STRUCTURE AND REACTIVITY OF CYCLIC IMIDO DERIVATIVES OF PHOSPHORIC ACID

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MASTER OF SCIENCE

by

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CONTENTS

ABSTRACT

New cyclic 1,3-diazaphospholidine-2,4,5-triones were synthesised and their solvolytic behaviour was studied.

Methanolysis of 2-methylamino (**24**) and 2-dimethylamino (**25**) derivatives showed evidence of cleavage of both imide P-N bonds. This indicates that the ring opening in these derivatives is much slower than the second P-N cleavage in the ring-opened intermediate (**30**, scheme 11). On the other hand, methanolysis of 1,3-dimethyl-2-phenoxy-1,3,2-diazaphospholidine-2,4,5-trione (**22**) yielded the product of the cleavage of only one P-N bond. This product (**26**, scheme 9) was relatively stable towards further solvolysis. This was taken by Mulliez[8] as evidence for the addition-elimination mechanism of solvolysis, since in such a case **22** would experience the usual rate accelerating effect upon the formation of the P^V intermediate with trigonal bipyramidal structure.

The crystal structures of **24** and **25** were determined in order to investigate the low reactivity of **24** and **25** to solvolysis. This low reactivity correlates with the small size (92.3 and 91.9° respectively) of their endocyclic N-P-N angle. In the case of these two compounds, this suggests that the driving force towards the formation of the P^V trigonal bipyramidal intermediate is reduced.

Aminolysis of **22** with ammonia and p-anisidine resulted in products which indicate that nucleophilic attack takes place exclusively at the phosphorus atom. In the aminolysis with p-anisidine, both P-O bond cleavage (displacement of phenol, **43**) and ring P-N bond cleavage (**44**) products were obtained. This can be explained in terms of pseudorotation of the initially formed P^V intermediate (**22A**, scheme 23). The aminolysis of **22** with ammonia yielded exclusively the ring-retained P-OPh bond cleavage product (**23**). This indicates that pseudorotation of the initially formed P^V intermediate (**22A**, scheme 20) is much faster than endocyclic P-N bond cleavage. Finally,amminolysis of **22** with benzylamine was performed.As reported by Mulliez[8], this reaction yielded the product (**45**) of the initial C-N cleavage, followed by ring closure.

Acidolysis studies were carried out in anhydrous TFA. These studies indicated that the low reactivity towards nucleophilic attack of 2-amino (**23**), 2-methylamino (**24**),2-dimethylamino (**25**) and 2-p-anisidino (**43**) derivatives may also be accounted for by the lowered electrophilicity of their phosphorus atom.

Finally, within the cyclic 1,3-diazaphospholidine-2,4,5-trione series the reactivity of the various compounds was found to be vastly different, depending on which substituents were present on the exocyclic N atom.

Part of the work reported in this thesis has been published; *viz.*;

Phosphoric Carboxylic Imides. Part 6. Structure and Reactivity of 1,3,2-diazaphospholidine-4,5-diones; Crystal Structure of 1,3-Dimethyl-2-methylamino-1,3,2-diazaphospholidine-2,4,5-trione,Alan T. Hutton, Tomasz A. Modro, Margaret L. Niven, and Sonia Scaillet, *J. Chem. Soc. Perkin Trans. II*, 17 (1986).

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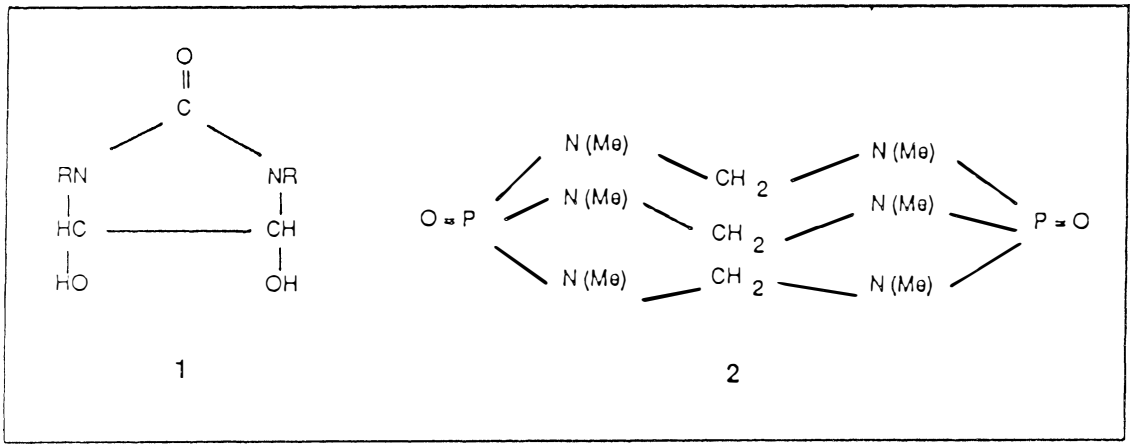
To my father.

