{CH}_2$-O-) appears as a doublet of quintets as shown in Figure 3.7. The presence of two signals indicates that the methylene protons are non-equivalent. The multiplicity of these signals appears to be much simpler than that predicted from theoretical considerations. In a study of systems containing non-equivalent methylene protons Hudson *et al.*[8] and other authors[9-11] have shown that geminal coupling of 9-10 Hz exists which results in AB spectra. In compounds of Type G the presence of geminal coupling would result in signals with at least 16 lines for each non-equivalent proton due to further coupling to the methyl protons and phosphorus (all the methylene protons in

Group	Chemical Shift (δ)[a]	Multiplicity	Coupling Constant (J Hz)
$(Me_2N)_2P(O)$-	2.51 - 2.55	dd	$^3J_{PNCH}$ 10.2
-NH-	4.69 - 5.21	dd[b]	-
-CH-	5.71 - 5.87	m	$^3J_{PNCH}$ 10.5-11.5
-NHC(O)-	7.94 - 9.34	d[c]	$^3J_{HNCH}$ 8.3-9.3

Table 3.4 The general ^1H NMR signals of compounds of Type D, $(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)R$.

a All spectra were recorded in DMSO-d_6 unless otherwise stated.
b Overlapping.
c Not resolved when R=CCl_3 group.
d When R^1=OC_4H_9 and triazolyl group the signal was present as two singlets. The reasons for this are discussed later (See p. 119) .
e Spectrum recorded in $CDCl_3$.

Group	Chemical Shift (δ)[a]	Multiplicity	Coupling Constant (J Hz)
$(Me_2N)_2P(O)$-	2.51 - 2.52	dd	$^3J_{PNCH}$ 10.2
-NH-	4.96 - 5.31	dd[b]	-
-CH-	5.75 - 5.76	m	$^3J_{PNCH}$ 10.2-11.0
-NHC(O)-	7.98 - 8.79	d	$^3J_{HNCH}$ 8.8-10.9
$-C(O)CH_2-$	3.25 - 5.1	s[d]	-

Table 3.5 The general ^1H NMR signals of compounds of Type E, $(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)CH_2R^1$. (See Table 3.4 for footnotes).

Group	Chemical Shift (δ)	Multiplicity	Coupling Constant (J Hz)
$(Me_2N)_2P(O)$-	2.7[e] 2.6	dd	$^3J_{PNCH}$ 10.0-10.2
-NH-	3.2[e] 5.4	dd[b] dd[b]	- -
-CH-	5.0[e] 4.8	dd dd	- $^3J_{PNCH}$ 7.8-8.1

Table 3.6 The general ^1H NMR signals of compounds of Type F, $(Me_2N)_2P(O)NHCH(CCl_3)OR^2$. (See Table 3.4 for footnotes).

Group	Chemical Shift (δ)[a]	Multiplicity	Coupling Constant (J Hz)
$\underline{CH_3}CH_2$-O-	1.18 - 1.23	t	$^3J_{HCCH}$ 7.1
$CH_3\underline{CH_2}$-O-	3.95 - 4.00	dq	-
-P-<u>NH</u>-<u>CH</u>-	5.64 - 5.94	m	$^3J_{PNCH}$ 10.7-12.2
-NHC(O)-	8.27 - 9.33	d[c]	$^3J_{HCNH}$ 7.8-9.3

Table 3.7 The general ^1H NMR signals of compounds of Type G, $(EtO)_2P(O)NHCH(CCl_3)NHC(O)R^3$. (See Table 3.4 for footnotes).

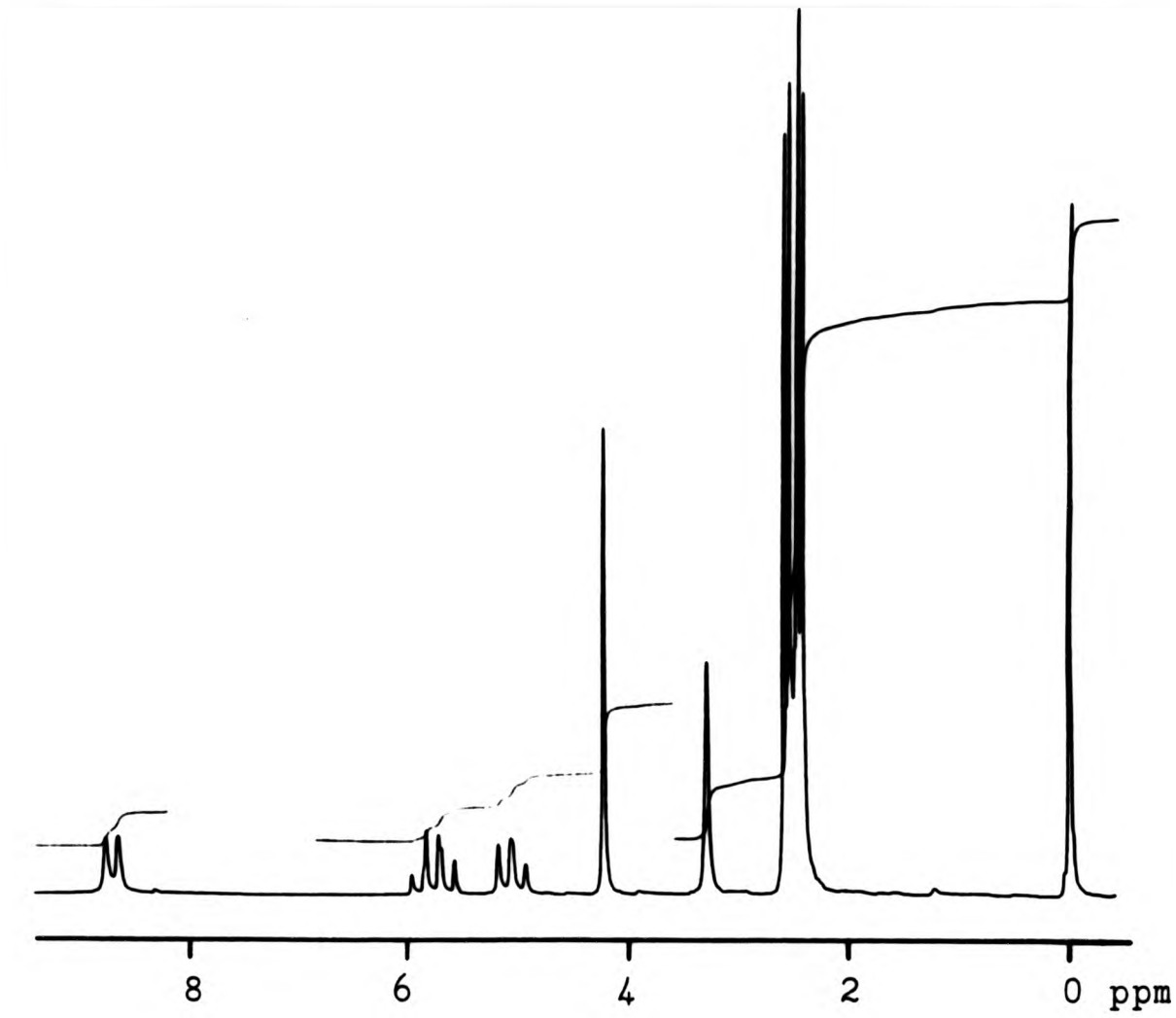


Figure 3.4 ^{1}H spectrum of compound D, R= CH_2Cl.

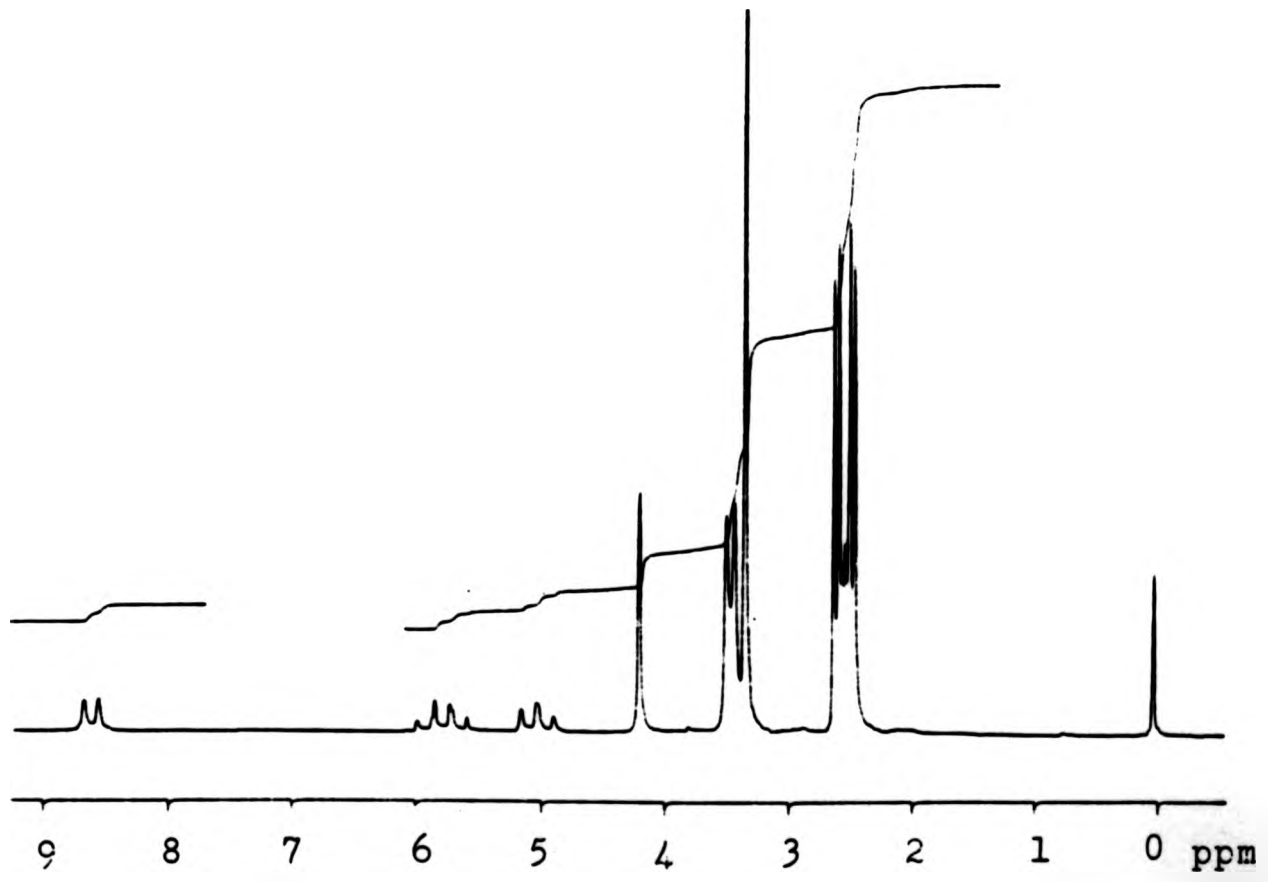


Figure 3.5 ^{1}H spectrum of compound E, R^1= $SC(S)NMe_2$.

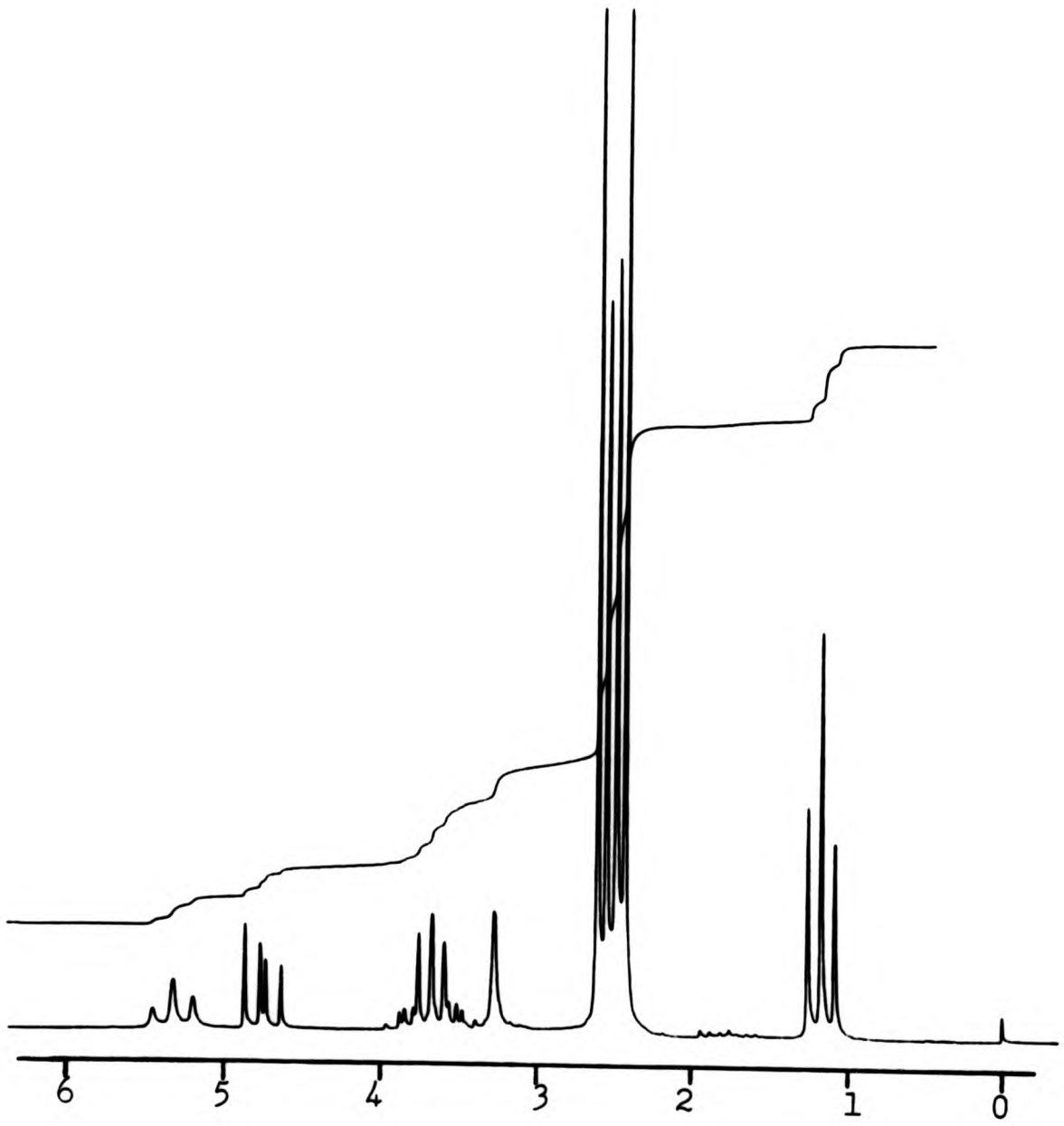
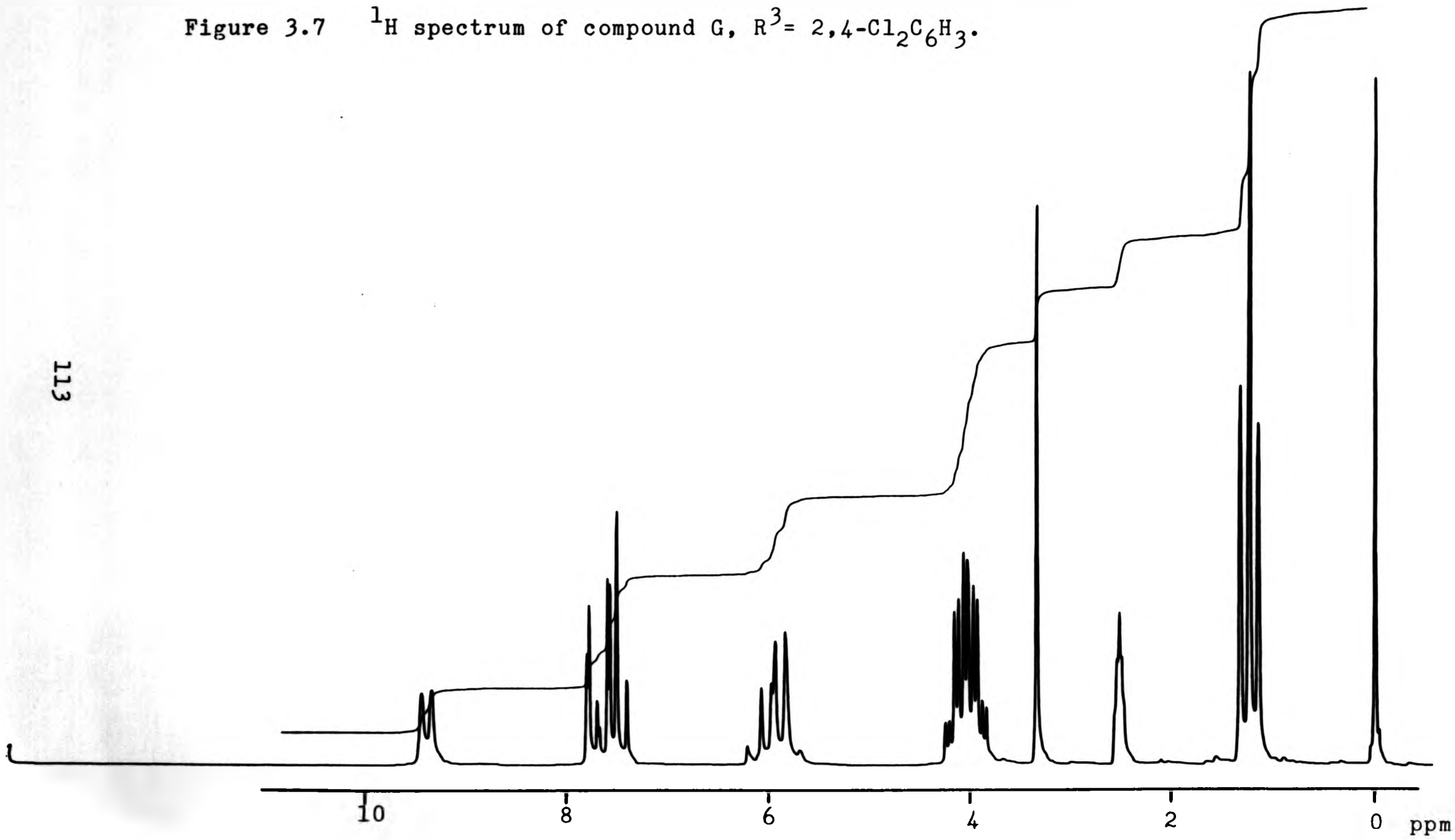


Figure 3.6 ^{1}H spectrum of compound F, R^{2}= OEt.

Figure 3.7 ^{1}H spectrum of compound G, R^{3}= 2,4-$Cl_2C_6H_3$.



compounds of Type G are predicted to be non-equivalent due to the presence of the chiral methine group, see later discussion). Hudson *et al.*[8] showed that the methylene protons of ethyl chlorosulphite (EtOS(O)Cl) gave rise to a signal approximating to two overlapping quartets, as have been observed for diethyl sulphite ($[EtO]_2S{=}O$),[11] although a detailed examination of the NMR spectrum of the latter showed that it was best analysed as an ABC_3 system.[10] In the case of diethyl sulphite the appearance of the signal as overlapping quartets was shown by Waugh *et al.*[9] to arise due to the difference in the chemical shifts of the non-equivalent protons being accidently so small that the additional lines were weak and could not be seen. Calculations by these workers based on a 0.05 ppm difference in the chemical shift of the geminal protons and geminal coupling of 10 Hz showed that the satellite lines would have intensities of 1-2% of the central components. Thus it would appear that in compounds of Type G the difference in the chemical shifts of the non-equivalent protons are accidently very small resulting in unobservable satellite peaks and effectively giving signals in which geminal coupling cannot be seen. If this is assumed to be the case, coupling to the methyl protons and phosphorus should yield signals with eight lines and the fact that signals appear as quintets indicates that $^3J_{HCCH} \approx {}^3J_{POCH} \approx$ 7 Hz. Non-equivalence of methylene protons is a common feature of tetraco-ordinated phosphorus and has been observed by other authors.[12-15] The reasons for such non-equivalence have been reported.[16-18] The non-equivalence within one group arises by its interaction with another of low symmetry (examples of such low symmetry groups are carbon and phosphorus carrying

three or four different substituents). The terminology used by Jennings[16] will be used during this discussion. A close examination of the diethoxy phosphoryl compounds synthesised (Type G) shows the existence of two types of prochiral centre, the phosphorus and the methylene group (Figure 3.8, marked with •) and one chiral centre, the methine group (marked with *). The phosphorus being linked *via* the nitrogen to the methine carbon can lead to the chemical shift non-equivalence of the ethoxy groups. However, as the methylene groups are linked to

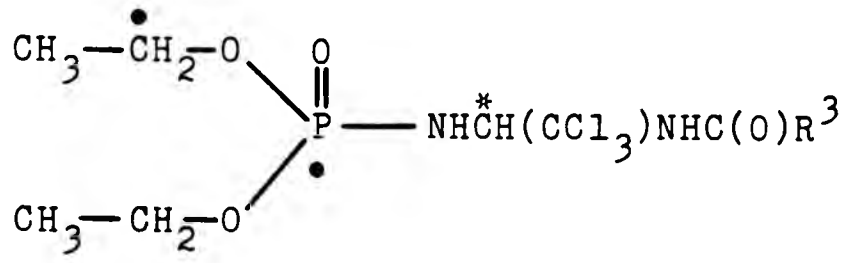
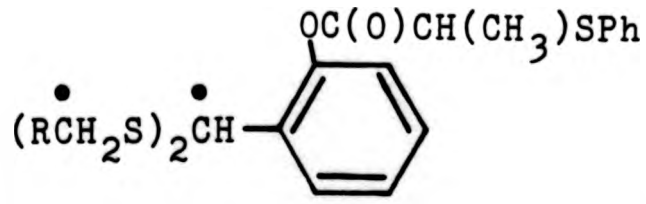


Figure 3.8. Diagram to show the two prochiral and chiral centres of our ethoxy compounds.

the phosphorus (which carries three different groups) *via* the oxygen, the geminal protons of these groups would be expected to be non-equivalent (anisochronous). Compounds containing two prochiral centres (106) have been studied[19-20] and found to show four signals for the geminal protons of the methylene groups. This effect has been described as "double



(106)

non-equivalence".[16] From the preceding discussion it would be expected that our diethoxy compounds would show double non-equivalence and that the four geminal protons of the methylene groups would give rise to four signals, each being split into a quintet by the methyl group and phosphorus. This effect is shown in Figure 3.9. The non-equivalence of the ethoxy

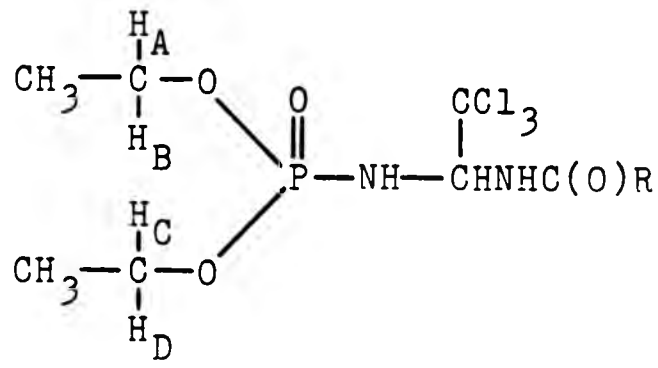


Figure 3.9. Structure showing the non-equivalence of the geminal protons of the methylene groups.

groups was indicated by ^{13}C NMR spectroscopy of these compounds which shows the signal due to the methylene groups as an overlapping doublet of doublets. This confirms the non-equivalence of the carbons and thus that of the ethoxy groups. The fact that only two overlapping signals appear for the geminal methylene protons instead of the predicted four indicates that the difference in the chemical shift between the protons H_A and H_B and that of protons H_C and H_D is very small thus resulting in much simpler spectra (i.e. overlapping quintets) than expected from theoretical considerations.

The observed non-equivalence of the dimethylamido groups in bis(dimethylamido)phosphoryl compounds can also be explained as follows: these compounds contain a prochiral phosphorus but

may also possess a second prochiral centre at the dimethylamido nitrogen if the pyrimidal inversion at nitrogen is slow on the time scale of the NMR experiment. The presence of two prochiral centres would be anticipated to give four signals for the methyl groups which would then be split into doublets by phosphorus. Only two doublets are observed in the ^{1}H NMR spectrum and only a single doublet in the ^{13}C spectrum for the bis-(dimethylamido)phosphoryl group. This would indicate that only one prochiral centre (the phosphorus) is present or that again chemical shifts are fortuitously the same for the different methyl groups.

The proton signal due to the amido proton of the -P-NH-CH- group of compounds of Types D, E, F and G was observed as an overlapping doublet of doublets which had a variable position. The position was greatly influenced by the solvent used. It exchanged slowly with D_2O. Where the compound had low solubility CD_3OD was used instead to avoid precipitation of the sample. The multiplicity of the signal arises from coupling to the methine (-CH-) proton and the phosphorus, and could sometimes be resolved into two separate doublets as shown in Figure 3.10. The variations in the shift of the signal are

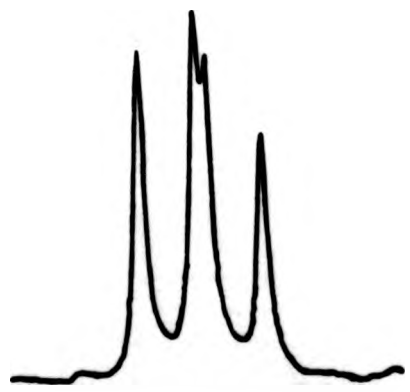


Figure 3.10. Signal for the amido proton demonstrating that it can be resolved into a doublet of doublets.

caused by differences in the degree of association through hydrogen-bonding between solute-solute and solvent-solute molecules. This association is concentration dependent. Such variations in the shifts of acidic protons e.g. those in -OH, $-NH_2$, -SH groups are a known feature of NMR spectroscopy.

The methine proton of compounds of Types D and E appears as a multiplet due to coupling to phosphorus, the phosphoramido proton, and the acetamido proton. Exchange of the acidic phosphoramido and acetamido protons using D_2O or CD_3OD reduces the signal to a doublet due to coupling to phosphorus ($^3J_{PNCH}$ 11 Hz). In the case of compounds of Type F in which no acetamido proton is present the signal appears as a doublet of doublets due to coupling to phosphorus and phosphoramido proton. In this case exchange of the phosphoramido proton using D_2O or CD_3OD reduces the signal to a doublet ($^3J_{PNCH}$ 8 Hz). As would be expected replacement of the -NHC(O)R group by -OR on the methine carbon affects the position of the chemical shift (moving the signal to higher field) and the coupling constant (see Table 3.4 and 3.6 for comparison). The signal due to the methine proton of compounds of Type G is further complicated by the fact that it overlaps with the signal from the phosphoramido proton when DMSO-d_6 is used as the solvent. This was confirmed by D_2O (or CD_3OD) exchange which resulted in the signal becoming a sharp doublet ($^3J_{PNCH}$ 11 Hz) corresponding to one proton by integration.

The signal for the acetamido proton of compounds of Types D, E and G appears as a broad doublet which is removed by D_2O (or CD_3OD) exchange. The doublet arises from coupling to the methine proton. As with the phosphoramido proton the

shift is variable. The reasons for this have been discussed previously. In compounds of Types D and G when R = R^3 = CCl_3 the doublet for this proton is not resolved and the signal appears as a broad singlet.

In compounds of Type E the methylene group of the -NHC(O)$\underline{CH_2}R^1$ moiety was generally observed as a singlet under the NMR conditions used. The chemical shift of this signal depended on the nature of R^1. However when R^1 was a butoxy or triazolyl group the signal appeared to be split into a doublet. In the case of the butoxy group this observation can be explained on the basis of the non-equivalence of geminal groups in prochiral centres. It has been shown that geminal non-equivalence can occur even if the prochiral and chiral centres are separated by upto 4 atoms.[21,22] Table 3.8 illustrates this point more clearly and shows that an increase in the distance between

$$(CH_3)_2\overset{\bullet}{C}H\text{- (X)- }\overset{*}{C}H(CH_3)Ph$$

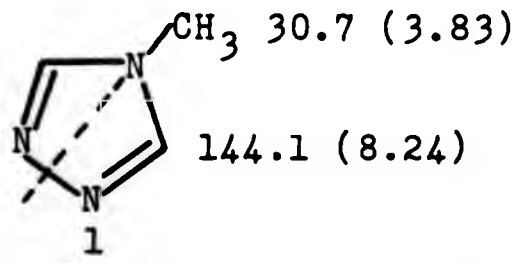
(107)

X	$\Delta\delta$ ppm	
	(CCl_4 soln.)	(benzene soln.)
—	0.182	0.133
-O-	0.067	0.013
$-OCH_2-$	0.005	0.008
$-OCH_2CH_2-$	0.042	0.030
$-OCH_2CH_2O-$	0.000	0.013
$-OCH_2CH_2OCH_2-$	0.000	0.000

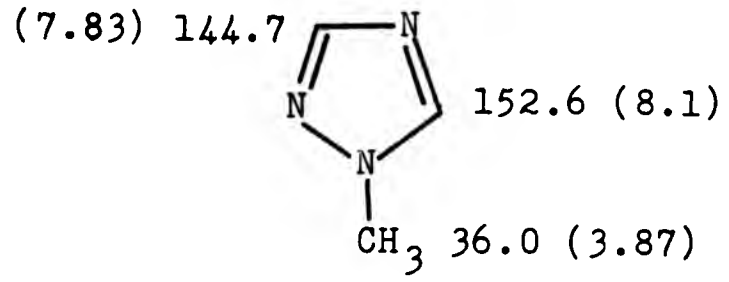
Table 3.8. Effects of distance between the prochiral and chiral centres on the observed geminal methyl non-equivalence ($\Delta\delta$) in compounds of Type 107.[21]

the prochiral and chiral centres generally reduces the non-equivalence although there is a reverse when X = 3 atoms. This latter point has been discussed by Jennings.[16] From this, one would expect that the geminal hydrogens of the methylene group of the $-NHC(O)CH_2R^1$ moiety should be non-equivalent as the chiral $-NH\overset{*}{C}H(CCl_3)NH-$ moiety is separated from it by only 2 atoms. Why this non-equivalence of the geminal protons of the methylene group was only observed when R^1 = butoxy is unclear.

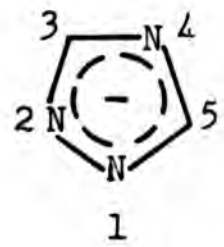
In the case when R^1 = 1,2,4-triazolyl the reasons for the appearance of two signals for the methylene group, at δ_H 4.94 and 5.07, are quite different. In addition to these two signals, three signals were observed in the triazolyl region of the spectrum at δ_H 7.98, 8.44 and 8.52. This indicated that two isomeric compounds were present which only differed in the way the triazolyl group was attached to the methylene moiety. These observations were supported by ^{13}C NMR data which showed two signals at δ_C 46.4 and 51.0 for the methylene group and three signals in the triazolyl region, δ_C 143.9, 145.5 and 151.5. A literature search showed that substitution at the 4 position by methyl in 1,2,4-triazoles results in only one signal in the ^1H NMR spectrum and one in the ^{13}C spectrum for the triazole ring due to a plane of symmetry as shown below. (The figures in brackets refer to the ^1H chemical shifts)[23,24] :



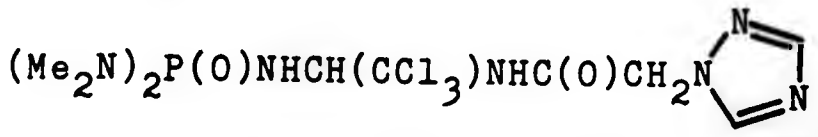
Substitution at the 1 or 2 position (which are equivalent) removes this plane of symmetry and gives rise to two signals for the protons and two for the carbons.[23,24]



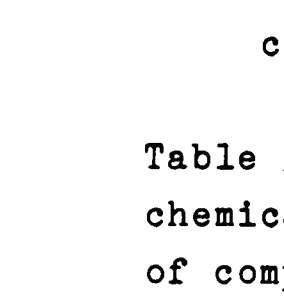
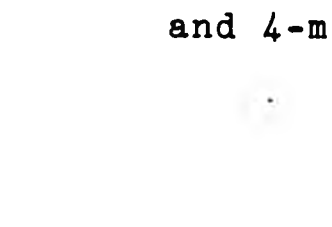
The production of isomeric triazolyl compounds in our synthesis of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-triazolylacetamidoethyl)phosphoric triamide can be explained by considering the 1,2,4-triazolyl anion, which was used in this reaction to have the resonance structure shown below with the negative charge delocalised. This would then allow nucleophilic attack



by any of the nitrogen atoms, with attack at N^1 and N^2 yielding the same isomeric compound as these positions are equivalent. The assignment of structures to the 1- and 4-substituted isomers of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-triazolylacetamidoethyl)phosphoric triamides (108 and 109) has been based on the ^1H NMR[23] and ^{13}C NMR[24] shifts of 1- and 4-methyl-1,2,4-

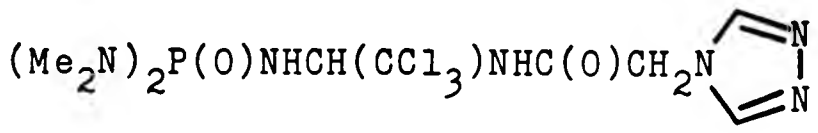


(108)

Structure*	Chemical shift (ppm)					
	^{1}H			^{13}C		
	CH_3	(CH_2R) H_A	H_B	CH_3	(CH_2R) H_A	H_B
	3.83[23]	8.24	8.24	30.7[24]	144.1	144.1
	4.94	8.44	8.44	46.4	143.9	143.9
	3.87[23]	7.83	8.10	36.0[24]	144.7	152.6
	5.07	7.98	8.52	51.0	145.5	151.5

* $-CH_2R$ corresponds to the methylene group of compounds 108 and 109.

Table 3.9 Comparison of observed ^{1}H and ^{13}C NMR chemical shifts for the methylene and triazolyl groups of compounds 108 and 109 with those reported for 1- and and 4-methyl substituted triazoles.



(109)

triazoles. The comparisons are shown fully in Table 3.9. Although a direct comparison of the chemical shifts of the methyl group and methylene group cannot be made, it can be seen that both the ^{1}H and ^{13}C signals for the methyl group of the 1-isomer appear further downfield than those for the 4-methyl isomer. Thus the signal originating from the methylene group at δ_H 5.07 can be assigned to the 1-isomer (108) and that at δ_H 4.94 to the 4-isomer (109). As can be seen from Table 3.9 the ^{1}H and ^{13}C chemical shifts of the 1- and 4- substituted triazolyl groups of compounds 108 and 109 are in good agreement with those of 1- and 4-methyl-1,2,4-triazole. The N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-triazol-1-yl-acetamidoethyl)phosphoric triamide (108) was found to be the major component, in agreement with the results of Atkinson et al.[25] who showed that alkylation of 1,2,4-triazole by methyl iodide in the presence of sodium methoxide in methanol gave the 1-methyl isomer (65%) as the major product.

3.3.2 ^{13}C NMR spectroscopy

The general ^{13}C chemical shifts and coupling constants due to phosphorus-carbon coupling for compounds of Types D, E, F and G are shown in Tables 3.10, 3.11, 3.12 and 3.13 respectively. Characteristic spectra for each type of compound are

Group	Chemical Shift (δ)[a]	Multiplicity	Coupling Constant (J Hz)
$(Me_2N)_2P(O)$-	36.1-36.2	d	$^2J_{PNC}$ 3.4-4.0
-CH-NH-	67.6-71.3	d	$^2J_{PNC}$ 4.4-5.4
$-CCl_3$	102.9-104.0	d	$^3J_{PNCC}$ 8.8-11.0

Table 3.10 The general ^{13}C NMR signals for compounds of Type D, $(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)R$.

a) All chemical shifts determined in DMSO-d_6 unless otherwise stated.

b) Chemical shift determined in $CDCl_3$.

Group	Chemical Shift (δ)[a]	Multiplicity	Coupling Constant (J Hz)
$(Me_2N)_2P(O)$-	36.2	d	$^2J_{PNC}$ 3.4-4.4
-CH-NH-	68.5-69.5	d	$^2J_{PNC}$ 5.1-5.9
$-CCl_3$	103.1-103.8	d	$^3J_{PNCC}$ 9.6-10.9
$-CH_2R^1$	34.7-70.8	s	-

Table 3.11 The general ^{13}C NMR signals for compounds of Type E, $(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)CH_2R^1$. (See footnotes above).

Group	Chemical Shift (δ)[a]	Multiplicity	Coupling Constant (J Hz)
$(Me_2N)_2P(O)$-	36.3 36.7[b]	d	$^2J_{PNC}$ 4.1
-CH-OR^2	91.0-92.7	d	$^2J_{PNC}$ 5.4-6.1
$-CCl_3$	101.8-102.2	d	$^3J_{PNCC}$ 9.5-10.2

Table 3.12 The general ^{13}C NMR signals for compounds of Type F, $(Me_2N)_2P(O)NHCH(CCl_3)OR^2$. (See Table 3.10 for footnotes).

Group	Chemical Shift (δ)[a]	Multiplicity	Coupling Constant (J Hz)
$\underline{CH_3}$-CH_2-O-	15.8-15.9	d	$^3J_{POCC}$ 6.6-8.1
CH_3-$\underline{CH_2}$-O-	61.9-62.4	dd	$^2J_{POC}$ 5 - 6
-CH-NH-	67.7-71.4	d	$^2J_{PNC}$ 3.7-5.1
$-CCl_3$	101.9-103.0	d	$^3J_{PNCC}$ 10.4-13.2

Table 3.13 The general ^{13}C NMR signals for compounds of Type G, $(EtO)_2P(O)NHCH(CCl_3)NHC(O)R^3$. (See Table 3.10 for footnotes).

shown in Figures 3.11, 3.12, 3.13 and 3.14 respectively.

The signal for the bis(dimethylamido)phosphoryl group of compounds of Types D, E and F appears as a doublet due to coupling to phosphorus ($^2J_{PNC}$ 4 Hz) at δ 36.2 when the spectra were recorded in DMSO-d_6. However in compounds of Type F the position of the signal was found to be solvent dependent, being observed at δ 36.7, in $CDCl_3$ but at the "normal" position, δ 36.2, when using DMSO-d_6.

The position of the methine carbon signal of compounds of Types D and F was found to be influenced by the nature of the groups R and R^2, probably because of their close proximity to the methine carbon. A downfield shift of the methine carbon signal occurs when the -NHC(O)X moiety is replaced by $-OR^2$ as in compounds of Type F, as a result of greater deshielding by the more electronegative oxygen. The signal always appears as a doublet due to coupling over two bonds to phosphorus ($^2J_{PNC}$ 4-6 Hz).

The signal for the trichloromethyl group of compounds of Types D, E, F and G appears at δ 102-104 and is a doublet due to coupling over three bonds to phosphorus ($^3J_{PNCC}$ 9-13 Hz). Variations in the chemical shift, although small, appear to be caused by structural changes and may be large enough to allow prediction of the chemical environment of this group (see Chapter 2 p. 44)

e.g.	$-CH(CCl_3)-NHX$	δ 101.9 - 104.0
	$-CH(CCl_3)-OR_2$	δ 101.8 - 102.2

Signals for the carbon atoms of the ethoxy groups of

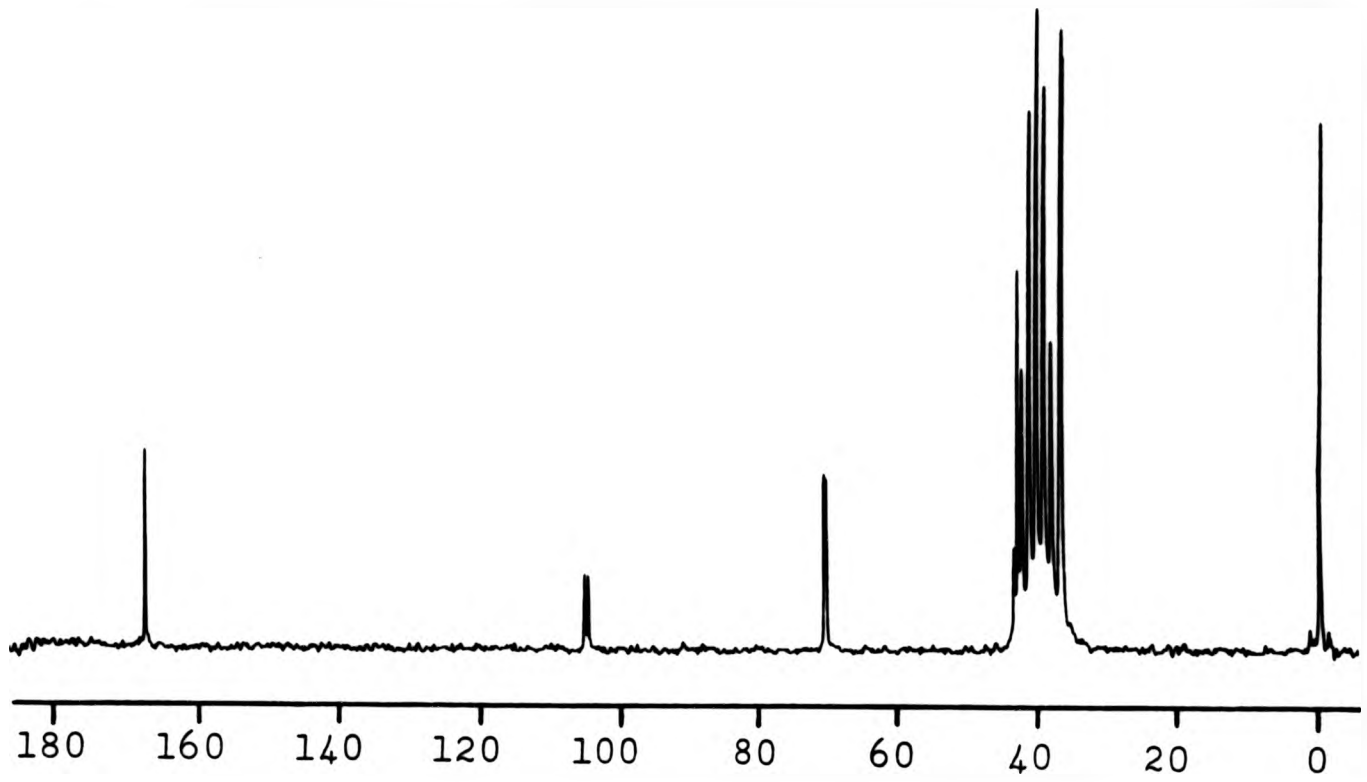


Figure 3.11 ^{13}C spectrum of compound D, R= CH_2Cl.

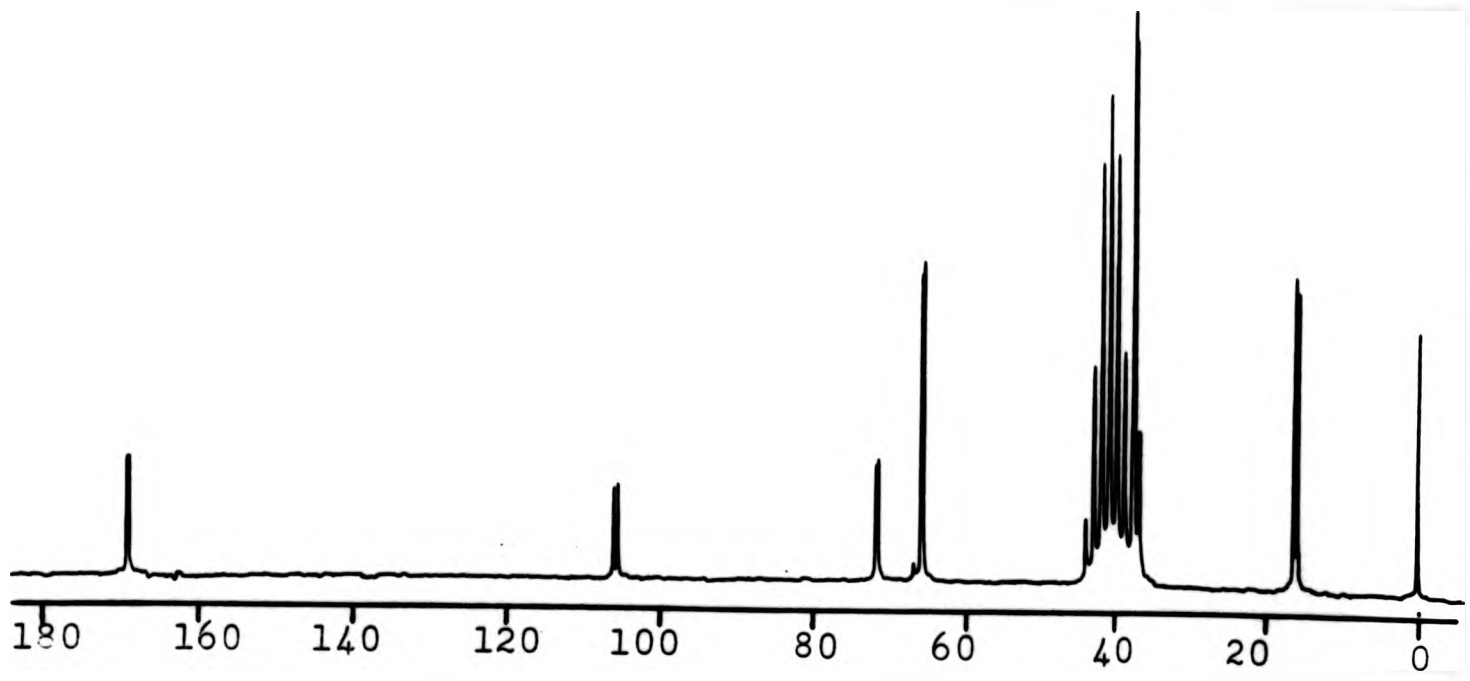


Figure 3.12 ^{13}C spectrum of compound E, R^1= $S_2P(OEt)_2$.

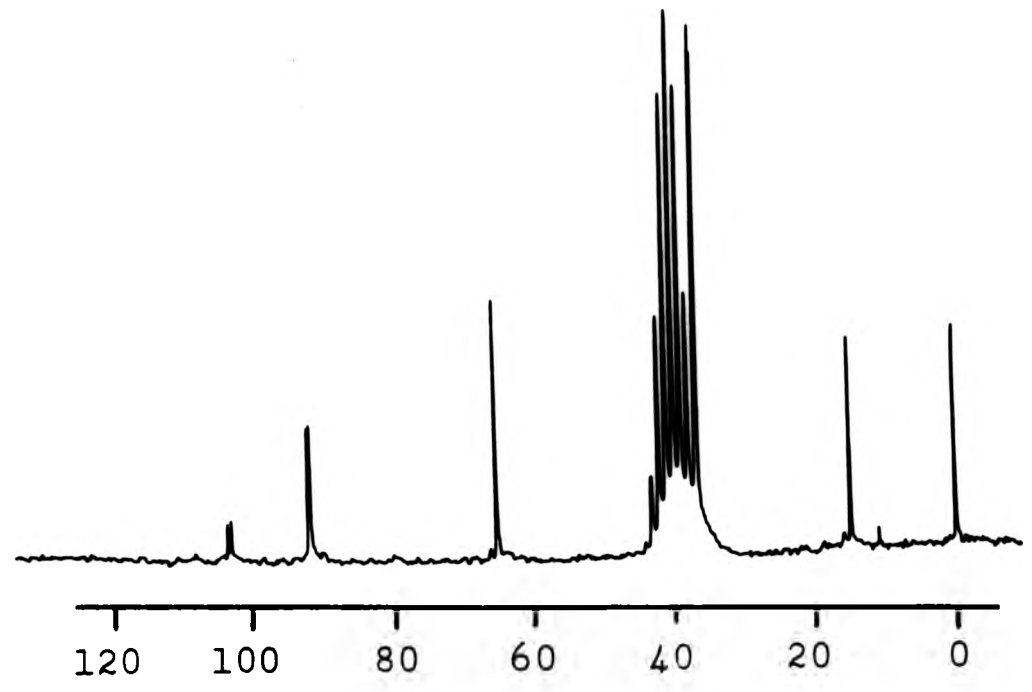


Figure 3.13 ^{13}C spectrum of compound F, R^2= OEt.

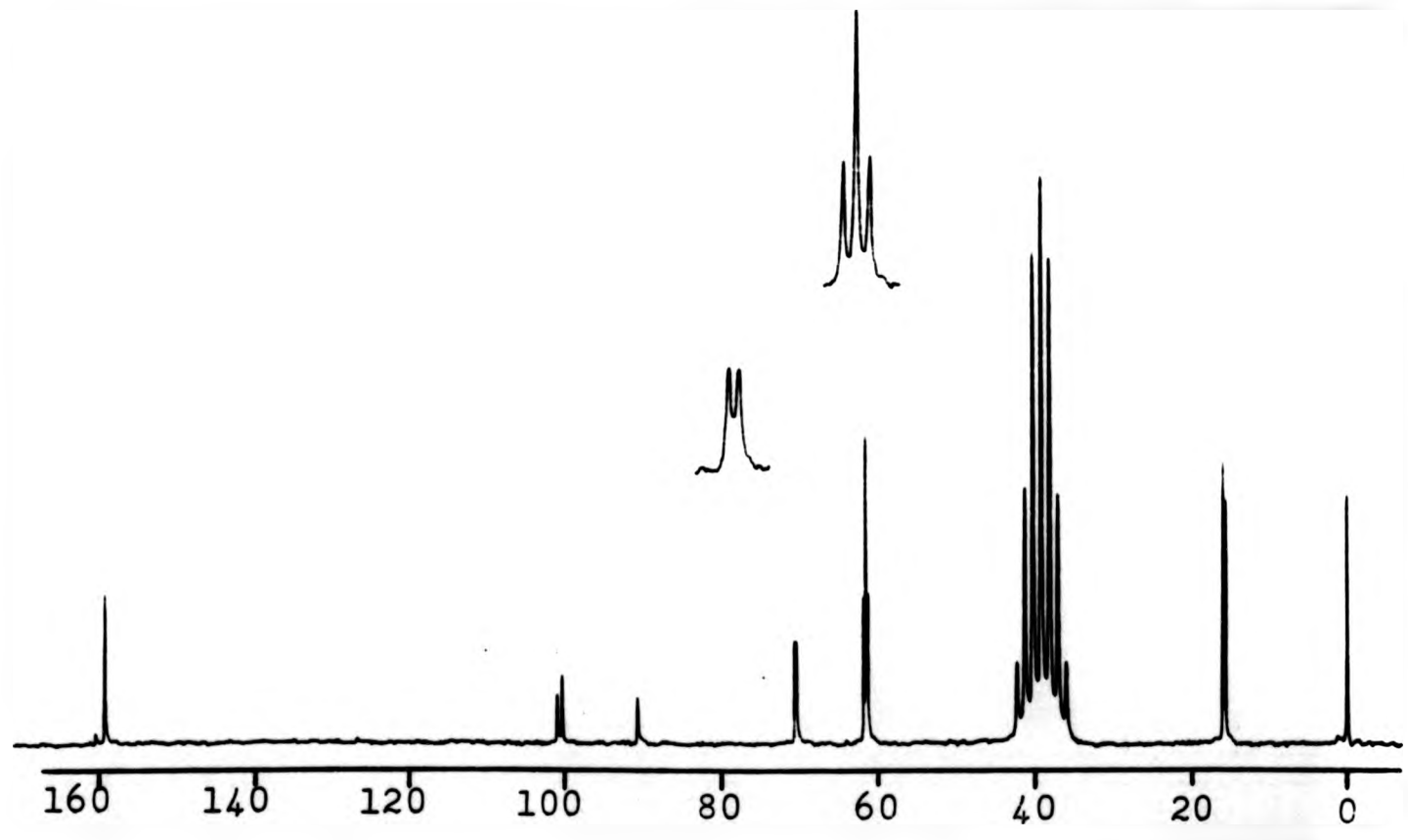


Figure 3.14 ^{13}C spectrum of compound G, R^3= CCl_3.

compounds of Type G occur at δ 15.9 (CH_3-) and at 62 (-CH_2-O-) and appear as a doublet ($^3J_{POCC}$ 7-8 Hz) and an overlapping doublet of doublets ($^2J_{POC}$ 5 Hz) respectively, due to coupling over two and three bonds to phosphorus. The multiplicity of the signal due to the methylene carbons is due to their non-equivalence (see section 3.3.1 p. 108).

An interesting observation was the variation in the chemical shift of the terminal methylene group of compounds of Type E. As would be expected this depended on the type of heteroatom linked to this group and the nature of the group R^1 containing the heteroatom. This variation is summarised in Table 3.14 and is due to the shielding or deshielding effects

Group (R^1)	δ CH_2
Cl	42.2
OC_4H_9	70.8
$SC_{12}H_{25}$	34.7
$SC(S)OC_2H_5$	38.7
$SC(S)NMe_2$	39.9
$SC(S)NEt_2$	40.6
$SP(S)(OEt)_2$	35.5
1,2,4-triazol-4-yl	46.4
1,2,4-triazol-1-yl	51.0

Table 3.14. The variation of the chemical shift position of the terminal methylene group of compounds of Type E, $(Me_2N)_2P(O)NHCH(CCl_3)NHCOCH_2R^1$.

caused by a) variations in the electronegativity of the groups, and b) anisotropic effects when the group contains π-electrons.

During this study it was found that two-bond phosphorus-carbon coupling ($^2J_{PXC}$ 3-6 Hz; X=O or N) was smaller than three bond phosphorus-carbon coupling ($^3J_{PXCC}$ 7-13 Hz; X=O or N). It would be anticipated that the further apart two coupling nuclei are the smaller the coupling interaction. This unusual effect has been observed in other phosphorus compounds[26] and a number of organometallic derivatives.[27]

3.3.3 ^{31}P NMR spectroscopy

The range of ^{31}P chemical shifts obtained for compounds of Type D, E, F and G are shown in Table 3.15. Proton decoupled

Compound type	^{31}P chemical shift (δ)[a]
D	+19.9 to +20.5
E	+19.3 to +20.3
F	+19.5 to +19.6
G	+5.3 to +6.1

a) All shifts reported are proton decoupled using DMSO-d_6 as the solvent and 80% H_3PO_4 as reference.

Table 3.15. ^{31}P chemical shifts for compounds of Types D, E, F and G.

spectra were normally recorded because of the complex nature of uncoupled spectra resulting from the large number of protons capable of coupling with the phosphorus within the phosphoryl moieties studied.

The overall range of the ^{31}P chemical shifts for the bis(dimethylamido)phosphoryl group of compounds D, E and F was found to be between +19.3 and +20.5 ppm, which represents a slight shift to higher field when compared with N,N,N',N'-tetramethylphosphoric triamide (+22.6 ppm). Therefore substitution of the amido group causes an up-field shift. This shift was invaluable in studying reaction mixtures for the presence of condensation products whose signals were well removed from that of the starting material. The ^{31}P chemical shift of O,O-diethyl phosphoramidate, $(EtO)_2P(O)NH_2$, has been reported to be +11.1 ppm.[28] When this is compared with the range observed during this study (+5.3 to +6.1 ppm) for compounds of Type G it can again be seen that a shift to higher field occurs on substituting the amido group.

The effect of replacing the dimethylamido groups on phosphorus by ethoxy was to shift the signal to higher field, i.e. more to negative values. This effect has been observed by other authors who have tried to develop empirical relationships for predicting chemical shifts when dimethylamido groups are replaced by ethoxy groups.[28-30] These have generally given poor correlation between calculated and observed results.

3.4 Mass spectrometry

The mass spectra of compounds D, E, F and G were determined by conventional electron impact (EI) ionisation and when this failed to give molecular ions the newer ionisation technique of fast atom bombardment (FAB) was used.

The quoted m/z values for fragment ions containing one or more chlorine atoms refer to ions containing only the ^{35}Cl isotope. Fragment ions containing chlorine give rise to characteristic isotope patterns depending on the number of chlorines present, the peaks being separated by two units due to the ^{35}Cl and ^{37}Cl isotopes (natural abundance of ^{35}Cl and ^{37}Cl isotopes is approximately 3:1). The expected isotope patterns for molecular and fragment ions containing up to six chlorine atoms are shown in Table 3.16 and can be used to confirm the numbers of chlorine atoms in these ions. However, in FAB mass spectra it was observed that these patterns were often disrupted and it was difficult to predict the number of chlorine atoms with certainty.

All the compounds of Types D, E, F and G yielded very complex spectra. Marked variations were observed between spectra obtained using EI and FAB conditions indicating different fragmentation pathways. The higher mass fragments were generally weak in electron impact spectra and only moderately stronger in FAB spectra. Several compounds failed to give molecular ions when using EI conditions, but did yield such ions (although weak) using FAB ionisation. Thus molecular weights for all compounds of Types D, E, F and G were confirmed by obtaining molecular ions in either their EI or FAB mass spectrum.

In this section the discussion will be limited to general observations concerning fragmentation pathways for compound Types D, E, F and G. Fragmentation pathways originating from the groups R, R^1, R^2 and R^3 will be omitted from the discussion

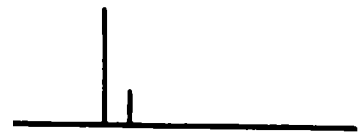
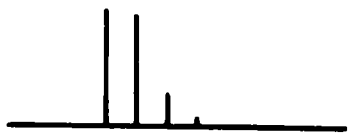
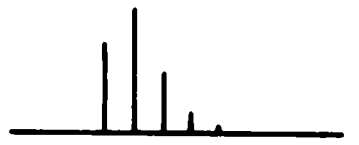
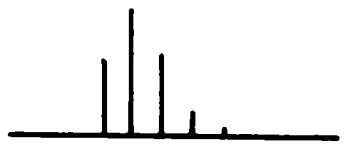
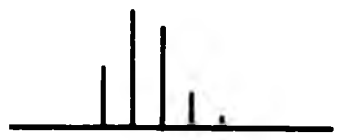
Number of chlorine atoms	Isotope pattern
1	
2	
3	
4	
5	
6	

Table 3.16 Expected isotopic patterns in the studied ionic species containing up to six chlorine atoms.

unless they are of special interest.

Accurate masses referred to throughout this discussion can be found in Table 3.23 at the end of this section.

(a) Compounds of type D, $(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)R$

In general these compounds gave weak molecular ions (0.3-4%) under EI conditions and their structures were confirmed by accurate mass measurements. Compounds in which R= CCl_3 and 2,4-$Cl_2C_6H_3$ failed to give molecular ions under EI conditions. However molecular ions (M+1) were obtained using FAB.

A typical spectrum obtained under EI conditions is shown in Figure 3.15. The spectra obtained for compound D (R=2,4-$Cl_2C_6H_3$) under EI and FAB conditions are shown in Figures 3.16 and 3.17 for comparison and also to show the different fragmentation pathways that occur. The main features of the spectra obtained from compounds of Type D under EI conditions, are shown in Table 3.17, from which it can be seen that most of the characteristic fragment ions are weak. As can be seen from Figure 3.15 very few ions appear above m/z 200.

A weak peak is given at M-44 corresponding to loss of a dimethylamido group, by all the compounds except that in which R=5,6-dihydro-2-methyl-1,4-oxathiin-3-yl.

A fragment ion at m/z 253 corresponding to M-44-RC≡N was observed for all these compounds. Accurate mass measurement showed this ion to have the elemental composition $C_4H_9N_2Cl_3O_2P$, whilst metastable analysis using linked scanning,[31] of the spectrum of the compound in which R=2-Me-furan-3-yl showed

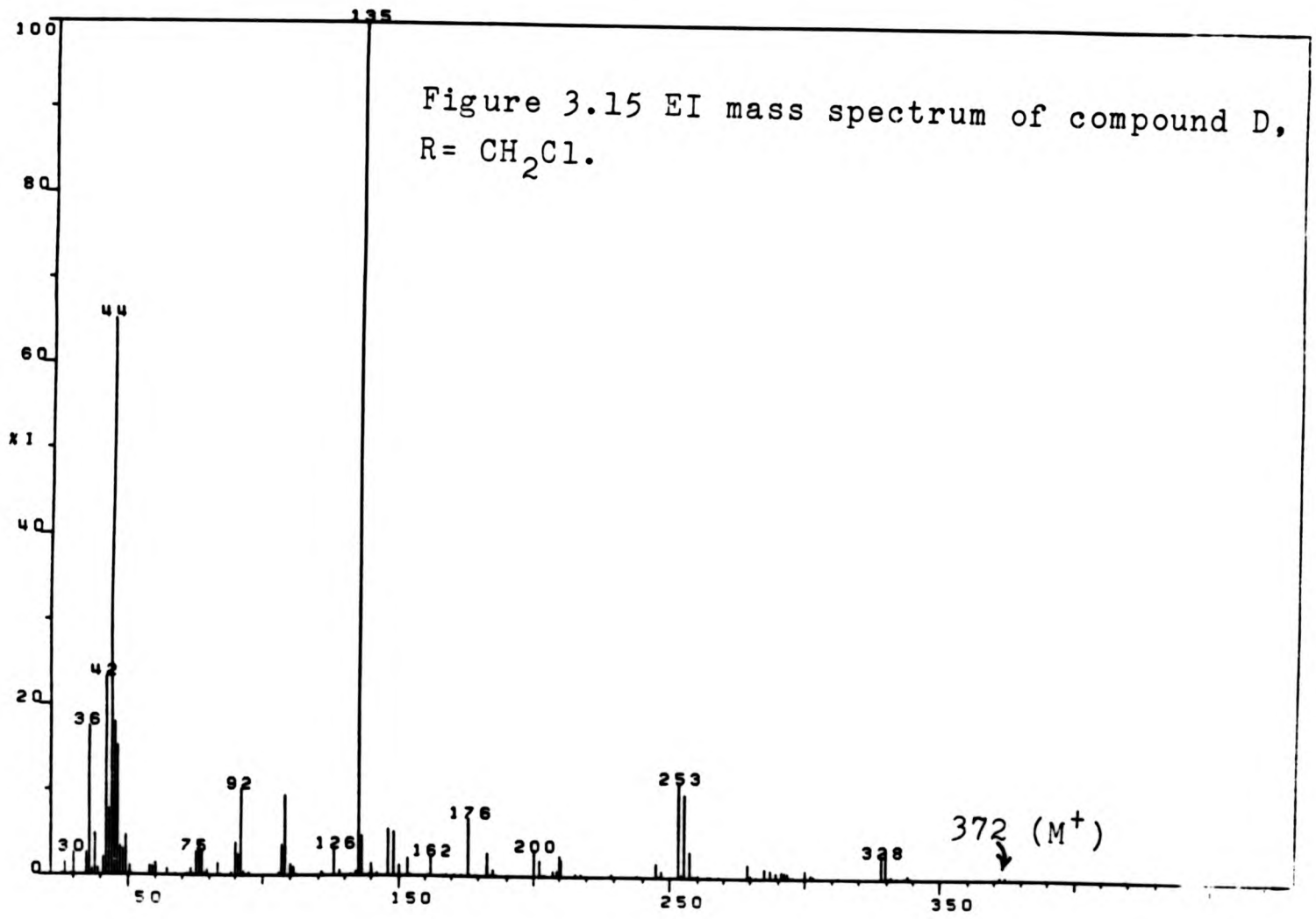


Figure 3.15 EI mass spectrum of compound D, R= CH_2Cl.

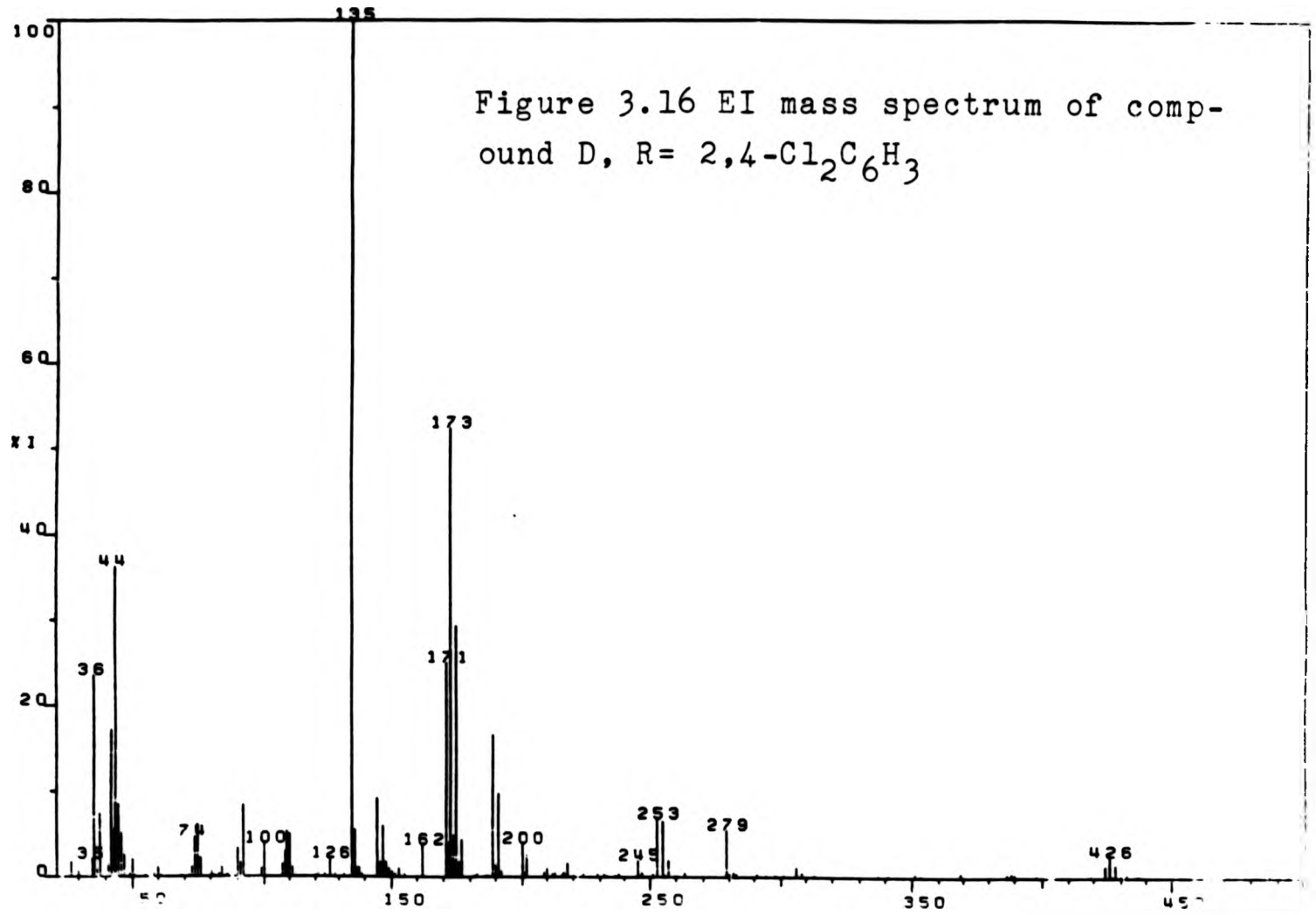


Figure 3.16 EI mass spectrum of compound D, R= 2,4-$Cl_2C_6H_3$

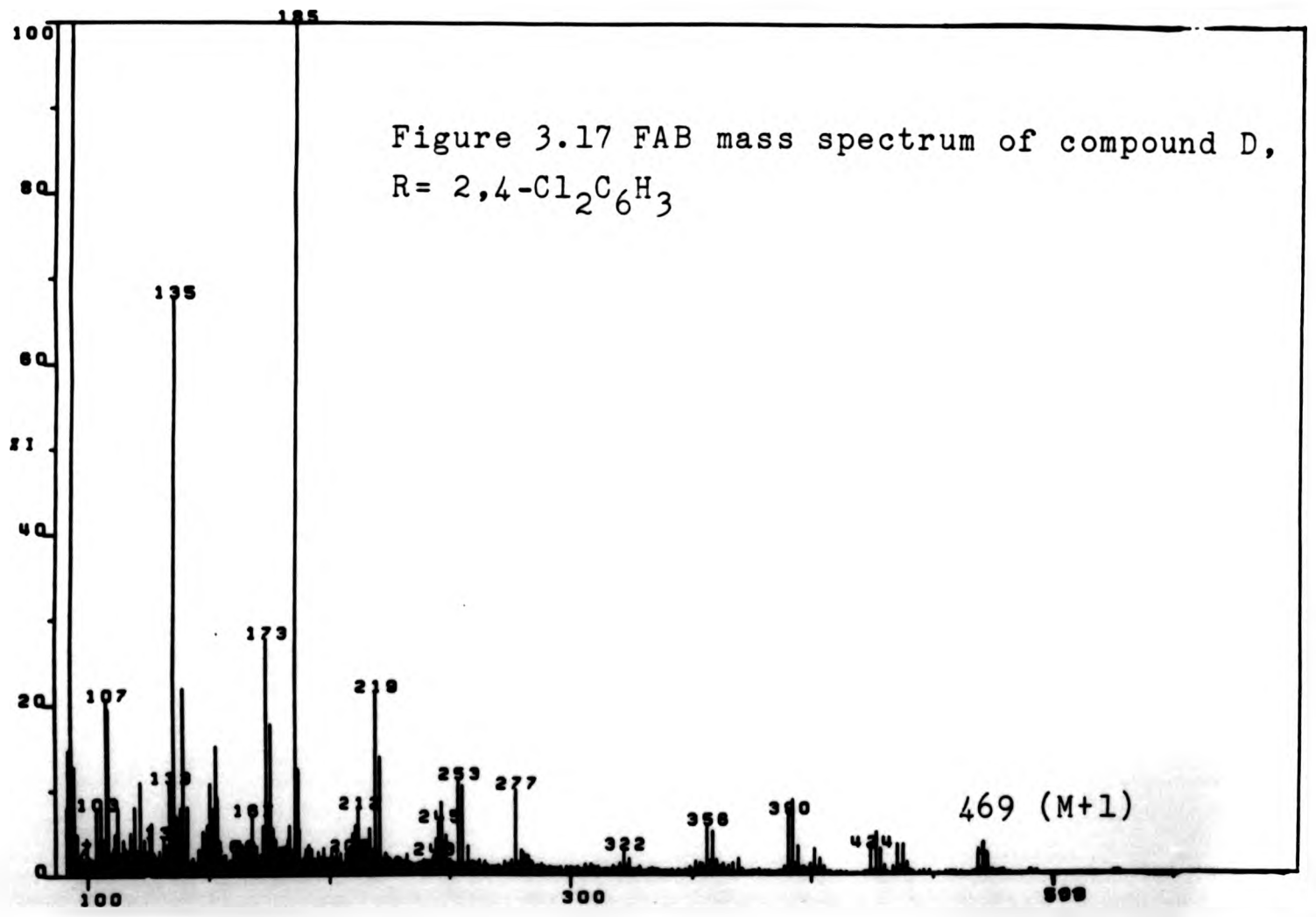


Figure 3.17 FAB mass spectrum of compound D, R= 2,4-$Cl_2C_6H_3$

Fragment ion	Compound*/Relative %						
	1	2	3	4	5	6	7
M^+	4	0	2	1	0	2	0.3
$M-N(CH_3)_2$	29	1	0	3	1	15	3
$M-N(CH_3)_2-RC\equiv N$	6	7	8	11	4	28	11
$M-CCl_3$	27	0	0	4	4	3	0
$M-CCl_3-RC\equiv N$	15	0	0	7	0	0	0
m/z 200	8	4	0	4	1	3	3
135	100	100	85	100	100	79	100
108	20	3	3	10	3	54	9
107	12	0	7	5	2	33	4
92	12	8	6	9	7	9	10
44	55	44	58	72	61	100	64

Table 3.17. General fragment ions obtained for compounds of Type D, $(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)R$.

*R = 1. CH_3; 2. $2,4\text{-}Cl_2C_6H_3$; 3. 5,6-dihydro-2-methyl-1,4-oxathiin-3-yl; 4. CHO; 5. CCl_3; 6. 2-Me-furan-3-yl; 7. CH_2Cl

this ion to be the daughter of the fragment ion at m/z 360. A possible pathway to the formation of the fragment ion at m/z 253 is shown in Figure 3.18 and involves the migration of a hydroxy group *via* a six-membered transition state. Hydroxy group migration becomes possible due to the proposed tautomerism shown in structures 110 and 111. The structure of the fragment ion at m/z 360 was also confirmed by accurate mass measurement. Hydroxy group transfers of this type are unknown in the mass spectrometry of purely organic compounds but have been reported in the fragmentations of a number of organometallic derivatives,[32] and other phosphorus compounds.[33,34] It is likely that the rearrangement is facilitated by the ability of phosphorus to use d-orbitals in the formation of the transition state (112) and by its tendency to retain the oxidation state +5.[34] Elimination of the RC≡N fragment in this rearrangement is further supported by observations which show that RC≡N can be charged and give rise to a peak at the corresponding m/z value. Table 3.18 shows the compounds which give rise to charged RC≡N fragments. The origin of the charged RC≡N fragments is unclear. It could be that the elimination from the molecular ion is such that the charge resides on the RC≡N fragment as shown in Figure 3.19. This proposal will need to be confirmed by metastable scanning. In the case in which R=2-Me-furan-3-yl it must be noted that the ion arising from the RC≡N fragment at m/z 107 cannot be differentiated by accurate mass measurement at a resolution of 10,000 from the ion of the same m/z value due to the fragment $C_2H_8N_2OP$. This latter fragment is observed for all compounds of this type but normally has a low

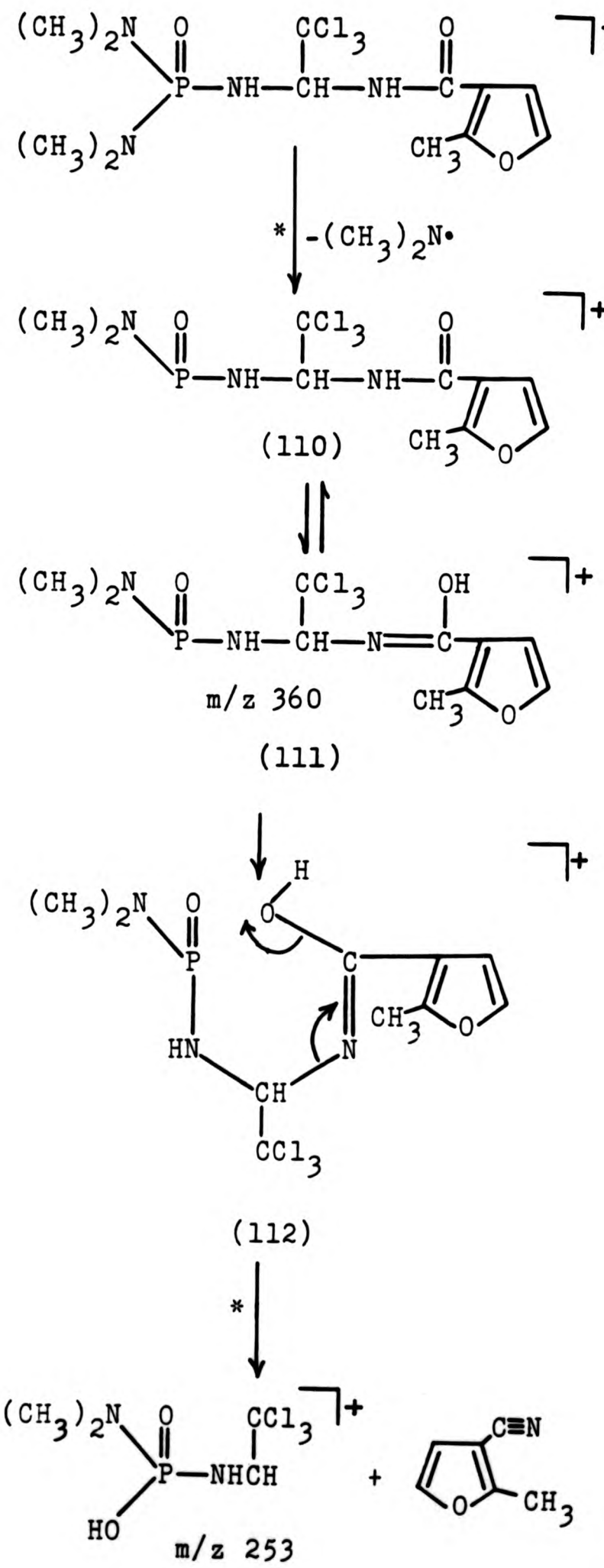


Figure 3.18 Scheme to show the formation of the fragment ion at m/z 253.

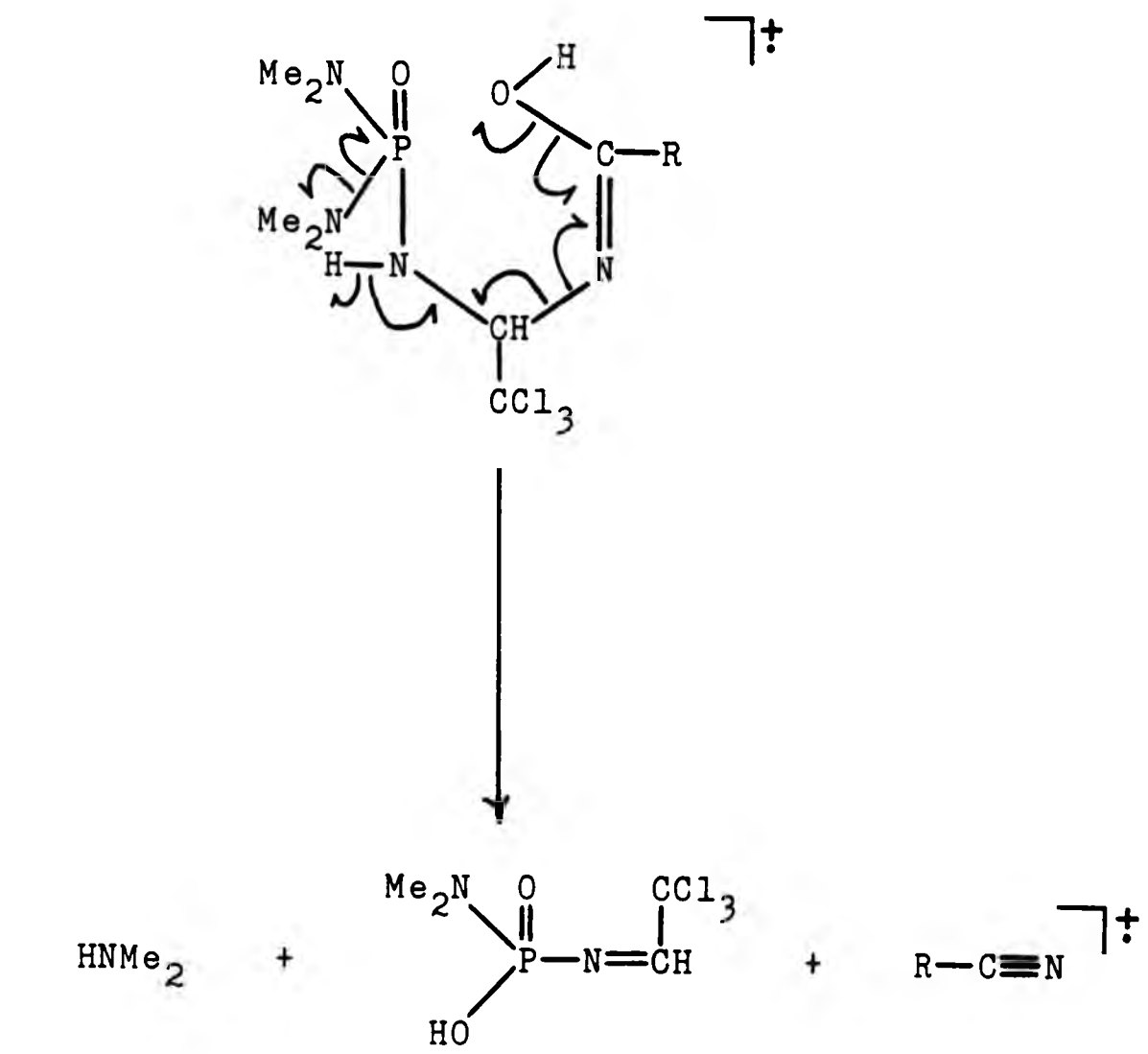


Figure 3.19. Scheme to show fragmentation leading to the charge residing on the RC≡N fragment.

relative abundance (2-12%). In the case in which R= 2-Me-furan-3-yl the relative abundance of the ion at m/z 107 was found to be 33% and thus it can be inferred that the ion of structure 113 is almost certainly contributing. This observation is further supported by the presence of a fragment ion at m/z 106. Accurate mass measurement showed this ion to have an elemental composition of C_6H_4NO, corresponding to the pyran structure (114), which could be formed by an analogous rearrangement to that which leads to tropylium from toluene. Accurate mass

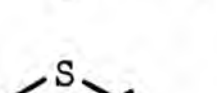
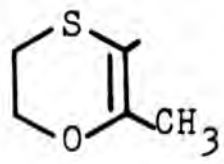
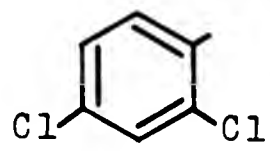
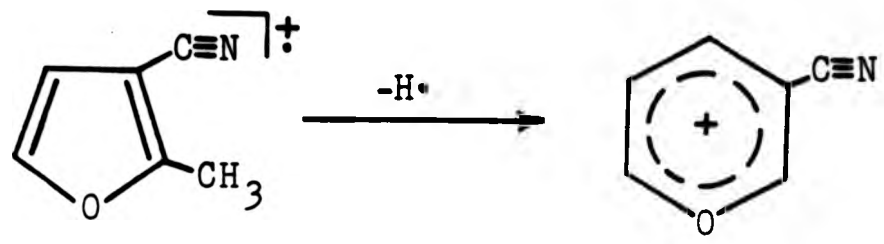
R	$RC\equiv N^+$ m/z	% Abundance	Accurate mass	
			Found	Requires
CH_3	41	12	-	-
CH_2Cl	75	3	74.9885	74.9875
	107	33	107.0378	107.0371
	141	31	141.0273	141.0248
	171	25	170.9631	170.9642

Table 3.18 Compounds of the type $(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)R$ which give rise to charged $RC\equiv N$ fragments.

measurements on the ion at m/z 107 are however required at much higher resolution in order to confirm its structure.



(113) (114)

Fragment ions at M-117, corresponding to simple loss of trichloromethyl group, were observed for compounds in which R= CH_3, CHO, CCl_3 and 2-Me-furan-3-yl. Losses involving the trichloromethyl group together with other fragments were also observed when R= 2,4-$Cl_2C_6H_3$, 5,6-dihydro-2-methyl-1,4-oxathiin-3-yl, and 2-Me-furan-3-yl. When R= 2,4-$Cl_2C_6H_3$ an ion at m/z 279 corresponding to M-CCl_3-2HCl was observed. In the cases in which R= 2-Me-furan-3-yl or 5,6-dihydro-2-methyl-1,4-oxathiin-3-yl, ions at m/z 242 and 276 respectively correspond to the successive loss of a dimethylamido group and of chloroform, i.e. M-NMe_2-$CHCl_3$. The compound in which R= CH_2Cl shows an ion at m/z 176 corresponding to the successive loss of dimethylamido and trichloromethyl groups, and chlorine i.e. M-$N(CH_3)_2$-CCl_3-Cl. An interesting loss of the trichloromethyl group was observed for compounds in which R= CH_3 or CHO. These compounds yielded fragment ions at m/z 179 corresponding to successive loss of the trichloromethyl group and of RC≡N, i.e. M-CCl_3-RC≡N. The loss of RC≡N may involve the hydroxy group

transfer which has already been discussed.