CHAPTER I

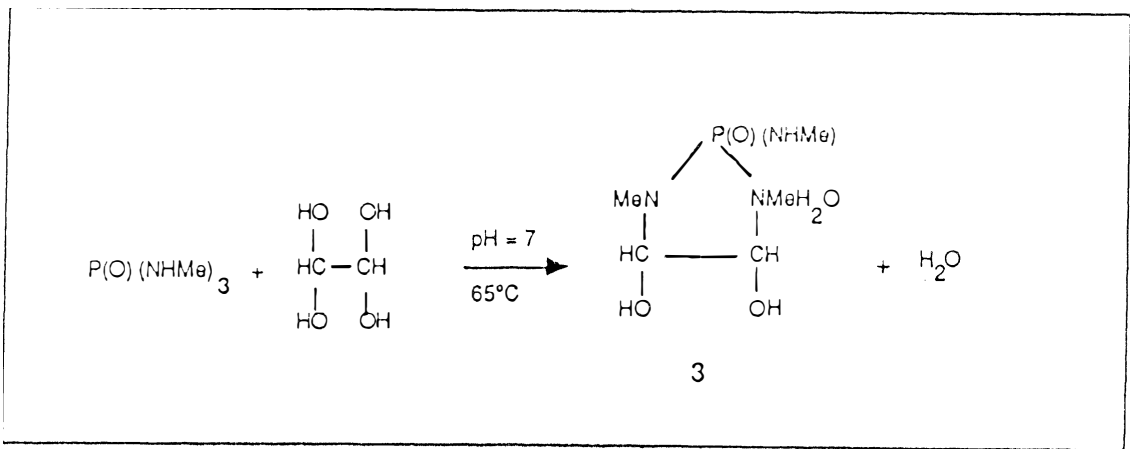
INTRODUCTION

INTRODUCTION

The use of 4,5-dihydroxy-2-imidazolidinones (1) for providing permanent press properties to cellulosic substrates has been extensively examined[1-5]. It has also been reported that a certain bi-cyclic phosphorimidate (2) imparts fire resistant properties to cellulosic material[6].

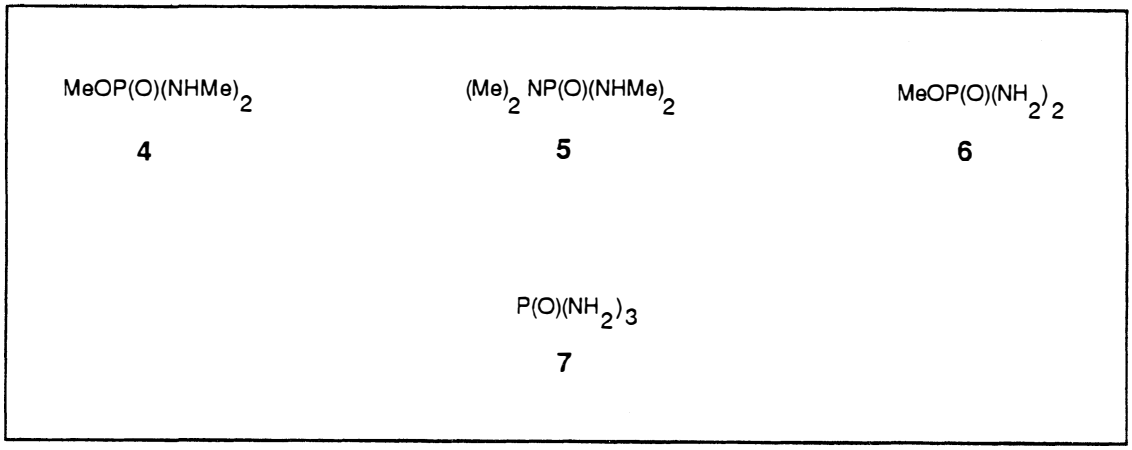


Schenkenberg and Williams proposed a method to synthesise new phospholidine species in which the carbonyl group of 1 was substituted by a phosphoryl group[7]. They proposed that such a new phospholidine could provide (when combined in a cellulosic matrix) the permanent press properties of 1 together with the long term fire retarding properties of 2. The synthesis of this new phospholidine, 1,3-dimethyl-2-methylamino-2-oxo-4,5-dihydroxy-1,3,2-diazaphospholidine monohydrate (3) was achieved via the reaction between aqueous glyoxal and N,N',N''-trimethylphosphoric triamide (reaction 1).