A fragment ion at m/z 200 is observed for all the compounds except that in which R= 5,6-dihydro-2-methyl-1,4-oxathiin-3-yl. Accurate mass measurement showed this to have the composition $C_4H_7Cl_2N_2OP$ and a possible route to its formation is shown in Figure 3.20, involving successive loss of HCl, the amido moiety and $CH_3N{=}CH_2$ group.

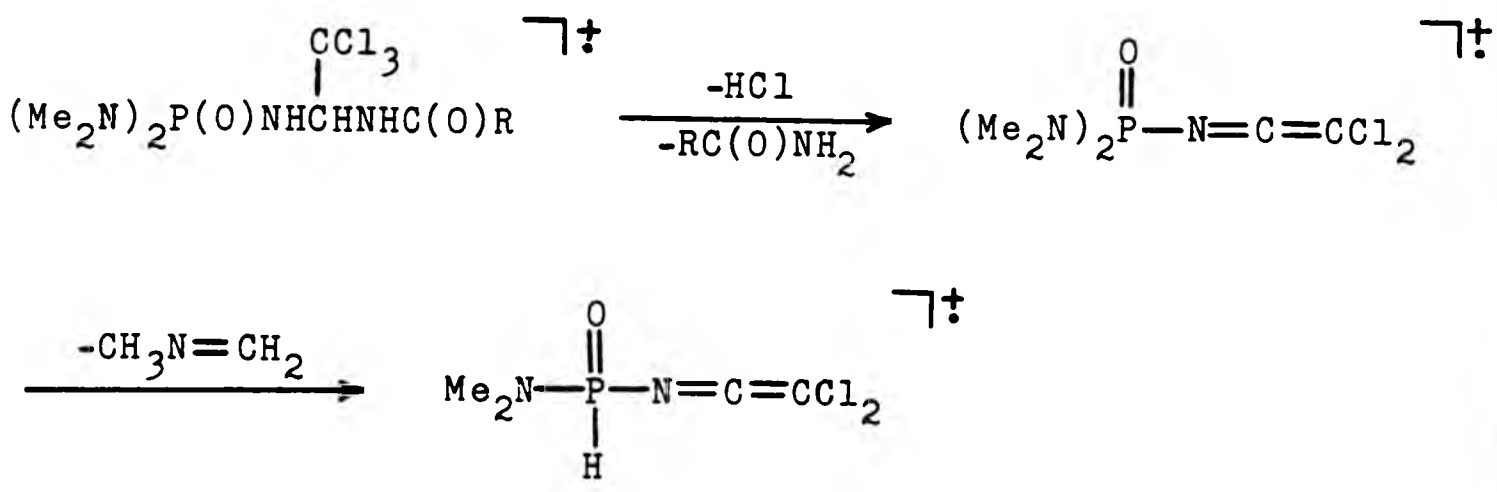
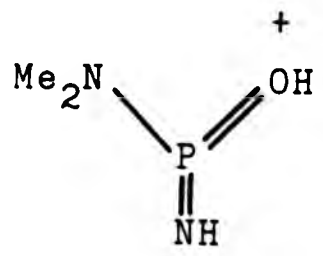


Figure 3.20. A possible route to the formation of the fragment ion at m/z 200.

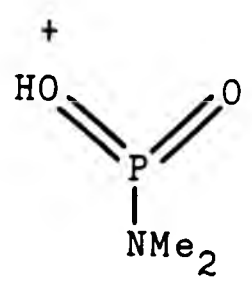
The major fragment ion in the mass spectra of these compounds was that at m/z 135. This was generally the base peak and corresponds to the fragment $(Me_2N)_2P(O)$, whose elemental composition was confirmed by accurate mass measurement. Only when R= 2-Me-furan-3-yl or 5,6-dihydro-2-methyl-1,4-oxathiin-3-yl was this not the base peak, the relative abundances being 79% and 85% respectively.

The fragment ions at m/z 107 and 108 were shown by

accurate mass measurements to have the elemental composition $C_2H_8N_2OP$ and $C_2H_7NO_2P$. All the compounds show these fragment ions and possible structures are given (115 and 116). The ion at m/z 92, which is given by all compounds of this type, was



m/z 107
(115)



m/z 108
(116)

shown by accurate mass measurement to have the elemental composition C_2H_7NOP. Metastable scanning showed this ion to be a daughter of that at m/z 135. It thus seems probable that the ion at m/z 92 is derived from the fragment ion at m/z 135 by loss of $CH_3N{=}CH_2$. An ion at m/z 44 which had a high relative abundance was present in all spectra. It was sometimes the base peak and corresponds to the dimethylamido group ($-NMe_2$).

The compounds where R= 2,4-$Cl_2C_6H_3$ or CCl_3 and which failed to give molecular ions under EI conditions yielded such ions using FAB ionisation. The most significant difference in the spectra obtained using these two types of ionisation was that fragment ions corresponding to successive substitution of chlorine by hydrogen were observed in both cases in the FAB spectra. The fact that the compounds contain two centres carrying chlorine i.e. R and the trichloromethyl group, made it difficult to determine which chlorine atoms were being replaced. In the case in which R= 2,4-$Cl_2C_6H_3$ this could not be determined but for R= CCl_3 evidence was obtained that it was the chlorine

atoms of the trichloromethyl group attached to the methine carbon. This effect is shown in Figure 3.21. The substitution of chlorine by hydrogen most probably occurs whilst the compound is in the glycerol which is used to introduce the sample into the instrument as such a process seems unlikely in the gas phase.

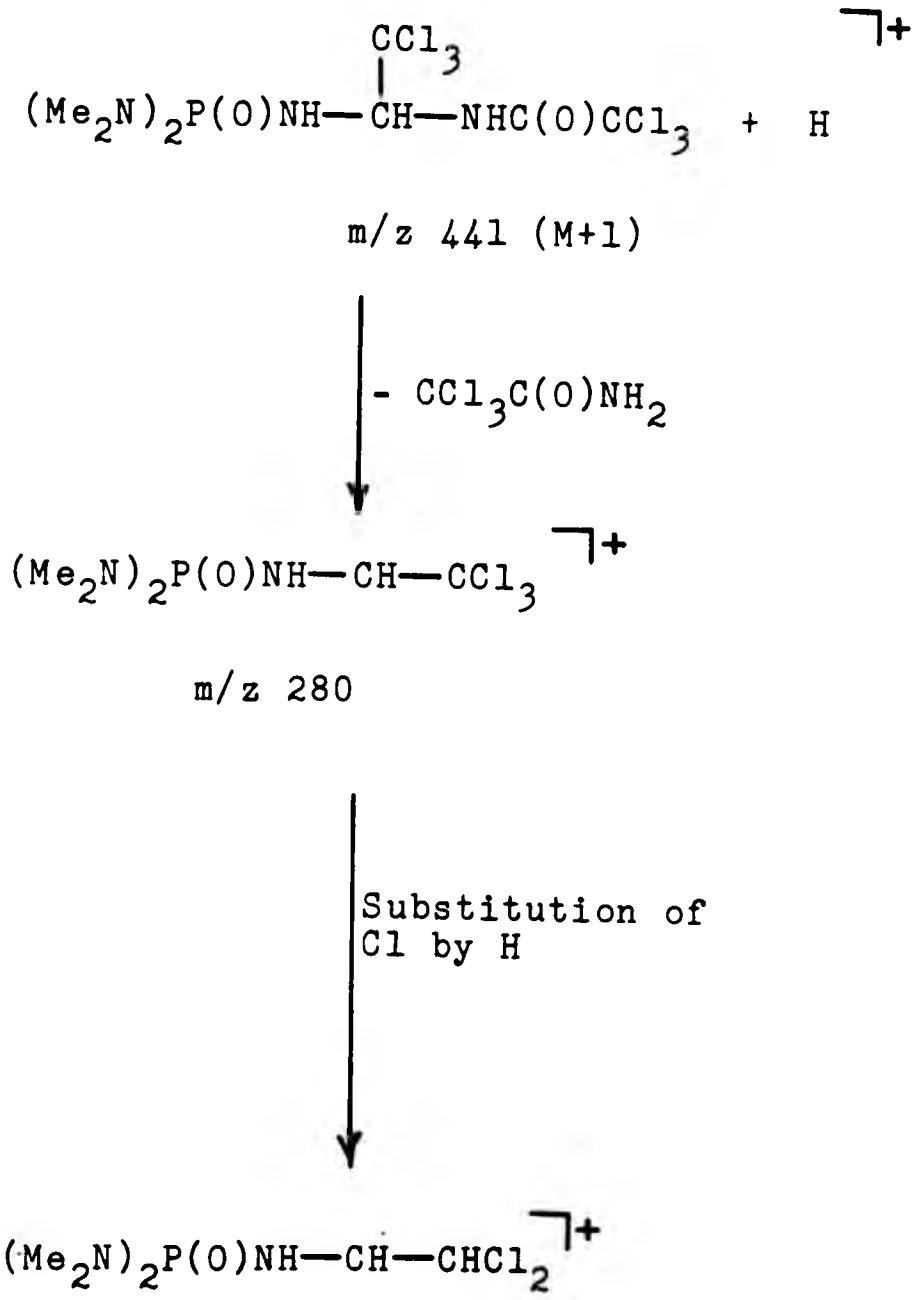


Figure 3.21. Substitution of Cl by H in the FAB mass spectrum of compound D (R= CCl_3)

(b) Compounds of Type E, $(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)CH_2R^1$

These compounds all gave weak molecular ions under EI conditions except the compound in which $R^1=SC_{12}H_{25}$, for which no molecular ion was observed. The generally observed fragment ions are shown in Table 3.19.

These compounds show fragment ions at m/z 253, 200, 135, 108, 107, 92 and 44 which are characteristic of the $(Me_2N)_2$-$P(O)NHCH(CCl_3)NHC(O)$ part of the molecule and their formation has been discussed in the previous section. In contrast to compounds of Type D these compounds do not generally show ions corresponding to the $M-N(CH_3)_2$ or to simple or complex loss of the trichloromethyl group. Only when $R^1=SP(S)(OEt)_2$ or 1,2,4-triazolyl are fragment ions corresponding to $M-N(CH_3)_2$ and $M-CCl_3$ observed. The base peak was always due to the fragment ion at m/z 135.

All the compounds except that in which R^1=1,2,4-triazolyl give an ion of low relative abundance at m/z 280. This ion corresponds to $M-NHC(O)CH_2R^1$ and its composition was confirmed by accurate mass measurement. Other ions originating from fragmentations of the $-NHC(O)CH_2R^1$ moiety were also observed, thus compound D (R^1=1,2,4-triazolyl, dimethyl dithiocarbamato or diethyl dithiocarbamato) gave ions corresponding to $M-CH_2R^1$. From the dithiocarbamato derivatives fragment ions corresponding to $M-R^1$ were also obtained.

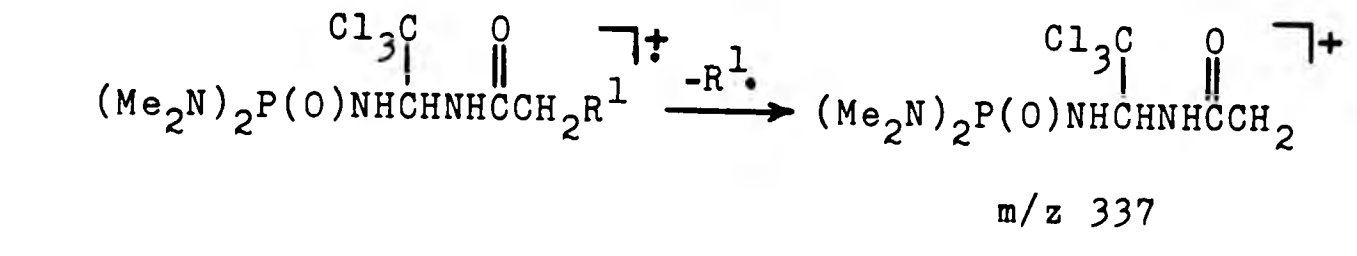
An ion at m/z 176, which was observed in the mass spectra of all compounds of Type D was also shown by accurate mass measurement to have the elemental composition $C_5H_{11}N_3O_2P$.

Fragment ion	Compound*/Relative %					
	1	2	3	4	5	6
M^+	0.6	0.4	1	1	1	0
$M-R^1$	0	0	0	5	8	0
$M-CH_2R^1$	0	5	0	2	2	0
$M-NHC(O)CH_2R^1$	6	0	4	4	8	4
$M-N(CH_3)_2-R^1CH_2C\equiv N$	39	9	31	3	2	6
m/z 200	2	3	4	3	3	0
176	3	3	11	2	6	6
135	100	100	100	100	100	100
108	10	8	12	2	3	3
107	6	3	8	2	2	2
92	9	9	14	8	8	7
44	59	58	24	58	59	39

Table 3.19 General fragment ions observed for compounds of Type E, $(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)CH_2R^1$.

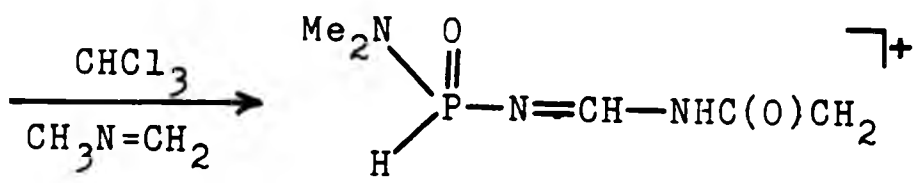
* R= 1. $SP(S)(OEt)_2$; 2. 1,2,4-triazolyl; 3. SC(S)OEt; 4. $SC(S)NMe_2$; 5. $SC(S)NEt_2$; 6. $SC_{12}H_{25}$

A possible structure for this ion is given (118) and it could be formed by successive loss of $R^1\cdot$, $CHCl_3$, and $CH_3N{=}CH_2$ from the molecular ion (see scheme below). The ion at m/z 337 (117), was observed in the spectra of some of these compounds.



m/z 337

(117)



(118)

(c) Compounds of Type F, $(Me_2N)_2P(O)NHCH(CCl_3)OR^2$

The spectra of these compounds were only recorded using FAB conditions and all yieled weak molecular ions at m/z M+1. Table 3.20 gives the other generally observed fragment ions.

The fragment ions at m/z 135 (base peak), 108, 107 and 92 have also been observed for compounds of Types D and E which also contain the bis(dimethylamido)phosphoryl group and their formation has previously been discussed.

All the compounds give ions at m/z 280, 246, 244, 210 and 176. The formation of these ions is shown in Figure 3.22. Loss of R^2OH from the molecular ion gives the ion at m/z 280 which can then undergo two types of fragmentation: a) substitution of Cl by hydrogen to give the ion at m/z 246 or b) loss of HCl to give the ion at m/z 244. Successive substitution of Cl by hydrogen of the ion at m/z 244 leads to the fragment ions

Fragment ion		Compound*/Relative %			
		1	2	3	4
M+H		7	3	2	1
MH^+-R^2OH		21	11	10	12
m/z	246	37	13	13	21
	244	9	7	6	11
	210	5	4	4	5
	176	2	4	8	5
	135	100	100	100	100
	108	2	29	26	17
	107	0	6	7	8
	92	4	8	11	13

Table 3.20 General fragment ions obtained for compounds of Type F, $(Me_2N)_2P(O)NHCH(CCl_3)OR^2$.

* R^2= 1. OCH_3; 2. OCH_2CH_3; 3. $O(CH_2)_3CH_3$;
4. $\underline{n}$-$OC_{12}H_{25}$

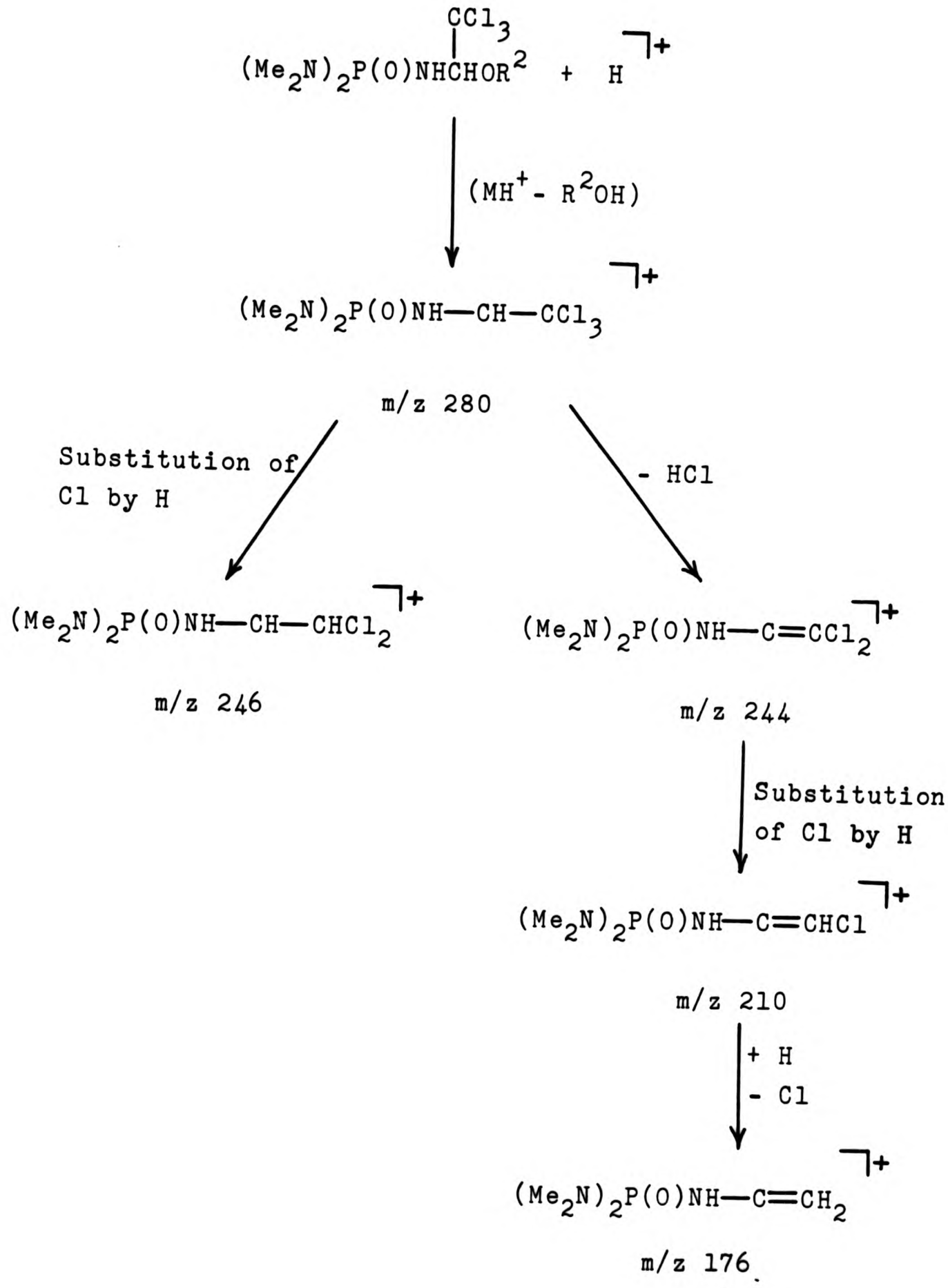


Figure 3.22 Scheme to show the formation of the fragment ions at m/z 280, 246, 244, 210, and 176 for compounds of Type F.

at m/z 210 and 176.

(d) Compounds of Type G, $(EtO)_2P(O)NHCH(CCl_3)NHC(O)R^3$

Only the compound in which R^3= 2-Me-furan-3-yl gave a molecular ion under EI conditions. Molecular ions were however obtained using FAB. Spectra obtained using EI and FAB conditions when R^3= CCl_3 are shown in Figures 3.23 and 3.24 for comparison. The general fragment ions obtained using EI and FAB are shown in Tables 3.21 and 3.22 respectively.

The EI spectra will be discussed first. All the compounds gave fragment ions corresponding to loss of the trichloromethyl group ($M-CCl_3$) and in the case in which R^3= CH_2Cl this was the base peak.

The compounds all yield an ion at m/z 254 and it was first thought that this originated by hydroxy group migration as shown in Figure 3.25. This type of rearrangement would be analogous to that already described for the bis(dimethylamido)-phosphoryl compounds of Types D and E. However, metastable linked scanning of the spectrum obtained for compound G (R= 2-Me-furan-3-yl) showed the precursor of the ion at m/z 254 to be that at m/z 282 and the latter to be a daughter of the molecular ion. No evidence in this case could be found that the ion at m/z 254 was itself a daughter of the molecular ion. A more probable mechanism for the formation of the fragment ion at m/z 254 is shown in Figure 3.26, which also illustrates the stepwise loss of ethylene leading to structure 119. The elemental composition of the ions at m/z 282, 254 and 226 was

at m/z 210 and 176.

(d) Compounds of Type G, $(EtO)_2P(O)NHCH(CCl_3)NHC(O)R^3$

Only the compound in which R^3= 2-Me-furan-3-yl gave a molecular ion under EI conditions. Molecular ions were however obtained using FAB. Spectra obtained using EI and FAB conditions when R^3= CCl_3 are shown in Figures 3.23 and 3.24 for comparison. The general fragment ions obtained using EI and FAB are shown in Tables 3.21 and 3.22 respectively.

The EI spectra will be discussed first. All the compounds gave fragment ions corresponding to loss of the trichloromethyl group ($M-CCl_3$) and in the case in which R^3= CH_2Cl this was the base peak.

The compounds all yield an ion at m/z 254 and it was first thought that this originated by hydroxy group migration as shown in Figure 3.25. This type of rearrangement would be analogous to that already described for the bis(dimethylamido)-phosphoryl compounds of Types D and E. However, metastable linked scanning of the spectrum obtained for compound G (R= 2-Me-furan-3-yl) showed the precursor of the ion at m/z 254 to be that at m/z 282 and the latter to be a daughter of the molecular ion. No evidence in this case could be found that the ion at m/z 254 was itself a daughter of the molecular ion. A more probable mechanism for the formation of the fragment ion at m/z 254 is shown in Figure 3.26, which also illustrates the stepwise loss of ethylene leading to structure 119. The elemental composition of the ions at m/z 282, 254 and 226 was

Fragment ion		Compound*/Relative %				
		1	2	3	4	5
M^+		0	0	0	4	0
$M-CCl_3$		32	30	81	13	100
$M-NHC(O)R^3$		0	0	10	15	1
m/z	254	1	5	3	4	3
	226	1	2	6	4	3
	164	8	12	33	16	23
	137	12	30	100	45	64
	109	12	35	94	30	64
	81	10	31	64	21	46

Table 3.21 General fragment ions obtained under EI conditions for compounds of Type G, $(EtO)_2P(O)NHCH(CCl_3)-NHC(O)R^3$.

* R^3= 1. $2,4-Cl_2C_6H_3$; 2. CHO; 3. CCl_3;
4. 2-Me-furan-3-yl; 5. CH_2Cl

Fragment ion	Compound*/Relative %			
	1	2	3	4
M+H	32	4	10	10
MH-34†	18	4	6	9
MH-$R^3C(O)NH_2$ (282)	37	6	74	25
MH-34-$R^3C(O)NH_2$ (248)	34	9	30	21
MH-$CHCl_3$-$C(O)R^3$+H (181)	30	7	31	21
MH-$CHCl_3$	11	2	4	9
m/z 164	7	3	9	7
154	100	100	100	100
137	5	9	6	9
126	25	11	36	35
109	17	4	11	20
98	56	13	59	50

Table 3.22 General fragment ions obtained under FAB conditions for compounds of Type F, $(EtO)_2P(O)NHCH(CCl_3)$-$NHC(O)R^3$.

* R= 1. CHO; 2. 2,4-$Cl_2C_6H_3$; 3. CCl_3; 4. CH_2Cl

†Substitution of chlorine by hydrogen to give a loss of 34

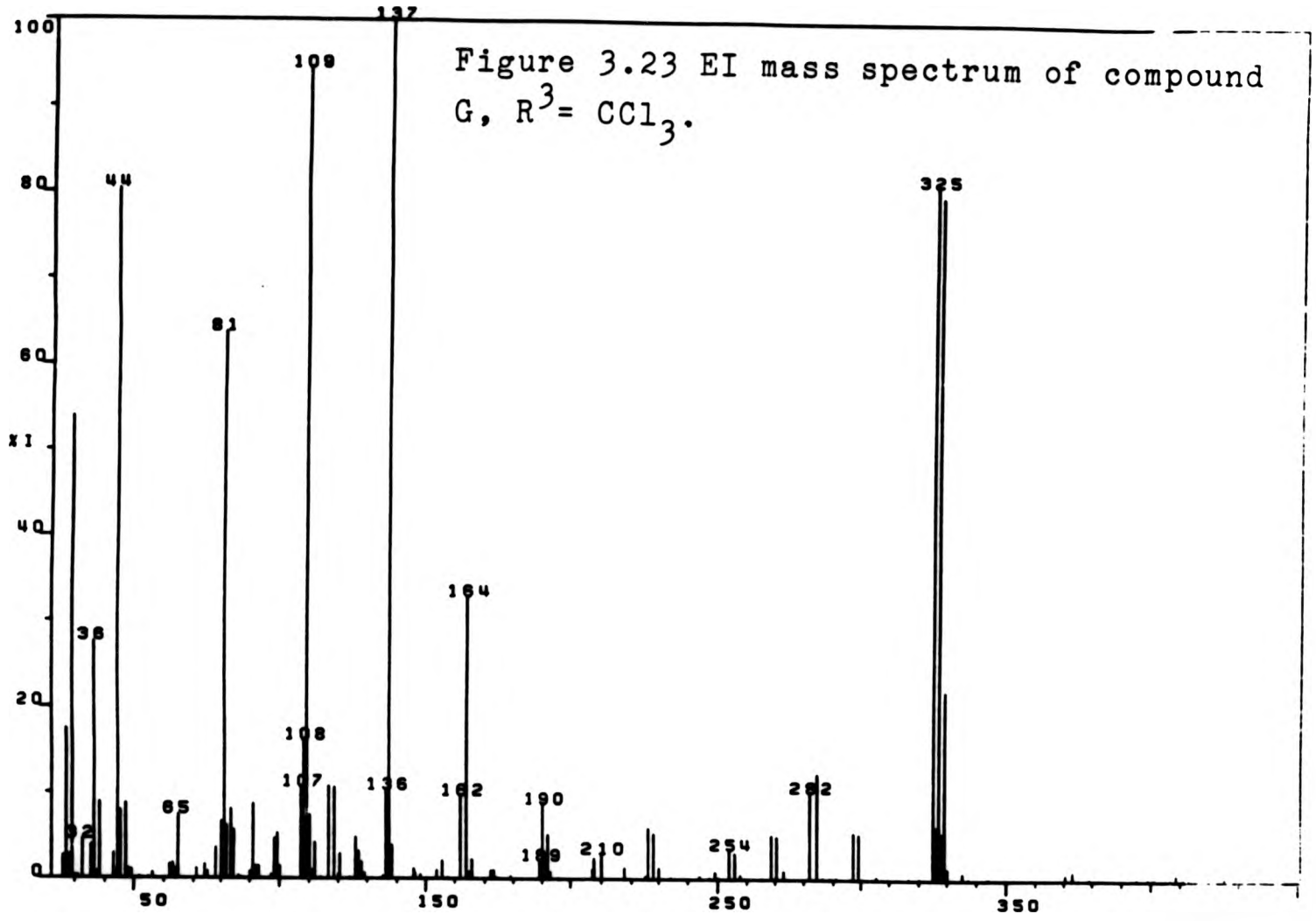


Figure 3.23 EI mass spectrum of compound G, $R^3 = CCl_3$.

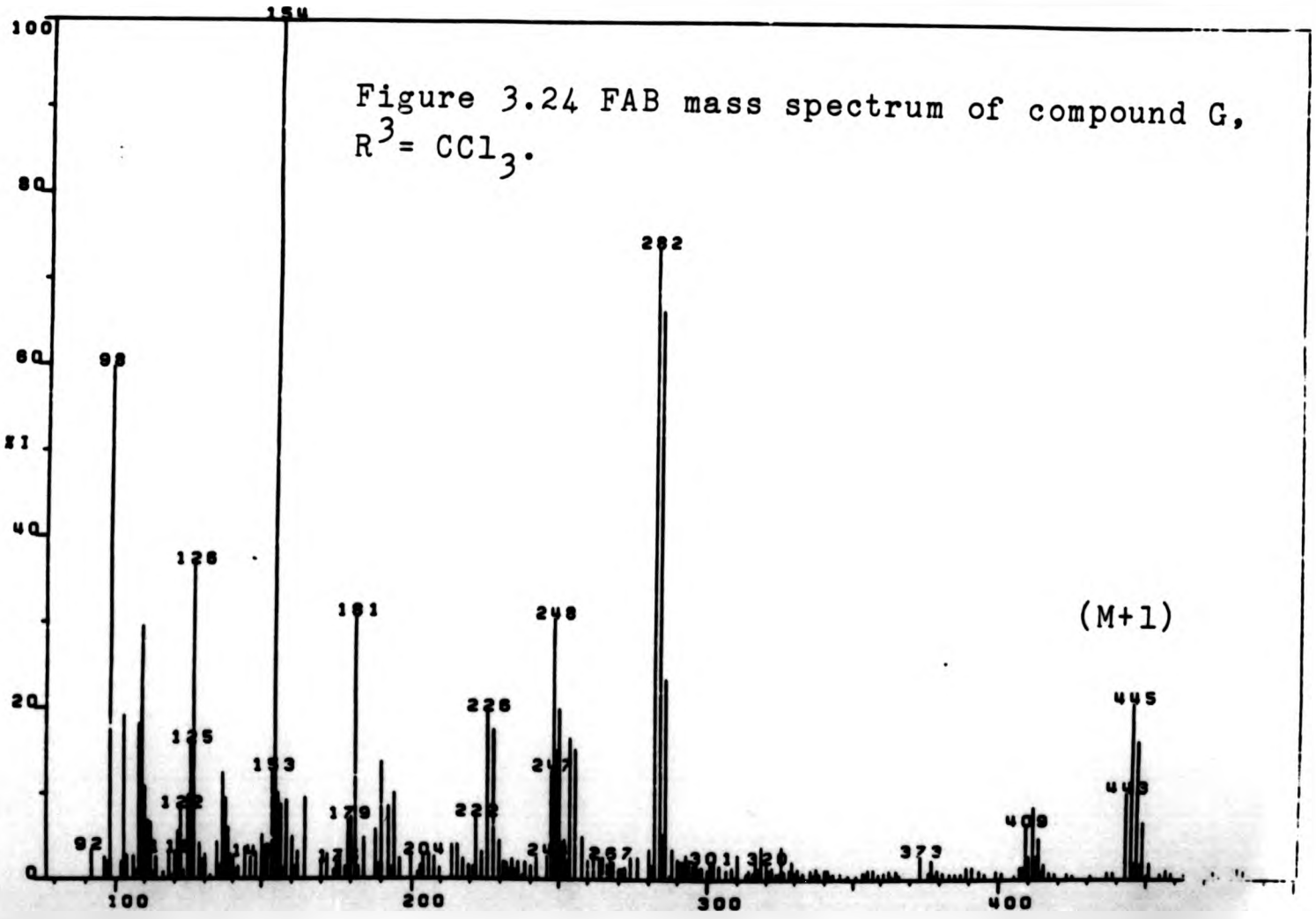
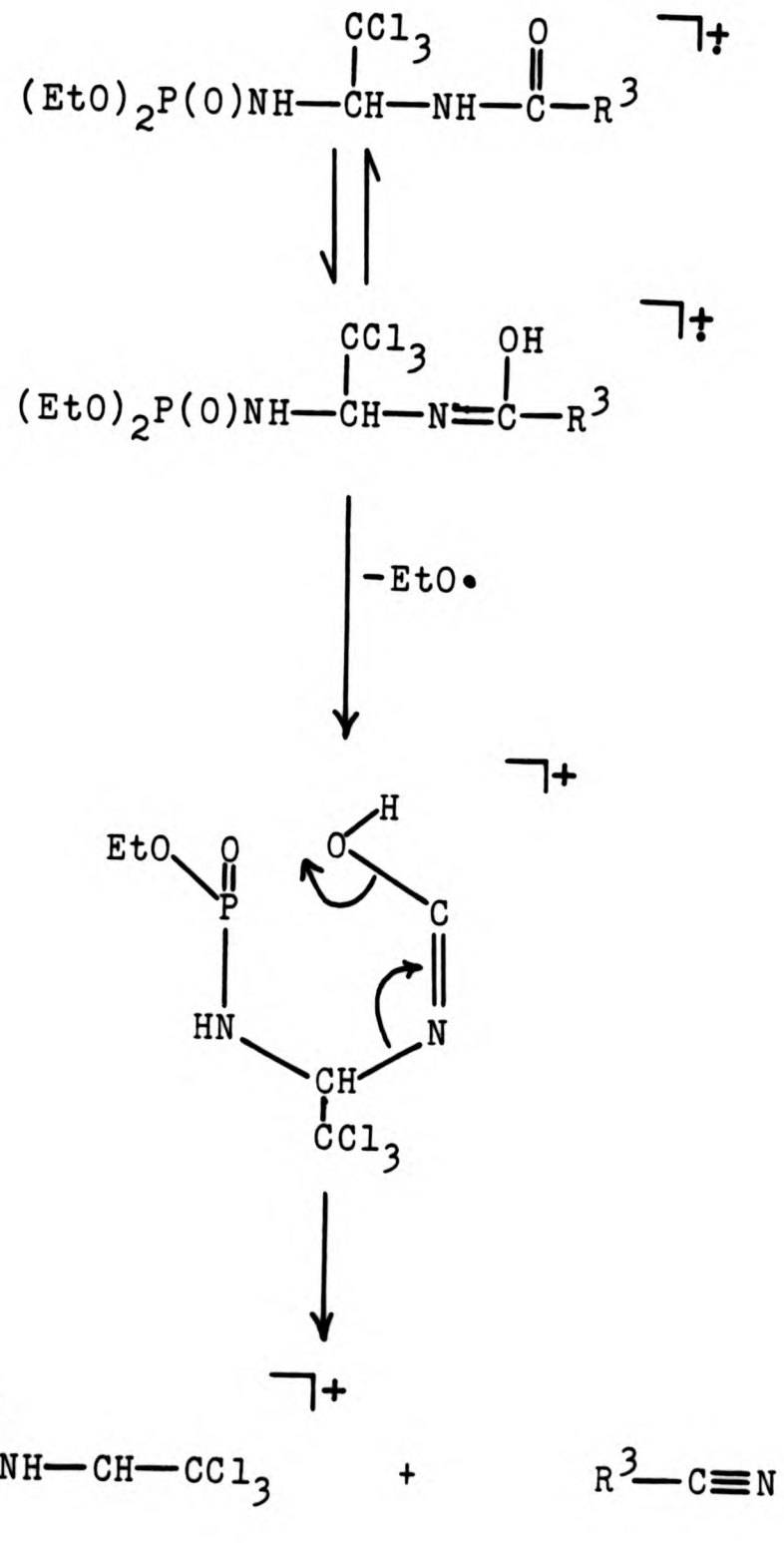


Figure 3.24 FAB mass spectrum of compound G, $R^3 = CCl_3$.



m/z 254

Figure 3.25. One of the possible routes to the fragment ion at m/z 254.

confirmed by accurate mass measurement. Loss of ethylene of

the type shown is a known feature of diethoxy phosphoryl compounds.[35-37]

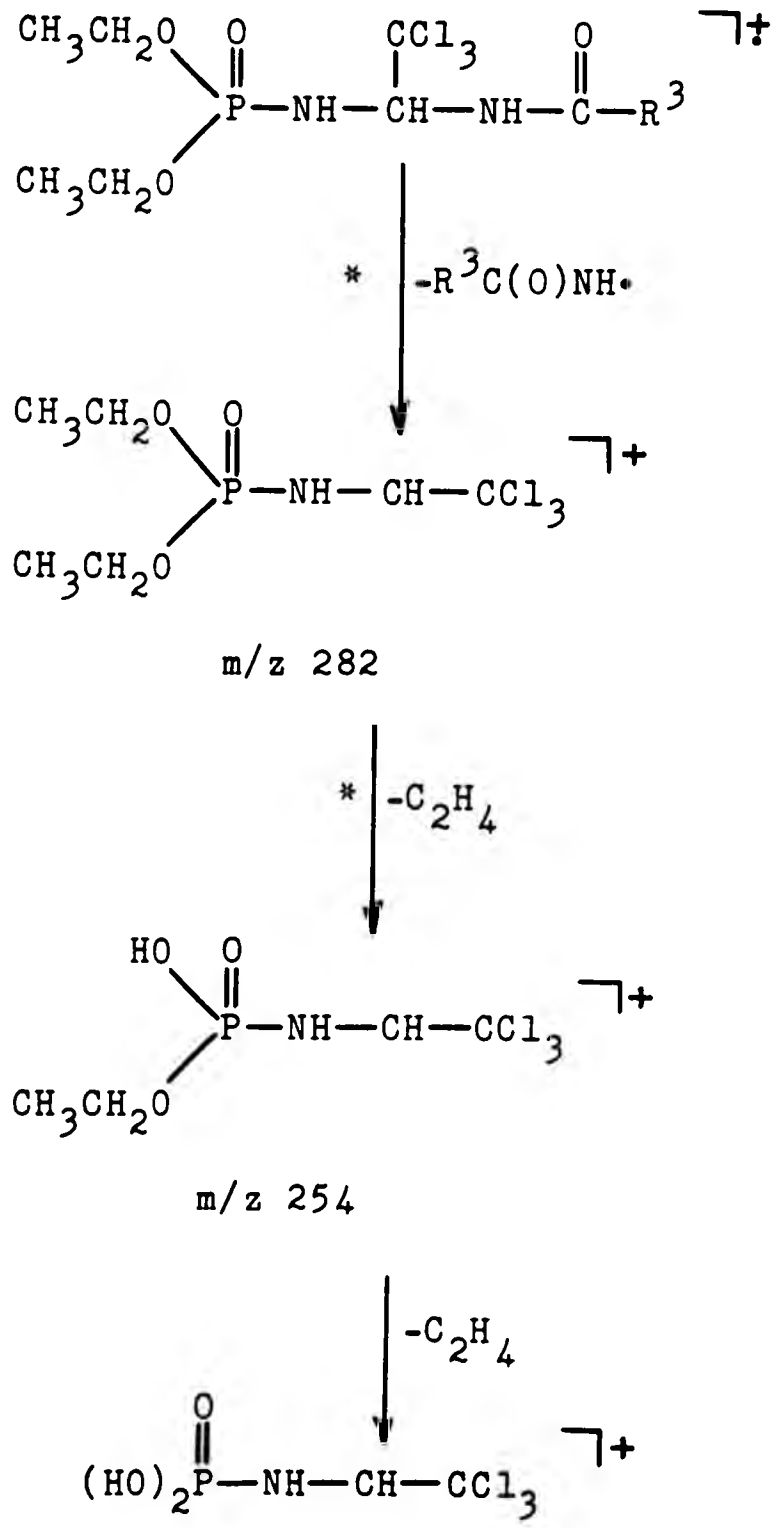
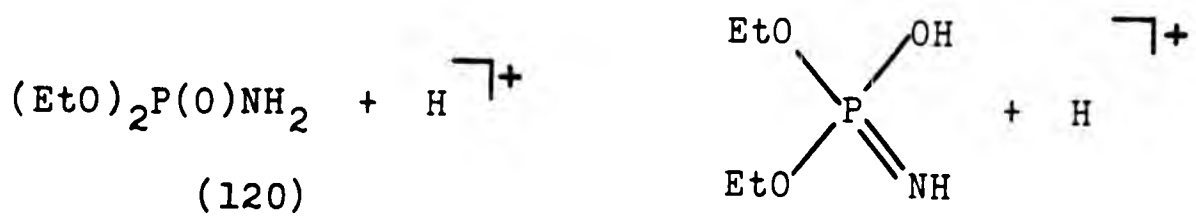


Figure 3.26. A mechanism for the probable formation of the fragment ion at m/z 254.

The compounds generally showed abundant fragment ions at m/z 164, 137, 109 and 81, whose elemental compositions were confirmed by accurate mass measurement. A route to their possible formation is shown in Figure 3.27. The fact that the ion at m/z 282 was not observed for all the compounds indicates that either simultaneous loss of $NHC(O)R^3$ and $CHCl_3$ occurs from the molecular ion or other routes exist leading to the fragment ion at m/z 164. Successive losses of HCN and of ethylene from the latter fragment ion yields the ions at m/z 137, 109 and 81.