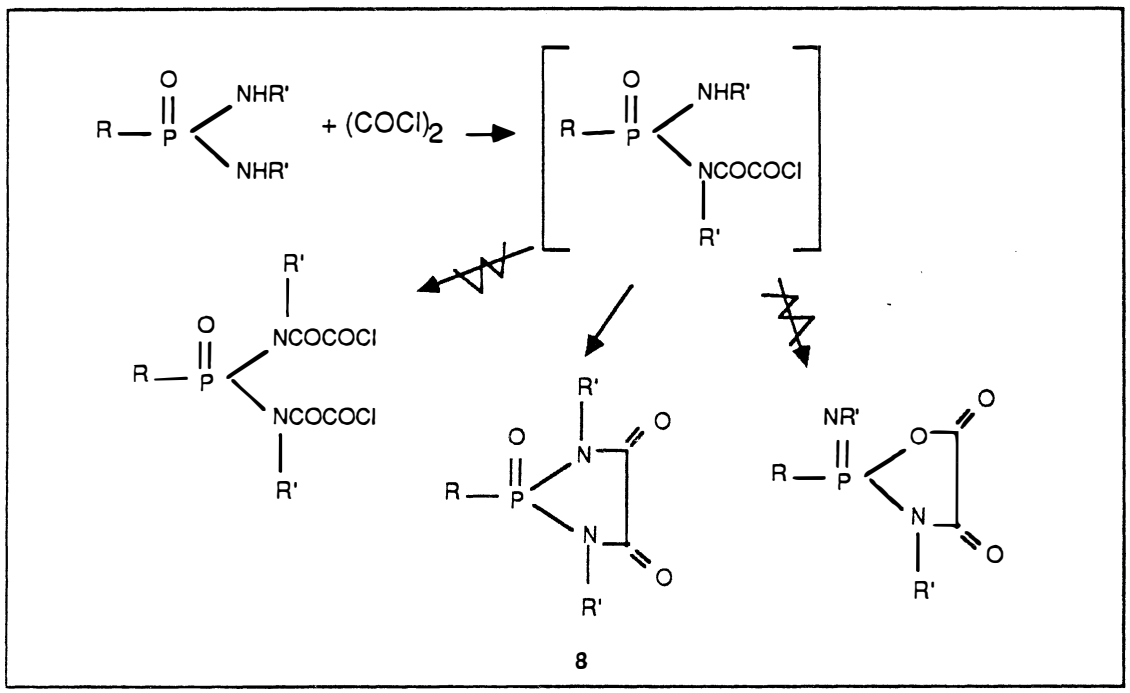
REACTION 1

Schenkenberg and Williams further reported that when other phosphoramidates (**4-7**) were substituted for N,N',N"-trimethyl-phosphoric triamide in reaction 1, no phospholidine structures were isolated.



Initially, reaction 1 was investigated using the method described by Schenkenberg and Williams[7] with the objective of studying both the stereochemical course of the reaction and the stereochemistry of the resulting diazaphospholidine formed. However, reaction 1 proved to be more complex than anticipated from the description provided by Schenkenberg and Williams. Consequently, these results could not be reproduced or substantiated.

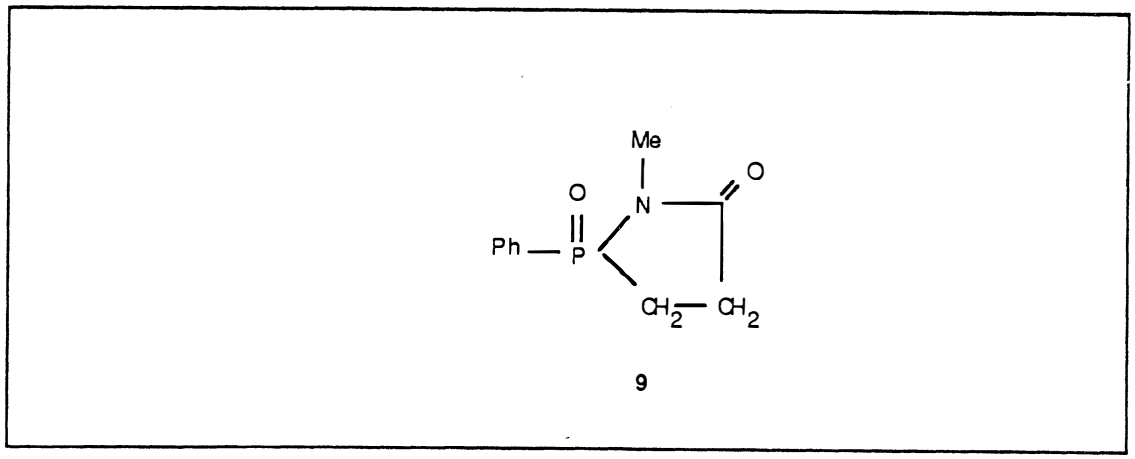
Another type of 5-membered cyclic phospholidines are those which were synthesised by Mulliez[8]. The syntheses involved the reaction of oxalyl chloride with various phosphordiamidates, as described in scheme 1. Prior to this paper[8], the synthesis of these kinds of compounds had already been reported[9], but involved only aromatic R' groups in the phosphordiamidate. Invariably, the reaction described by Mulliez[8] yielded 5-membered cyclic phospholidine-2,4,5 triones (**8**, scheme 1).



8

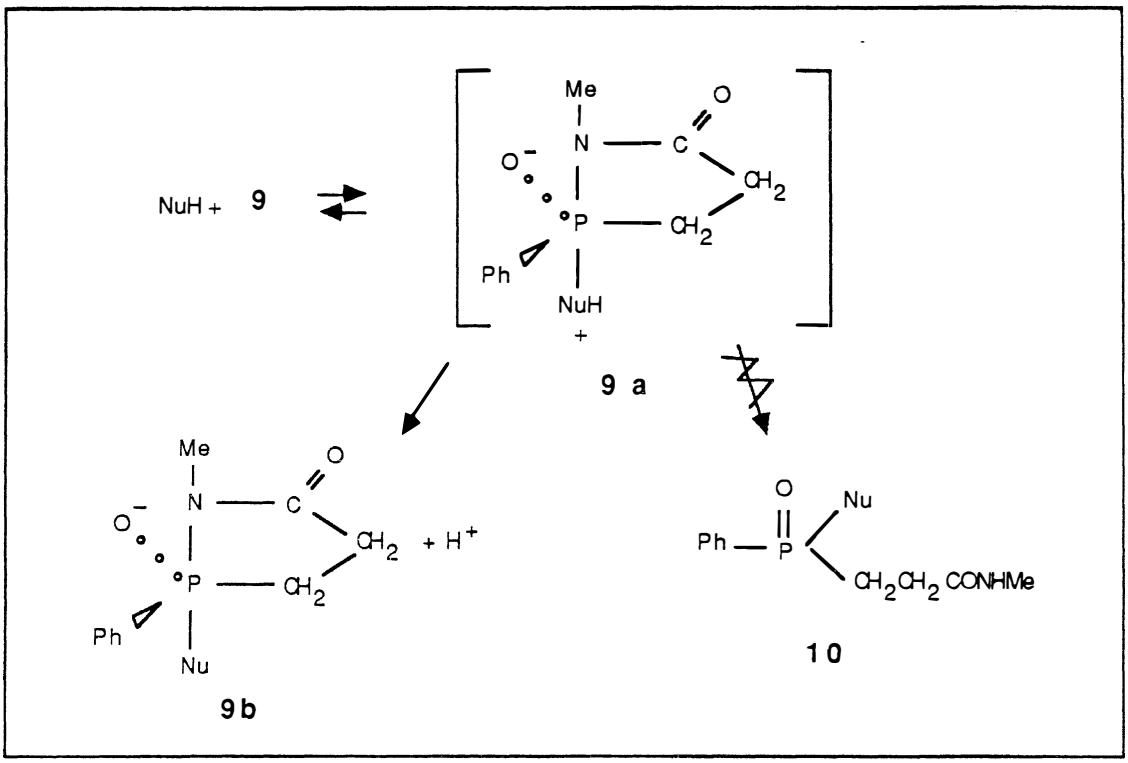
Scheme 1

Mulliez and his co-workers also investigated the hypothesis that, in 5-membered cyclic phosphordiamidates, nucleophilic attack by amines at the level of the phosphoryl centre does not take place unless pseudorotation of the formed pentacoordinated intermediate is possible[10]. This hypothesis was derived from work done on **9**, in which there was complete absence of aminolysis when **9** was exposed to dry benzylamine in a THF solution.



9

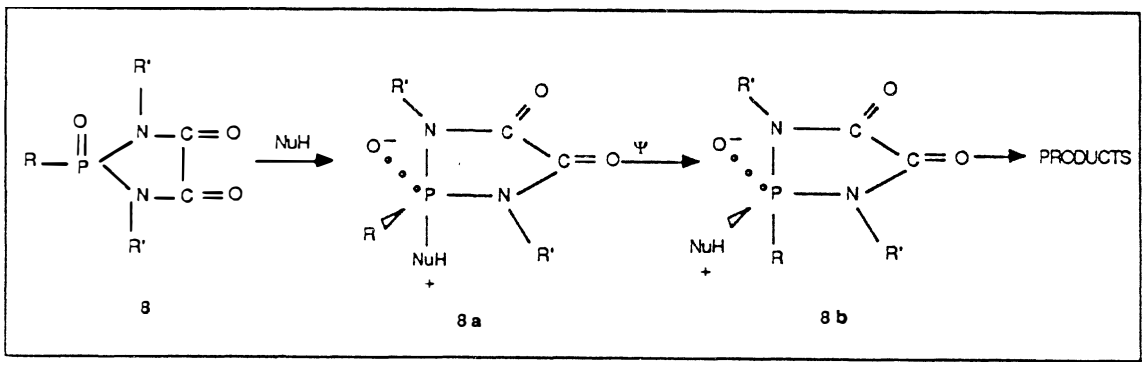
Given that the generally accepted mechanism for nucleophilic substitution at the P^{iv} included in a pentagonal cycle is by addition-elimination[11] (following a nucleophilic attack by the amine onto the phosphoryl group), the only intermediate that could have been formed is the zwitterion **9a** (scheme 2).



Scheme 2

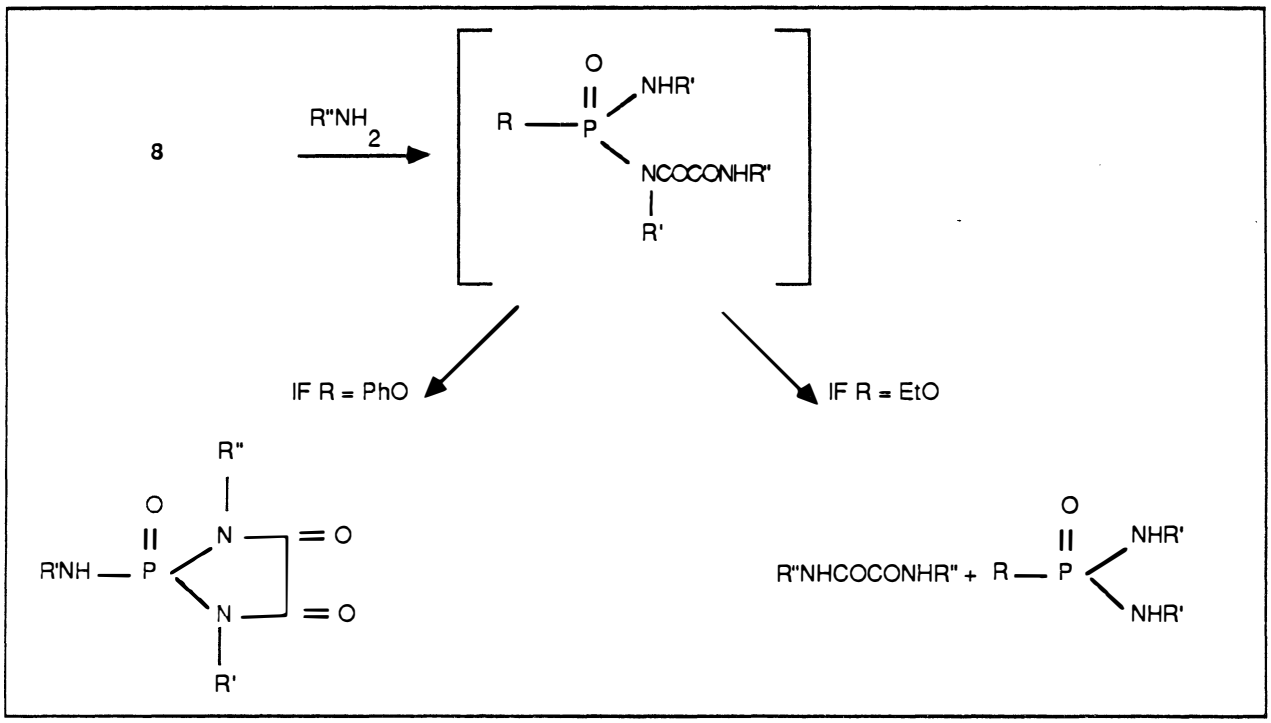
Mulliez observed base-catalysed methanolysis of **9** and therefore concluded that the pathway from intermediate **9a** to **9b** in scheme 2 is the rate determining step. The intermediate **9a** may be formed when groups such as -OH or -OR are in the apical position (as is the case with methanol as the nucleophile), due to the apicophilicity of those groups. However, when the attacking nucleophile is an amine, the deprotonation of this amine in the apical position is highly unfavourable. Mulliez hypothesised that this is because the ammonium nitrogen is more apicophilic than the deprotonated form. Consequently, the only pathway for aminolysis is the return of the zwitterion **9a** (scheme 2) to the original nucleophile and to **9**, thereby explaining the absence of aminolysis.