Under FAB conditions the compounds all gave $(M+H)^+$ molecular ions, but the base peak in all cases was the fragment ion at m/z 154 (Table 3.22). This ion was not significant in the EI spectra indicating that a different fragmentation pathway was being followed. This m/z value corresponds to the composition $C_4H_{12}NO_3P+H$ and possible structures are shown (120 and 121). Structure 121 can be derived from a McLafferty type



rearrangement involving a six membered transition state and the phosphoryl group as shown in Figure 3.28. Successive loss of two molecules of ethylene from the ion at m/z 154 will then account for the ions at m/z 126 and 98. The fragment ions observed at $M-CCl_3$, m/z 282, 164, 137 and 109 were observed in both the EI and FAB spectra. In the former case the ions at

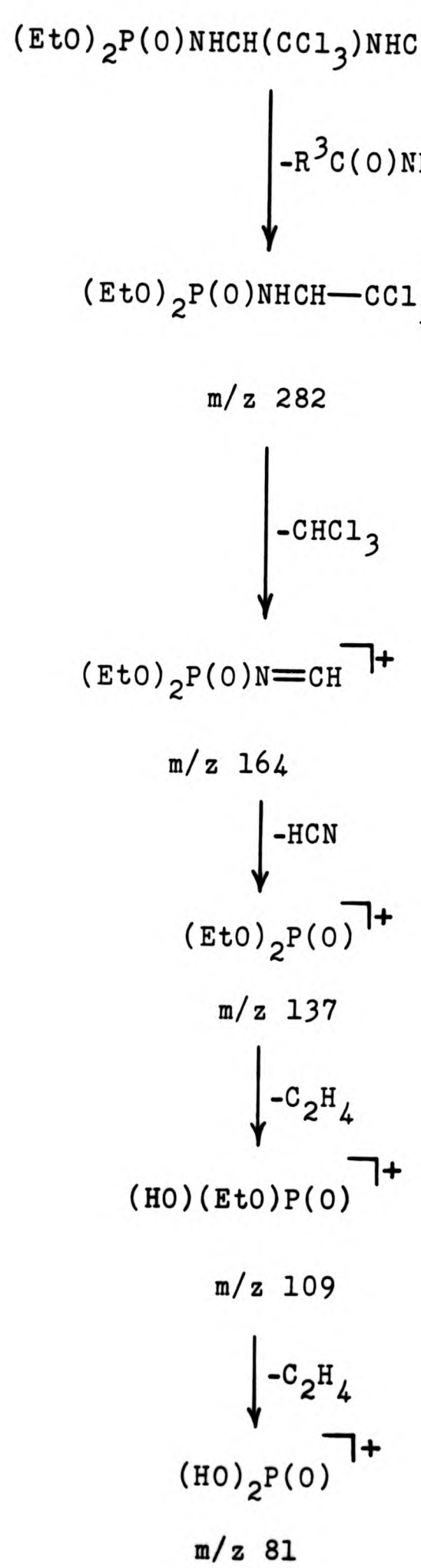
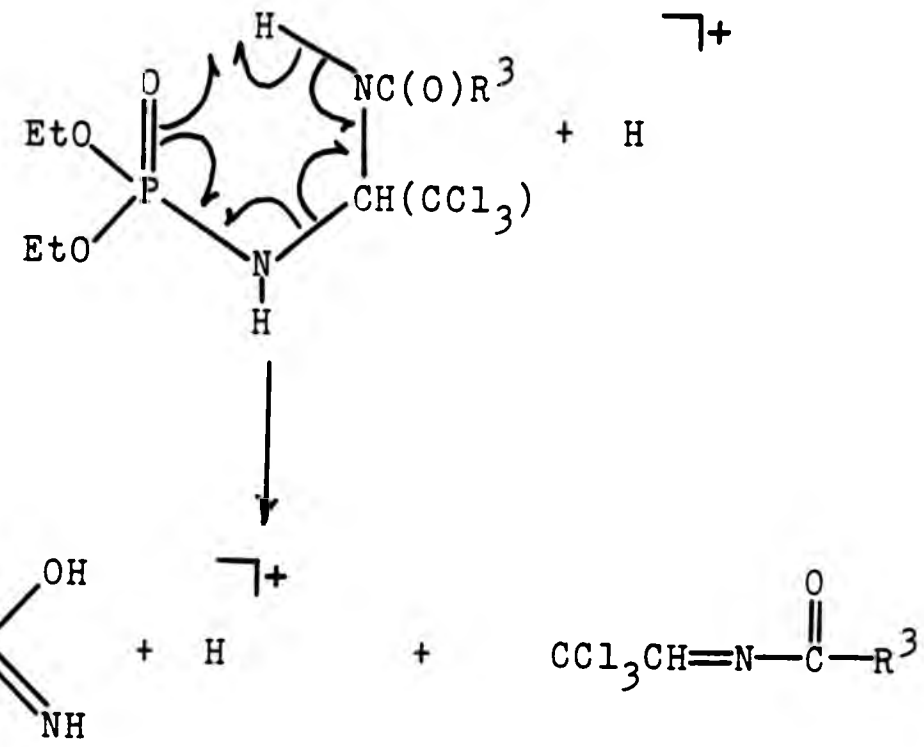


Figure 3.27 A possible route to the fragment ions at m/z 164, 137, 109, and 81.



(121)

Figure 3.28. Proposed rearrangement for the formation of structure 121.

M-CCl_3 and m/z 282 arise by the initial loss of a radical (CCl_3•, $R^3C(O)NH$•) from the molecular ion, and in the FAB spectrum by loss of the corresponding molecules $CHCl_3$ or $R^3C(O)$-NH_2 from the $(M+1)^+$ ion.

A number of fragment ions which involved replacement of Cl by H (i.e. a loss of 34 mass units) were also observed, the most general being (MH-34) which was observed for all the compounds. A fragment ion at m/z 181 corresponding to [MH-$CHCl_3$-$C(O)R^3$+H] was also observed for all the compounds.

Compound type	Ion (m/z)	Assignment	Accurate mass	
			Measured	Calculated
D	360	$C_{10}H_{14}Cl_3N_3O_3P$	359.9833	359.9838
	253	$C_4H_9Cl_3N_2O_2P$	252.9454	252.9466
	200	$C_4H_7Cl_3N_2OP$	199.9690	199.9673
	135	$C_4H_{12}N_2OP$	135.0679	135.0687
	108	$C_2H_7NO_2P$	108.0205	108.0214
	107	$C_2H_8N_2OP$	107.0378	107.0374
	106	C_6H_4NO	106.0282	106.0293
	92	C_2H_7NOP	92.0264	92.0266
E	280	$C_6H_{14}Cl_3N_3OP$	279.9933	279.9940
	176	$C_5H_{11}N_3O_2P$	176.0594	176.0588
G	282	$C_6H_{12}Cl_3NO_3P$	281.9636	281.9620
	254	$C_4H_8Cl_3NO_3P$	253.9303	253.9307
	226	$C_2H_4Cl_3NO_3P$	225.8995	225.8994
	164	$C_5H_{11}NO_3P$	164.0475	164.0477
	137	$C_4H_{10}O_3P$	137.0366	137.0367
	109	$C_2H_6O_3P$	109.0054	109.0055
	81	H_2O_3P	80.9719	80.9742

Table 3.23 Accurate mass measurements.

3.5 The X-ray crystal structure of $(Me_2N)_2P(O)NHCH(CCl_3)NMe_2$

The structure determined by X-ray crystallography was that predicted from ^1H and ^{31}P NMR data and is shown in Figure 3.29.

Crystal data, tables of co-ordinates, thermal parameters, bond lengths, bond angles and non-bonding distances are given in Appendix 1 (Tables 1-7).

The structure is not monomeric due to intermolecular hydrogen bonding between the oxygen of the phosphoryl group and the amido proton. The non-bonding distance between the hydrogen and oxygen atoms of 2.03 Å is less than the value of 2.2 Å below which hydrogen-bonding can be assumed to be present,[38] and shows that this interaction is strong. A study of the various non-bonding distances in the crystal shows this to be the only hydrogen-bonding present, leading to a structure composed of infinite chains of molecules joined together through the phosphoryl oxygen and the amido proton. Part of such a chain is shown in Figure 3.30.

The configuration around the phosphorus was found to be approximately tetrahedral with bond angles varying between 101.8° and 120.2° (mean value of these angles was 109.4 (5)°). The two P-NMe_2 and P-NH bond lengths of 1.647 Å, 1.649 Å, and 1.645 Å respectively are identical within experimental error. A literature search using the SERC Crystal Structure Search Retrieval (CSSR) data base of X-ray crystal structures showed that no other structures containing the $(Me_2N)_2P(O)NH$- moiety have been determined and thus no direct comparison of P-N bond

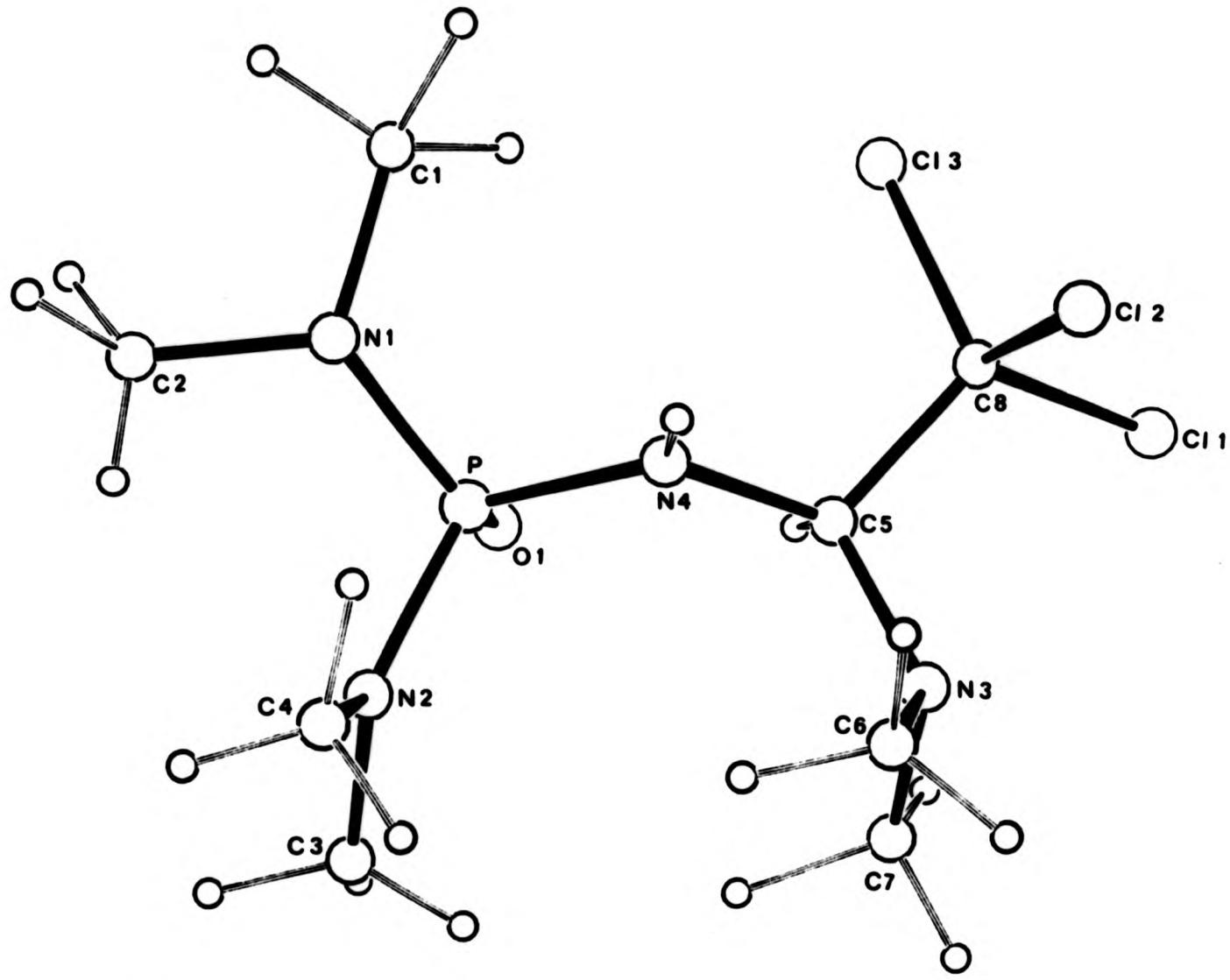


Figure 3.29 X-ray crystal structure of $(Me_2N)_2P(O)NHCH(CCl_3)NMe_2$

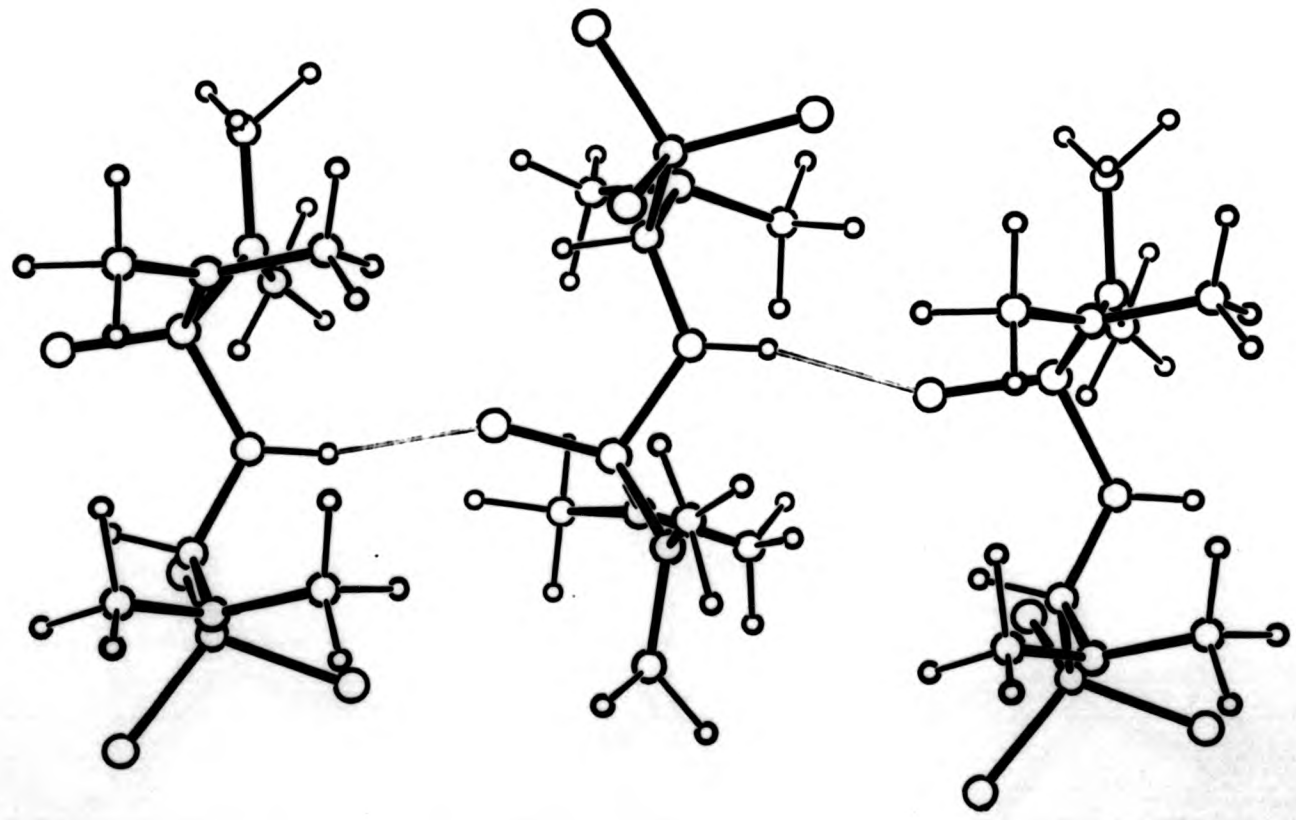
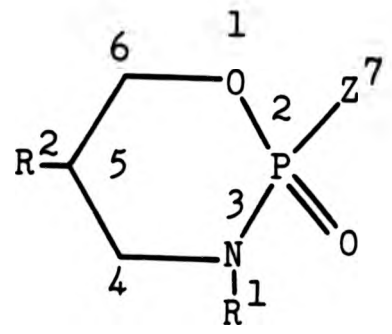


Figure 3.30 Diagram to show hydrogen-bonding in $(Me_2N)_2P(O)NHCH(CCl_3)NMe_2$.

lengths could be made. However, the determined P-N bond lengths are in good agreement with those determined for 1,3,2-oxaza-phosphorinanes (122, 123 and 124 see Table 3.23 for values).[39-41]



where
R^1= H, R^2=H, Z=$N(CH_2CH_2Cl)_2$ (122)
R^1=CH_2CH_2Cl, R^2=H, Z=$NHCH_2CH_2Cl$ (123)
R^1=H, R^2=Cl, Z=$N(CH_2CH_2Cl)_2$ (124)

A P=O bond length of 1.498 Å was determined which was found to be significantly longer than the P=O bond length reported for triphenylphosphine oxide,[42] tri-O-tolylphosphine oxide[43] and O,O-dimethyl-(1-hydroxy-2,2,2-trichloroethyl)-phosphonate ($[MeO]_2P(O)CH(CCl_3)OH$)[44] (see Table 3.24 for values), indicating that in $(Me_2N)_2P(O)NHCH(CCl_3)NMe_2$ the P=O bond has more single bond character and thus it is more highly polarised than in the former compounds.

Compound	Bond lengths (Å)		
	P=O	$P-N_3$	$P-N_7$
$Ph_3P=O$ [42]	1.46(1)	-	-
$(O-CH_3C_6H_5)_3P=O$ [43]	1.473	-	-
$(MeO)_2P(O)CH(CCl_3)OH$ [44]	1.426	-	-
122 [39]	1.470(4)	1.625(5)	1.630(4)
123 [40]	1.47	1.62	1.61
124 [41]	1.484(2)	1.626(2)	1.631(2)

Table 3.24 P=O and P-N bond lengths reported in the literature.

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CHAPTER 4

BIOLOGICAL TESTING

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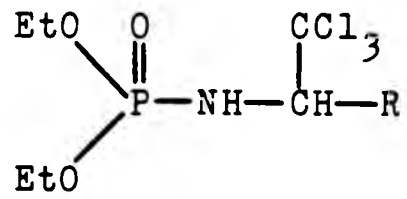
4.1 Introduction

A considerable number of organophosphorus compounds have been investigated for fungicidal activity and some have been developed commercially (see Chapter 1).

Recent studies on a series of O,O-diethyl N-(1-hydroxy-2,2,2-trichloroethyl)phosphoramidates (125) indicated that replacement of one of the ethoxy groups by dimethylamido in the compound in which R= imidazolyl, led to an increase in fungitoxicity.[1] Compounds (125) in which both the ethoxy groups were replaced by dimethylamido could not be obtained (see Chapter 1) and thus structure-activity studies could not be extended.



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The need to synthesise compounds which contained the bis(dimethylamido)phosphoryl group together with the trichloromethyl group in order to extend structure activity studies led to the synthesis of compounds of Types A and B. Compounds of Type C were also synthesised in the hope that some structure-activity correlation could be obtained between this type of compound and compounds of Type A.

Preliminary results from fungicidal screening and phytotoxicity tests are reported.

$(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)R^1$ ..... Type A

$(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)R^2$ ..... Type B

$(EtO)_2P(O)NHCH(CCl_3)NHC(O)R^3$ ..... Type C

4.2 Methods

4.2.1 Mycelial growth on agar (in vitro)

The fungi Piricularia oryzae, Rhizoctonia solani, Botrytis cinerea, Septoria nodorum, Fusarium avenaceum and Dreschlera sativa were used in these tests.

The test compounds were suspended in agar to give final concentrations of 300 ppm. The suspension was then sterilised and shaken thoroughly to distribute the compound evenly before pouring it into standard (9 cm diameter) Petri plates. A 5 mm plug with growing mycelia was placed upside down in the centre of each plate and the plates were then incubated at 28 ^{o}C. The growth diameter was measured and compared with untreated (control) plates.

4.2.2 Seed treatment (in vivo)

Spring-barley (Tellus#374) infected with Pyrenophora teres (subdivision Ascomycotina) conidial stage of Dreschlera teres and winter-wheat (Holme#3055) infected with Leptosphaeria nodorum (subdivision Ascomycotina) conidial stage Septoria nodorum were used in these experiments. The seeds were treated (10 min. in a laboratory seed treatment machine)

$(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)R^1$ ..... Type A

$(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)R^2$ ..... Type B

$(EtO)_2P(O)NHCH(CCl_3)NHC(O)R^3$ ..... Type C

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with formulations containing 20% (w/w or w/v) of test compound. When the compounds were sufficiently soluble in water, aqueous solutions were used. Compounds insoluble in water were applied as powders. The dosage rate was 2 cm^3 (2 g) per kilo of seed. 200 Seeds of each treatment were placed on a moistened filter-paper and incubated at 10 °C (3 days) and then at 20 °C (4 days). The coleoptiles and roots of the seeds were examined for disease symptoms and compared with untreated (control) seeds.

Inhibition of fungal growth in both *in vitro* and *in vivo* tests was assessed by visual comparison with untreated plates or seeds (control). The results are reported on a scale of 1 to 5 where:-

1 = 0 to 25%
2 = 26 to 50%
3 = 51 to 75%
4 = 76 to 99%
5 = 100%

4.2.3 Phytotoxicity tests

Seeds of winter-wheat and spring-barley from seed treatment tests were planted in moist sand and placed in a growing chamber at 10 °C (4 days) then at 20 °C (6-7 days).The germination and plant development were then assessed.

In germination tests, every seed (200) was examined and those germinating normally were counted. The

results are given as a relative percentage of seeds germinating normally in untreated control batches (i.e. 0= no significant effect; positive values= better in treated seeds than untreated; negative values= adverse effect on germination).

In the plant development tests early plant development (growth retardation and evenness) was assessed by visual observation and graded on a scale of 1-5 (control= 4).

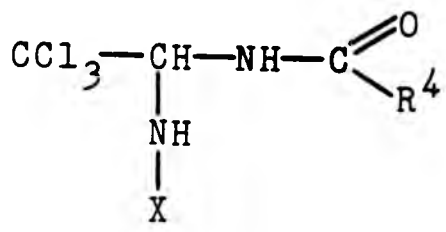
4.3 Results

The results obtained for compounds of Types A, B, and C are shown in Tables 4.1, 4.2, and 4.3 respectively.

4.4 Discussion

None of the compounds tested showed significantly high levels of activity against the organisms used in this preliminary screening. Some of the compounds of each series showed low activity against one or two of the fungal pathogens, but none showed a wide spectrum of activity. No structure- activity correlations could be obtained because of the low level of activity, which makes comparisons between compounds unreliable due to variable and sometimes large experimental errors. Tests at higher concentrations (*ca*. 1000 ppm) against the pathogens *Piricularia oryzae*, *Dreschlera teres* and *Septoria nodorum*, for which the compounds have generally shown some weak effect, may however yield useful structure-activity correlations.

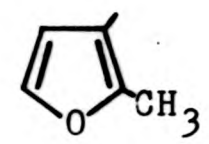
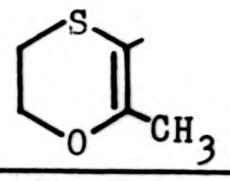
Compounds of the type 126, (where X= alkyl or aryl and R^4= H), synthesised by other workers as triforine analogues[2,3] were shown to exhibit good *in vivo* activity in leaf disc and systemic tests against powdery mildews of cucumber (caused by *Sphaerotheca fuliginea*) and that of wheat and barley (caused by *Erysiphe graminis*), but poor *in vitro* activity against a number of pathogens including *Botrytis cinerea* and *Septoria nodorum.*[2] The compounds synthesised in the present study (126, where X= $(EtO)_2P(O)$ or $(Me_2N)_2P(O)$ and R^4= H, alkyl, aryl etc.) are analogues of these compounds. It is therefore desirable that the new compounds reported in this thesis should be screened for activity against powdery mildews so that a better indication of their potential as fungicides can be obtained.



(126)

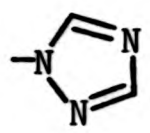
Compounds of Types A and B as a whole showed no phytotoxic effects, with some of the compounds of Type A improving the plant development of wheat. Compounds of Type C which contain the $(EtO)_2P(O)$ group, showed a small adverse effect on the germination of both wheat and barley, although this did not seem to affect plant development.

Table 4.1 Fungicidal screening and phytotoxicity test results for compounds of Type A, $(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)R^1$

Comp. No.*	R^1	in vitro[A]						in vivo[B]		Germination[C]		Bonitet	
		P.o.	R.s.	B.c.	S.n.	F.a.	D.s.	D.t.	S.n.	W	B	W	B
28	H	2	1	-	-	-	-	2	1	0	0	4.5	4
21	CH_3	1	1	-	-	-	-	1	1	0	0	4.5	3.5
26	CH_2Cl	1	1	-	-	-	-	2	1	+5	0	4.5	4
67	CCl_3	1	-	1	1	1	1	-	1	0	-	-	-
22	2,4-$Cl_2C_6H_3$	2	1	-	-	-	-	1	2	0	0	4.5	4
68		1	1	1	1	1	1	-	1	0	-	-	-
69		1	1	1	1	1	1	-	1	0	-	-	-
Panoctine[D]		5	4	5	5	1	4	2	3	+5	0	-	-

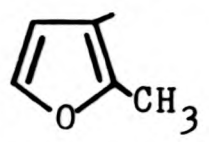
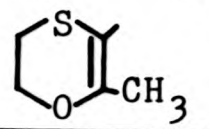
(see p. 177 for footnotes)

Table 4.2 Fungicidal screening and phytotoxicity test results for compounds of Type B, $(Me_2N)_2P(O)NHCH(CCl_3)NHC(O)CH_2R^2$

Comp. No.*	R^2	in vitro[A]						in vivo[B]	Germination[C]
		P.o.	R.s.	B.c.	S.n.	F.a.	D.s.	S.n.	W
42	$SC(S)OEt$	1	1	1	1	1	1	1	0
43	$SC(S)NMe_2$	1	1	1	1	1	1	1	0
44	$SC(S)NEt_2$	1	1	1	1	1	1	1	0
45		1	1	1	1	1	1	1	0
46	$S_2P(OEt)_2$	1	1	1	1	1	1	1	0
Panoctine[D]		5	4	5	5	1	4	3	+5

(see p. 177 for footnotes)

Table 4.3 Fungicidal screening and phytotoxicity test results for compounds of Type C, $(EtO)_2P(O)NHCH(CCl_3)NHC(O)R^3$

Comp. No.*	R^3	in vitro[A]		in vivo[B]		Germination[C]		Bonitet	
		P.o.	R.s.	D.t.	S.n.	W	B	W	B
29	H	1	1	1	1	-5	-5	3.5	4
14†	CH_3	2	1	1	1	-5	-5	4	4
27	CH_2Cl	1	1	1	1	0	0	4	4
30	CCl_3	1	1	1	1	-5	-5	4	4
25	$2,4\text{-}Cl_2C_6H_3$	1	1	1	1	0	-5	3	4
31		1	1	1	1	-5	0	4	3.5
19†		1	1	1	1	-5	0	4	4
Panoctine[D]		5	4	2	3	+5	0	-	-

(see p.177 for footnotes)

Footnotes to Tables 4.1, 4.2, and 4.3

* The Polytechnic of North London (PNL) registry number.

† These compounds were not synthesised during this programme.

A Tests at 300 ppm against the following:- P.o.= Piricularia oryzae; R.s.= Rhizoctonia solani; B.c.= Botrytis cinerea; S.n.= Septoria nodorum; F.a.= Fusarium avenaceum; D.s.= Dreschlera sativa.

B Tests using 20% (w/v or w/w) formulations at 2 cm^3 (2 g) per kilo of seeds against the following:- D.t.= Dreschlera teres; S.n.= Septoria nodorum.

C W= Winter-wheat (Holme # 3055); B= Spring-barley (Tellus # 374).

D Commercial Panoctine; obtained by guanidation of technical 1,17-diamino-9-azaheptadecane.[4]

\- Not tested.

References

1. P.J. Eccles, H.R. Hudson and M. Pianka, Unpublished work.
2. G.A. Carter, K. Chamberlain and R.L. Wain, Ann. Appl. Biol., 75, 49 (1973).
3. D. Brown and D. Woodcock, Pestic. Sci., 6, 347 (1975).
4. J.A.C. Bjorkland, Saltsjo-Boo and A.R. Reuterhall, Ger. Offen. 2,647,915 May 1977. Chem. Abstr., 87, 17304w (1977).

CHAPTER 5

EXPERIMENTAL

5.1 Starting materials and reagents

Ammonia gas	B.O.C. Ltd.
Dimethylamine	B.D.H. Ltd.
Phosphoryl chloride	B.D.H. Ltd.
O,O-Diethyl N-(1,2,2,2-tetrachloroethyl)-phosphoramidate	P. Eccles
Chloral	B.D.H. Ltd.
Thionyl chloride	B.D.H. Ltd.
Triethylamine	Hopkins and Williams
Pyridine	B.D.H. Ltd.
2,4-Dichlorobenzoic acid	Aldrich Chemical Co. Ltd.
2-Methyl-furan-3-carboxylic acid	KenoGard
Acetamide	B.D.H. Ltd.
N-Methylacetamide	Aldrich Chemical Co. Ltd.
Chloroacetamide	Aldrich Chemical Co. Ltd.
Trichloroacetamide	Aldrich Chemical Co. Ltd.
Formamide	B.D.H. Ltd.
N-Methylformamide	Aldrich Chemical Co. Ltd.
Potassium ethyl xanthate	Hopkins and Williams
Sodium dimethyldithio-carbamate	Hopkins and Williams
Sodium diethyldithio-carbamate	Hopkins and Williams
Sodium salt of 1,2,4-triazole	Aldrich Chemical Co. Ltd.
Sodium salt of imidazole	Aldrich Chemical Co. Ltd.

Dodecanol	Aldrich Chemical Co. Ltd.
Dodecanethiol	Aldrich Chemical Co. Ltd.
Ethanethiol	Aldrich Chemical Co. Ltd.
Butan-1-ol	B.D.H. Ltd.
Imidazole	Aldrich Chemical Co. Ltd.
2-Piperidone	Aldrich Chemical Co. Ltd.
Ethyl α-chloroaceto-acetate	P. Eccles
Sodium metal	B.D.H. Ltd.
Potassium metal	B.D.H. Ltd.
Sodium hyroxide	B.D.H. Ltd.
Potassium hydroxide	B.D.H. Ltd.
Sodium bicarbonate	B.D.H. Ltd.
Sodium chloride	B.D.H. Ltd.
Magnesium chloride	B.D.H. Ltd.
Ammonium chloride	B.D.H. Ltd.

5.2 Purification of starting materials, reagents and solvents

These were generally used without further purification.

Triethylamine was dried over potassium hydroxide and redistilled collecting the fraction boiling between 89 and 90 °C.

Solvents were dried as follows:-

(a) Benzene and toluene were dried over sodium wire.

(b) Methanol and ethanol were dried over molecular sieve (E.Merck type 3 Å).

5.3 Analytical methods

5.3.1 Infrared spectroscopy

Infrared spectra were recorded as potassium bromide discs on Pye Unicam SP2000 and SP3-200 double beam spectrophotometers.

5.3.2 Electronic spectra

Ultraviolet spectra were recorded using a Pye Unicam SP1800 double beam spectrophotometer.

5.3.3 Nuclear magnetic resonance spectroscopy (N.M.R.)

Routine ^{1}H N.M.R. spectra were obtained using a Perkin-Elmer R12B continuous wave spectrometer at a field of 60 MHz.

Higher field ^{1}H N.M.R. spectra were recorded at 80.02 MHz on a Brucker WP-80 Fourier transform spectrometer. ^{13}C and ^{31}P N.M.R. spectra were also recorded on this instrument using fields of 20.12 and 32.40 MHz respectively.

Chemical shifts for ^{1}H and ^{13}C spectra are given relative to the internal standard tetramethylsilane (TMS).

^{31}P chemical shifts are given relative to 85% phosphoric acid contained in an external capillary tube. The chemical shifts are reported as positive downfield with respect

to the standard.

5.3.4 Mass spectrometry

Routine mass spectra were recorded using an A.E.I. MS9 double focusing instrument.

High resolution electron impact (EI) spectra were recorded at the Physico-Chemical Measurements Unit, Harwell, using a V.G. Micromass ZAB-1F double focusing instrument at an electron energy of 70 eV using direct insertion and temperature scanning upto 170 ^{o}C. Accurate mass measurements were carried out at 10,000 resolution.

The mass spectra of compounds which failed to give molecular ions under EI conditions were recorded on the same instrument using a VG Fast Atom Bombardment (FAB) source and probe. Samples were prepared by dissolving or mulling in glycerol. Spectra were recorded by direct insertion of the sample into a primary beam of xenon atoms produced by an ion gun (Ion Tech Ltd.) operating at 1.0 mA and 8 KV.

5.3.5 Carbon, hydrogen and nitrogen analysis

All analyses for carbon, hydrogen and nitrogen were carried out in the Department of Chemistry using a Perkin-Elmer 240B microanalyser.

5.3.6 Chlorine analysis

A sample of the compound was accurately weighed by difference in a gelatine capsule. This was then inserted into a platinum basket together with a fuse of filter paper. The fuse was lit and the basket quickly placed into a 3 L flask previously charged with a solution of sodium hydroxide (ca. 10 pellets in 20 cm^3 of distilled water) and oxygen. After combustion was complete the flask was allowed to clear of fumes by allowing it to stand (30-60 mins). The contents of the flask were then transferred to a 250 cm^3 beaker with thorough washing to ensure complete transfer. The resultant solution was acidified with concentrated nitric acid using methyl red as indicator and titrated potentiometrically with 0.1 mol dm^{-3} silver nitrate solution.

5.3.7 Phosphorus analysis

An accurately weighed sample of the compound was transferred into a Kjeldahl flask together with concentrated sulphuric acid (15 cm^3) and a selenium Kjeldahl catalyst tablet. The flask was fitted with a water reservoir and suck back trap to isolate the contents from the atmosphere. The mixture was then heated under reflux until it was clear and colourless (1-4 hours). The system was allowed to cool and concentrated nitric acid (15 cm^3) was added. After this addition the mixture was heated under reflux until the evolution of nitrous oxide fumes had ceased and a colourless solution remained (2-4 hours). The solution was allowed to cool, diluted to about 100 cm^3 with distilled water and

transferred with thorough washing to a 600 cm^3 beaker. The solution was cooled in ice and neutralised with concentrated ammonia solution, then made just acid with 4 M hydrochloric acid, using methyl red as indicator. Magnesia mixture (containing 20% NH_4Cl and 10% $MgCl_2$)(25 cm^3) was added and the solution was made just alkaline using ammonia solution. A precipitate formed which was allowed to ripen overnight and then filtered off using a sintered glass crucible (No. 4). It was washed with dilute ammonia solution and redissolved in hot 4 M hydrochloric acid. Magnesia mixture (3 cm^3) was added to the resulting solution, which was then neutralised with dilute ammonia solution using methyl red as indicator. The precipitate that formed was left to ripen overnight, whence it was filtered off into an accurately weighed sintered glass crucible (No. 4). It was then washed successively with dilute ammonia solution (2 x 15 cm^3), ethanol (2 x 15 cm^3) and diethyl ether (2 x 15 cm^3), air dried and placed in a desiccator. The precipitate was weighed as magnesium ammonium phosphate hexahydrate ($MgNH_4PO_4.6H_2O$) and the phosphorus content of the original sample determined.

5.4 Abbreviations and a general note

5.4.1 Abbreviations

b = Broad

d = Doublet

dd = Doublet of doublets

dquin = Double quintet

FAB = Fast atom bombardment

^{1}H-BB = Proton broad band decoupled

m = Multiplet

odd = Overlapping doublet of doublets

q = Quartet

SFORD = Single frequency off-resonance decoupled

s = Singlet

t = Triplet

5.4.2 General note

The ^{1}H spectra of bis(dimethylamido)phosphoryl compounds obtained using DMSO-d_6 as solvent, generally gave an integration for the bis(dimethylamido)phosphoryl group which was greater than the expected 12 protons. This was due to residual solvent peaks which have a chemical shift of 2.5 ppm. The contribution of these residual peaks to the integration was dependent on the solubility of the sample.

Preparation of N,N,N',N'-tetramethylphosphorodiamidic chloride

Dimethylamine (177.6 g, 3.94 mol) was added dropwise (2 hours), from a dropping funnel cooled with a mixture of Cardice and acetone, to a well-stirred solution of phosphoryl chloride (151.8 g, 0.99 mol) in dry light petroleum (b.p. 60-80 °C) (1000 cm^3), which was cooled in ice. After the addition was complete, the reaction mixture was allowed to reach room temperature and then stirred for a further one hour. The dimethylamine hydrochloride which precipitated was filtered off in a closed sinter and washed well with benzene (3 x 75 cm^3). The solvent was then removed *in vacuo* and the residue distilled under reduced pressure, using a 15 cm column packed with Fenske glass helices to give N,N,N',N'-tetramethylphosphorodiamidic chloride (133.2 g, 79%), b.p. 66-68 °C at 0.1 mmHg (Lit.[1] 79-82 °C at 0.6 mmHg)(Found: Cl, 21.4. Calc. for $C_4H_{12}ClN_2OP$: Cl, 20.9%); δ(ppm): $^{31}P(^1H\text{-BB}, CDCl_3)$ 30.7.

Preparation of N,N,N',N'-tetramethylphosphoric triamide

Anhydrous ammonia gas was passed through a mechanically stirred solution of N,N,N',N'-tetramethylphosphorodiamidic chloride (23.52 g, 0.14 mol) in dry light petroleum (b.p. 60-80 °C)(500 cm^3) for four hours. A white solid separated. This solid was filtered off and washed with light petroleum (2 x 50 cm^3). The solid was then shaken with

chloroform (1 x 150 cm^3, 2 x 50 cm^3). The remaining white solid was filtered off and dried to give ammonium chloride (5.41 g, 73%). The filtrate was then evaporated to dryness using a rotary evaporator to give a white solid which was recrystallised from benzene to give N,N,N',N'-tetramethylphosphoric triamide (10.2 g, 49%), m.p. 108-110 °C (Lit.[2] 108 °C)(Found: P, 20.3. Calc. for $C_4H_{14}N_3OP$: P, 20.5%); $\lambda_{max}(CHCl_3)$: 242 nm (ε = 1.99 m^2mol^{-1}); δ(ppm): $^1H(CDCl_3)$ 2.66 (d, $^3J_{PNCH}$ 10.0, -P-N-$\underline{CH}_3$); $^{31}P(^1H\text{-BB}, CDCl_3)$ 22.6; m/z(%): 151(25, M^+), 108(17), 107(41), 88(3), 45(62), 44(100), 43(12), 42(18).

Preparation of N-(1-hydroxy-2,2,2-trichloroethyl)-acetamide

Equimolar amounts of chloral hydrate (36.5 g, 0.223 mol) and acetamide (13.16 g, 0.223 mol) were placed in a 100 cm^3 round-bottomed flask fitted with a reflux condenser. The mixture was then heated on a water-bath until it solidified (approx. 1 hour). The solid was washed well with distilled water (3 x 50 cm^3) to remove any unreacted starting materials. The resultant white solid was recrystallised from dilute alcohol to give N-(1-hydroxy-2,2,2-trichloroethyl)acetamide (27.35 g, 59%), m.p. 153-154 °C (Lit.[3] 158 °C)(Found: C, 23.1; H, 2.9; N, 6.3. Calc. for $C_4H_6Cl_3NO_2$: C, 23.3; H, 2.9; N, 6.8%).

Preparation of N-(1,2,2,2-tetrachloroethyl)acetamide

Thionyl chloride (8.92 g, 0.075 mol) and N-(1-hydroxy-2,2,2-trichloroethyl)acetamide (10.32 g, 0.05 mol) were heated under reflux, with stirring until the evolution of gases had ceased. To the hot, stirred reaction mixture, was then added light petroleum (b.p. 60-80 °C) which caused the precipitation of an off-white solid. The solid was filtered off, washed with light petroleum, and recrystallised from light petroleum (b.p. 60-80 °C) to give N-(1,2,2,2-tetrachloroethyl)acetamide (8.08 g, 72%), m.p. 128-129 °C (Lit.[4] 130-132 °C)(Found: C, 20.2; H, 2.4; N, 5.8. Calc. for $C_4H_5Cl_4NO$: C, 21.4; H, 2.2; N, 6.2%); $\lambda_{max}(CHCl_3)$: 242 nm (ε = 2.56 m^2mol^{-1}).

Preparation of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-acetamidoethyl)phosphoric triamide

Triethylamine (1.67 g, 0.016 mol) was added to a solution of N-(1,2,2,2-tetrachloroethyl)acetamide (3.71 g, 0.016 mol) in dry benzene (25 cm^3). A white precipitate formed immediately. The flask was stoppered and shaken gently. The mixture was allowed to stand for about fifteen minutes after which time, the solid was filtered off and washed with benzene (3 x 5 cm^3). The solid was dried to give triethylamine hydrochloride (1.81 g, 80%). To the combined filtrate and washings was then added N,N,N',N'-tetramethylphosphoric triamide (2.49 g, 0.016 mol). Benzene was then added to dissolve all the phosphoric triamide and the mixture allowed to stand for two days. A white solid crystallised. This was filtered off,

and recrystallised from a mixture of chloroform and light petroleum (b.p. 60-80 °C) to give N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-acetamidoethyl)phosphoric triamide (1.92 g, 34%), m.p. 200-202 °C (decomp.)(Found: C, 28.3; H, 5.3; N, 16.2; Cl, 30.9; P, 9.3; M^+, 338.0243. $C_8H_{18}Cl_3N_4O_2P$ requires: C, 28.3; H, 5.4; N, 16.5; Cl, 31.3; P, 9.1%; M^+, 338.0233); $\lambda_{max}(CHCl_3)$: 242 nm (ε = 2.80 m^2mol^{-1}); ν_{max}(KBr): 1685 (C=O), 1200 (P=O) cm^{-1}; δ(ppm): ^1H(DMSO-d_6) 1.92 (3H, s, -CO$\underline{CH_3}$), 2.51 (>12H,† dd, $^3J_{PNCH}$ 10.2, -P-N-$\underline{CH_3}$), 4.69 (1H, odd,† exchanges on shaking with D_2O, -P-$\underline{NH}$-CH-NH-), 5.67 (1H, m, becomes a doublet on shaking with D_2O, $^3J_{PNCH}$ 10.8, -P-NH-$\underline{CH}$-NH-), 8.36 (1H, d, $^3J_{HCNH}$ 9.1, exchanges on shaking with D_2O, -CH-$\underline{NH}$-CO-); ^{13}C(DMSO-d_6) 22.5 (s, -CO$\underline{CH_3}$), 36.2 (d, $^2J_{PNC}$ 3.7, -P-N-$\underline{CH_3}$), 68.9 (d, $^3J_{PNC}$ 5.1, -P-NH-$\underline{CH}$-NH-), 103.7 (d, $^3J_{PNCC}$ 11.0, -P-NH-CH-$\underline{CCl_3}$), 168.5 (s, C=O); $^{31}P(^1H$-BB, DMSO-d_6) 20.1; m/z(%): 338(4, M^+), 294(29), 253(57), 221(27), 218(11), 200(8), 179(15), 146(12), 146(12), 135(100), 108(20), 107(12), 44(55), 42(27).