Based on the above observations, Mulliez[8] synthesised 5-membered cyclic phospholidines which were able, under nucleophilic attack by amines, to form intermediates in which pseudorotation was possible. Pseudorotation is a phenomenon described by F.H.Westheimer, to explain the abnormally high reactivity of phosphoric derivatives, in which the phosphorus atom is constrained in a 5-membered ring[12]. According to the generally accepted theory[12] (scheme 3), significant release of strain is achieved when two endocyclic bonds of a substrate attain an apical-equatorial configuration in the intermediate bipyramidal structure (intermediate **8a** in scheme 3). If the formed intermediate (**8a**) can then undergo pseudorotation, so that the 5-membered ring is in the apical-equatorial configuration with the electronegative atoms in the apical position (**8b**, scheme 3), then the reaction would be facilitated by the departure of the electronegative leaving group from the apical position.



Scheme 3

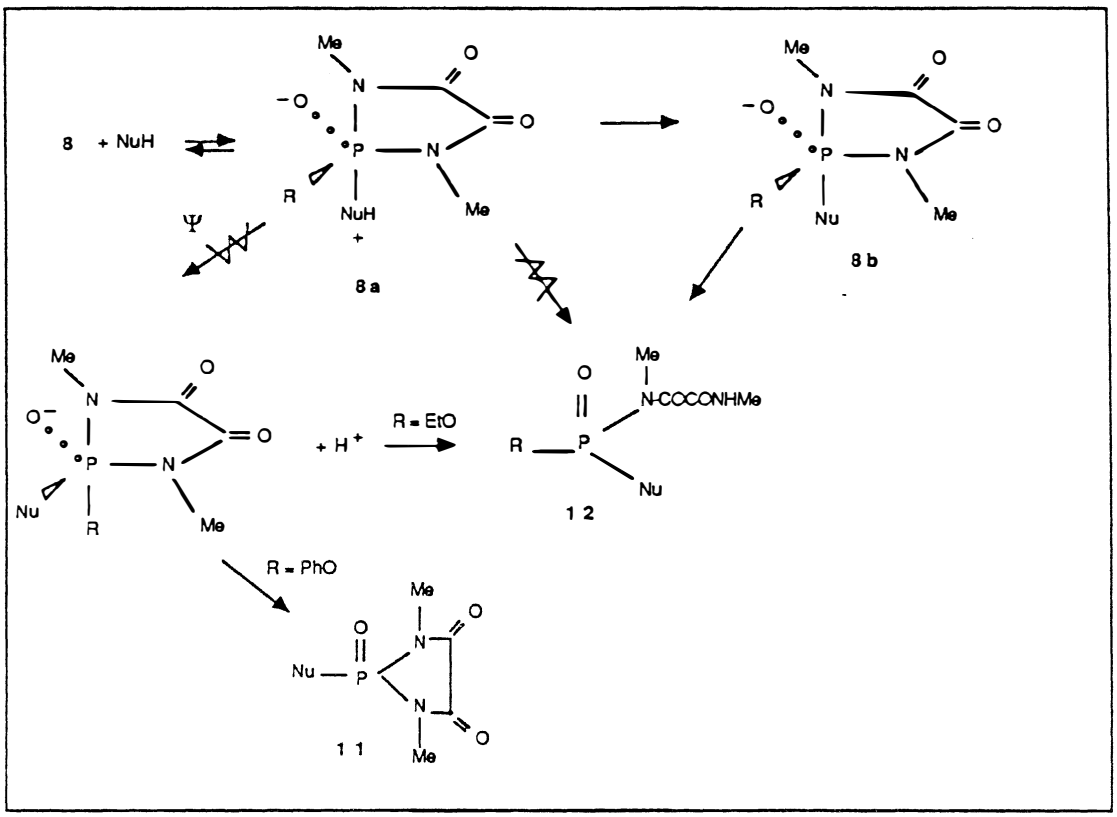
Mulliez therefore chose to synthesise compounds with electronegative R groups (R= PhO, EtO and R'= Me, $PhCH_2$), as is represented by **8** in scheme 3. He then reacted these compounds with a series of amines[8] (NH_2R'' where R''= Me, Me_2CH, Me_2CHCH_2, $PhCH_2$). The results obtained[8] led him to the conclusion that aminolysis was slower at the level of the phosphoryl group in 5-membered cyclic phosphordiamidates than at the level of the carbonyl group, even when pseudorotation was possible (scheme 4).