Preparation of 2,4-dichlorobenzamide

Thionyl chloride (98.4 g, 0.83 mol, 60 cm^3) was added to 2,4-dichlorobenzoic acid (38.28 g, 0.20 mol) and the mixture heated under gentle reflux, with stirring, until the evolution of gases had ceased (approx. 4 hours). The excess thionyl chloride was then removed in vacuo, to leave a brown liquid which was distilled under reduced pressure to yield

† See abbreviations and the general note on p. 186.

2,4-dichlorobenzoyl chloride (24.87 g, 69%) b.p. 127-129 °C / 20 mmHg (Lit.[5] 146-149 °C / 28 mmHg). The 2,4-dichloro - benzoyl chloride was then dissolved in benzene (100 cm^3) and anhydrous ammonia gas passed through the stirred solution for 30 minutes. The resulting white solid was filtered off and the filtrate evaporated to dryness *in vacuo* to yield a white solid. The solids were combined and shaken well with distilled water (2 X 150 cm^3). The remaining white solid was filtered off and recrystallised from a mixture of IMS and water to yield 2,4-dichlorobenzamide (18.14 g, 80%) m.p. 188-189 °C (Lit.[6] 193-194 °C)(Found: C, 44.8; H, 2.9; N, 7.0 Calc. for $C_7H_5Cl_2NO$: C, 44.2; H, 2.6; N, 7.4%).

Preparation of *N*-(1-hydroxy-2,2,2-trichloroethyl)-2,4-dichlorobenzamide

Chloral (7.41 g, 0.05 mol) was added to 2,4-dichloro - benzamide (9.56 g, 0.05 mol) and the mixture heated on a water-bath for 2 hours. The resulting off-white solid was recrystallised from methanol/water to yield *N*-(1-hydroxy-2,2,2-trichloroethyl)-2,4-dichlorobenzamide (11.06 g, 66%) m.p. 146-148 °C* (Lit.[7] 155-157 °C)(Found: C, 32.1; H, 1.9; N, 4.2. Calc. for $C_9H_6Cl_5NO_2$: C, 32.0; H, 1,8; N, 4.1%).

* Melting point appears to vary with rate of heating. If heated very slowly softens at ~146 °C melting completely at ~184 °C i.e. conversion to 2,4-dichlorobenzamide.

Preparation of N-(1,2,2,2-tetrachloroethyl)-2,4-dichlorobenzamide

Thionyl chloride (36.1 g, 0.30 mol, 22 cm^3) was added to finely powdered N-(1-hydroxy-2,2,2-trichloroethyl)-2,4-dichlorobenzamide (10.0 g, 0.03 mol) and the mixture was heated under reflux for 3 hours, with stirring, on a water-bath. The mixture was allowed to stand overnight. The excess thionyl chloride was then removed under reduced pressure and light petroleum (b.p. 60-80 °C) added to the resultant yellow oil. This resulted in the formation of a white solid, which was filtered off and recrystallised from light petroleum (b.p. 60-80 °C) to give N-(1,2,2,2-tetrachloroethyl)-2,4-dichlorobenzamide (7.56 g, 72%), m.p. 124-125 °C (Found: C, 31.8; H, 1.7; N, 4.2. $C_9H_5Cl_6ON$ requires: C, 30.3; H, 1.4; N, 3.9%).

Preparation of N,N,N',N'-tetramethyl-N"-[2,2,2-trichloro-1-(2,4-dichlorobenzamido)ethyl] phosphoric triamide

Triethylamine (1.15 g, 0.011 mol) was added to a solution of N-(1,2,2,2-tetrachloroethyl)-2,4-dichlorobenzamide (4.02 g, 0.011 mol) in dry benzene (100 cm^3). A white precipitate formed immediately. The flask was stoppered and shaken gently. The mixture was allowed to stand for about fifteen minutes, after which the solid was filtered off, washed with benzene (3 X 15 cm^3) and dried to give triethyl-

amine hydrochloride (1.59 g, 102%). To the combined filtrate and washings was added solid N,N,N',N'-tetramethylphosphoric triamide (1.73 g, 0.011 mol). The mixture was shaken to dissolve the phosphoric triamide and allowed to stand overnight. A white solid crystallised out which was filtered off, washed well with benzene, and recrystallised from aqueous ethanol to give N,N,N',N'-tetramethyl-N"-[2,2,2-trichloro-1-(2,4-dichlorobenzamido)ethyl]phosphoric triamide (3.27 g, 62%), m.p. 205-206 °C (decomp.)(Found: C, 33.3; H, 4.0; N, 11.9; Cl, 38.1; P, 6.5; M+1, 469.0. $C_{13}H_{18}Cl_5N_4O_2P$ requires: C, 33.2; H, 3.8; N, 11.9; Cl, 37.7; P, 6.6%; M+1, 469.0); ν_{max}(KBr): 1670 (C=O), 1200 (P=O) cm^{-1}; δ(ppm): ^{1}H(DMSO-d_6) 2.55 (>12H, dd, $^3J_{PNCH}$ 10.2, -P-N-CH$_3$), 4.75 (1H, odd, exchanges using CD_3OD as solvent, -P-NH-CH-), 5.87 (1H, m, becomes a doublet using CD_3OD, $^3J_{PNCH}$ 10.7, -P-NH-CH-NH-), 7.55 (3H, m, aromatic protons), 9.11 (1H, d, $^3J_{HCNH}$ 8.8, exchanges using CD_3OD, -CH-NH-CO-); ^{13}C(DMSO-d_6) 36.2 (d, $^2J_{PNC}$ 4.0, -P-N-CH$_3$), 69.4 (d, $^2J_{PNC}$ 5.1, -P-NH-CH-NH-), 103.4 (d, $^3J_{PNCC}$9.6, -P-NH-CH-CCl$_3$), 127.5, 129.5, 130.2, 131.3, 134.5, 135.2 (s, aromatic carbons), 164.4 (s, C=O); ^{31}P(^{1}H-BB, DMSO-d_6) 19.9; m/z(%): 424(1), 279(5), 253(7), 200(4), 189(16), 173(53), 171(25), 135(100), 44(36), 36(24); FAB 469(3, M+1), 424(4), 390(11), 356(9), 253(16), 219(26), 173(40), 135(100), 107(30).

Preparation of diethyl N-[2,2,2-trichloro-1-(2,4-dichlorobenzamido)ethyl]phosphoramidate

Diethyl N-(1,2,2,2-tetrachloroethyl)phosphoramidate (5.07 g, 0.016 mol) was dissolved in dry benzene (100 cm^3). Triethylamine (1.62 g, 0.016 mol) was then added to this solution. A white precipitate formed immediately. The flask was stoppered, shaken gently and allowed to stand for fifteen minutes. The white precipitate was filtered off, washed with benzene (3 X 15 cm^3) and dried to give triethylamine hydrochloride (2.12 g, 96%). The filtrate and washings were combined and to this was added 2,4-dichlorobenzamide (2.99 g, 0.016 mol). The mixture was then heated under reflux, with stirring and the exclusion of moisture on a water-bath. Benzene was added to the hot reaction mixture in order to dissolve the 2,4-dichlorobenzamide which still remained. This resulted in a colourless solution which was heated under reflux for a further six hours. On cooling, a white solid crystallised out, which was filtered off and recrystallised from aqueous ethanol. The recrystallised solid was filtered off, air dried, ground and dried in a vacuum oven at 90 ^{o}C at 0.1 mmHg for several hours in order to remove residual solvent, to yield diethyl N-[2,2,2-trichloro-1-(2,4-dichlorobenzamido)ethyl] phosphoramidate (4.66 g, 62%), m.p. 203-204 ^{o}C(Found: C, 33.1; H, 3.4; N, 6.0; Cl, 37.8; P, 6.5; M+1, 470.8. $C_{13}H_{16}Cl_5N_2O_4P$ requires: C, 33.0; H, 3.4; N, 5.9; Cl, 37.6; P, 6.6%; M+1, 470.9); ν_{max}(KBr): 1662 (C=O), 1245 (P=O) cm^{-1}; δ(ppm): ^{1}H(DMSO-d_6) 1.23 (6H, t, $^{3}J_{HCCH}$ 7.1, -P-O-CH_2-$\underline{CH}_3$), 4.00 (4H, dquin, -P-O-$\underline{CH}_2$-CH_3), 5.91 (2H, m, becomes a doublet of 1H on shaking with D_2O, $^{3}J_{PNCH}$ 11.23,

-P-NH-CH-NH-), 7.54 (3H, m, aromatic protons), 9.33 (1H, d, $^{3}J_{HCNH}$ 7.8, exchanges with D_2O , -CH-NH-CO-); ^{13}C(DMSO-d_6) 15.9 (d, $^{3}J_{POCC}$ 7.4, -P-O-CH_2-CH_3), 62.1 (dd, $^{2}J_{POC}$ 5.1, -P-O-CH_2-CH_3), 69.6 (d, $^{2}J_{PNC}$ 5.1, -P-NH-CH-NH-), 102.4 (d, $^{3}J_{PNCC}$ 12.5, -P-NH-CH(CCl_3)NH), 127.4, 129.4, 130.3, 131.3, 134.4, 135.2 (s, aromatic carbons), 164.9(s, C=O); $^{31}P(^{1}H$-BB, DMSO-d_6) 5.9; m/z(%): 398(3), 173(100), 164(8), 145(10), 137(12), 109(12), 81(10); FAB 471(4, M+1), 437(4), 403(2), 211(49), 186(27), 181(7), 154(100), 139(19), 126(11), 98(13).

Preparation of ethyl 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylate

A solution of 2-mercaptoethanol (16.0 g, 0.2 mol) and ethyl α-chloroacetoacetate (33.0 g, 0.2 mol) in benzene (200 cm^3), was stirred vigorously. To this stirred solution was added dropwise (1 hour), a solution of sodium bicarbonate (22.0 g, 0.26 mol) in water (200 cm^3). The reaction mixture was then stirred for a further 2 hours. The aqueous layer was saturated with sodium chloride and the benzene layer was separated. The aqueous layer was extracted with benzene (3 X 30 cm^3), and the combined extracts dried over anhydrous sodium sulphate. The solution was filtered and toluene-4-sulphonic acid (0.2 g) was added to the filtrate. The mixture was refluxed in a Dean and Stark apparatus in order to remove water (3.1 cm^3, 0.17 mol, 86%). The solvent was then removed in vacuo and the residue distilled under reduced pressure

to give ethyl 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylate (20.52 g, 55%), b.p. 129-132 °C at 20 mmHg(Lit.[8] b.p. 120-122 °C at 15 mmHg); δ(ppm): ^{1}H(60 MHz, $CDCl_3$) 1.3 (3H, t, -O-CH_2-$\underline{CH_3}$), 2.3 (3H, s, -S-C=C($\underline{CH_3}$)-O-), 3.0 (2H, t, -S-$\underline{CH_2}$-CH_2-O-), 4.2 (4H, m, -O-$\underline{CH_2}$-CH_3, -S-CH_2-$\underline{CH_2}$-O-).

Preparation of 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylic acid

A solution of sodium hydroxide (6.50 g, 0.16 mol) in distilled water (25 cm^3) was added to a solution of ethyl 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylate (15.23 g, 0.081 mol) in ethanol (15 cm^3). The reaction mixture was then heated under reflux for three hours, allowed to cool and then acidified with dilute hydrochloric acid. An off white solid precipitated which was filtered off, washed well with distilled water and dried in vacuo to give 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylic acid (12.51 g, 97%), m.p. 176-178 °C (Lit.[8] 179-181 °C).

Preparation of 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylic acid amide

Thionyl chloride (42.6 g, 0.36 mol, 26 cm^3) was added dropwise to a solution of 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylic acid (11.6 g, 0.0725 mol) in chloroform (35 cm^3). The reaction mixture was then heated under reflux for three hours. The solvent and other volatiles were removed

in vacuo to give the crude acid chloride. This was dissolved in benzene (100 cm^3). The solution was cooled in ice and vigorously stirred. Anhydrous ammonia gas was then passed through the solution until the exothermic reaction had subsided. An off white solid was formed, which was filtered off and recrystallised from water (approx. 500 cm^3) and a little charcoal. The resultant white solid was filtered off, washed with water and dried *in vacuo* to give 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylic acid amide (6.80 g, 59%), m.p. 170-172 °C (Lit.[8] m.p. 174.5-175 °C)(Found: C, 44.4; H, 5.7; N, 8.5. Calc. for $C_6H_9NO_2S$: C, 45.3; H, 5.7; N, 8.8%); δ(ppm): ^1H(DMSO-d_6) 2.04 (3H, s, -S-C(CONH)=C($\underline{CH_3}$)-O-), 2.97 (2H, t, -S-$\underline{CH_2}$-CH_2-O-), 4.22 (2H, t, -S-CH_2-$\underline{CH_2}$-O-), 7.08 (2H, bs, -CO$\underline{NH_2}$); ^{13}C(DMSO-d_6, symbols in brackets give multiplicity of signals in the SFORD spectrum) 20.2 (q, $-CH_3$), 24.1 (t, -S-$\underline{CH_2}$-CH_2-O-), 65.6 (t, -S-CH_2-$\underline{CH_2}$-O-), 99.0 (s, -S-$\underline{C}$($CONH_2$)=C(CH_3)-O-), 151.2 (s, -S-C($CONH_2$)=$\underline{C}$(CH_3)-O-), 167.6 (s, $-C(O)NH_2$).

Preparation of 5,6-dihydro-2-methyl-1,4-oxathiin-3-[*N*-(1'-hydroxy-2',2',2'-trichloroethyl)]carboxamide

To a well stirred suspension of 5,6-dihydro-2-methyl-1,4-oxathiin-3-carboxylic acid amide (3.90 g, 0.0245 mol) in chloroform (25 cm^3) was added a solution of chloral (3.62 g, 0.0246 mol) in chloroform (15 cm^3) and the mixture heated under reflux for three hours. This resulted in a

colourless solution, from which a white solid crystallised on cooling. The solid was filtered off and recrystallised from a mixture of chloroform and light petroleum (b.p. 40-60 °C) to yield 5,6-dihydro-2-methyl-1,4-oxathiin-3-[N-(1'-hydroxy-2',2',2'-trichloroethyl)] carboxamide(4.22 g, 56%), m.p. 132-133 °C (Lit.[9] m.p. 141-143 °C)(Found: C, 31.3; H, 3.3; N, 4.6. Calc. for $C_8H_{10}Cl_3NO_3S$: C, 31.3; H, 3.3; N, 4.6%); δ(ppm): ^1H(DMSO-d_6) 2.05 (3H, s, $-CH_3$), 3.00 (2H, t, -S-$\underline{CH_2}$-CH_2-O-), 4.26 (2H, m, -S-CH_2-$\underline{CH_2}$-O-), 5.75 (1H, dd, $^3J_{HCOH}$ 6, -NH-$\underline{CH}$-OH), 7.75 (1H, d, $^3J_{HCOH}$ 6.3, -NH-CH-$\underline{OH}$), 8.10 (1H, d, $^3J_{HCNH}$ 8.8, -$\underline{NH}$-CH-OH); ^{13}C(DMSO-d_6) 20.4 ($-CH_3$), 23.9 (-S-$\underline{CH_2}$-CH_2-O-), 66.0 (-S-CH_2-$\underline{CH_2}$-O-), 80.0 (NH-$\underline{CH}$-OH), 98.1 (-S-$\underline{C}$=C-O-), 102.4 ($-CCl_3$), 152.7 (-S-C=$\underline{C}$-O-), 165.7 (C=O).

Preparation of N,N,N',N'-tetramethyl-N"-[2,2,2-trichloro-1-(5',6'-dihydro-2'-methyl-1',4'-oxathiin-3'-carboxamido)ethyl] phosphoric triamide

Thionyl chloride (15.6 g, 0.13 mol, 9.5 cm^3), was added dropwise,to a stirred boiling solution of 5,6-dihydro-2-methyl-1,4-oxathiin-3- N-(1'-hydroxy-2',2',2'-trichloroethyl) carboxamide (4.0 g, 0.013 mol) in chloroform (30 cm^3). After the addition was complete, the mixture was heated under reflux for a further three hours. The solvent, excess thionyl chloride and any other volatiles were then removed in vacuo to give a yellow oil which failed to crys-

tallise from light petroleum (b.p. 40-60 °C). The solvent was again removed *in vacuo* and the residue put under high vacuum for two hours. The residue was dissolved in benzene (100 cm^3). To this solution was added triethylamine (1.34 g, 0.013 mol). The flask was stoppered, shaken gently and allowed to stand for fifteen minutes. The white solid which had formed immediately, was filtered off, washed with benzene (3 X 30 cm^3) and dried as triethylamine hydrochloride (1.71 g, 94%). It was identified by ^1H NMR. To the combined filtrate and washings was added *N*,*N*,*N*',*N*'-tetramethylphosphoric triamide (1.97 g, 0.013 mol) and the mixture allowed to stand overnight. An off-white solid crystallised out, which was filtered off and recrystallised from aqueous ethanol to give *N*,*N*,*N*',*N*'-tetramethyl-*N*"-[2,2,2-trichloro-1-(5',6'-dihydro-2'-methyl-1',4'-oxathiin-3'-carboxamidoethyl)]phosphoric triamide (3.19 g, 56%). This was shown by ^1H, ^{13}C NMR, mass spectrometry and elemental analysis to contain benzene. The analytical sample was obtained by repeatedly recrystallising the compound from aqueous ethanol, followed by grinding the solid to a fine powder and drying *in vacuo* at 100 °C at 0.1 mmHg for several hours each time. m.p. 197-198 °C(decomp.) (Found: C, 32.8; H, 5.0; N, 12.6; P, 6.8; M^+, 438.0205. $C_{12}H_{22}Cl_3N_4O_3PS$ requires: C, 32.8; H, 5.0; N, 12.7; P, 7.0%; M^+, 438.0215); ν_{max}(KBr): 1665 (C=O), 1180 (P=O) cm^{-1}; δ(ppm): ^1H(DMSO-d_6) 2.07 (3H, s, -C=C-$\underline{CH}_3$), 2.51 (12H, dd, $^3J_{PNCH}$ 10.2, -P-N-$\underline{CH}_3$), 3.04 (2H, t, -S-$\underline{CH}_2$-CH_2-O-), 4.29 (2H, q, -S-CH_2-$\underline{CH}_2$-O-), 5.01 (1H, exchanges when using CD_3OD as

solvent, -P-NH-CH-), 5.78 (1H, m, becomes a doublet using CD_3OD, $^3J_{PNCH}$ 11.0, -P-NH-CH-NH-), 7.94 (1H, d, $^3J_{HCNH}$ 9.3, exchanges using CD_3OD, -CH-NH-CO-); ^{13}C(DMSO-d_6) 20.3 (s, -S-C=C(CH_3)-O-), 23.8 (s, -S-CH_2-CH_2-O-), 36.1 (d, $^2J_{PNC}$ 3.4, -P-N-CH_3), 66.1 (s, -S-CH_2-CH_2-O-), 69.2 (d, $^2J_{PNC}$ 4.7, -P-NH-CH-NH-), 97.7 (s, -S-C=C-O-), 103.9 (d, $^3J_{PNCC}$ 9.5, -P-NH-CH-CCl_3), 153.1 (s, -S-C=C-O-), 164.5 (s, C=O); ^{31}P (^{1}H-BB, DMSO-d_6) 20.3; m/z(%): 438(2, M^+), 276(21), 253(8), 159(10), 143(25), 141(31), 135(85), 87(13), 44(58), 43(100), 42(21).

Preparation of N-(1-hydroxy-2,2,2-trichloroethyl)-formamide

Chloral (44.1 g, 29.0 cm^3, 0.3 mol) was added dropwise with stirring to formamide (13.5 g, 0.3 mol) and the mixture cooled in ice until the addition was complete. The mixture was allowed to reach room temperature when an exothermic reaction took place. The mixture was allowed to stand for a further two hours at room temperature. A pale yellow resinous solid was obtained, which when triturated with hot chloroform solidified to give N-(1-hydroxy-2,2,2-trichloroethyl)formamide (40.1 g, 69%), m.p. 116-117 °C (Lit.[10] m.p. 118 °C).

Preparation of N-(1,2,2,2-tetrachloroethyl)formamide

Thionyl chloride (68.0 g, 41.5 cm^3, 0.57 mol) was added

to N-(1-hydroxy-2,2,2-trichloroethyl)formamide (20.0 g, 0.1 mol) and the mixture gently heated under reflux with stirring for three hours. The excess thionyl chloride was removed under reduced pressure to give a yellow oil. Petroleum (b.p. 60-80 °C) was then added to the warm, well stirred oil, which resulted in the precipitation of an off white solid. The solid was filtered off and recrystallised from petroleum (b.p. 60-80 °C) to give N-(1,2,2,2-tetrachloroethyl)formamide (6.35 g, 29%), m.p. 99-100 °C (Lit.[4] m.p. 95-97 °C)(Found: C, 16.6; H, 1.7; N, 6.9. Calc. for $C_3H_3Cl_4NO$: C, 17.1; H, 1.4; N, 6.6%).

Preparation of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-formamidoethyl)phosphoric triamide

To a solution of N-(1,2,2,2-tetrachloroethyl)formamide (6.0 g, 0.028 mol) in dry benzene (100 cm^3) was added triethylamine (2.94 g, 0.029 mol). A white precipitate formed immediately. The flask was stoppered and shaken gently. The mixture was allowed to stand for 15 minutes after which the solid was filtered off and washed with benzene (2 X 50 cm^3) to give triethylamine hydrochloride (3.83 g, 96%). To the combined filtrate and washings was then added N,N,N',N'-tetramethylphosphoric triamide (4.31 g, 0.029 mol) and the mixture left to stand overnight. A white solid crystallised out, which was filtered off and recrystallised from a mixture of chloroform and light petroleum (b.p. 60-80 °C) to give

N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-formamidoethyl)-phosphoric triamide (5.73 g, 61%), m.p. 190-191 °C (decomp.) (Found: C, 26.1; H, 4.9; N, 17.4; Cl, 32.9; P, 9.4; M^+, 324.0061. $C_7H_{16}Cl_3N_4O_2P$ requires: C, 25.8; H, 4.9; N, 17.2; Cl, 32.7; P, 9.5%; M^+, 324.0076); ν_{max}(KBr): 1675 (C=O), 1185 (P=O) cm^{-1}; δ(ppm): ^1H(DMSO-d_6) 2.51 (12H, dd, $^3J_{PNCH}$ 10.2, -P-N-CH$_3$), 5.21 (1H, odd, exchanges when CD_3OD was used as solvent, -P-NH-CH-NH-), 5.81 (1H, m, becomes a doublet using CD_3OD, $^3J_{PNCH}$ 10.5, -P-NH-CH-NH-), 8.15 (1H, d, $^3J_{HNCH}$ 1.2, becomes singlet using CD_3OD, -NH-CHO), 8.65 (1H, bd, $^3J_{HCNH}$ 9.3, exchanges using CD_3OD, -CH-NH-CO-), ^{13}C(DMSO-d_6) 36.2 (d, $^2J_{PNC}$ 3.7, -P-N-CH$_3$), 67.6 (d, $^2J_{PNC}$ 5.1, -P-NH-CH-NH-), 103.4 (d, $^3J_{PNCC}$ 10.3, -P-NH-CH-CCl$_3$), 160.4 (s, C=O); ^{31}P(^1H-BB, DMSO-d_6) 20.1; m/z(%): 324(1, M^+), 280(3), 279(3), 260(6), 253(11), 207(4), 200(4), 179(7), 135(100), 108(10), 107(5), 92(9), 44(72), 36(19).

Preparation of diethyl N-(2,2,2-trichloro-1-formamidoethyl)phosphoramidate

Diethyl N-(1,2,2,2-tetrachloroethyl)phosphoramidate (14.61 g, 0.046 mol) was dissolved in dry benzene (120 cm^3). Triethylamine (4.64 g, 0.046 mol) was then added to this solution. A white precipitate formed immediately. The flask was stoppered, shaken gently and allowed to stand for 15 minutes. The white precipitate was filtered off and washed with benzene (2 X 50 cm^3) and dried to give triethylamine

hydrochloride (6.20 g, 98%). To the combined filtrate and washings was then added formamide (2.02 g, 0.045 mol) and the mixture refluxed with stirring and the exclusion of moisture for three hours. The mixture was allowed to stand overnight which resulted in a white solid crystallising out. The white solid was filtered off, washed with benzene (2 X 25 cm^3) and diethyl ether (2 X 25 cm^3) to give diethyl N-(2,2,2-trichloro-1-formamidoethyl)phosphoramidate (10.30 g, 70%), m.p. 146-147 °C (Found: C, 26.5; H, 4.4; N, 8.3; Cl, 32.5; P, 9.2; M+1, 326.98. $C_7H_{14}Cl_3N_2O_4P$ requires: C, 25.6; H, 4.3; N, 8.5; Cl, 32.5; P, 9.5%; M+1, 326.98); ν_{max}(KBr): 1670 (C=O), 1240 (P=O) cm^{-1}; δ(ppm): ^{1}H(DMSO-d_6) 1.20 (6H, t, $^3J_{HCCH}$ 7.1, -P-O-CH_2-$\underline{CH}_3$), 3.95 (4H, dquin, -P-O-$\underline{CH}_2$-CH_3), 5.94 (2H, m, becomes doublet using CD_3OD as solvent, $^3J_{PNCH}$ 10.7, -P-$\underline{NH}$-$\underline{CH}$-NH-), 8.16 (1H, d, becomes singlet using CD_3OD, -NH$\underline{CHO}$), 8.83 (1H, bd, $^3J_{HNCH}$ 9.3, exchanges using CD_3OD, -CH-$\underline{NH}$-CHO); ^{13}C(DMSO-d_6) 15.9 (d, $^3J_{POCC}$ 7.4, -P-O-CH_2-$\underline{CH}_3$), 61.9 (odd, -P-O-$\underline{CH}_2$-CH_3), 67.7 (d, $^2J_{PNC}$ 5.1, -P-NH-$\underline{CH}$-CCl_3), 102.4 (d, $^3J_{PNCC}$ 12.5, -P-NH-CH-$\underline{CCl}_3$), 160.7 (s, C=O); ^{31}P(^{1}H-BB, DMSO-d_6) 6.1; m/z(%): 262(6), 254(5), 247(5), 226(3), 209(30), 181(100), 164(12), 153(28), 137(30), 125(46), 109(35), 98(16), 81(31), 80(19); FAB 327(32, M+1), 293(18), 282(37), 248(34), 214(14), 209(11), 181(30), 154(100), 126(25), 109(17), 98(56).

Preparation of N-(1-hydroxy-2,2,2-trichloroethyl)-trichloroacetamide

Anhydrous chloral (18.3 g, 11.9 cm^3, 0.12 mol) was added to trichloroacetamide (10.0 g, 0.062 mol). The stirred reaction mixture was then heated under reflux with the exclusion of moisture for seven hours. The reaction mixture was then allowed to cool a little and diethyl ether (25 cm^3) was added, to give a colourless solution which was stored at -18 °C overnight. A white crystalline solid was formed which was filtered off and recrystallised from diethyl ether to give N-(1-hydroxy-2,2,2-trichloroethyl)trichloroacetamide (8.47 g, 44%), m.p. 127-129 °C (Lit.[11] m.p. 115 °C. The method given in this reference did not yield the required compound) (Found: C, 15.6; H, 1.01; N, 4.5. Calc. for $C_4H_3Cl_6NO_2$: C, 15.5; H, 0.97; N, 4.5%); δ(ppm): ^1H(60 MHz, DMSO-d_6) 5.7 (1H, dd, $^3J_{HCOH}$ 7, becomes a singlet on shaking with D_2O, -NH-CH-OH), 8.1 (1H, d, $^3J_{HCOH}$ 7, exchanges with D_2O, -NH-CH-OH), 9.4 (1H, d, $^3J_{HNCH}$ 7, exchanges with D_2O, -NH-CH-OH); ^{13}C(DMSO-d_6): 83.0 (-NH-CH-OH), 92.3 (CCl_3CONH), 101.6 (-NHCH-CCl_3), 161.4 (C=O).

Preparation of N-(1,2,2,2-tetrachloroethyl)-trichloroacetamide

Thionyl chloride (31.2 g, 19.0 cm^3, 0.26 mol) was added to N-(1-hydroxy-2,2,2-trichloroethyl)trichloroacetamide (8.3 g, 0.027 mol) and the mixture heated under reflux for three hours. The excess thionyl chloride was removed *in vacuo* to give a white solid. The solid was heated with light

petroleum (b.p. 40-60 °C) (350 cm^3). Not all the solid dissolved thus the mixture was filtered hot and the residue was examined by ^1H NMR. It was shown to be trichloroacetamide. The filtrate was stored at 4 °C overnight which resulted in a white solid crystallising out. This solid was filtered off and also shown by ^1H NMR to trichloroacetamide. The filtrate was evaporated to dryness *in vacuo* to give a white solid which was recrystallised from light petroleum (b.p. 60-80 °C)(approx. 50 cm^3) to give N-(1,2,2,2-tetrachloroethyl)trichloroacetamide (3.05 g, 35%), m.p. 97-99 °C (Found: C, 14.4; H, 0.86; N, 4.7; Cl, 76.4; $C_4H_2Cl_7NO$ requires: C, 14.4; H, 0.61; N, 4.3; Cl, 75.6%); δ(ppm): ^1H(60 MHz, DMSO-d_6) 5.8 and 6.7 ca. ratio 3:1 (1H, d, $^3J_{HNCH}$ 9, -NH-CH-Cl), 9.4 and 10.7 ca. ratio 3:1 (1H, d, $^3J_{HNCH}$ 9, exchanges with D_2O, -NH-CH-Cl).

Preparation of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-trichloroacetamidoethyl)phosphoric triamide

Triethylamine (0.46 g, 0.0046 mol) was added to a solution of N-(1,2,2,2-tetrachloroethyl)trichloroacetamide (1.50 g, 0.0046 mol) in dry benzene (25 cm^3). A white solid formed immediately. The flask was stoppered, shaken gently and allowed to stand for fifteen minutes. The solid was filtered off, washed with benzene (3 X 10 cm^3) and dried to give triethylamine hydrochloride (0.61 g, 97%). To the combined filtrate and washings was added N,N,N',N'-tetramethylphosphoric triamide (0.69 g, 0.0046 mol) and the mixture allowed to

stand overnight. A white solid crystallised out which was filtered off, washed well with benzene, and recrystallised from a mixture of chloroform and light petroleum (b.p. 60-80 °C) to give N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-trichloroacetamidoethyl)phosphoric triamide.(0.87 g, 43%), m.p. 180-181 °C (decomp.) (Found: C, 21.7; H, 3.4; N, 12.4; P, 7.2; M+1, 440.95. $C_8H_{15}Cl_6N_4O_2P$ requires: C, 21.7; H, 3.4; N, 12.6; P, 7.0%; M+1, 440.91); ν_{max}(KBr): 1710 (C=O), 1168 (P=O) cm^{-1}; δ(ppm): ^{1}H(DMSO-d_6) 2.54 (12H, dd, $^3J_{PNCH}$ 10.2, -P-N-CH$_3$), 4.98 (1H, odd, exchanges with D_2O, -P-NH-CH-NH-), 5.71 (1H, m, becomes doublet on shaking with D_2O, $^3J_{PNCH}$ 11.5, -P-NH-CH-NH-), 9.34 (1H, bs, exchanges with D_2O, -CH-NH-CO-); ^{13}C(DMSO-d_6) 36.1 (d, $^2J_{PNC}$ 3.4, -P-N-CH$_3$), 71.3 (d, $^2J_{PNC}$ 5.4, -P-NH-CH-CCl$_3$), 92.2 (s, -COCCl$_3$), 102.9 (d, $^3J_{PNCC}$ 8.8, -P-NH-CH-CCl$_3$), 160.5 (s, C=O); ^{31}P(^{1}H-BB, DMSO-d_6) 20.2; m/z(%): 396(1), 323(4), 253(4), 235(2), 135(100), 126(3), 108(3), 92(7), 44(61); FAB 441(1, M+1), 280(10), 253(10), 246(9), 244(4), 221(4), 200(2), 135(100), 126(9), 121(10), 107(18), 108(17), 92(15), 44(61).

Preparation of diethyl N-(2,2,2-trichloro-1-trichloroacetamidoethyl)phosphoramidate

Diethyl N-(1,2,2,2-tetrachloroethyl)phosphoramidate (10.80 g, 0.034 mol) was dissolved in dry benzene (100 cm^3). Triethylamine (3.44 g, 0.034 mol) was then added to this solution. A white precipitate formed immediately. The flask

was stoppered, shaken gently and allowed to stand for fifteen minutes. The white precipitate was filtered off, washed with benzene (2 X 50 cm^3) and dried to give triethylamine hydrochloride (4.60 g, 98%). The filtrate and washings were combined. To the combined filtrate and washings was then added trichloroacetamide (5.51 g, 0.034 mol) and the mixture heated under reflux with stirring for eight hours. The mixture was allowed to stand overnight which resulted in a white solid crystallising out. The white solid was filtered off and boiled with diethyl ether (150 cm^3) on a water-bath, in order to remove any unreacted trichloroacetamide. The mixture was filtered hot and the remaining white solid recrystallised from benzene to give diethyl N-(2,2,2-trichloro-1-trichloroacetamidoethyl)phosphoramidate (10.11 g, 67%), m.p. 183-184 °C (Found: C, 21.3; H, 3.1; N, 6.3; Cl, 47.9; P, 7.1; M+1, 442.84. $C_8H_{13}Cl_6N_2O_4P$ requires: C, 21.6; H, 2.9; N, 6.3; Cl, 47.9; P, 7.0%; M+1, 442.88); ν_{max}(KBr): 1700 (C=O), 1245 (P=O) cm^{-1}; δ(ppm): ^{1}H(DMSO-d_6) 1.24 (6H, t, $^3J_{HCCH}$ 7.1, -P-O-CH_2-$\underline{CH}_3$), 4.00 (4H, dquin, -P-O-$\underline{CH}_2$-CH_3), 5.64 (2H, bd, sharpens and reduces to 1H on shaking with D_2O, $^3J_{PHCH}$ 12.2, -P-$\underline{NH}$-$\underline{CH}$-NH), 9.32 (1H, bs, exchanges with D_2O, -CH-$\underline{NH}$-CO); ^{13}C(DMSO-d_6) 15.9 (d, $^3J_{POCC}$ 7.4, -P-O-CH_2-$\underline{CH}_3$), 62.4 (odd, -P-O-$\underline{CH}_2$-CH_3), 71.4 (d, $^2J_{PNC}$ 3.7, -P-NH-$\underline{CH}$-), 90.7 (s, -CO$\underline{CCl}_3$), 101.9 (d, $^3J_{PNCC}$ 10.4, -P-NH-CH-$\underline{CCl}_3$), 160.8 (s, C=O); ^{31}P(^{1}H-BB, DMSO-d_6) 5.3; m/z(%): 325(81), 297(6), 282(10), 254(3), 226(6), 190(9), 164(33), 137(100), 126(5), 117(10), 109(94), 108(16), 107(10), 81(64), 44(81); FAB 443(10, M+1), 409(6), 282(74),

254(16), 248(30), 226(20), 190(14), 181(31), 154(100), 126(36), 103(19), 98(59).

Preparation of 2-methyl-furan-3-carboxamide

Redistilled thionyl chloride (42.7 g, 70.0 cm^3, 0.36 mol) was added to 2-methyl-furan-3-carboxylic acid (20.5 g, 0.16 mol) and the mixture heated at 40 °C for five hours. The excess thionyl chloride was removed under reduced pressure to give an orange oil. This oil was distilled under reduced pressure using a short Vigreux column to give 2-methyl-furan-2-carboxylic acid chloride as a colourless liquid (18.9 g, 82%) b.p. 38-39 °C at 3.5 mmHg. The chloride was dissolved in petroleum (b.p. 60-80 °C)(350 cm^3) and anhydrous ammonia passed through the well stirred solution for three hours. The resulting white solid was filtered off and extracted with diethyl ether (100 cm^3) and chloroform (2 X 100 cm^3). The remaining white solid, ammonium chloride (6.67 g, 95%) was filtered off. The extracts were combined and the solvent removed *in vacuo*, to give a white solid. This solid was recrystallised from benzene to give 2-methyl-furan-3-carboxamide (15.2 g, 93%), m.p. 85-86 °C (Lit.[12] m.p. 90 °C)(Found: C, 58.9; H, 5.8; N, 11.4. Calc. for $C_6H_7NO_2$: C, 57.6; H, 5.6; N, 11.2%).

Preparation of *N*-(1-hydroxy-2,2,2-trichloroethyl)-2'-methyl-furan-3'-carboxamide

Chloral (17.7 g, 11.6 cm^3, 0.12 mol) was added to 2-methyl-furan-3-carboxamide (5.0 g, 0.04 mol) and the mixture heated under reflux, with stirring and the exclusion of moisture for three hours. The reaction mixture was allowed to cool and taken up in hot diethyl ether. To this was added hot petroleum (b.p. 40-60 °C) and the mixture stored at -18 °C overnight. A white solid and some brown resinous material precipitated out. The solid was carefully filtered off leaving the bulk of the resinous material behind. The filtrate was evaporated to dryness *in vacuo* to give an orange oil which was treated in a similar fashion to the originial reaction mixture. This yielded several other crops of off-white crystals over a period of two weeks. The various crops of crystals were combined and recrystallised from a mixture of diethyl ether and petroleum (b.p. 40-60 °C), with a little charcoal, to yield **N-(1-hydroxy-2,2,2-trichloroethyl)-2'-methyl-3'-carboxamide** as a white solid (5.4 g, 50%), m.p. 122-123 °C (decomp.)(Found: C, 35.5; H, 3.2; N, 4.8; Cl, 39.0. $C_8H_8Cl_3NO_3$ requires: C, 35.2; H, 2.9; N, 5.1; Cl, 39.1%); δ(ppm): ^1H(60 MHz, $CDCl_3$/DMSO-d_6) 2.5 (3H, s, $-CH_3$), 6.0 (1H, d, $^3J_{HNCH}$ 9, becomes a singlet on shaking with D_2O, -NH-CH-OH), 6.9 (1H, d, $^3J_{HCCH}$ 3, -O-CH=CH- ring), 7.3 (1H, d, $^3J_{HCCH}$ 3, -O-CH=CH- ring), 7.8 (1H, d, exchanges with D_2O, -NH-CH-).

Preparation of N,N,N',N'-tetramethyl-N''-[2,2,2-trichloro-1-(2'-methyl-furan-3'-carboxamidoethyl)]phosphoric triamide

Thionyl chloride (23.6 g, 14.4 cm^3, 0.20 mol) was added to N-(1-hydroxy-2,2,2-trichloroethyl)-2'-methyl-3'-carboxamide (5.4 g, 0.02 mol) and the mixture heated at 40 °C for one hour. The reaction was completed by heating the mixture under reflux for a further one hour. The excess thionyl chloride was removed *in vacuo* to give an orange oil which failed to crystallise from petrol (b.p. 40-60 °C). The petrol was removed under reduced pressure and the residue dissolved in diethyl ether. Removal of diethyl ether under reduced pressure yielded an off-white solid. This was placed under high vacuum to remove traces of thionyl chloride and used without further purification. The solid was dissolved in dry benzene (100 cm^3) and triethylamine added (2.01 g, 0.02 mol). A white solid formed immediately. The reaction mixture was allowed to stand for fifteen minutes. The solid was filtered off, washed with benzene (3 X 50 cm^3) and dried as triethylamine hydrochloride (2.6 g, 95%). It was identified by ^1H NMR. To the combined filtrate and washings was added N,N,N',N'-tetramethylphosphoric triamide (3.0 g, 0.02 mol) and the mixture allowed to stand for two days. The benzene was removed under reduced pressure to give an orange oil. This oil was triturated with hot diethyl ether to give an off-white solid. The solid was filtered off and extracted with hot acetone (150 cm^3). The remaining solid was filtered off from the hot solution to give N,N,N',N'-tetramethyl-N''-[2,2,2-trichloro-1-(2'-methyl-furan-3'-carboxamido)ethyl] phosphoric triamide (2.27 g, 28%), m.p. 185-186 °C (decomp.)(Found: C, 35.2; H, 4.9; N, 13.7; Cl, 26.3; P, 7.5; M^+, 404.0332. $C_{12}H_{20}Cl_3N_4O_3P$ requires: C, 35.5; H, 4.9; N,

Thionyl chloride (23.6 g, 14.4 cm^3, 0.20 mol) was added to N-(1-hydroxy-2,2,2-trichloroethyl)-2'-methyl-3'-carboxamide (5.4 g, 0.02 mol) and the mixture heated at 40 °C for one hour. The reaction was completed by heating the mixture under reflux for a further one hour. The excess thionyl chloride was removed *in vacuo* to give an orange oil which failed to crystallise from petrol (b.p. 40-60 °C). The petrol was removed under reduced pressure and the residue dissolved in diethyl ether. Removal of diethyl ether under reduced pressure yielded an off-white solid. This was placed under high vacuum to remove traces of thionyl chloride and used without further purification. The solid was dissolved in dry benzene (100 cm^3) and triethylamine added (2.01 g, 0.02 mol). A white solid formed immediately. The reaction mixture was allowed to stand for fifteen minutes. The solid was filtered off, washed with benzene (3 X 50 cm^3) and dried as triethylamine hydrochloride (2.6 g, 95%). It was identified by ^1H NMR. To the combined filtrate and washings was added N,N,N',N'-tetramethylphosphoric triamide (3.0 g, 0.02 mol) and the mixture allowed to stand for two days. The benzene was removed under reduced pressure to give an orange oil. This oil was triturated with hot diethyl ether to give an off-white solid. The solid was filtered off and extracted with hot acetone (150 cm^3). The remaining solid was filtered off from the hot solution to give N,N,N',N'-tetramethyl-N''-[2,2,2-trichloro-1-(2'-methyl-furan-3'-carboxamido)ethyl] phosphoric triamide (2.27 g, 28%), m.p. 185-186 °C (decomp.)(Found: C, 35.2; H, 4.9; N, 13.7; Cl, 26.3; P, 7.5; M^+, 404.0332. $C_{12}H_{20}Cl_3N_4O_3P$ requires: C, 35.5; H, 4.9; N,

13.8; Cl, 26.3; P, 7.6%; M^+, 404.0338); ν_{max}(KBr): 1667 (C=O), 1180 (P=O) cm^{-1}; δ(ppm): ^1H(DMSO-d_6) 2.51 (15H, usdd, -P-N(CH_3)$_2$ and CH_3 in furan ring), 4.73 (1H, odd, resolves into a doublet of doublets, exchanges with D_2O, -P-NH-CH-), 5.86 (1H, m, resolves to three doublets; becomes sharp doublet on shaking with D_2O, $^3J_{PNCH}$ 11.2, -P-NH-CH-NH-), 6.78 (1H, d, $^3J_{HCCH}$ 2.0, -O-CH=CH- ring), 7.59 (1H, d, $^3J_{HCCH}$ 2.0, -O-CH=CH- ring), 8.22 (1H, d, $^3J_{HCNH}$ 8.8, exchanges with D_2O, -CH-NH-CO-); ^{13}C(DMSO-d_6) 13.1 (s, -CH_3 furan ring), 36.1 (d, $^2J_{PNC}$ 3.7, -P-N-CH_3), 69.0 (d, $^2J_{PNC}$ 4.4, -P-NH-CH-), 104.0 (d, $^3J_{PNCC}$ 10.3, -P-NH-CH-CCl_3), 108.8 (s, -O-CH=CH- ring), 115.0 (s, -O-C=C-CONH ring), 141.3 (s, -O-CH=CH- ring), 156.7 (s, -O-C(CH_3)=C- ring), 161.7 (s, C=O); ^{31}P(^1H-BB, DMSO-d_6) 20.5; m/z(%): 404 (2, M^+), 360(15), 359(6), 323(5), 253(28), 242(26), 200(3), 172(10), 162(3), 153(9), 146(8), 135(79), 109(91), 108(74), 107(33), 106(16), 92(9), 44(100).