Scheme 4

As a means of comparison, Mulliez also undertook methanolysis studies conducted in neutral and basic conditions. The results of these experiments (see scheme 5) indicated that although nucleophilic attack took place at the phosphoryl centre, the expected pseudorotation did not occur[8]. This conclusion was derived from the absence of closed ring compounds (**11**) amongst the products (scheme 5) even when good leaving groups (eg. R=PhO) were present in the substrate.

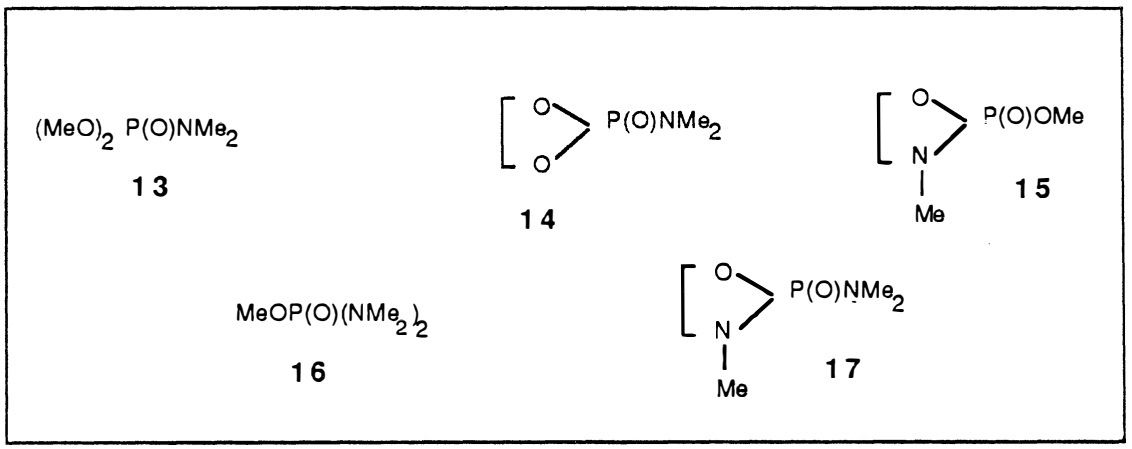
Instead, the pentacoordinated intermediate formed was deprotonated (from intermediate **8a** to intermediate **8b** in scheme 5) in a rate determining step, which was supported by the basic catalysis observed.



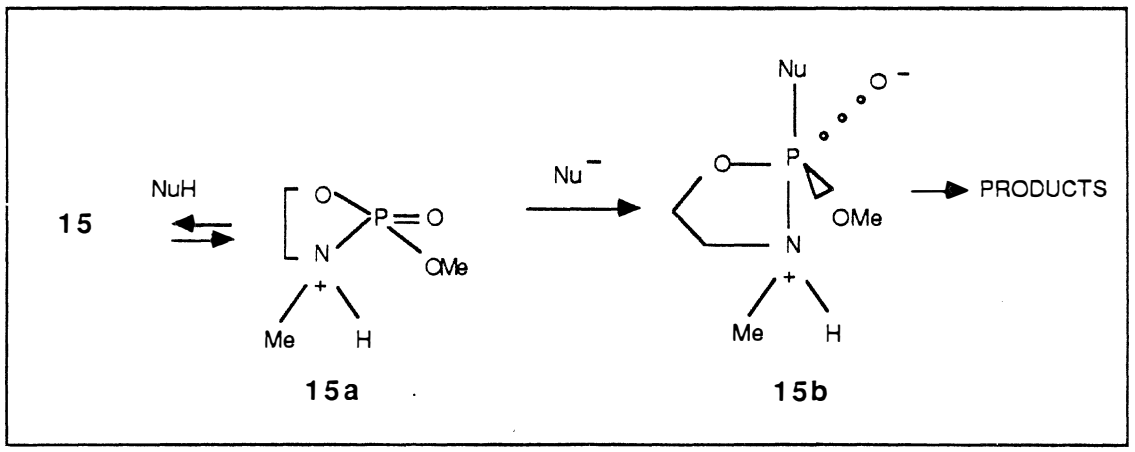
Scheme 5

The work of Mulliez was of great interest to our research group as it introduced a novel method for the synthesis of 5-membered cyclic phosphordiimidates in which the OPNR'CO moiety was included. These compounds involving a mixed phosphoric-carboxylic imides have formed the subject of our laboratory's research interest from both structural and reactivity points of view. Our research group has made some contributions to a detailed understanding of the chemical and structural properties of these types of compounds and investigations into their nucleophilic[13], solvolytic[14] and structural[15] properties have been conducted.

Additionally, a study involving the synthesis of compounds **13** to **17** was conducted in our laboratories[16] on the acid-catalysed solvolytic behaviour of acyclic and cyclic (5-membered ring) phosphoramidates and phosphordiamidates. The P-N bond cleavage of these compounds was monitored by proton NMR.



Theoretically, the rate determining step in the cleavage of the P-N bond of the cyclic 5-membered phosphoramidates could be due to either: (1) Nucleophilic attack on the O-protonated substrate; or (2) Nucleophilic attack on the N-protonated substrate, from which a pentacoordinated intermediate could be formed, as illustrated in scheme 6.