Preparation of diethyl N-[2,2,2-trichloro-1-(2'-methylfuran-3'-carboxamido)ethyl]phosphoramidate

Diethyl N-(1,2,2,2-tetrachloroethyl)phosphoramidate (11.80 g, 0.037 mol) was dissolved in dry benzene (100 cm^3). Triethylamine (3.76 g, 0.037 mol) was then added to this solution. A white precipitate formed immediately. The mixture was allowed to stand for fifteen minutes. The white precipitate was then filtered off, washed with benzene (2 X 50 cm^3) and dried to give triethylamine hydrochloride (4.93 g, 97%).

To the combined filtrate and washings was then added 2-methyl-furan-3-carboxamide (4.66 g, 0.37 mol) and the mixture heated under reflux with stirring and the exclusion of moisture for seven hours. The mixture was allowed to stand overnight. A white solid crystallised out which was filtered off and recrystallised from benzene to give diethyl N-[2,2,2-trichloro-1-(2'-methyl-furan-3'-carboxamido)ethyl] phosphoramidate (9.64 g, 64%), m.p. 169-170 °C (Found: C, 36.5; H, 4.8; N, 6.9; Cl, 26.1; P, 7.7; M^+, 406.0006. $C_{12}H_{18}Cl_3N_2O_5P$ requires: C, 35.3; H, 4.4; N, 6.9; Cl, 26.1; P, 7.6%; M^+, 406.0018); ν_{max}(KBr): 1642 (C=O), 1240 (P=O) cm^{-1}; δ(ppm): ^1H(DMSO-d_6) 1.18 (6H, t, $^3J_{HCCH}$ 7.1, -P-O-CH_2-$\underline{CH}_3$), 2.53 (3H, s, $-CH_3$ in ring), 3.97 (4H, dquin, -P-O-$\underline{CH}_2$-CH_3), 5.69 (2H, m, reduces to 1H doublet on shaking with D_2O, $^3J_{PNCH}$ 11.5, -P-$\underline{NH}$-$\underline{CH}$-NH-). 6.80 (1H, d, $^3J_{HCCH}$ 2.0, -O-CH=$\underline{CH}$- ring), 7.60 (1H, d, $^3J_{HCCH}$ 2.0, -O-$\underline{CH}$=CH- ring), 8.27 (1H, d, $^3J_{HNCH}$ 8.3, exchanges with D_2O, -CH-$\underline{NH}$-CO-); ^{13}C(DMSO-d_6) 13.2 (s, $-CH_3$ furan ring), 15.8 (d, $^3J_{POCC}$ 8.1, -P-O-CH_2-$\underline{CH}_3$), 62.1 (dd, $^2J_{POC}$ 2.9, -P-O-$\underline{CH}_2$-CH_3), 69.0 (d, $^2J_{PNC}$ 4.4, -P-NH-$\underline{CH}$-NH-), 103.0 (d, $^3J_{PNCC}$ 13.2, -P-NH-CH-$\underline{CCl}_3$), 108.9 (s, -O-CH=$\underline{CH}$- furan ring), 114.9 (s, -O-C=$\underline{C}$-CONH- ring), 141.3 (s, -O-$\underline{CH}$=CH- ring), 157.0 (s, -O-$\underline{C}(CH_3)$=C- ring), 162.0 (s, C=O); ^{31}P(H-BB, DMSO-d_6) 5.8; m/z(%): 406(4, M^+), 282(15), 254(4), 226(4), 190(3), 164(16), 154(36), 137(45), 125(26), 109(100), 108(19), 81(21), 69(18).

Preparation of N-(1-hydroxy-2,2,2-trichloroethyl)-chloroacetamide

Chloral (29.52 g, 0.20 mol) was added dropwise to a refluxing suspension of chloroacetamide (18.73 g, 0.20 mol) in chloroform (100 cm^3). The mixture was heated under reflux for three hours. The mixture was allowed to cool and the resulting white solid filtered off and washed with chloroform (2 X 20 cm^3) to give N-(1-hydroxy-2,2,2-trichloroethyl)chloroacetamide (41.7 g, 88%), m.p. 128-130 °C (Lit.[4] m.p. 139-140 °C)(Found: C, 20.3; H, 2.2; N, 6.1. Calc. for $C_4H_5Cl_4NO_2$: C, 19.9; H, 2.1; N, 5.8%).

Preparation of N-(1,2,2,2-tetrachloroethyl)-chloroacetamide

Thionyl chloride (37.7 g, 23.0 cm^3, 0.32 mol) was added to N-(1-hydroxy-2,2,2-trichloroethyl)chloroacetamide (15.0 g, 0.062 mol) and the mixture heated under gentle reflux, with stirring until the evolution of gases had ceased (approx. 3 hours). The excess thionyl chloride was removed *in vacuo* and then petroleum (b.p. 40-60 °C) was added to the hot well stirred residue. A white solid formed which was filtered off and recrystallised from petroleum (b.p. 40-60 °C) to give N-(1,2,2,2-tetrachloroethyl)chloroacetamide (10.2 g, 63%), m.p. 74.5-75.5 °C (Lit.[4] m.p. 74-75 °C)(Found: Cl, 68.1. Calc. for $C_4H_4Cl_5NO$: Cl, 68.4%).

Preparation of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)phosphoric triamide

Triethylamine (3.52 g, 0.035 mol) was added to a solution of N-(1,2,2,2-tetrachloroethyl)chloroacetamide (9.00 g, 0.035 mol) in dry benzene (75 cm^3). A white precipitate formed immediately. The flask was stoppered and shaken gently. The mixture was allowed to stand for fifteen minutes, after which the solid was filtered off, washed with benzene (3 X 20 cm^3) and dried to give triethylamine hydrochloride (4.7 g, 98%). To the combined filtrate and washings was added N,N,N',N'-tetramethylphosphoric triamide (5.27 g, 0.035 mol) and the mixture allowed to stand for two days. An off white solid crystallised which was filtered off and recrystallised from a mixture of chloroform and light petroleum (b.p. 60-80 °C) to give N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)phosphoric triamide (5.80 g, 45%), m.p. 187-188 °C (decomp.)(Found: C, 25.4; H, 4.4; N, 15.0; Cl, 38.3; P, 8.1; M^+, 371.9836. $C_8H_{17}Cl_4N_4O_2P$ requires: C, 25.7; H, 4.5; N, 15.0; Cl, 38.0; P, 8.3%; M^+, 371.9842); ν_{max}(KBr): 1680 (C=O), 1190 (P=O) cm^{-1}; δ(ppm): ^1H(DMSO-d_6) 2.52 (>12H, dd, $^3J_{PNCH}$ 10.2, -P-N-CH$_3$), 4.24 (2H, s, COCH$_2$Cl), 5.07 (1H, odd, exchanges with D_2O, -P-NH-CH-NH-), 5.77 (1H, m, becomes a doublet on shaking with D_2O, $^3J_{PNCH}$ 11.0, -P-NH-CH-NH-), 8.70 (1H, d, $^3J_{HCNH}$ 9.0, exchanges with D_2O, -CH-NH-CO-); ^{13}C(DMSO-d_6) 36.1 (d, $^2J_{PNC}$ 3.4, -P-N-CH$_3$), 42.2 (s, -CO-CH$_2$Cl), 69.4 (d, $^2J_{PNC}$ 5.4, -P-NH-CH-NH-), 103.2 (d, $^3J_{PNCC}$ 10.2, -P-NH-CH-CCl$_3$), 165.4 (s, C=O); ^{31}P (^1H-BB, DMSO-d_6) 20.1; m/z(%): 372(0.3, M^+), 328(3), 253(11), 200(3), 176(7), 146(6), 135(100), 108(9), 92(10), 44(64).

Preparation of diethyl N-(2,2,2-trichloro-1-chloroacetamidoethyl)phosphoramidate

Diethyl N-(1,2,2,2-tetrachloroethyl)phosphoramidate (12.75 g, 0.04 mol) was dissolved in dry benzene (100 cm^3). Triethylamine (4.04 g, 0.04 mol) was added to this solution and the mixture allowed to stand for fifteen minutes. A white solid which had precipitated was filtered off, washed with benzene (2 X 50 cm^3) and dried to give triethylamine hydrochloride (5.30 g, 96%). To the combined filtrate and washings was added chloroacetamide (3.73 g, 0.04 mol) and the mixture heated under reflux for three hours. The mixture was allowed to stand overnight. A white solid crystallised which was filtered off and extracted with hot diethyl ether (2 X 50 cm^3) to remove unreacted starting materials. The remaining solid was recrystallised from benzene to give diethyl N-(2,2,2-trichloro-1-chloroacetamidoethyl)phosphoramidate (4.90 g, 33%), m.p. 183-184 ^{o}C (Found: C, 25.5; H, 4.2; N, 7.6; Cl, 37.9; P, 8.2; M+1, 375.0. $C_8H_{15}Cl_4N_2O_4P$ requires: C, 25.5; H, 4.0; N, 7.45; Cl, 37.9; P, 8.2%; M+1, 375.0); ν_{max}(KBr): 1670 (C=O), 1230 (P=O) cm^{-1}; δ(ppm): ^{1}H(DMSO-d_6) 1.21 (6H, t, $^{3}J_{HCCH}$ 7.1, -P-O-CH_2-$\underline{CH}_3$), 4.00 (4H, dquin, -P-O-$\underline{CH}_2$-CH_3), 4.25 (2H, s, -CO-$\underline{CH}_2$Cl), 5.88 (2H, m, becomes 1H doublet using CD_3OD as solvent, $^{3}J_{PNCH}$ 10.7, -P-$\underline{NH}$-$\underline{CH}$-NH-). 8.89 (1H, d, $^{3}J_{HCNH}$ 8.8, exchanges using CD_3OD, -CH-$\underline{NH}$-CO-); ^{13}C(DMSO-d_6) 15.9 (d, $^{3}J_{POCC}$ 6.6, -P-O-CH_2-$\underline{CH}_3$), 42.1 (s, -CO-$\underline{CH}_2$Cl), 62.0 (odd, -P-O-$\underline{CH}_2$-CH_3), 69.5 (d, $^{2}J_{PNC}$ 5.1,

-P-NH-<u>CH</u>-NH-), 102.2 (d, $^{3}J_{PNCC}$ 12.5, -P-NH-CH-<u>CCl</u>$_3$), 165.7 (s, C=O); $^{31}P(^{1}H$-BB, DMSO-d_6) 5.9; m/z(%): 257(100), 181(33), 164(23), 153(42), 137(64), 125(31), 109(64), 108(11), 98(10), 81(46); FAB 375(10, M+1), 341(9), 307(3), 282(25), 274(4), 257(9), 254(8), 248(21), 247(10), 192(10), 181(21), 154(100), 126(35), 125(18), 109(20), 108(11), 98(50).

Preparation of <u>O</u>,<u>O</u>-diethyl dithiophosphoric acid potassium salt

To a refluxing well stirred solution of absolute ethanol (18.40 g, 0.04 mol) in dry benzene (100 cm^3) was added phosphorus pentasulphide (22.23 g, 0.10 mol) in small portions. After the addition was complete the mixture was heated under reflux until the evolution of H_2S ceased and a clear solution remained (approx. 8 hours). Powdered potassium hydroxide (11.22 g, 0.20 mol) was added and the mixture shaken on a mechanical shaker, for one hour. The white solid which was formed was filtered off and washed well with benzene (3 X 50 cm^3) and diethyl ether (3 X 50 cm^3). The white solid was then extracted with AnalaR acetone (200 cm^3). The acetone solution was then evaporated to dryness under reduced pressure and the residue recrystallised from a mixture of acetone and diethyl ether to give <u>O</u>,<u>O</u>-diethyl dithiophosphoric acid potassium salt (23.28 g, 52%), m.p. 190-191 °C (Lit.[13] m.p. 200-201 °C)(Found: C, 21.1; H, 4.5; P, 14.0. Calc. for $C_4H_{10}KO_2PS_2$: C, 21.4; H, 4.5; P, 13.8%).

Preparation of N,N,N',N'-tetramethyl-N"-[2,2,2-trichloro-1-{(diethoxyphosphinothioylthio)acetamido}ethyl]phosphoric triamide

To a well stirred, refluxing solution of N,N,N',N'-teramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)-phosphoric triamide (4.0 g, 0.011 mol) in dry methanol (100 cm^3) was added a solution of O,O-diethyl dithiophosphoric acid potassium salt (2.40 g, 0.011 mol) in acetone (30 cm^3). The mixture was heated under reflux for six hours and then filtered hot to remove some precipitated potassium chloride. The solvent was removed in vacuo to give an off white solid which was recrystallised from a mixture of chloroform and diethyl ether to give N,N,N',N'-tetramethyl-N"-[2,2,2-trichloro-1-{(diethoxyphosphinothioylthio)acetamido}ethyl]phosphoric triamide (3.76 g, 67%), m.p. 125-127 °C (The compound melts, resolidifies and decomposes at 154-155 °C)(Found: C, 27.5; H, 5.3; N, 10.7; P, 11.9; M^+, 522.0012. $C_{12}H_{27}Cl_3N_4O_4P_2S_2$ requires: C, 27.5; H, 5.2; N, 10.7; P, 11.8%; M^+, 522.0014); ν_{max}(KBr): 1668 (C=O); 1180 (P=O) cm^{-1}; δ(ppm): ^1H(DMSO-d_6) 1.29 (6H, t, -P-O-CH_2-$\underline{CH}_3$), 2.52 (>12H, dd, $^3J_{PNCH}$ 10.2, -P-N-$\underline{CH}_3$), 3.69 (2H, d, $^3J_{PSCH}$ 14.2, -P-S-$\underline{CH}_2$-CO-), 4.13 (4H, m, -P-O-$\underline{CH}_2$-CH_3), 4.96 (1H, odd, exchanges with D_2O, -P-$\underline{NH}$-CH-NH-), 5.76 (1H, m, becomes a doublet on shaking with D_2O, $^3J_{PNCH}$ 10.2, -P-NH-$\underline{CH}$-NH-), 8.79 (1H, d, $^3J_{HCNH}$ 9.3, -NH-CH-$\underline{NH}$-CO-); ^{13}C(DMSO-d_6) 15.5 (d, $^3J_{POCC}$ 7.9, -P-O-CH_2-$\underline{CH}_3$), 35.5 (d, $^2J_{PSC}$ 3.4, -P-S-$\underline{CH}_2$-CO-), 36.2 (d, $^2J_{PNC}$ 3.4,

-P-N-$\underline{CH}_3$), 63.8 (d, $^2J_{POC}$ 5.7, -P-O-$\underline{CH}_2$-CH_3), 69.5 (d, $^2J_{PNC}$ 5.1, -P-NH-$\underline{CH}$-NH-), 103.2 (d, $^3J_{PNCC}$ 10.2, -P-NH-CH-$\underline{CCl}_3$), 166.0 (d, $^3J_{PSCC}$ 6.2, -P-S-CH_2-$\underline{CO}$-NH-); $^{31}P(^1H$-BB, DMSO-d_6) 20.0 ($(Me_2N)_2P(O)N$-), 91.7 $((EtO)_2P(S)S$-); m/z(%): 522(0.6, M^+), 478(5), 405(4), 280(6), 253(39), 226(12), 227(12), 171(10), 153(7), 146(10), 135(100), 125(11), 108(10), 107(6), 97(25), 92(9), 65(10), 44(59).

Preparation of dodecanethiol potassium salt

To a solution of dodecanethiol(9.7 g, 0.048 mol) in dry benzene (50 cm^3) was added powdered potassium hydroxide (2.7 g, 0.048 mol) and the mixture shaken for eight hours. The mixture was allowed to stand overnight. The off white solid was filtered off using a closed sinter to give dodecanethiol potassium salt (6.04 g, 52%). Elemental analysis showed it to be approximately 80% pure and it was used without further purification.

Preparation of N,N,N',N'-tetramethyl-N"-[2,2,2-trichloro-1-{(dodecylthio)acetamido}ethyl] phosphoric triamide

To a well stirred, refluxing solution of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)-phosphoric triamide (4.0 g, 0.011 mol) in methanol (50 cm^3) was added dropwise a solution of dodecanethiol potassium

salt (2.57 g, 0.011 mol) in methanol (30 cm^3). After the addition was complete the mixture was heated under reflux for a further two hours. The mixture was hot filtered to remove precipitated potassium chloride and stored at -18 °C overnight. A white solid crystallised which was filtered off. The filtrate was evaporated to dryness <u>in vacuo</u> and the residue taken up in hot diethyl ether. The etheral solution was stored at -18 °C overnight to yield more white solid. The solids were combined and recrystallised from diethyl ether to yield <u>N,N,N',N'-tetramethyl-N"-[2,2,2-trichloro-1-{(dodecylthio)acetamido}ethyl]phosphoric triamide</u> (2.36 g, 51%, based on dodecanethiol potassium salt being 80%), m.p. 108-109 °C (decomp.)(Found: C, 44.6; H, 7.6; N, 10.5; Cl, 19.6; P, 5.8; M+1, 539.1. $C_{20}H_{42}Cl_3N_4O_4PS$ requires: C, 44.5; H, 7.8; N, 10.4; Cl, 19.7; P, 5.6%; M+1, 539.2); ν_{max}(KBr): 1660 (C=O), 1185 (P=O) cm^{-1}; δ(ppm): ^{1}H(DMSO-d_6) 0.70 (3H, m, -S-$(CH_2)_{11}$-<u>CH_3</u>), 1.24 (22H, bs with shoulder, -S-<u>CH_2</u>-(<u>CH_2</u>)$_{10}$-), 2.52 (>12H, dd, $^3J_{PNCH}$ 10.2, -P-N-<u>CH_3</u>), 3.25 (2H, s, -CO-<u>CH_2</u>-S-), 4.99 (1H, odd, exchanges with D_2O, -P-<u>NH</u>-CH-NH-), 5.75 (1H, m, becomes a doublet on shaking with D_2O, $^3J_{PNCH}$ 10.8, -P-NH-<u>CH</u>-NH-), 8.45 (1H, d, $^3J_{HCNH}$ 9.3, exchanges with D_2O, -CH-<u>NH</u>-CO-); ^{13}C(DMSO-d_6) 13.8, 22.0, 28.2, 28.5, 28.6, 28.9, 31.2, 31.8 (s, C_{12} chain), 34.7 (s, -CO-<u>CH_2</u>-S-), 36.2 (d, $^2J_{PNC}$ 3.7, -P-N-<u>CH_3</u>), 69.4 (d, $^2J_{PNC}$ 5.1, -P-NH-<u>CH</u>-NH-), 103.8 (d, $^3J_{PNCC}$ 9.6, -P-NH-CH(<u>CCl_3</u>)NH-), 168.2 (s, C=O); ^{31}P(^{1}H-BB, DMSO-d_6) 20.0; m/z(%): 338(5), 280(4), 253(6), 201(23), 176(6), 135(100),

97(5), 92(7), 83(8), 69(6), 61(6), 59(94), 57(13), 55(25), 44 (39), 43(29), 41(25); FAB 539(3, M+1), 505(4), 280(3), 253(12), 246(11), 219(15), 212(8), 176(8), 152(28), 135(100), 108(16), 107(19), 92(15).

Preparation of N,N,N',N'-tetramethyl-N"-[2,2,2-trichloro-1-(triazolylacetamido)ethyl]phosphoric triamide

To a well stirred, refluxing solution of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)-phosphoric triamide (4.0 g, 0.011 mol) in dry methanol (100 cm^3) was added dropwise a solution of 1,2,4-triazole sodium salt (0.97 g, 0.011 mol) in dry methanol (50 cm^3). The mixture was then heated under reflux for four hours. The mixture was hot filtered and the solvent removed *in vacuo* to give a yellow oil. The yellow oil was crystallised from a mixture of chloroform and petrol (b.p. 40-60 °C). The off white solid obtained was recrystallised from a mixture of chloroform and diethyl ether to give N,N,N',N'-tetramethyl-N"-[2,2,2-trichloro-1-(triazolylacetamido)ethyl]-phosphoric triamide (1.32 g, 30%), m.p. 182-183 °C (decomp.) (Found: C, 28.2; H, 4.7; N, 24.3; Cl, 26.6; P, 7.6; M^+, 405.0406. $C_{10}H_{19}Cl_3N_7O_2P$ requires: C, 29.5; H, 4.7; N, 24.1; Cl, 26.2; P, 7.6%; M^+, 405.0402); ν_{max}(KBr): 1670 (C=O), 1180 (P=O) cm^{-1}; δ(ppm): ^1H(DMSO-d_6) 2.51 (>12H, dd, $^3J_{PNCH}$ 10.2, -P-N-CH_3), 5.1 (3H, m, reduces to two singlets of 2H on shaking with D_2O, -P-NH-CH, -COCH_2N< 1 and 4 isomers), 5.79, (1H, m, reduces to a doublet with D_2O, $^3J_{PNCH}$ 10.5, -NH-CH-NH-),

7.98 (s, 1-sub. triazole), 8.44 (s, 4-sub. triazole), 8.52 (s, 1-sub. triazole), 8.86 (1H, d, $^{3}J_{HCNH}$ 10.9, exchanges with D_2O, -CH-NH-CO-); ^{13}C(DMSO-d_6) 36.2 (d, $^{2}J_{PNC}$ 3.4, -P-N-CH_3), 46.4 (s, -CO-CH_2- 4-sub. triazole), 51.0 (s, -CO-CH_2-, 1-sub. triazole), 69.3 (d, $^{2}J_{PNC}$ 5.4, -P-NH-CH-NH-), 103.1 (d, $^{3}J_{PNCC}$ 10.9, -P-NH-CH-CCl_3), 143.9 (s, C_1 and C_2 in 4-sub. triazole), 145.5 (s, C_1, 1-sub. triazole), 151.5 (s, C_2, 1-sub. triazole), 165.4 (s, C=O); ^{31}P(^{1}H-BB, DMSO-d_6) 20.0; m/z(%): 405(0.4, M^+), 361(2), 324(5), 318(6), 253(9), 200(3), 176(3), 173(4), 146(5), 135(100), 109(18), 108(8), 92(9), 83(12), 55(8), 44(58).

Preparation of N,N,N',N'-tetramethyl-N"-[2,2,2-trichloro-1-{(ethoxythiocarbonylthio)acetamido}ethyl]phosphoric triamide

To a well stirred, refluxing solution of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)-phosphoric triamide (4.0 g, 0.011 mol) in ethanol (100 cm^3) was added a solution of potassium ethyl xanthate (1.71 g, 0.011 mol) in distilled water (20 cm^3). The mixture was heated under reflux for three hours. The solvent was then removed *in vacuo* to yield an off white solid which was recrystallised from a mixture of ethanol and water with a little charcoal, to yield N,N,N',N'-tetramethyl-N"-[2,2,2-trichloro-1-{(ethoxythiocarbonylthio)acetamido}ethyl]phosphoric triamide (3.64 g, 74%), m.p. 184-185 °C(decomp)(Found: C, 28.8; H, 4.7; N, 12.3; P, 6.8; M^+, 457.9933. $C_{11}H_{22}Cl_3N_4O_3PS_2$ requires: C, 28.7; H, 4.8;

N, 12.2; P, 6.7%; M^+, 457.9936); ν_{max}(KBr): 1675 (C=O), 1190 (P=O) cm^{-1}; δ(ppm): ^1H(DMSO-d_6) 1.36 (3H, t, -C(S)OCH$_2$<u>CH$_3$</u>), 2.51 (>12H, dd, $^3J_{PNCH}$ 10.2, -P-N(<u>CH$_3$</u>)$_2$), 4.03 (2H, s, -CO-<u>CH$_2$</u>-S-), 4.62 (2H, q, -C(S)-O-<u>CH$_2$</u>-CH$_3$), 4.98 (1H, odd, exchanges using CD_3OD as solvent, -P-<u>NH</u>-CH-), 5.76 (1H, m, becomes doublet using CD_3OD, $^3J_{PNCH}$ 10.2, -P-NH-<u>CH</u>-NH-), 8.71 (1H, d, exchanges using CD_3OD, $^3J_{HCNH}$ 8.8, -CH-<u>NH</u>-CO-); ^{13}C(DMSO-d_6) 13.4 (s, -C(S)O-CH$_2$-<u>CH$_3$</u>), 36.2 (d, $^2J_{PNC}$ 3.7, -P-N-<u>CH$_3$</u>), 38.7 (s, -CO-<u>CH$_2$</u>-S-C(S)-), 69.5 (d, $^2J_{PNC}$ 5.1, -P-NH-<u>CH</u>-CCl$_3$), 70.6 (s, -CO-C(S)O-<u>CH$_2$</u>-CH$_3$), 103.3 (d, $^3J_{PNCC}$ 9.6, -P-NH-CH-<u>CCl$_3$</u>), 165.5 (s, C=O), 212.8 (s, C=S); $^{31}P(^1H$-BB, DMSO-d_6) 20.0; m/z(%): 458(1, M^+), 280(4), 253(31), 200(4), 179(13), 176(11), 163(16), 161(8), 146(10), 135(100), 119(6), 108(12), 107(8), 92(14), 91(7), 90(7), 73(8), 76(7), 44(24).

<u>Preparation of N,N,N',N'-tetramethyl-N"-[2,2,2-trichloro-1-{(dimethylthiocarbamoylthio)acetamido}ethyl]-phosphoric triamide</u>

To a well stirred, refluxing solution of <u>N</u>,<u>N</u>,<u>N'</u>,<u>N'</u>-tetramethyl-<u>N"</u>-(2,2,2-trichloro-1-chloroacetamidoethyl)-phosphoric triamide (4.0 g, 0.011 mol) in methanol (100 cm^3) was added dropwise a solution of sodium dimethyl dithiocarbamate(dihydrate) (1.92 g, 0.011 mol) in methanol (30 cm^3). The mixture was then heated under reflux for three hours. The mixture was allowed to cool and a little charcoal was

added. The mixture was then heated under reflux for another ten minutes and filtered hot. The solvent was removed *in vacuo* and the resulting off white solid washed well with distilled water to remove sodium chloride. The remaining solid was recrystallised from a mixture of chloroform and petrol (b.p. 40-60 °C) with a little charcoal to give **N,N,N',N'-tetramethyl-N"-[2,2,2-trichloro-1-{(dimethythiocarbamoylthio)acetamido}ethyl] phosphoric triamide** (4.28 g, 87%), m.p. 191-192 °C (decomp.)(Found: C, 28.6; H, 4.8; N, 15.4; P, 6.9; M^+, 457.0092. $C_{11}H_{23}Cl_3N_5O_2PS_2$ requires: C, 28.8; H, 5.0; N, 15.3; P, 6.8%; M^+, 457.0096); ν_{max}(KBr): 1668 (C=O), 1175 (P=O) cm^{-1}; δ(ppm): ^{1}H(DMSO-d_6) 2.51 (>12H, dd, $^3J_{PNCH}$ 10.2, -P-N-$\underline{CH}_3$), 3.43 (6H, d, -C(S)N($\underline{CH}_3$)$_2$), 4.15 (2H, s, -CO-$\underline{CH}_2$-S-), 4.99 (1H, odd, exchanges when using CD_3OD as solvent, -P-$\underline{NH}$-CH-), 5.75 (1H, m, becomes a doublet using CD_3OD, $^3J_{PNCH}$ 10.7, -P-NH-$\underline{CH}$-NH-), 8.57 (1H, d, $^3J_{HCNH}$ 8.8, exchanges using CD_3OD, -CH-$\underline{NH}$-CO-); ^{13}C(DMSO-d_6) 36.2 (d, $^2J_{PNC}$ 3.7, -P-N-$\underline{CH}_3$), 40.6 (s, -CO-$\underline{CH}_2$-S-), 41.3 (s, -C(S)N($\underline{CH}_3$)$_2$), 45.3 (s, C(S)N($\underline{CH}_3$)$_2$), 69.4 (d, $^2J_{PNC}$ 5.1, -P-NH-$\underline{CH}$-NH-), 103.5 (d, $^3J_{PNCC}$ 10.3, -P-NH-CH-$\underline{CCl}_3$), 166.1 (s, C=O), 194.2 (s, C=S); ^{31}P(^{1}H-BB, CD_3OD) 19.3; m/z(%): 457(1, M^+), 369(5), 324(2), 280(4), 253(3), 200(3), 178(9), 160(6), 135(100), 120(5), 92(8), 88(71), 73(6), 44(58).

Preparation of N,N,N',N'-tetramethyl-N"-[2,2,2-trichloro-1-{(diethylthiocarbamoylthio)acetamido}ethyl] phosphoric triamide

To a well stirred, refluxing solution of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)-phosphoric triamide (4.0 g, 0.011 mol) in methanol (100 cm^3) was added a solution of sodium diethyl dithiocarbamate (trihydrate) (2.41 g, 0.011 mol) in methanol (30 cm^3). The reaction mixture was heated under reflux for three hours, allowed to cool and a little charcoal added. The mixture was heated under reflux for a further ten minutes and then filtered hot. The solvent was removed *in vacuo* to give a resinous brown solid which was recrystallised from a mixture of chloroform and diethyl ether and a little charcoal to give N,N,N',N'-tetramethyl-N"-[2,2,2-trichloro-1-{(diethylthiocarbamoylthio)acetamido}ethyl]phosphoric triamide as an off white solid (3.41 g, 66%), m.p. 171-172 °C (decomp.)(Found: C, 31.9; H, 5.6; N, 14.4; P, 6.3; M^+, 485.0397. $C_{13}H_{27}Cl_3N_5O_2PS_2$ requires: C, 32.1; H, 5.5; N, 14.4; P, 6.4%; M^+, 485.0409); ν_{max}(KBr): 1670 (C=O), 1188 (P=O) cm^{-1}; δ(ppm): ^{1}H(DMSO-d_6) 1.21 (6H, m, -C(S)CH_2-$\underline{CH_3}$), 2.51 (>12H, dd, $^3J_{PNCH}$ 10.2, -P-N-$\underline{CH_3}$), 3.94 (4H, m, -C(S)-$\underline{CH_2}$-CH_3), 4.15 (s, -CO$\underline{CH_2}$S-), 5.01 (1H, odd, exchanges with D_2O, -P-$\underline{NH}$-CH-NH-), 5.75 (1H, m, becomes a doublet on shaking with D_2O, $^3J_{PNCH}$ 10.7, -P-NH-$\underline{CH}$-NH-), 8.52 (1H, d, $^3J_{HCNH}$ 9.3, exchanges with D_2O, -CH-$\underline{NH}$-CO-); ^{13}C(DMSO-d_6) 11.8 (d, -N-CH_2-$\underline{CH_3}$), 36.2 (d, $^2J_{PNC}$ 4.4, -P-N-$\underline{CH_3}$), 39.9 (s, -CO-$\underline{CH_2}$-S-), 48.1 (d, -N-$\underline{CH_2}$-CH_3), 69.4 (d, $^2J_{PNC}$ 5.9, -P-NH-$\underline{CH}$-NH-), 103.5 (d, $^3J_{PNCC}$ 9.6, -P-NH-CH-$\underline{CCl_3}$), 166.2 (s, C=O), 192.8 (s, C=S); ^{31}P(^{1}H-BB, DMSO-d_6) 20.1; m/z(%): 485(1, M^+), 369(8), 338(5), 324(2),

280(8), 253(2), 206(6), 200(3), 190(10), 176(6), 148(13), 135(100), 116(47), 92(8), 88(30), 72(18), 60(23), 44(59).

Reaction of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)phosphoric triamide with sodium dodecyloxide

A solution of sodium dodecyloxide was prepared by heating small pieces of sodium (0.32 g, 0.0139 mol) with dodecan-1-ol (10 cm^3) at 120 °C for 36 hours. Acetone (30 cm^3) was added to this solution to give a suspension. This suspension was added dropwise to a well stirred refluxing suspension of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)phosphoric triamide (4.0 g, 0.011 mol) in dry tetrahydrofuran (200 cm^3). The mixture was then heated under reflux for three hours. The reaction mixture turned black. It was filtered hot and the tetrahydrofuran removed *in vacuo* to give a black oil. Trituration of the oil with diethyl ether (450 cm^3) gave a black solid (0.3 g) which was not investigated further. To the filtrate was added a little charcoal and the mixture heated on a water-bath for fifteen minutes. It was filtered hot and the volume reduced to approximately 100 cm^3, *in vacuo*. Storage overnight at -18 °C gave an off white precipitate. This was filtered off and recrystallised from a mixture of benzene and petrol (b.p. 40-60 °C) and a little charcoal, to give an off white solid (0.2 g) which was investigated by ^1H and ^{31}P NMR. δ(ppm): ^1H(DMSO-d_6)

2.51 (dd), 4.01 (s), 4.23 (s), 5.06 (m), 6.24 (m), 7.44 (bd), 8.69 (d). D_2O exchange removes signals at 5.06, 7.44, 8.69 and reduces the signal at 6.24 to a doublet. Integration shows peaks at δ 4.23, 5.06, 6.24 and 8.69 to be in the ratio of 2:1:1:1 and the peaks at δ 4.01 and 7.44 are in the ratio of 1:1. Comparison of the chemical shifts with N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)phosphoric acid and chloroacetamide shows this to be a mixture of these two compounds in the ratio of 1:3.4 respectively (based on integration of $-CH_2$ group). $^{31}P(^1H$-BB, DMSO-d_6) 20.7. Only a single phosphorus species could be observed corresponding to N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)phosphoric triamide.

The filtrate was worked up in the following way: The solvent was removed *in vacuo* to give an orange oil. The oil which contained the excess dodecanol used as solvent, was then distilled under reduced pressure. The dodecanol was removed (b.p. 105-110 °C at 0.1 mmHg) and petrol (b.p. 60-80 °C) was added to the residue which had undergone extensive decomposition during the distillation. A black tar separated. The petrol was carefully decanted off and stored at -18 °C overnight. The tar was not investigated further. An off white solid (0.3 g) crystallised from the petrol and identified by ^1H, ^{13}C and ^{31}P NMR to be N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-dodecyloxyethyl)phosphoric triamide. δ(ppm): ^1H(DMSO-d_6) 0.85 (3H, m, CH_3-$(CH_2)_{10}$-CH_2-O-), 1.24 (20H, s, CH_3-$(CH_2)_{10}$-CH_2-O-), 2.55 (12H, dd, $^3J_{PNCH}$ 10.0, -P-N-CH_3), 3.65 (2H,

m, CH_3-$(CH_2)_{10}$-$\underline{CH_2}$-O-), 4.83 (1H, dd, becomes a doublet on shaking with D_2O, $^3J_{PNCH}$ 8.1, -P-NH-$\underline{CH}$-O-), 5.40 (1H, odd, exchanges with D_2O, -P-$\underline{NH}$-CH-O-); ^{13}C(DMSO-d_6) 13.8, 22.0, 25.4, 28.7, 29.0, 31.2 (s, C_{12} chain), 36.3 (d, $^2J_{PNC}$ 4.1, -P-N-$\underline{CH_3}$), 68.9 (s, -NH-CH-O-$\underline{CH_2}$-R), 91.2 (d, $^2J_{PNC}$ 6.1, -P-NH-$\underline{CH}$-O-), 102.2 (d, $^3J_{PNCC}$ 9.5, -P-NH-CH-$\underline{CCl_3}$); $^{31}P(^1H$-BB, DMSO-d_6) 19.5.

Reaction of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)phosphoric triamide with potassium dodecyloxide

A solution of potassium dodecyloxide was made by heating potassium metal (0.42 g, 0.011 mol) at 100 °C with dodecan-1-ol (50 cm^3). This solution was added dropwise to a well stirred refluxing suspension of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)phosphoric triamide in pentan-3-one (200 cm^3). The mixture was then heated under reflux for three hours and hot filtered. The solvent was removed *in vacuo* to give a yellow liquid which was a solution of the products in dodecanol. Petrol (b.p. 60-80 °C) (500 cm^3) was added and the mixture stored at -18 °C for two days. An off white solid crystallised (0.8 g) which was filtered off and recrystallised from a mixture of chloroform and petrol to give unreacted N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)phosphoric triamide which was identified by ^1H, ^{13}C and ^{31}P NMR.

The filtrate was worked up in the following way: The petrol was removed under reduced pressure and the residue distilled to remove dodecanol (b.p. 100-118 ^{o}C at 0.02 mmHg). The residue underwent decomposition during distillation. Petrol (b.p. 60-80 ^{o}C) was added to the residue which caused the precipitation of a brown solid. This was filtered off and not investigated further. The filtrate was evaporated to dryness *in vacuo* to give an orange oil which was extracted with hot petrol (b.p. 60-80 ^{o}C) (200 cm^{3}) and the hot petrol filtered off from an insoluble resinous material. The filtrate was stored at -18 ^{o}C for several days. An off white solid (0.2 g) crystallised which was filtered off and identified as *N,N,N',N'*-tetramethyl-*N"*-(2,2,2-trichloro-1-dodecyloxyethyl)-phosphoric triamide which was shown by elemental analysis and ^{1}H NMR to be slightly contaminated by the starting material. (Found: C, 44.2; H, 8.1; N, 9.3; M+1, 466.0. $C_{18}H_{39}Cl_3N_3O_2P$ requires: C, 46.3; H, 8.4; N, 9.0%; M+1, 466.2; δ(ppm): ^{1}H($CDCl_3$) 0.88 (3H, m, $\underline{CH}_3$-$(CH_2)_{10}$-CH_2-O-), 1.25 (20H, s, -CH_3-$(\underline{CH}_2)_{10}$-CH_2-O-), 2.67 (12H, dd, $^{3}J_{PNCH}$ 10.2, -P-N-$\underline{CH}_3$), 3.12 (1H, odd, -P-$\underline{NH}$-CH-O-), 3.81 (2H, m, -CH_3-$(CH_2)_{10}$-$\underline{CH}_2$-O-), 4.97 (1H, dd, -P-NH-$\underline{CH}$-O-); ^{13}C($CDCl_3$) 14.1, 22.7, 26.1, 29.4, 29.7, 32.0 (s, C_{12} chain), 36.7 (d, $^{2}J_{PNC}$ 4.1, -P-N-$\underline{CH}_3$), 70.9 (s, -NH-CH-O-$\underline{CH}_2$-R), 91.0 (d, $^{2}J_{PNC}$ 6.1, -P-NH-$\underline{CH}$-O-), 101.9 (d, $^{3}J_{PNCC}$ 10.2, -P-NH-CH-$\underline{CCl}_3$); ^{31}P(^{1}H-BB, $CDCl_3$) 19.2; m/z(%): FAB 466(1, M+1), 348(2), 280(12), 253(2), 246(21), 244(11), 210(5), 153(4), 135(100), 126(4), 108(17), 107(8), 92(13).

Reaction of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)phosphoric triamide with sodium butoxide

A solution of sodium butoxide was made by adding sodium metal (0.25 g, 0.011 mol) in small pieces to refluxing butan-1-ol (30 cm^3) and the mixture heated under reflux until all the sodium had dissolved. This solution was added dropwise to a well stirred refluxing solution of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)-phosphoric triamide (4.0 g, 0.011 mol) in butanol (100 cm^3). After addition was complete, the mixture was heated under reflux for one hour. The reaction mixture was hot filtered and the solvent removed *in vacuo* to give a dark brown oil. This oil was extracted with hot diethyl ether (200 cm^3). The ether was carefully decanted with filtration from insoluble material. The filtrate volume was reduced *in vacuo* and stored at -18 °C for several days. An off white solid crystallised (0.68 g) which was filtered off. The filtrate was worked up to yield more solid. The solids were recrystallised in different batches from diethyl ether to yield off white solids which were identified as N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-butoxyethyl)phosphoric triamide (1.07 g, 28%), m.p. 115-116 °C (decomp.)(Found: C, 33.4; H, 6.5; N, 11.8; M+1, 354.01. $C_{10}H_{23}Cl_3N_3O_2P$ requires: C, 33.9; H, 6.5; N, 11.8%; M+1, 354.07); δ(ppm): $^1H(CDCl_3)$ 0.92 (3H, m, $\underline{CH_3}$-$(CH_2)_2$-CH_2-O-), 1.49 (4H, m, -CH_3-$(\underline{CH_2})_2$-CH_2-O-), 2.68 (12H, dd,

$^{3}J_{PNCH}$ 10.2, -P-N-$\underline{CH}_3$), 3.39 (1H, odd, -P-$\underline{NH}$-CH-O-), 3.83 (2H, q, -CH_3-$(CH_2)_2$-$\underline{CH}_2$-O-), 4.99 (1H, dd, -P-NH-$\underline{CH}$-O-); $^{13}C(CDCl_3)$ 13.9, 19.2, 31.7 (s, C_4 chain), 36.7 (d, $^{2}J_{PNC}$ 4.1, -P-N-$\underline{CH}_3$), 70.5 (s, -NH-CH-O-$\underline{CH}_2$-R), 91.0 (d, $^{2}J_{PNC}$ 5.4, -P-NH-$\underline{CH}$-O-), 101.9 (d, $^{3}J_{PNCC}$ 10.2, -P-NH-CH-$\underline{CCl}_3$); $^{31}P(^{1}H\text{-BB}, CDCl_3)$ 19.2; m/z(%): FAB 354(2, M+1), 318(3), 280(10), 246(13), 244(6), 210(4), 164(8), 135(100), 126(4), 121(6), 108(26), 107(7), 92(11).

Reaction of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)phosphoric triamide with imidazole sodium salt in methanol

A solution of imidazole sodium salt (0.96 g, 0.011 mol) in dry methanol (30 cm^3) was added dropwise to a well stirred refluxing solution of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)phosphoric triamide (4.0 g, 0.011 mol) in dry methanol (100 cm^3). The mixture was heated under reflux for three hours. The solvent was then removed in vacuo to yield an orange oil. This was crystallised from a mixture of chloroform and petrol (b.p. 40-60 °C) to give an off white solid (0.6 g) which was shown by ^{1}H NMR to be starting material. The filtrate was evaporated to dryness and the residue re-crystallised from diethyl ether to give an off white solid (0.35 g) which was identified as N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-methoxyethyl)phosphoric triamide, m.p. 157-158 °C (decomp.)(Found: C, 26.3; H, 5.5; N, 13.8; M+1,

312.0. $C_7H_{17}Cl_3N_3O_2P$ requires: C, 26.9; H, 5.4; N, 13.4%, M+1, 312.0); δ(ppm): ^{1}H(DMSO-d_6) 2.56 (12H, dd, $^3J_{PNCH}$ 10.2, -P-N-$\underline{CH}_3$), 3.35 (3H, s, -O-$\underline{CH}_3$), 4.75 (1H, dd, becomes a doublet on shaking with D_2O, $^3J_{PNCH}$ 7.8, -P-NH-$\underline{CH}$-O-), 5.44 (1H, odd, exchanges with D_2O, -P-$\underline{NH}$-CH-O-); ^{13}C(DMSO-d_6) 36.3 (d, $^2J_{PNC}$ 4.1, -P-N-$\underline{CH}_3$), 56.5 (s, -O-$\underline{CH}_3$), 92.7 (d, $^2J_{PNC}$ 6.1, -P-NH-$\underline{CH}$-O-), 101.8 (d, $^3J_{PNCC}$ 9.5, -P-N-CH-$\underline{CCl}_3$): ^{31}P(^{1}H-BB, DMSO-d_6) 19.6; m/z(%): FAB 312(7, M+1), 280(21), 246(37), 244(9), 210(5), 135(100).

Reaction between imidazole and chloroacetamide in the presence of sodium ethoxide

To a well stirred refluxing solution of imidazole (6.29 g, 0.0925 mol) in dry benzene (250 cm^3) was added sodium metal (2.13 g, 0.0925 mol). Absolute ethanol (100 cm^3) was then added and the mixture heated under reflux until all the sodium had dissolved. Chloroacetamide (8.65 g, 0.0925 mol) was then added and the mixture heated under reflux for three hours. An off white precipitate formed which was hot filtered from the reaction mixture, and dried as sodium chloride (5.9 g, 109%). The solvent was removed *in vacuo* to give a dark brown solid. The solid was extracted with hot chloroform (200 cm^3) and diethyl ether (200 cm^3). The remaining solid was recrystallised from a mixture of propan-1-ol and diethyl ether to give 1-acetamido-imidazole (7.23 g, 63%), m.p. 168-170 °C (decomp.)(Lit.[14] 182-183 °C) (Found: C, 47.1; H, 5.4; N, 31.0; M^+, 125.1. Calc. for

$C_5H_7N_3O$: C, 48.0; H, 5.6; N, 33.6%; M^+, 125.1); δ(ppm): ^1H(DMSO-d_6) 4.63 (2H, s, -$\underline{CH_2}$-CO-), 6.87, 7.08, 7.58 (3H, s, imidazole protons), 7.25 (2H, bs, exchanges with D_2O, -CH_2-CO-$\underline{NH_2}$); ^{13}C(DMSO-d_6) 48.4 (-$\underline{CH_2}$-$CONH_2$), 120.6, 127.7, 138.1 (imidazole carbons), 168.8 (C=O); m/z(%): 125(100, M^+), 82(40), 81(82), 55(12), 54(39), 44(26), 41(8), 40(9).

The chloroform and diethyl ether used in the extraction were combined and evaporated to dryness in vacuo to give an oil with some solid. The residue was heated with diethyl ether (100 cm^3) and the remaining solid filtered off. This solid (0.7 g) was shown to be 1-acetamido-imidazole by ^1H NMR. Work up of the filtrate gave a white crystalline solid which was identified as 1-ethoxy-acetamide (0.5 g, 6%); δ(ppm): ^1H(DMSO-d_6) 1.14 (3H, t, -CH_2-$\underline{CH_3}$), 3.47 (2H, q, -$\underline{CH_2}$-CH_3), 3.75 (2H, s, -O-$\underline{CH_2}$-CO-), 7.17 (2H, bs, exchanges with D_2O, -CH_2-CO-$\underline{NH_2}$); ^{13}C(DMSO-d_6) 14.8 (-CH_2-$\underline{CH_3}$), 66.1 (-$\underline{CH_2}$-O-CH_2-CO-), 69.4 (-CH_2-O-$\underline{CH_2}$-CO-), 171.7 (C=O).

Reaction of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)phosphoric triamide with imidazole in the presence of sodium ethoxide

To a solution of imidazole (0.65 g, 0.010 mol) in absolute ethanol (30 cm^3) was added sodium metal (0.21 g, 0.009 mol) in small pieces, and the mixture stirred until all the sodium metal had reacted. This solution was then added dropwise to a well stirred refluxing solution of

N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-chloroacetamidoethyl)phosphoric triamide (3.23 g, 0.009 mol) in absolute ethanol (75 cm^3). After the addition was complete the mixture was heated under reflux for a further 2 hours. The solvent was then removed *in vacuo* to give an orange oil which solidified on standing. This solid was extracted with hot diethyl ether. Most of the solid dissolved and the mixture was filtered hot. A small off-white residue (0.18 g) was collected which gave a precipitate when tested with silver nitrate indicating that it was probably sodium chloride. The filtrate was then placed on a water-bath until it boiled and light petroleum (b.p. 40-60 °C) was added. The mixture was then stored overnight at -18 °C. A white solid (0.30 g) crystallised which was filtered off and investigated by ^1H NMR. It was shown to consist of mainly one component δ_H(DMSO-d_6) 4.02 (s), 7.66 (bs) ppm with integration showing these peaks to be in the ratio 1:1. Comparison of these shifts with chloroacetamide shows these compounds to be the same. The filtrate volume was reduced *in vacuo* and stored at -18 °C overnight. A further white solid crystallised (1.39 g) which was filtered off and investigated by ^1H, ^{13}C and ^{31}P NMR. It was shown to consist mainly of a single phosphorus species δ_P(DMSO-d_6) 19.7 ppm and imidazole. This solid was taken up in chloroform (100 cm^3) and washed with distilled water (3 X 50 cm^3). The chloroform was dried over magnesium sulphate and the solvent removed using a rotary evaporator to yield an off-white solid which was recrystallised from diethyl ether to give

N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-ethoxyethyl)-phosphoric triamide (0.54 g, 18%), m.p. 152-153 °C (decomp.) (Found: C, 29.4; H, 5.9; N, 13.0; M+1, 325.9. $C_8H_{19}Cl_3N_3O_2P$ requires: C, 29.4; H, 5.8; N, 12.7%; M+1, 326.0); δ(ppm): ^1H(DMSO-d_6) 1.18 (3H, t, $-OCH_2\underline{CH}_3$), 2.55 (>12H, dd, $^3J_{PNCH}$ 9.8, $-P-N-\underline{CH}_3$), 3.72 (2H, m, $-O\underline{CH}_2CH_3$), 4.84 (1H, dd, $-P-NH-\underline{CH}(CCl_3)-O-$), 5.42 (1H, odd, exchanges with D_2O, $-P-\underline{NH}-CH(CCl_3)-O-$); ^{13}C(DMSO-d_6) 14.8 (s, $-OCH_2\underline{CH}_3$), 36.2 (d, $^2J_{PNC}$ 4.1, $-P-N-\underline{CH}_3$), 64.3 (s, $-O\underline{CH}_2CH_3$), 90.9 (d, $^2J_{PNC}$ 6.1, $-P-NH-\underline{CH}(CCl_3)-O-$), 102.1 (d, $^3J_{PNCC}$ 10.2, $-P-NH-CH(\underline{CCl}_3)-O-$); $^{31}P(^1H$-BB, DMSO-d_6) 19.6; m/z(%): FAB 326(3, M+1), 290(4), 280(11), 246(13), 244(7), 210(4), 176(4), 152(3), 135(100), 108(29), 92(8).

Preparation of 1-(1'-hydroxy-2',2',2'-trichloroethyl)-imidazole

To a stirred solution, cooled in ice, of imidazole (6.8 g, 0.10 mol) in dry benzene (20 cm^3), a solution of chloral (14.7 g, 0.10 mol) in benzene (10 cm^3) was added, at such a rate as to maintain the temperature below 20 °C. The mixture was then stirred for a further 2 hours at room temperature. The solvent was removed *in vacuo* to give a yellow oil which was crystallised from a mixture of diethyl ether and light petroleum (b.p. 30-40 °C) to give 1-(1'-hydroxy-2',2',2'-trichloroethyl)imidazole (15.62 g, 73%), m.p. 92-94 °C (Lit.[15] 90-92 °C)(Found: C, 28.0; H, 2.5;

N, 13.3. Calc. for $C_5H_5Cl_3N_2O$: C, 27.9; H, 2.3; N, 13.0%); δ(ppm): ^{1}H(60 MHz, acetone-d_6) 6.7 (1H, bs, -CH(CCl_3)-OH), 7.2 (2H, s, imidazole protons), 8.0 (1H, s, imidazole proton), 10.8 (1H, s, exchanges with D_2O, -CH(CCl_3)-OH).

Reaction of 1-(1'-hydroxy-2',2',2'-trichloroethyl)-imidazole with thionyl chloride

To a cooled solution of 1-(1'-hydroxy-2',2',2'-trichloroethyl)imidazole (2.15 g, 0.01 mol) in dry chloroform (20 cm^3) was added dropwise a solution of thionyl chloride (1.78 g, 0.15 mol) in chloroform (10 cm^3). The reaction was exothermic and the addition was made keeping the temperature below 10 °C. A white precipitate formed on addition of thionyl chloride. The mixture was allowed to stand for 15 minutes. The white precipitate was filtered off and the solvent removed *in vacuo*. The residue was placed under high vacuum to give an off white solid, identified as imidazole hydrochloride (0.42 g, 40%), m.p. 145-147 °C (Lit.[16] 145 °C)(Found: Cl, 39.2. Calc. for $C_3H_5ClN_2$: Cl, 33.9%); δ(ppm): ^{1}H(60 MHz, DMSO-d_6) 7.7 (2H, d, imidazole protons), 9.2 (1H, m, imidazole proton), 12.9 (2H, bs, exchanges with D_2O, -NH, =$\overset{+}{N}$H imidazole).

Reaction of 1-(1'-hydroxy-2',2',2'-trichloroethyl)-imidazole with thionyl chloride using pyridine as solvent

The procedure adopted was analogous to that in the

previous experiment with pyridine substituted for chloroform. A yellowish precipitate formed which was filtered off and not investigated. The solvent and excess thionyl chloride were removed *in vacuo* to give a yellow oil. TLC of this oil using chloroform:methanol, 1:1 on silica plates, showed this to be made up of at least four components (R_f 0.71, 0.47, 0.25 and a brown baseline residue), and that it contained no starting material (R_f 0.56).

The residue was dissolved in chloroform (50 cm^3) and the chloroform extracted with distilled water. TLC of the chloroform and water layers showed that most of the components had been extracted into the water layer, leaving one major component (R_f, 0.71) in the chloroform layer. Removal of the chloroform *in vacuo* and study of the residue by NMR gave the following result: δ(ppm): ^1H(60 MHz, $CDCl_3$) 6.8, 7.1, 7.4, 7.6, 7.7, 8.0, 8.1, 8.6. Peak at 8.1 exchanges with D_2O.

As the chemical shifts for pyridine (δ , 8.6(α H), 7.6 (β), 7.0(γ)) and pyridine hydrochloride are similar to those of imidazole compounds, it was somewhat difficult to assign peaks with any certainty. However, the peaks at δ 6.8, 7.4, 8.0 are in the ratio of 1:2:1. These shifts compare favourably with those of *N*-(1'-hydroxy-2',2',2'-trichloroethyl)-imidazole and can tentatively be proposed as those expected from *N*-(1',2',2',2'-tetrachloroethyl)imidazole.

Reaction of 1-(1'-hydroxy-2',2',2'-trichloroethyl)imidazole with *N*,*N*,*N*',*N*'-tetramethylphosphorodiamidic chloride

To a stirred solution of 1-(1'-hydroxy-2',2',2'-trichloroethyl)imidazole (4.31 g, 0.02 mol) and triethylamine (2.02 g, 0.02 mol) in dry chloroform (50 cm^3) was added, dropwise a solution of N,N,N',N'-tetramethylphosphorodiamidic chloride (3.41 g, 0.02 mol) in dry chloroform (10 cm^3). No heat was evolved on addition. The mixture was then heated under reflux for one hour, allowed to cool and the chloroform extracted with distilled water (3 X 25 cm^3). Both the organic and aqueous layers were collected and the solvent removed *in vacuo*.

The aqueous layer yielded an off white solid which was shown by ^1H NMR to be triethylamine hydrochloride.

The organic layer yielded a yellow oil which gave the following ^1H NMR: δ(ppm): ^1H(60 MHz, $CDCl_3$) 2.7 (dd, $^3J_{PNCH}$ 10, -P-N-$\underline{CH_3}$), 7.2 (2H, m, imidazole protons), 7.9 (1H, bs, imidazole proton). Comparison with the ^1H NMR of 1-(N,N,N',N'-tetramethylphosphorodiamidic)imidazole (δ ($CDCl_3$): 2.72, 7.22, 7.95) indicates that the two compounds are the same.[16a]

Reaction of 1-(1'-hydroxy-2',2',2'-trichloroethyl)imidazole with N,N,N',N'-tetramethylphosphoric triamide

A solution of 1-(1'-hydroxy-2',2',2'-trichloroethyl)imidazole (1.89 g, 0.009 mol) and N,N,N',N'-tetramethylphosphoric triamide (1.33 g, 0.009 mol) in benzene (100 cm^3) was heated under Dean and Stark conditions for an hour. No water could be detected (expected 0.15 cm^3), but a yellow oil deposited. The solvent was removed *in vacuo* to give a brown resinous

material. This was dissolved in chloroform and studied by TLC using chloroform:methanol (1:1) on silica plates. The mixture was shown to consist of four major components R_f 0.89, 0.66, 0.54 and a baseline residue of which two were the starting materials (R_f 0.66, phosphoramide; 0.54, 1-(1'-hydroxy-2',2',2'-trichloroethyl)imidazole). The reaction mixture was not investigated further.

Preparation of N-methyl-N-(1-hydroxy-2,2,2-trichloroethyl)formamide

Chloral (29.4 g, 0.20 mol) was added dropwise to N-methylformamide (12.0 g, 0.20 mol) and the mixture stirred during the addition. An exothermic reaction started at once. Approximately 30 minutes after all the chloral had been added the mixture began to solidify. The mixture was allowed to stand for a further two hours. The solid was treated with water, filtered and dried. The resulting off white solid was recrystallised from benzene to give N-methyl-N-(1-hydroxy-2,2,2-trichloroethyl)formamide (30.62 g, 74%), m.p. 102-103 °C (Lit.[17] m.p. 111 °C)(Found: C, 23.7; H, 3.1; N, 7.0. Calc. for $C_4H_6Cl_3NO_2$: C, 23.2; H, 2.9; N, 6.8%)

Preparation of N-methyl-N-(1,2,2,2-tetrachloroethyl)-formamide

N-methyl-N-(1-hydroxy-2,2,2-trichloroethyl)formamide

(10.1 g, 0.049 mol) and thionyl chloride (23.0 g, 14.0 cm^3, 0.19 mol) were heated under reflux with stirring for one hour. The excess thionyl chloride was removed under reduced pressure to give a yellow oil. The oil was dissolved in chloroform (100 cm^3). The chloroform solution was then washed with aqueous sodium carbonate solution (5%, 2 X 50 cm^3), followed by aqueous sodium chloride (10%, 2 X 50 cm^3) and dried over sodium sulphate. Evaporation of the solvent *in vacuo* yielded a yellow liquid which was crystallised from petrol (b.p. 40-60 °C) by taking it up in the minimum amount of hot petrol and storing overnight at -18 °C. The off white solid formed was filtered off and recrystallised from petroleum (b.p. 40-60 °C) to give *N*-methyl-*N*-(1,2,2,2-tetrachloroethyl)formamide (3.46 g, 31%), m.p. 42-43 °C (Lit.[17] m.p. 42-44 °C)(Found: C, 20.6; H, 2.2; N, 6.1. Calc. for $C_4H_5Cl_4NO$: C, 21.3; H, 2.2; N, 6.2%); δ(ppm): ^1H(60 MHz, $CDCl_3$) 3.1, 3.2 (ratio 1:1, s, -N-$\underline{CH_3}$), 6.1, 6.9 (ratio 1:1, s, CCl_3-$\underline{CH}$-$N(CH_3)$-C-), 8.2, 8.4 (ratio 1:1, s, -$N(CH_3)$-$\underline{CHO}$); $^{13}C(CDCl_3)$ 27.2, 30.7 (ratio 1:1, -$N(\underline{CH_3})$-CHO); 75.3, 83.8 (ratio 1:1, -$\underline{CH}$-$N(CH_3)$-); 98.7, 99.6 (ratio 1:1, $\underline{CCl_3}$-CH-N-); 162.9, 163.8 (ratio 1:1, -$N(CH_3)$-$\underline{CHO}$).

Reaction of *N*-methyl-*N*-(1,2,2,2-tetrachloroethyl)formamide with *N*,*N*,*N*',*N*'-tetramethylphosphoric triamide in the presence of pyridine

To a solution of *N*-methyl-*N*-(1,2,2,2-tetrachloroethyl)-

formamide (2.28 g, 0.010 mol) and pyridine (0.99 g, 0.013 mol) in benzene (20 cm^3) was added N,N,N',N'-tetramethylphosphoric triamide (1.84 g, 0.012 mol) and the mixture heated under reflux, with stirring for five hours. Some decomposition occured with a yellow oil separating out. Evaporation of the solvent *in vacuo* gave a yellow oil which gave the following ^1H NMR. δ(ppm): ^1H(60 MHz, $CDCl_3$) 2.6 (d, J 10), 3.0, 3.1, 3.2, 6.3, 6.9, 8.2, 8.5 (s). The doublet at δ 2.6 and the peaks at 3.1, 3.2, 6.3, 6.9, 8.2 and 8.5 can be assigned to the starting materials. No peaks corresponding to the expected condensation product were observed indicating that no reaction had taken place.

Reaction of N-methyl-N-(1,2,2,2-tetrachloroethyl)formamide with N,N,N',N'-tetramethylphosphoric triamide in the presence of triethylamine

To a solution of N-methyl-N-(1,2,2,2-tetrachloroethyl)-formamide (2.27 g, 0.010 mol) and triethylamine (1.26 g, 0.012 mol) in toluene (20 cm^3) was added N,N,N',N'-tetramethylphosphoric triamide (1.87 g, 0.012 mol). The mixture was heated under reflux, with stirring for three hours. A white precipitate formed after 15 minutes. After three hours the mixture was filtered hot to yield a white solid which was identified by ^1H NMR as triethylamine hydrochloride (1.21 g, 88%, based on chloro compound). On cooling the filtrate a

white solid crystallised which was identified by melting point and ^{1}H NMR to be N,N,N',N'-tetramethylphosphoric triamide (1.19 g, 64% of starting weight). The solvent was removed from the filtrate *in vacuo* to give a yellow oil. Initial ^{1}H NMR showed this to be contaminated by N,N,N',N'-tetramethylphosphoric triamide. The oil was dissolved in benzene (50 cm^3), washed with water to remove the residual phosphoric triamide, and dried over magnesium sulphate. The solvent was removed *in vacuo* to give a yellow oil. δ(ppm): ^{1}H(60 MHz, $CDCl_3$) 3.0, 3.1 (3H, s, ratio 1:7), 8.0, 8.2 (1H, s, ratio 1:7); ^{13}C($CDCl_3$) 29.8, 33.3 (ratio 7:1), 122.4, 129.9, 160.9 and 161.9 (ratio 7:1). A peak at 128.4 appears in the ^{13}C which is due to benzene (δ 128.5). Toluene the original solvent used shows no peaks in the ^{13}C (Lit.[18] 21.3, 137.4, 129.2, 128.4, 125.6) and thus the peaks can be assigned with some certainty. This data indicates the structure CCl_2=C(Cl)N(CH_3)CHO .

Reaction of N-methyl-N-(1,2,2,2-tetrachloroethyl)formamide with triethylamine: Preparation of N-methyl-N-(1,2,2-trichloroethenyl)formamide

To a solution of N-methyl-N-(1,2,2,2-tetrachloroethyl)-formamide (6.92 g, 0.0308 mol) in dry toluene (50 cm^3) was added triethylamine (3.12 g, 0.0309 mol) and the mixture heated under reflux for three hours with the exclusion of moisture. The solution became a dark orange colour and an

off-white precipitate formed. The mixture was filtered hot and the solid identified as triethylamine hydrochloride (3.27 g, 77%) by ^{1}H NMR. The filtrate was then worked up by removing the solvent *in vacuo* and distilling the residue under reduced pressure to yield *N*-methyl-*N*-(1,2,2-trichloroethenyl)formamide as a colourless liquid (2.65 g, 46%), b.p. 94-98 °C at 22 mmHg. δ(ppm): ^{1}H(DMSO-d_6) 2.97, 3.15 ca. ratio 2:1 (singlets, -N(*CH*$_3$)-), 8.14, 8.33 ca. ratio 2:1 (singlets, -N(CH$_3$)-*CHO*); ^{13}C(DMSO-d_6) 29.4, 33.1 ca. ratio 3:1 (singlets, -N(*CH*$_3$)-), 121.3 (s, CCl_2=*CCl*-), 130.0 (s, *CCl*$_2$=CCl-), 162.0, 162.5 ca. ratio 3:1 (singlets, -N(CH$_3$)-*CHO*); m/z(%): 152(94), 124(69), 108(22), 69(49), 58(100); FAB 188(100, M+1), 152(58), 124(41), 108(25), 109(53), 95(47).

Preparation of *N*-(1'-hydroxy-2',2',2'-trichloroethyl)-2-piperidone

Chloral (36.8 g, 0.25 mol) was added to 2-piperidone (9.9 g, 0.1 mol) and the mixture heated under reflux with stirring for three hours. The excess chloral was removed *in vacuo* to give an off white resinous material which was recrystallised from a mixture of diethyl ether and light petroleum (b.p. 40-60 °C) to give *N*-(1'-hydroxy-2',2',2'-trichloroethyl)-2-piperidone (13.2 g, 54%), m.p. 97-99 °C (Lit.[19] No data given)(Found: C, 34.3; H, 4.0; N, 5.6; Cl, 42.9. Calc. for $C_7H_{10}Cl_3NO_2$: C, 34.1, H, 4.1; N, 5.7; Cl, 43.2%).

Preparation of N-(1',2',2',2'-tetrachloroethyl)-2-piperidone and reaction with N,N,N',N'-tetramethylphosphoric triamide

Thionyl chloride (23.8 g, 14.5 cm^3, 0.2 mol) was added to N-(1'-hydroxy-2',2',2'-trichloroethyl)-2-piperidone (4.93 g, 0.02 mol) and the mixture heated under reflux until the evolution of gases had ceased (approx. 1 hour). The excess thionyl chloride was removed *in vacuo* and the resulting yellow oil was placed under high vacuum until constant weight was obtained. The yellow oil was weighed (4.93 g, 93%) and the IR spectrum recorded. This indicated that the reaction was complete due to the lack of the -OH peak.

The yellow oil was dissolved in benzene (25 cm^3). This solution was added simultaneously with a solution of triethylamine (2.02 g, 0.02 mol) in benzene (25 cm^3) to a solution of N,N,N',N'-tetramethylphosphoric triamide (3.03 g, 0.02 mol) in benzene (50 cm^3). The mixture was then heated under reflux for three hours and allowed to stand overnight. A white solid precipitated which was filtered off and identified by ^1H NMR as triethylamine hydrochloride (0.95 g, 35%). The solvent was removed *in vacuo* from the filtrate to give a yellow solid which was recrystallised from benzene and shown by ^1H NMR and melting point to be unreacted N,N,N',N'-tetramethylphosphoric triamide (1.55 g, 51%).

Reaction of chloral with acetanilide

Chloral (10.9 g, 0.074 mol) was added to acetanilide (5.03 g, 0.037 mol) and the mixture heated under reflux for three hours with the exclusion of moisture. The excess chloral was removed in vacuo to give an off white solid (6.0 g). This was recrystallised from water to give acetanilide (1.6 g) identified by melting point, IR and ^{1}H NMR.

The reaction was repeated using a much longer reaction time (48 hours) and under dry nitrogen to reduce decomposition. Removal of the excess chloral again gave an off white solid (5.5 g) indicating that no condensation had taken place. Recrystallisation of the solid gave acetanilide (1.37 g) identified as before. Work up of the filtrate gave a residue (0.8 g) identified as acetanilide by ^{1}H NMR.

These results indicate that no reaction had taken place.

Reaction of chloral with N-methylacetamide

Chloral (14.75 g, 0.1 mol) was added dropwise with stirring to N-methylacetamide (7.30 g, 0.1 mol). The reaction was exothermic. The mixture was heated under reflux for four hours and allowed to stand overnight. Attempted crystallisation of the resulting oil by scratching and cooling in Cardice/acetone failed. ^{1}H NMR showed that some reaction had taken place but that the bulk of the starting material was unchanged. The mixture was allowed to stand for two days, during which a white solid crystallised. This was filtered off and washed with a little diethyl ether to yield N-methyl-

N-(1-hydroxy-2,2,2-trichloroethyl)acetamide (0.55 g, 2.5%), m.p. 94-95 °C (Lit.[20] No data given)(Found: C, 26.8; H, 3.6; N, 6.1. Calc. for $C_5H_8Cl_3NO_2$: C, 27.2; H, 3.6; N, 6.3%); δ(ppm): ^{1}H(60 MHz, DMSO-d_6) 2.1 (3H, s, $\underline{CH_3}$CO-), 3.0 (3H, s, -N($\underline{CH_3}$)), 6.4 (1H, d, becomes singlet on shaking with D_2O, -$\underline{CH}$-OH), 7.8 (1H, d, exchanges with D_2O, -CH-$\underline{OH}$).

The reaction was repeated using 24 and 48 hour reaction times and using an excess of chloral. This failed to improve the yield of the desired product.

Reaction of 1-(1'-hydroxy-2',2',2'-trichloroethyl)imidazole with dimethylcarbamoyl chloride

To a stirred solution of 1-(1'-hydroxy-2',2',2'-trichloroethyl)imidazole (10.82 g, 0.05 mol) in chloroform (50 cm^3), cooled in ice were added solutions of dimethylcarbamoyl chloride (5.38 g, 0.05 mol) in benzene (10 cm^3) and pyridine (4.77 g, 0.05 mol) in benzene (10 cm^3), simultaneously. The mixture was then stirred for two hours at room temperature. The resulting solution was washed well with distilled water (3 X 50 cm^3), dried over sodium sulphate and the solvent removed <u>in vacuo</u>. TLC using a mixture of chloroform/ethyl-acetate/methanol (3:1:0.5) on silica showed the mixture to be made up of three components (R_f 0.69, 0.50 and 0.35) of which that at R_f 0.50 was the main component. No starting material (R_f 0.28) could be detected. Column chromatography using the same conditions as TLC yielded four fractions

whose TLC indicated that the first fraction contained one component (R_f 0.48) and the others a mixture of components. Only the first fraction was investigated further. The solvent was removed *in vacuo* to give a yellow oil (1.04 g) which failed to crystallise from a mixture of diethyl ether and petrol (b.p. 30-40 °C). The solvent was again removed *in vacuo* and the residue investigated by ^{1}H NMR. The spectrum was quite complex but peaks at δ(ppm) 3.0, 7.1, 7.5 and 8.3 could clearly be seen when taking into account residual solvent peaks. The peak at δ 3.0 was due to the $-C(O)NMe_2$ group and the peaks at δ 7.1, 7.5 and 8.3 are in the imidazole proton region. No peak consistent with the presence of the $-CH(CCl_3)$ group could be seen, indicating that C-N bond cleavage had occurred.

Reaction of *N*,*N*,*N*',*N*'-tetramethylphosphoric triamide with chloral

Experiment 1. To a well stirred, cooled solution of *N*,*N*,*N*',*N*'-tetramethylphosphoric triamide (1.00 g, 0.0066 mol) in benzene* (30 cm^3) was added a solution of chloral (0.98 g, 0.0066 mol) in benzene (10 cm^3) under anhydrous conditions using silica gel as the drying agent. After addition was complete the reaction mixture was allowed to come to room temperature and the mixture stirred for three hours. The solvent and

* Benzene was AnalaR grade dried over sodium.

any unreacted chloral were removed *in vacuo* using a rotary evaporator (bath temperature 30 °C) followed by two hours under high vacuum (0.1 mmHg). The mixture was allowed to stand overnight in a desiccator and the ^{1}H and ^{31}P NMR spectra recorded, δ(ppm): $^{1}H(CDCl_3)$ 2.64 (d, J 10, $(Me_2N)_2P{=}O$ species), 2.85, 2.96 (dimethylformamide. Literature[21] δ 2.88, 2.97), 3.43 (bs, $-P-NH_2$ starting material), 3.67 (m, -P-NH-CH- product of condensation), 5.18 (dd, J 7.5, -P-NH-CH- product of condensation), 7.34 (s, benzene and $CHCl_3$ present as residual solvent or in the case of the latter as a reaction product), 7.63, 8.00 (unassigned), 9.07 (bs, chloral); $^{31}P(^{1}H\text{-BB}, CDCl_3)$ 23.1(100*), 20.5(53), 11.7(6, multiplet), 5.8(7, multiplet), -6.6(22), -6.8(42), -7.5(18), -9.3(27). A total of 41 peaks were recorded in the ^{31}P spectrum. The peak in the ^{31}P at δ 23.1 corresponds to the starting material and indicates that the reaction has not gone to completion.

Experiment 2. The same conditions as in the previous experiment were used and the reaction time extended to 3 days. A resinous material separated. The benzene was decanted off and the solvent removed *in vacuo*. The ^{13}C and ^{31}P spectra of this fraction were recorded, $^{13}C(DMSO\text{-}d_6/CDCl_3)$ 34.5 (s, $-N(\underline{CH}_3)_2$), 36.7 (d, J 3.1, $-P-N(\underline{CH}_3)_2$), 41.6, 42.2 ($-N(CH_3)_2$

*The ^{31}P signals are quoted relative to the largest peak in the spectrum (100%) in order to give some information on the relative importance of each peak. The percentages are based on peak height.

of dimethylformamide), 77.4, 79.2, 79.9, 80.6 (s, unassigned), 83.2 (d, J 4.3, -P-NH-CH-), 85.2 (d, J 4.9, -P-NH-CH-), 101.4 (d, J 9.8, -P-NH-CH-CCl_3), 102.4 (d, J 9.2, -P-NH-CH-CCl_3), 157.3 (s, unassigned -C=O), 158.9 (d, J 8, possibly -P-NHCHO), 162.3 (s, C=O, dimethylformamide). A total of 111 peaks were recorded of which the quoted peaks (with the exception of those at 101.4 and 102.4) could clearly be seen. $^{31}P(^{1}H$-BB, DMSO-d_6/$CDCl_3$) 22.9(92), 20.4(70), 20.2(100), 10.0(19, multiplet), 5.3(15, multiplet), -0.4(21), -6.5(10, multiplet), -10.0 (10, multiplet). A total of 56 peaks were recorded.

The ^{13}C and ^{31}P spectra of the resinous material were also recorded, ^{13}C(DMSO-d_6/CD_3OD) 34.6 (s, -N(CH_3)$_2$), 36.8 (d, J 2.9, -P-N(CH_3)$_2$), 49.1, 75.5, 79.5 (s, unassigned), 86.3 (d, J 12.5), 93.6 (d, J 19), 101.8 (s, -CCl_3), 160.0 (m, C=O). The peak at δ 34.6 was by far the biggest peak in the spectrum (approx. ten times larger than any other peak). The peaks at δ 36.8 are very small indicating that few compounds containing the -P-N$(CH_3)_2$ group exist in this fraction. $^{31}P(^{1}H$-BB, DMSO-d_6/CD_3OD) 23.9(22), 20.7(11), 16.1(13), 10.1, 9.4(23, 32 respectively. Largest peaks in a multiplet), -0.1(56), -0.5 (65), -0.7(67), -4.0(100), 7.7(28, highest peak in the multiplet), -10.0(76), -21.8(16, multiplet). The ^{31}P spectrum contains 83 peaks. However the spectrum shows that very few phosphoric triamide species exist i.e. δ 23.9, 20.7 and that many of the other compounds contain P-O bonds. Successive replacement of P-N bonds for P-O bonds moves the ^{31}P to more negative shifts i.e. upfield. P-N bond cleavage was also suppor-

ted by the ^{13}C spectrum of this fraction.

Experiment 3. The same conditions as in the previous experiment were used with the reaction time extended to 4 days. GLC was used to detect and monitor any chloroform and dimethylformamide which were expected as reaction products.

Determination of chloroform

Conditions: 6' glass, 10% Apiezon column
Column temperature of 50 °C
FID detector

TIME DAYS	% $CHCl_3$* OF THEORETICAL
1	46
2	36
4	18

Determination of dimethylformamide(DMF)

Conditions: 6' glass, 10% EGSS-X on Celite column
Column temperature of 120 °C
FID detector

TIME DAYS	% DMF* OF THEORETICAL
1	20
2	26
4	20

*Determined by standard addition method.

Standard solutions of the reagents used in the reaction were made and these were checked for the presence of chloroform and DMF. No chloroform or DMF could be detected in the starting materials.

A resinous material had been formed during the course of the reaction. The benzene was decanted off and removed *in vacuo* to give a white resinous solid. Recrystallisation of this solid from a mixture of benzene and petrol (b.p. 60-80 °C) gave large crystals of a solid which was identified as *N*,*N*,*N*',*N*'-tetramethyl-*N*"-(2,2,2-trichloro-1-dimethylaminoethyl)phosphoric triamide (12 mg), δ(ppm): $^{1}H(CDCl_3)$ 2.52 (6H, s, $-N(\underline{CH_3})_2$), 2.70 (12H, dd, $^{3}J_{PNCH}$ 10.0, $-P-N(\underline{CH_3})_2$), 2.99 (1H, m, -P-NH-CH-), 4.70 (1H, dd, -P-NH-CH-N-); $^{31}P(^{1}H\text{-BB}, CDCl_3)$ 19.7. The structure was confirmed by X-ray crystallography.

Attempted fractional recrystallisation of the resinous material from a number of solvents failed to yield any compounds which could be identified.

Reaction of hexamethylphosphoric triamide with chloral

To a solution of hexamethylphosphoric triamide (HMPT) (1.8565 g, 0.010 mol) in dry benzene (25 cm^3) contained in a 100 cm^3 round-bottomed flask, was added a solution of chloral (1.5405 g, 0.010 mol) in benzene (25 cm^3). The flask was stoppered and allowed to stand. Analysis of the mixture by glc after 16, 48 and 96 hours showed that no chloroform or dimethylfomamide were present. Standards containing 0.01 mol of chloroform, dimethylformamide, HMPT and chloral

in benzene (25 cm^3) were also run to ensure that the starting materials were pure and that the conditions used were able to detect small amounts of chloroform and/or dimethylformamide which were expected as reaction products. After 16 days of standing the solvent was removed <u>in vacuo</u> and the residue investigated by ^{31}P NMR. This showed a single peak $\delta_P(CDCl_3)$ 25.9 which when compared with the HMPT ($\delta_P(CDCl_3)$ 25.6) used in the experiment showed that no reaction had taken place.

<u>Preparation of 1-butoxyacetamide</u>

A solution of sodium butoxide was prepared by adding small pieces of sodium metal (5.03 g, 0.22 mol) to refluxing butanol (50 cm^3). The solution was cooled, and then added dropwise (with care as reaction was exothermic) to a well stirred refluxing solution of chloroacetamide (20.0 g, 0.21 mol) in butanol (50 cm^3). The reaction mixture went dark brown and a white solid separated. After the addition was complete the reaction mixture was heated under reflux for a further 30 minutes. It was then filtered hot, to yield an off-white solid (13.15 g) which gave a precipitate with silver nitrate indicating that it was sodium chloride (theoretical weight 12.3 g based on chloroacetamide). The solvent was removed from the filtrate using a rotary evaporator to yield a dark brown oil which crystallised on standing. This residue was taken up in chloroform (150 cm^3) and washed with distilled water (2 X 50 cm^3). The chloroform layer was then dried over

magnesium sulphate and the chloroform removed *in vacuo*. This gave a yellow oil which was crystallised from diethyl ether to give *1-butoxyacetamide* (5.23 g, 19%), m.p. 68-70 °C (Found: C, 55.0; H, 9.7; N, 10.8. $C_6H_{13}NO_2$ requires: C, 55.0; H, 9.9; N, 10.7%); δ(ppm): ^{1}H(60 MHz, $CDCl_3$) 0.9 (3H, t, $-CH_2-\underline{CH}_3$), 1.5 (4H, m, $-O-CH_2-(\underline{CH}_2)_2-CH_3$), 3.5 (2H, t, $-O-\underline{CH}_2-CH_2-$), 3.9 (2H, s, $-\underline{CH}_2-O-CH_2CH_2-$), 6.7 (2H, bs, exchanges with D_2O, $-CO\underline{NH}_2$); m/z(%): 131(9, M^+), 116(22), 101(16), 99(21), 74(12), 73(11), 69(21), 60(33), 57(100), 44(45), 41(78).

Preparation of 1-butoxy-N-(1'-hydroxy-2',2',2'-trichloroethyl)acetamide

To a solution of 1-butoxyacetamide (4.96 g, 0.038 mol) in chloroform (75 cm^3) was added chloral (5.62 g, 0.038 mol). The mixture was heated under reflux with stirring and the exclusion of moisture for 3 hours. The solvent was then removed using a rotary evaporator to give a yellow oil, which on attempted recrystallisation from light petroleum (b.p. 40-60 °C) yielded an off white solid and an oil. The solid was filtered off and identified as *1-butoxy-N-(1'-hydroxy-2',2',2'-trichloroethyl)acetamide* (1.22 g, 12%), m.p. 52-53 °C (Found: C, 34.7; H, 5.0; N, 5.0. $C_8H_{14}NO_3Cl_3$ requires: C, 34.5; H, 5.0; N, 5.0%); δ (ppm): ^{1}H($CDCl_3$) 0.94 (3H, t, $-CH_2\underline{CH}_3$), 1.52 (4H, m, $-CH_2(\underline{CH}_2)_2CH_3$), 3.54 (2H, t, $-O-\underline{CH}_2-CH_2-$), 4.01 (2H, s, $-\underline{CH}_2-O-CH_2-CH_2-$), 5.89, 5.96 (2H, overlapping signals, reduces to 1H on shaking with D_2O, $-NH-\underline{CH}(CCl_3)-\underline{OH}$), 7.55 (1H,

bd, exchanges with D_2O, -CO-<u>NH</u>-CH(CCl_3)-); $^{13}C(CDCl_3)$ 13.9 (-CH_2<u>CH_3</u>), 19.2 (-CH_2-CH_2-<u>CH_2</u>-CH_3), 31.5 (-O-CH_2-<u>CH_2</u>-CH_2-), 77.1 (-O-<u>CH_2</u>-CH_2-), 78.7 (-CO-<u>CH_2</u>-O-), 80.6 (-NH<u>CH</u>(CCl_3)-), 100.8 (-NHCH(<u>CCl_3</u>)-), 171.5 (C=O).