Scheme 6

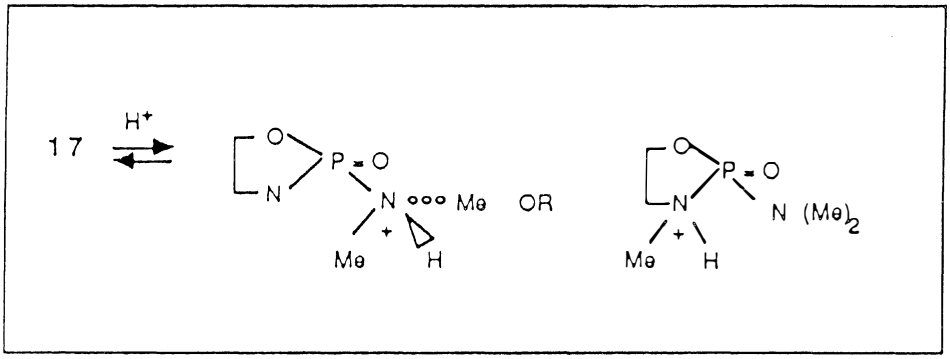
When as in the first case, the rate determinig step involves the nucleophilic attack at the O-protonated substrate, then cyclic phosphoramidates should solvolyse with rates comparable to those of acyclic systems. However if the latter is the case, then we would expect a significant rate enhancement of the P-N bond cleavage of the cyclic phosphoryl systems, wherein the N and P atoms are incorporated into a 5-membered ring, as predicted by Westheimer's theory[12]. In this case the strongly electronegative ammonium nitrogen should preferentially occupy the apical position as

illustrated by intermediate **15b** of scheme 6, and thus be suitably orientated for the P-N bond cleavage step.

The results of our laboratory's study[16] on the acid-catalysed solvolytic behaviour of compounds **13** to **17** indicated that although the reactivities of the acyclic phosphoramidates (**13** and **16**) were not significantly lower than the reactivities of the cyclic phosphoramidates (**14**,**15** and **17**), nucleophilic attack took place on the N-protonated substrate. This conclusion was based on the observation of the relative reactivity of the endocyclic P-N bond in compound **15**, which was found to be significantly greater than that of the exocyclic bond in the isomeric amide (**14**). The observed rate acceleration [k_2(**15**)/k_2(**14**)=4x10^3] could only be rationalised if, in the rate determining step, direct nucleophilic attack took place at the N-protonated species.

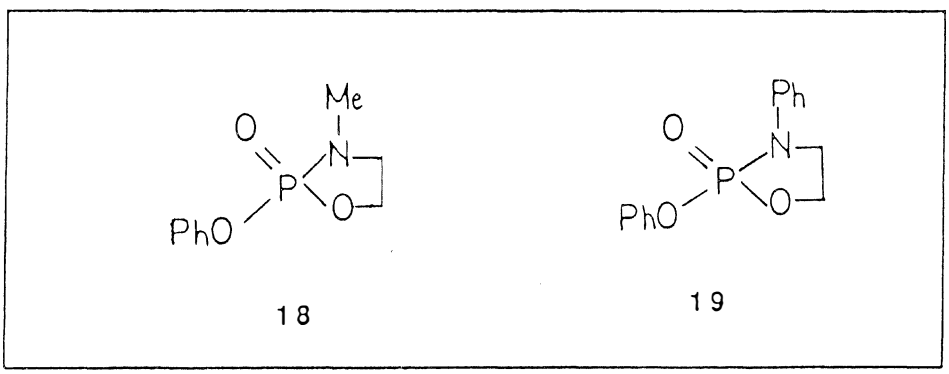
Direct nucleophilic attack on the N-protonated species would form a trigonal bipyramidal intermediate, (**15b** in scheme 6) in which the strongly electronegative ammonium nitrogen would preferentially occupy the apical position. P-N cleavage could then take place, permitting the amino group to depart. In the case of compound **14**, nucleophilic attack on the N-protonated substrate would result in the formation of a trigonal bipyramidal intermediate in which the strongly electronegative ammonium nitrogen would be placed in an unfavourable equatorial position, thereby explaining the relative unreactivity of **14** to nucleophilic attack.

The other important result obtained from our laboratory's study[16] relevant to the work presented in this thesis is the relative unreactivity of **17** when compared to **15**. Since the only difference between these two compounds is the exocyclic group, it could be expected that **17** and **15** should behave very similarly. However, the higher basicity of the exocyclic NMe_2 group in **17** inhibits the ring opening P-N cleavage because of the low concentration of the N (endo) protonated form. In addition to this basicity effect, the protonation of the exocyclic NMe_2 group is further favoured for steric reasons. This is due to the tendency of the exocyclic ammonium ion to allow for P-N rotation, thereby minimizing the torsional strain at the tetrahedral ammonium nitrogen (as illustrated in scheme 7). This phenomenon is particularly relevant to this report, as it was also observed in the acid-catalysed solvolytic behaviour of the 5-membered cyclic phospholidine systems presented in this thesis.