Preparation of <u>N</u>,<u>N</u>,<u>N</u>',<u>N</u>'-tetramethyl-<u>N</u>"-(2,2,2-trichloro-1-butoxyacetamidoethyl)phosphoric triamide

Thionyl chloride (45.9 g, 0.38 mol, 28.0 cm^3) was added to crude 1-butoxy-<u>N</u>-(1'-hydroxy-2',2',2'-trichloroethyl)acetamide (9.4 g, 0.034 mol) and the mixture heated under reflux with stirring until the evolution of gases had ceased. The excess thionyl chloride was removed under reduced pressure and the residue placed under high vacuum for 2 hours. This residue was dissolved in dry benzene (100 cm^3) and triethylamine (3.82 g, 0.038 mol) was added. A white precipitate formed immediately and the mixture was allowed to stand for 15 minutes. The precipitate was then filtered off, washed with benzene (2 X 50 cm^3), dried and weighed as triethylamine hydrochloride (4.0 g, 77%). It was identified by ^1H NMR. To the combined filtrate and washings was added <u>N</u>,<u>N</u>,<u>N</u>',<u>N</u>'-tetramethylphosphoric triamide (5.72 g, 0.038 mol) and the mixture allowed to stand for 2 days. No solid crystallised, hence the solvent was removed using a rotary evaporator. Fractional crystallisation from diethyl ether yielded two solids. The first solid (2.03 g) was shown by ^1H NMR to be unreacted phosphoric triamide, the second (2.99 g) was shown to be a mixture of phosphoric tri-

amide and the required product. This second solid was taken up in chloroform (100 cm^3) and washed with water (3 X 50 cm^3) to remove the phosphoric triamide. The chloroform layer was dried over magnesium sulphate and the solvent removed *in vacuo* to yield an off-white solid. This solid was recrystallised from a mixture of benzene and light petroleum (b.p. 60-80 °C) to yield **N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-butoxy-acetamidoethyl)phosphoric triamide** (0.97 g, 6%), m.p. 137-138 °C (decomp.)(Found: C, 34.2; H, 6.3; N, 13.1; M+1, 411.0. $C_{12}H_{26}Cl_3N_4O_3P$ requires: C, 35.0; H, 6.3; N, 13.6%; M+1, 411.1); δ(ppm): ^1H(DMSO-d_6) 0.89 (3H, t, $-CH_2-(CH_2)_2-\underline{CH_3}$), 1.48 (4H, m, $-CH_2-(\underline{CH_2})_2-CH_3$), 2.51 (12H, dd, $^3J_{PNCH}$ 10.2, $-P-N-\underline{CH_3}$), 3.48 (2H, t, $^3J_{PNCH}$ 6.3, $-O-\underline{CH_2}-(CH_2)_2-CH_3$), 3.94, 3.95 (2H, singlets, $-CO-\underline{CH_2}-O-CH_2-$), 5.31 (1H, odd, exchanges using CD_3OD as solvent, $-P-\underline{NH}-CH-NH-$), 5.76 (1H, m, reduces to a doublet using CD_3OD as solvent, $^3J_{PNCH}$ 11.0, $-P-NH-\underline{CH}-NH-$), 7.98 (1H, d, $^3J_{HCNH}$ 9.3, exchanges using CD_3OD as solvent, $-CH-\underline{NH}-CO-$); ^{13}C(DMSO-d_6) 13.7 (s, $-CH_2-(CH_2)_2-\underline{CH_3}$), 18.6 (s, $-CH_2-\underline{CH_2}-CH_2-CH_3$), 31.0 (s, $-CH_2-\underline{CH_2}-CH_2-CH_3$), 36.1 (d, $^2J_{PNC}$ 4.1, $-P-N-\underline{CH_3}$), 68.5 (d, $^2J_{PNC}$ 7, $-P-NH-\underline{CH}-NH-$), 69.4 (s, $-CO-CH_2-O-\underline{CH_2}-$), 70.8 (s, $-CO-\underline{CH_2}-O-$), 103.8 (d, $^3J_{PNCC}$ 10.2, $-P-NH-CH(\underline{CCl_3})-$), 168.6 (s, C=O); $^{31}P(^1H$-BB, DMSO-d_6) 20.3; m/z(%): FAB 411(5, M+1), 377(5), 366(9), 332(9), 280(4), 253 (12), 246(11), 219(12), 212(5), 152(25), 135(100), 108(13), 107(13), 92(11).

Preparation of 1-dodecyloxyacetamide

A solution of potassium dodecyloxide was prepared by adding small pieces of potassium metal (8.34 g, 0.21 mol) to a refluxing, well stirred solution of dodecan-1-ol (39.8 g, 0.21 mol) in dry benzene (250 cm^3). The mixture was heated under reflux with stirring until all the potassium metal had dissolved (ca. 24 hours). To this mixture was then added chloroacetamide (20.0 g, 0.21 mol) in small portions as the reaction was exothermic. After addition was complete the reaction mixture was heated under reflux for a further one hour. The solvent was then removed using a rotary evaporator to yield a brown resinous material, which was recrystallised from diethyl ether to give 1-dodecyloxyacetamide as an off white solid (18.3 g, 36%). δ(ppm): ^1H(60 MHz, $CDCl_3$) 0.9 (3H, m, $-(CH_2)_{11}\underline{CH_3}$), 1.3 (20H, m, $-OCH_2(\underline{CH_2})_{10}CH_3$), 3.4 (2H, t, $-O\underline{CH_2}(CH_2)_{10}-$), 3.8 (2H, s, $-C(O)\underline{CH_2}OCH_2-$), 6.5 (2H, bs, exchanges with D_2O, $-\underline{NH_2}$); $^{13}C(CDCl_3)$ 14.1, 22.8, 26.1, 29.5, 29.7, 32.0 (C_{12} chain), 70.2 ($-O\underline{CH_2}(CH_2)_{10}-$), 72.0 ($-C(O)\underline{CH_2}OCH_2-$), 173.4 (C=O).

Preparation of 1-dodecyloxy-N-(1'-hydroxy-2',2',2'-trichloroethyl)acetamide

To a solution of 1-dodecyloxyacetamide (5.0 g, 0.02 mol) in dry toluene (100 cm^3) was added chloral (3.1 g, 0.02 mol). The mixture was heated under reflux with stirring and the exclusion of moisture for 3 hours. The solvent was removed

in vacuo to give a yellow oil, which was recrystallised from a mixture of diethyl ether and petrol (b.p. 40-60 °C) to yield 1-dodecyloxy-N-(1'-hydroxy-2',2',2'-trichloroethyl)-acetamide (4.23 g, 54%), m.p. 73-75 °C; δ(ppm): $^{1}H(CDCl_3)$ 0.88 (3H, m, $-(CH_2)_{11}\underline{CH_3}$), 1.27 (20H, m, $-OCH_2(\underline{CH_2})_{10}CH_3$), 3.53 (2H, t, $-O\underline{CH_2}(CH_2)_{10}-$), 4.00 (2H, s, $-C(O)\underline{CH_2}O-CH_2-$), 5.93 (1H, d, $-NH-\underline{CH}(CCl_3)OH$), 6.38 (1H, bs, -OH), 7.52 (1H, d, $-\underline{NH}-CH-$); $^{13}C(CDCl_3)$ 14.1, 22.7, 29.4, 31.9 (C_{12} chain), 69.8 ($-O\underline{CH_2}(CH_2)_{10}-$), 72.3 ($-C(O)\underline{CH_2}O-$), 80.4 ($-NH-\underline{CH}-$), 100.9 ($-CCl_3$), 171.6 (C=O).

Preparation of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-dodecyloxyacetamidoethyl)phosphoric triamide

Thionyl chloride (8.8 g, 5.4 cm^3, 0.074 mol) was added to a solution of crude 1-dodecyloxy-N-(1'-hydroxy-2',2',2'-trichloroethyl)acetamide (2.9 g, 0.0074 mol) in benzene (30 cm^3) and the mixture heated under reflux with stirring until the evolution of gases had ceased. The solvent and excess thionyl chloride were removed in vacuo and the residue placed under high vacuum for 3 hours. This residue was dissolved in dry benzene (30 cm^3) and triethylamine (0.77 g, 0.0076 mol) was added. A white precipitate formed immediately and the mixture was allowed to stand for 15 minutes. The precipitate was then filtered off, washed with benzene (3 x 10 cm^3) and weighed as triethylamine hydrochloride (0.87 g, 85%). It was identified by ^{1}H N.M.R. To the combined filtrate and washings was added N,N,N',N'-tetramethylphosphoric triamide (1.15 g, 0.0076 mol)

and the mixture allowed to stand for 3 days. The solvent was removed using a rotary evaporator to give an orange oil which was taken up in chloroform (50 cm^3) and washed with distilled water (3 x 25 cm^3) to remove any unreacted phosphoric triamide. The chloroform layer was dried over magnesium sulphate and the solvent removed *in vacuo* to yield an oil which failed to crystallise from a number of solvents. Investigation of this oil by ^1H, ^{13}C and ^{31}P N.M.R. showed that some of the starting materials remained but that the major component was *N,N,N',N'*-tetramethyl-*N"*-(2,2,2-trichloro-1-dodecyloxy-acetamidoethyl)phosphoric triamide (*ca.* 70%); δ(ppm): $^1H(CDCl_3)$ 0.88 (m, $-(CH_2)_{10}\underline{CH_3}$), 1.26 (m, $-(\underline{CH_2})_{10}CH_3$), 2.66 (d, $^3J_{PNCH}$ 10.2, -P-N-$\underline{CH_3}$), 3.54 (m, $-O\underline{CH_2}(CH_2)_{10}-$), 3.98 (s, $-C(O)\underline{CH_2}OCH$ -), 5.88 (m, -NH-$\underline{CH}$-NH-), 7.74 (d, $^3J_{HCNH}$ 9.7, -CH-$\underline{NH}$-C(O)-); $^{13}C(CDCl_3)$ 14.1, 22.7, 26.0, 29.4, 32.0 (C_{12} chain), 36.7 (d, $^2J_{PNC}$ 3.4, -P-N-$\underline{CH_3}$), 70.0 (s, $-O\underline{CH_2}(CH_2)_{10}-$), 72.1 (d, $^2J_{PNC}$ 5.4, -P-NH-$\underline{CH}$-), 72.2 (s, $-C(O)\underline{CH_2}OCH_2-$), 102.9 (d, $^3J_{PNCC}$ 9.5, -P-NH-CH($\underline{CCl_3}$)-), 169.7 (C=O); $^{31}P(^1H\text{-BB}, CDCl_3)$ 19.6.

Reaction of *N,N,N',N'*-tetramethyl-*N"*-(2,2,2-trichloro-1-acetamidoethyl)phosphoric triamide with sodium ethoxide

Sodium metal (0.1428 g, 0.006 mol) was added to absolute ethanol (25 cm^3) and the mixture was allowed to stand until all the sodium metal had dissolved. This sodium ethoxide solution was added dropwise to a refluxing, well stirred solution of *N,N,N',N'*-tetramethyl-*N"*-(2,2,2-trichloro-1-acet-

amidoethyl)phosphoric triamide (2.0 g, 0.006 mol) in absolute ethanol (100 cm^3). A white precipitate formed after 5 minutes. The mixture was heated under reflux for 3 hours and then hot filtered. A solid (0.22 g) was collected which gave a precipitate with aqueous silver nitrate (which dissolved in concentrated ammonia) indicating that it was sodium chloride. The solvent was removed from the filtrate using a rotary evaporator to yield an orange oil. Fractional crystallisation from diethyl ether and storing overnight at -18 ^{o}C yielded two solids (combined weight 0.51 g) which were shown by spectroscopic methods to be a mixture of two compounds:-

1) N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-ethoxyethyl)phosphoric triamide

a) δ_H(DMSO-d_6)

Mixture	Authentic sample	Multiplicity	Assignment
1.18	1.18	t	$-OCH_2\underline{CH}_3$
2.52	2.55	dd	-P-N-$\underline{CH}_3$
3.72	3.72	m	$-O\underline{CH}_2CH_3$
4.84	4.84	dd	-NH-CH-O-
5.42	5.42	m	-P-NH-CH-

b) δ_C(DMSO-d_6)

See next page for table.

Mixture	Authentic sample	Multiplicity	Assignment
14.8	14.8	s	$-OCH_2\underline{CH}_3$
36.2	36.2	d	$-P-N-\underline{CH}_3$
64.3	64.3	s	$-O\underline{CH}_2CH_3$
90.9	90.9	d	$-P-NH-\underline{CH}-$
101.7	102.1	d	$-CCl_3$

c) $\delta_P(DMSO-d_6)$

Mixture : 19.6

Authentic sample: 19.6

2) N,N,N,N'-tetramethyl-N"-(dichloroacetyl)phosphoric triamide $(Me_2N)_2P(O)NHC(O)CHCl_2$

a) Molecular weight by FAB mass spectrometry

Found : 261.0 (M^+)

$C_6H_{14}Cl_2N_3O_2P$ requires: 261.0

b) $\delta_H(DMSO-d_6)$ 2.52 (d, $-P-N-\underline{CH}_3$), 6.56 (d, $^4J_{PNCCH}$ 2.0, $-P-NH-C(O)\underline{CHCl}_2$).

c) $\delta_C(DMSO-d_6)$ 36.2 (d, $-P-N-\underline{CH}_3$), 68.9 (d, $^3J_{PNCC}$ 29.2, $-P-NH-C(O)\underline{CHCl}_2$), 162.5 (d, $^2J_{PNC}$ 2.7, C=O).

d) $\delta_P(DMSO-d_6)$ 22.4

Reaction of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-acetamidoethyl)phosphoric triamide with sodium ethanethiolate

To a solution of ethanethiol (0.362 g, 0.0058 mol) in absolute ethanol (25 cm^3) was added sodium hydroxide (0.22 g, 0.0055 mol) and the mixture stirred until all the sodium hydroxide had dissolved. The resulting solution of sodium ethanethiolate was added dropwise to a refluxing, well stirred solution of N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-acetamidoethyl)phosphoric triamide (2.0 g, 0.0059 mol) in absolute ethanol (100 cm^3). A white precipitate formed after 5 minutes. The mixture was heated under reflux for 3 hours and then hot filtered. A solid (0.16 g) was collected which gave a precipitate with aqueous silver nitrate (this dissolved on addition of concentrated ammonia) indicating that it was sodium chloride. The solvent was removed from the filtrate using a rotary evaporator to yield an orange oil. Trituration of this oil with chloroform yielded a white solid (0.5 g) which was filtered off and identified as the phosphoric triamide starting material by spectroscopic methods. The filtrate was transferred to a separating funnel and washed well with distilled water. The two layers were separated. Removal of the water under reduced pressure from the water layer yielded an off white solid (1.1 g) which was identified as phosphoric triamide starting material. The chloroform layer was dried over magnesium sulphate, filtered and the solvent removed under reduced pressure to yield an orange oil.

Fractional crystallisation from diethyl ether yielded two compounds which could be fully characteried by spectroscopic techniques :-

1) N,N,N',N'-tetramethyl-N"-(dichloroacetyl)phosphoric triamide (0.27 g, 19%).

a) Molecular weight by FAB mass spectrometry

Found : 261.0 (M^+)

$C_6H_{14}Cl_2N_3O_2P$ requires: 261.0

b) $\delta_H(CDCl_3)$ 2.63 (d, -P-N-$\underline{CH}_3$), 5.99 (s, -$\underline{CHCl}_2$).

c) $\delta_C(CDCl_3)$ 36.4 (d, $^2J_{PNC}$ 3.4, -P-N-$\underline{CH}_3$), 69.6 (d, $^3J_{PNCC}$ 33.9, -$\underline{CHCl}_2$), 162.5 (d, $^2J_{PNC}$ 4.7, C=O).

d) $\delta_P(CDCl_3)$ 23.9

2) N,N,N',N'-tetramethyl-N"-(2,2-dichloro-1-ethoxyethyl)-phosphoric triamide (0.03 g, 2%).

$(Me_2N)_2P(O)NHCH(CHCl_2)OCH_2CH_3$

a) Molecular weight by FAB mass spectrometry

Found : 292.0 (M+1)

$C_8H_{20}Cl_2N_3O_2P$ requires: 292.1 (M+1)

b) $\delta_H(CDCl_3)$ 1.24 (t, $-OCH_2\underline{CH}_3$), 2.68 (dd, $-P-N-\underline{CH}_3$), 3.16 (m, -P-NH-CH- , exchanges with D_2O), 3.77 (m, $-O\underline{CH}_2CH_3$), 4.88 (m, -P-NH-CH-), 5.78 (dd, $-\underline{CHCl}_2$).

c) $\delta_P(CDCl_3)$ 19.5

Preparation of N-(2,2,2-trichloroethylidene)acetamide

To a mechanically stirred suspension of N-(1,2,2,2-tetrachloroethyl)acetamide (63.4 g, 0.28 mol) in dry diethyl ether (250 cm^3) cooled in ice was added triethylamine (28.4 g, 0.28 mol) dropwise. After the addition was complete the mixture was allowed to reach room temperature and stirred for a further 45 minutes. A white solid remained which was filtered off as triethylamine hyrochloride (37.8 g, 98%). It was identified by ^1H N.M.R. The solvent was then removed from the filtrate using a rotary evaporator to give a yellow oil. This oil was distilled under reduced pressure to yield N-(2,2,2-trichloroethylidene)acetamide as a pale yellow liquid which discoloured rapidly in light (39.4 g, 74%), b.p. 41-44 °C at 0.1 mmHg (Lit.[21] 45°C at 0.6 mmHg); n_D^{25} 1.4873 (Lit.[21] n_D^{20} 1.4900); $\lambda_{max}(CH_3CO_2CH_2CH_3)$ 252 (21.31), 268 (16.49) nm (ε/m^2mol^{-1}); δ(ppm): ^1H(60 MHz, $CDCl_3$) 2.3 (3H, s, $-C(O)CH_3$), 7.9 (1H, s, $CCl_3\underline{CH}$=); $^{13}C(CDCl_3)$ 24.3 ($-CH_3$), 93.0 ($-CCl_3$), 154.4 ($CCl_3\underline{CH}$=), 182.9 (C=O).

Kinetic investigation of the reaction between

N-(2,2,2-trichloroethylidene)acetamide and N,N,N',N'-tetramethylphosphoric triamide using ultraviolet spectroscopy

Method 1. Generation of N-(2,2,2-trichloroethylidene)-acetamide in situ.

This study was carried out using chloroform as the solvent which contains ethanol as stabiliser. The ethanol was removed by washing the chloroform with half its volume of distilled water five times. It was then dried over magnesium sulphate overnight and redistilled from phosphorus pentoxide.

Stock solutions containing 1.78×10^{-2} mol dm^{-3} of N-(1,2,2,2-tetrachloroethyl)acetamide, triethylamine and N,N,N',N'-tetramethylphosphoric triamide in chloroform were made up. These stock solutions were freshly prepared for each experiment. The solutions were placed in a water-bath at 20 °C and allowed to come to equilibrium. Using a dry box, 1 cm^3 of N-(1,2,2,2-tetrachloroethyl)acetamide solution was transferred to a 25 cm^3 graduated flask using a pipette. A further 5 cm^3 of chloroform was added, followed by 1 cm^3 of triethylamine solution and 1 cm^3 of phosphoric triamide solution. The volume was made up to the mark and shaken well. Some of this solution was transferred to a 1 cm silica U.V. cell which was then sealed with wax to exclude atmospheric moisture. A single band at λ_{max} 278 nm was observed. Repetitive scanning at various intervals from 1 to 8 hours was used to monitor the decay of the band at λ_{max} 278 nm over a period of 4 days. Experiments using N-(1,2,2,2-tetra-

chloroethyl)acetamide and the phosphoric triamide in the molar ratios of 1:1, 1:2 and 2:1 were carried out. Analysis of the data indicated that the reaction was first order. This was contrary to the expected result of second order. A large negative peak appeared in the spectrum during the course of each investigation which may have interfered with the results and thus it was decided to investigate the reaction kinetics further.

Method 2. Using previously prepared N-(2,2,2-trichloroethylidene)acetamide

This work was carried out using ethyl acetate as the solvent which had been dried by standing over freshly activated molecular sieve (E.Merck type 4 Å) for at least 24 hours.

A solution of N-(2,2,2-trichloroethylidene)acetamide (0.04114 g, 30 µl) in ethyl acetate (25 cm^3) was prepared in a dry box. Some of this solution was transferred to a 1 cm silica U.V. cell and the cell sealed with wax in order to exclude atmospheric moisture. Repetitive scanning at various intervals from 1 to 8 hours was used to monitor the decay of the peak at λ_{max} 252 nm over a period of 4 days. Over this period the absorbance decreased from 1.86 to 1.68 indicating that this peak could be used for kinetic investigations and that interfering nucleophiles such as water could be successfully excluded.

Investigation of the reaction between N,N,N',N'-tetramethylphosphoric triamide and N-(1,2,2,2-tetrachloro-

ethyl)acetamide in the absence of a tertiary base by ^{1}H N.M.R.

A solution of N-(1,2,2,2-tetrachloroethyl)acetamide (0.01 g, 4.44×10^{-4} mol) was made up in the minimum amount of deuterated chloroform ($CDCl_3$)(ca. 1 cm^3) and the ^{1}H N.M.R. recorded: $\delta_H(CDCl_3)$ 2.1 (3H, s, -C(O)$\underline{CH}_3$), 6.5 (1H, d, -NH-$\underline{CH}$-), 7.0 (1H, bs, -$\underline{NH}$-CH-). To this solution was added N,N,N',N'-tetramethylphosphoric triamide (0.0671 g, 4.44×10^{-4} mol) and the spectrum rerun: $\delta_H(CDCl_3)$ 2.2 (s, -C(O)$\underline{CH}_3$), 2.6 (d, -P-N-$\underline{CH}_3$), 6.6 (d, -NH-$\underline{CH}$-), 8.8 (bs, -$\underline{NH}$-CH-). The mixture was heated to 50 °C on a water-bath and the spectrum rerun. No change in the spectrum was observed. This reaction mixture was then allowed to stand for five days and the ^{1}H spectrum recorded: $\delta_H(CDCl_3)$ 2.0 (s), 2.2 (s), 2.3 (s), 2.7 (m), 5.6 (d), 6.6 (d), 7.8 (bs), 9.3 (bs). The peaks at δ 2.2, 6.6 and 7.8 corresponding to the N-(1,2,2,2-tetrachloroethyl)acetamide were the most prominent peaks indicating that much of this remained unchanged.

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APPENDICES

APPENDIX 1

X-ray crystallographic data for N,N,N',N'-tetramethyl-N"-(2,2,2-trichloro-1-dimethylaminoethyl)phosphoric triamide

Crystal Data. $C_8H_{20}Cl_3N_4OP$, M= 324.0440. Monoclinic, a= 14.735(3), b= 10.450(2), c= 10.275(3) Å, β= 101.90(3)°, V= 1548.15 $Å^3$, space group $P2_1/n$, Z= 4, D_x= 1.39 g cm^{-3}, F(000)= 680, $\mu(Mo\text{-}K_\alpha)$= 6.23 cm^{-1}.

Data Collection and Refinement. 1640 unique observed data collected using a Philips PW1100 diffractometer (with $F>6\sigma(F)$, $3\leq\theta\leq25°$). All non-hydrogen atoms with anisotropic thermal parameters and H-atoms are included in the refinement at found positions, final R= 0.0745 and R_w= 0.0733 with $w= 1/[\sigma^2(F)]$.

TABLE 1 Fractional atomic co-ordinates and thermal parameters ($Å^2$) for N,N,N',N'-tetramethyl-N''-(2,2,2-trichloro-1-dimethylaminoethyl)phosphoric triamide

Atom	x	y	z	U_{iso} or U_{eq}
P	0.7508(1)	0.3509(1)	0.1859(2)	0.038(1)
N(1)	0.8445(4)	0.4187(5)	0.1530(6)	0.051(4)
N(2)	0.6705(4)	0.3831(5)	0.0527(6)	0.051(4)
N(3)	0.5916(4)	0.4084(5)	0.4045(6)	0.052(4)
N(4)	0.7364(4)	0.4316(4)	0.3175(5)	0.037(3)
O(1)	0.7504(3)	0.2107(4)	0.2161(5)	0.051(3)
C(1)	0.9259(5)	0.4407(9)	0.2545(10)	0.079(6)
C(2)	0.8656(6)	0.4039(9)	0.0221(10)	0.085(7)
C(3)	0.6005(5)	0.2910(8)	-0.0090(8)	0.067(5)
C(4)	0.6524(6)	0.5154(7)	0.0023(8)	0.067(6)
C(5)	0.6886(5)	0.3744(5)	0.4122(7)	0.040(4)
C(6)	0.5612(5)	0.5334(8)	0.3431(9)	0.072(6)
C(7)	0.5295(6)	0.3075(9)	0.3446(10)	0.083(6)
C(8)	0.7421(5)	0.3967(6)	0.5578(7)	0.050(4)
Cl(1)	0.6909(2)	0.2991(2)	0.6664(2)	0.087(2)
Cl(2)	0.7376(2)	0.5589(2)	0.6100(2)	0.076(1)
Cl(3)	0.8599(2)	0.3514(2)	0.5790(2)	0.079(2)

TABLE 2 Fractional atomic co-ordinates for the hydrogen atoms for N,N,N',N'-tetramethyl-N''-(2,2,2-trichloro-1-dimethylaminoethyl)phosphoric triamide

Atom	x	y	z
H(1c)	0.9671	0.4973	0.3329
H(2c)	0.9014	0.4736	-0.0265
H(3c)	0.5955	0.1881	-0.0039
H(4c)	0.5858	0.5554	0.0082
H(6c)	0.6050	0.6152	0.3748
H(1a)	0.9139	0.4026	0.3338
H(1b)	0.9807	0.4710	0.2000
H(2a)	0.8087	0.3997	-0.0325
H(2b)	0.9202	0.3547	0.0159
H(3a)	0.5514	0.2947	0.0390
H(3b)	0.6055	0.2857	-0.1094
H(4a)	0.6515	0.5248	-0.0970
H(4b)	0.7087	0.5643	0.0624
H(4n)	0.7458	0.5215	0.3260
H(5)	0.6991	0.2799	0.4008
H(6a)	0.5670	0.5361	0.2394
H(6b)	0.5005	0.5580	0.3767
H(7a)	0.5269	0.2866	0.2282
H(7b)	0.4616	0.3096	0.3413
H(7c)	0.5525	0.2213	0.3976

TABLE 2 Fractional atomic co-ordinates for the hydrogen atoms for N,N,N',N'-tetramethyl-N''-(2,2,2-trichloro-1-dimethylaminoethyl)phosphoric triamide

Atom	x	y	z
H(1c)	0.9671	0.4973	0.3329
H(2c)	0.9014	0.4736	-0.0265
H(3c)	0.5955	0.1881	-0.0039
H(4c)	0.5858	0.5554	0.0082
H(6c)	0.6050	0.6152	0.3748
H(1a)	0.9139	0.4026	0.3338
H(1b)	0.9807	0.4710	0.2000
H(2a)	0.8087	0.3997	-0.0325
H(2b)	0.9202	0.3547	0.0159
H(3a)	0.5514	0.2947	0.0390
H(3b)	0.6055	0.2857	-0.1094
H(4a)	0.6515	0.5248	-0.0970
H(4b)	0.7087	0.5643	0.0624
H(4n)	0.7458	0.5215	0.3260
H(5)	0.6991	0.2799	0.4008
H(6a)	0.5670	0.5361	0.2394
H(6b)	0.5005	0.5580	0.3767
H(7a)	0.5269	0.2866	0.2282
H(7b)	0.4616	0.3096	0.3413
H(7c)	0.5525	0.2213	0.3976

TABLE 3 Anisotropic thermal parameters ($Å^2$)

for N,N,N',N'-tetramethyl-N''-(2,2,2-trichloro-1-dimethylaminoethyl)phosphoric triamide

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
P	0.049(1)	0.015(1)	0.050(1)	-0.001(1)	0.005(1)	0.003(1)
N(1)	0.050(4)	0.036(3)	0.067(4)	-0.003(3)	0.017(3)	0.001(3)
N(2)	0.074(4)	0.026(3)	0.053(4)	-0.002(3)	-0.009(3)	-0.007(3)
N(3)	0.046(4)	0.037(3)	0.071(4)	0.004(3)	0.005(3)	-0.007(3)
N(4)	0.051(4)	0.015(3)	0.046(3)	0.000(2)	0.001(3)	-0.000(2)
O(1)	0.078(3)	0.008(2)	0.067(3)	0.003(2)	0.011(3)	0.008(2)
C(1)	0.043(5)	0.096(7)	0.097(7)	0.025(6)	0.008(5)	-0.020(5)
C(2)	0.074(6)	0.070(6)	0.112(8)	-0.013(6)	0.048(6)	-0.008(5)
C(3)	0.071(6)	0.066(6)	0.064(5)	-0.021(5)	0.011(5)	-0.021(5)
C(4)	0.104(7)	0.036(4)	0.062(5)	0.013(4)	-0.018(5)	0.011(4)
C(5)	0.062(5)	0.014(3)	0.046(4)	-0.003(3)	-0.001(4)	0.000(3)
C(6)	0.059(5)	0.054(5)	0.103(7)	0.024(5)	0.023(5)	0.027(4)
C(7)	0.057(5)	0.082(6)	0.110(8)	-0.005(6)	-0.000(5)	-0.034(5)

table 3 continued

C(8)	0.075(5)	0.025(3)	0.051(5)	-0.001(3)	-0.000(4)	0.008(3)
Cl(1)	0.135(2)	0.064(1)	0.063(1)	0.027(1)	0.020(1)	-0.002(1)
Cl(2)	0.120(2)	0.034(1)	0.073(1)	-0.021(1)	0.004(1)	-0.001(1)
Cl(3)	0.075(1)	0.081(2)	0.081(2)	0.003(1)	-0.020(1)	0.025(1)

TABLE 4 Bond lengths (Å)

for N,N,N',N'-tetramethyl-N''-(2,2,2-trichloro-1-dimethylaminoethyl)phosphoric triamide

P	-N(1)	1.647(7)	P	-N(2)	1.649(6)
P	-N(4)	1.645(6)	P	-O(1)	1.498(4)
N(1)	-C(1)	1.436(10)	N(1)	-C(2)	1.449(13)
N(2)	-C(3)	1.458(10)	N(2)	-C(4)	1.481(9)
N(3)	-C(5)	1.459(10)	N(3)	-C(6)	1.479(10)
N(3)	-C(7)	1.447(10)	N(4)	-C(5)	1.444(9)
C(5)	-C(8)	1.558(9)	C(8)	-Cl(1)	1.789(8)
C(8)	-Cl(2)	1.783(7)	C(8)	-Cl(3)	1.769(8)

TABLE 5 Bond angles (°)

for N,N,N',N'-tetramethyl-N''-(2,2,2-trichloro-1-dimethylaminoethyl)phosphoric triamide

N(2)	-P	-N(1)	103.3(3)	N(4)	-P	-N(1)	101.8(3)
N(4)	-P	-N(2)	112.7(3)	O(1)	-P	-N(1)	120.2(3)
O(1)	-P	-N(2)	109.8(3)	O(1)	-P	-N(4)	108.9(3)
O(1)	-P	-N(2)	109.8(3)	O(1)	-P	-N(4)	108.9(3)
C(1)	-N(1)	-P	121.9(6)	C(2)	-N(1)	-P	119.6(5)
C(2)	-N(1)	-C(1)	112.6(7)	C(3)	-N(2)	-P	123.3(5)
C(4)	-N(2)	-P	121.8(5)	C(4)	-N(2)	-C(3)	113.8(6)
C(6)	-N(3)	-C(5)	116.4(6)	C(7)	-N(3)	-C(5)	111.8(6)
C(7)	-N(3)	-C(6)	110.7(6)	C(5)	-N(4)	-P	120.4(4)
N(4)	-C(5)	-N(3)	118.2(5)	C(8)	-C(5)	-N(3)	108.2(6)
C(8)	-C(5)	-N(4)	111.3(6)	Cl(1)	-C(8)	-C(5)	108.6(5)
Cl(2)	-C(8)	-C(5)	112.8(4)	Cl(2)	-C(8)	-Cl(1)	107.9(4)
Cl(3)	-C(8)	-C(5)	111.6(5)	Cl(3)	-C(8)	-Cl(1)	107.5(4)
Cl(3)	-C(8)	-Cl(2)	108.3(4)				

TABLE 6 Intermolecular distances (Å)

for N,N,N',N'-tetramethyl-N''-(2,2,2-trichloro-1-dimethylaminoethyl)phosphoric triamide

H(6b)	...N(3)	2.88	-1	1.0	1.0	1.0
O(1)	...N(4)	2.95	2	1.0	-1.0	0.0
H(6c)	...O(1)	2.69	2	1.0	0.0	0.0
Cl(2)	...O(1)	3.74	2	1.0	0.0	0.0
H(4b)	...O(1)	2.71	2	1.0	0.0	0.0
H(4n)	...O(1)	2.03	2	1.0	0.0	0.0
Cl(3)	...H(1c)	2.98	-1	2.0	1.0	1.0
Cl(1)	...C(3)	3.84	1	0.0	0.0	1.0
Cl(2)	...C(3)	3.70	2	1.0	0.0	0.0
Cl(2)	...H(3c)	3.19	2	1.0	0.0	0.0
Cl(3)	...C(4)	3.60	2	1.0	-1.0	0.0
Cl(3)	...H(4c)	3.36	2	1.0	-1.0	0.0
Cl(3)	...C(7)	3.69	-2	1.0	1.0	1.0
H(2a)	...Cl(1)	3.39	1	0.0	0.0	-1.0
H(3b)	...Cl(1)	2.85	1	0.0	0.0	-1.0
H(6b)	...Cl(1)	3.14	-1	1.0	1.0	1.0
Cl(2)	...Cl(1)	3.42	2	1.0	0.0	1.0
H(7b)	...Cl(2)	3.37	-1	1.0	1.0	1.0
H(3b)	...Cl(2)	3.31	2	1.0	-1.0	0.0
H(4a)	...Cl(3)	3.42	2	1.0	0.0	0.0
H(4b)	...Cl(3)	3.40	2	1.0	0.0	0.0
H(3a)	...Cl(3)	3.31	-2	0.0	1.0	0.0
H(7a)	...Cl(3)	2.99	-2	0.0	1.0	0.0
H(7b)	...Cl(3)	3.27	-2	0.0	1.0	0.0

TABLE 7 Intramolecular distances (Å)

for N,N,N',N'-tetramethyl-N''-(2,2,2-trichloro-1-dimethylaminoethyl)phosphoric triamide

N(3)	...P	3.62	C(1)	...P	2.70
C(2)	...P	2.68	C(3)	...P	2.74
H(3c)	...P	3.18	C(4)	...P	2.74
C(5)	...P	2.68	Cl(3)	...P	4.03
H(1a)	...P	2.62	H(2a)	...P	2.61
H(2b)	...P	3.33	H(3a)	...P	3.07
H(4b)	...P	2.58	H(4n)	...P	2.30
H(5)	...P	2.59	N(2)	...N(1)	2.59
N(4)	...N(1)	2.55	O(1)	...N(1)	2.73
H(1c)	...N(1)	2.44	H(2c)	...N(1)	2.25
C(4)	...N(1)	3.10	H(1a)	...N(1)	1.94
H(1b)	...N(1)	2.04	H(2a)	...N(1)	1.88
H(2b)	...N(1)	2.08	H(4b)	...N(1)	2.53
H(4n)	...N(1)	2.74	N(4)	...N(2)	2.74
O(1)	...N(2)	2.58	C(2)	...N(2)	2.96
H(3c)	...N(2)	2.33	H(4c)	...N(2)	2.18
H(2a)	...N(2)	2.38	H(3a)	...N(2)	1.96
H(3b)	...N(2)	2.02	H(4a)	...N(2)	2.11
H(4b)	...N(2)	1.97	N(4)	...N(3)	2.49
H(6c)	...N(3)	2.20	C(8)	...N(3)	2.44
Cl(1)	...N(3)	3.01	Cl(2)	...N(3)	3.11
H(4n)	...N(3)	2.82	H(5)	...N(3)	2.08
H(6a)	...N(3)	2.13	H(6b)	...N(3)	2.04
H(7a)	...N(3)	2.26	H(7b)	...N(3)	2.15
H(7c)	...N(3)	2.03	O(1)	...N(4)	2.56

table 7 continued

C(1)	...N(4)	3.00	C(4)	...N(4)	3.34
C(6)	...N(4)	2.85	H(6c)	...N(4)	2.87
C(7)	...N(4)	3.38	C(8)	...N(4)	2.48
Cl(2)	...N(4)	3.28	Cl(3)	...N(4)	3.04
H(1a)	...N(4)	2.60	H(4b)	...N(4)	2.92
H(5)	...N(4)	1.94	H(6a)	...N(4)	2.69
C(3)	...O(1)	2.97	H(3c)	...O(1)	2.87
C(5)	...O(1)	2.93	H(5)	...O(1)	2.30
C(2)	...C(1)	2.40	H(2c)	...C(1)	2.85
Cl(3)	...C(1)	3.78	H(2b)	...C(1)	2.60
H(4n)	...C(1)	3.02	C(4)	...C(2)	3.32
H(1b)	...C(2)	2.33	H(4b)	...C(2)	2.95
C(4)	...C(3)	2.46	H(4c)	...C(3)	2.78
H(4a)	...C(3)	2.76	H(7a)	...C(3)	2.87
H(2a)	...C(4)	2.69	H(3a)	...C(4)	2.81
H(3b)	...C(4)	2.69	H(6a)	...C(4)	2.97
C(6)	...C(5)	2.50	H(6c)	...C(5)	2.79
C(7)	...C(5)	2.41	Cl(1)	...C(5)	2.72
Cl(2)	...C(5)	2.79	Cl(3)	...C(5)	2.75
H(4n)	...C(5)	2.04	H(6a)	...C(5)	2.81
H(7a)	...C(5)	2.87	H(7c)	...C(5)	2.54
C(7)	...C(6)	2.41	C(8)	...C(6)	3.40
Cl(2)	...C(6)	3.38	H(4n)	...C(6)	2.76
H(7a)	...C(6)	2.84	H(7b)	...C(6)	2.76
Cl(2)	...H(6c)	2.84	Cl(1)	...C(7)	3.65
H(5)	...C(7)	2.46	H(6a)	...C(7)	2.72
H(6b)	...C(7)	2.68	H(4n)	...C(8)	2.73
H(5)	...C(8)	2.02	Cl(2)	...Cl(1)	2.89

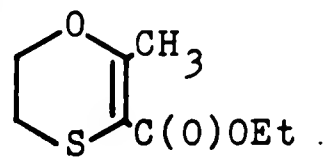
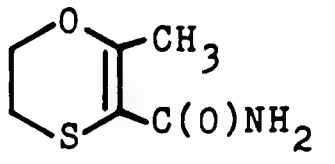
All

table 7 continued

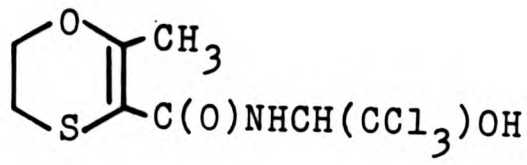
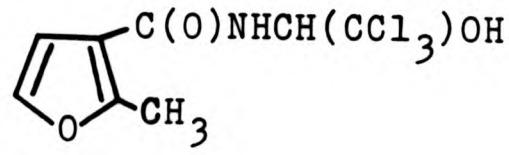
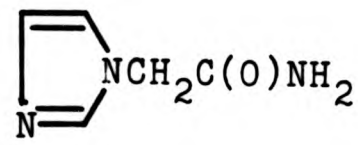
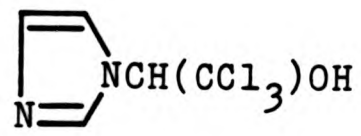
Cl(3)	...Cl(1)	2.87	H(5)	...Cl(1)	2.76
H(7c)	...Cl(1)	3.18	Cl(3)	...Cl(2)	2.88
H(4n)	...Cl(2)	2.97	H(1a)	...Cl(3)	2.84
H(4n)	...Cl(3)	3.31	H(5)	...Cl(3)	2.78

APPENDIX 2

Spectroscopic data reported for intermediates synthesised during this project

Compound	Spectroscopic data	Page
$(Me_2N)_2P(O)Cl$	^{31}P	187
$(Me_2N)_2P(O)NH_2$	UV, ^{1}H, ^{31}P and ms*	187
$CH_3C(O)NHCH(CCl_3)Cl$	UV and ^{1}H	188, 265
$CCl_3C(O)NHCH(CCl_3)OH$	^{1}H and ^{13}C	203
$CCl_3C(O)NHCH(CCl_3)Cl$	^{1}H	204
$CCl_3CH(Cl)N(CH_3)CHO$	^{1}H and ^{13}C	238
$CCl_2=C(Cl)N(CH_3)CHO$	^{1}H, ^{13}C and ms	241
$CCl_3CH(OH)N(CH_3)C(O)CH_3$	^{1}H	244
$CH_3(CH_2)_2CH_2OCH_2C(O)NH_2$	^{1}H and ms	251
$C_4H_9OCH_2C(O)NHCH(CCl_3)OH$	^{1}H and ^{13}C	252
$C_{12}H_{25}OCH_2C(O)NH_2$	^{1}H and ^{13}C	255
$C_{12}H_{25}OCH_2C(O)NHCH(CCl_3)OH$	^{1}H and ^{13}C	255
$CCl_3CHN=C(O)CH_3$	UV, ^{1}H and ^{13}C	262
	^{1}H	195
	^{1}H and ^{13}C	196

* ms= Mass spectrum.

Compound	Spectroscopic data	Page
	^{1}H and ^{13}C	197
	^{1}H	208
	^{1}H and ^{13}C	231
	^{1}H	234

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