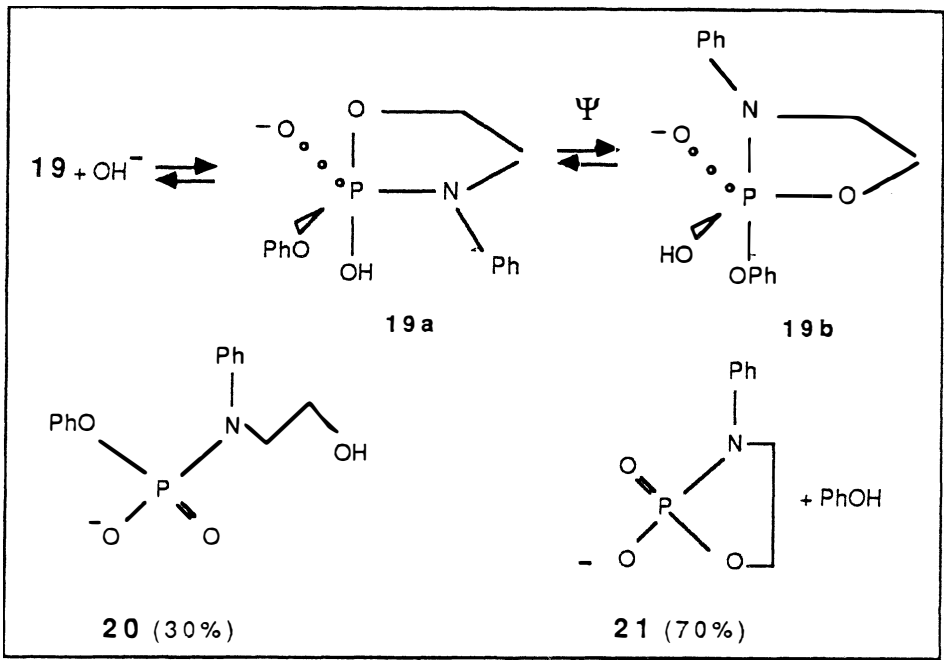
Scheme 7

Finally, a study on the base-catalysed solvolytic behaviour of cyclic phosphoramidates, similar to those studied by Mulliez[8,10], was carried out by Brown and co-workers[17]. The hydrolysis of compounds **18** and **19**, amongst others, was studied by means of U.V.-visible spectrophotometry.



18 **19**

It was found that most of the products formed involved retention of configuration accompanied by loss of phenol (as illustrated in scheme 8). The release of the phenolate ion can only be explained if pseudorotation of the initially formed intermediate takes place (see scheme 8).



Scheme 8

Thus, pseudorotation of **19a** (scheme 8) takes place, even though this places the N-phenyl group in an unfavourable apical position (as opposed to the more favourable O-apical position). Moreover, Brown et al argued that the formation of comparable yields of cyclic (70%) and open chain acids (30%) for **19** (scheme 8) was due to the higher apicophilicity of the PhO over the PhN group, which causes an equilibrium to be formed between **19a** and **19b**.

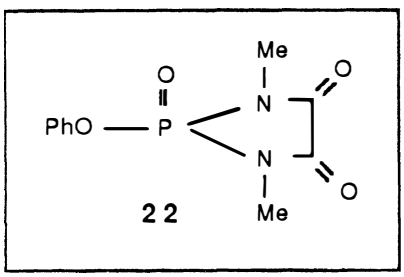
For compound **18**, an equivalent mechanistic pathway operates which involves pseudorotation of the intermediate formed following base-catalysed nucleophilic attack. This places the N-methyl group in a relatively unfavourable apical position. In contrast to intermediate **19b** (scheme 8), this pseudorotated intermediate formed from **18** is not stabilised and consequently 91% of the product found is present as the closed ring product (see compound **21**, scheme 8).

It is interesting to compare these results with the findings of Mulliez. When Mulliez performed base-catalysed solvolysis on **8** (scheme 5) in the cases where R=PhO, the release of phenol was not observed thereby suggesting that pseudorotation did not take place.

This indicates that the overriding apicophilicity of the PhO group is only one of many criterias which have to be taken into consideration when analysing the solvolytic behaviour of these types of 5-membered ring systems.

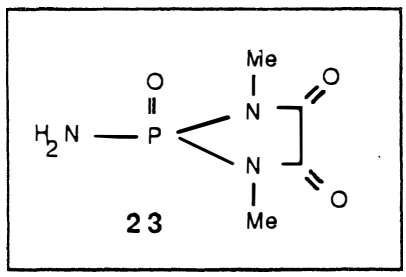
The studies discussed so far suggest that many factors determine the solvolytic behaviour of the 5-membered cyclic phospholidine compounds and it follows that these variables need to be characterised in order to facilitate the industrial use of such compounds. Consequently the synthesis and study of a series of 5-membered cyclic phospholidine compounds forms the basis of the present study.

With the aim of investigating factors which determine the mechanistic pathway of nucleophilic attack in 5-membered cyclic phospholidines, a series of compounds (**22** to **25**) resembling those compounds studied by Mulliez[8] were synthesised. Compounds **23-25** differed from the above due to the presence of a third exocyclic amido group. 1,3-dimethyl-2-phenoxy-1,3,2-diazaphospholi-dine-2,4,5-trione (**22**), studied by Mulliez[8], was used as a reference sample. The solvolytic behaviour of each of these compounds **22** to **25** was investigated, as well as their reactions with amines. Furthermore, a crystal study of compounds **24** and **25** was carried out in an attempt to correlate structure with chemical behaviour. Finally, a fragmentation pattern study, under conditions of electron-impact, was also performed.



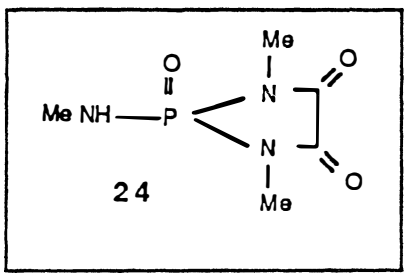
22

PHENOXYDIMET



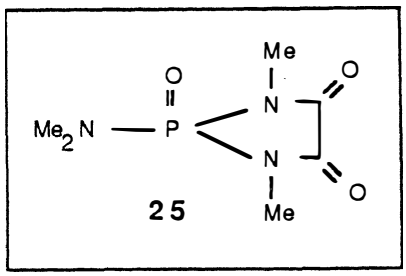
23

DIMET



24

TRIMET



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TETRAMET

It was hoped that the studies described above would permit identification of the factors influencing the nucleophilic attack of 5-membered cyclic phospholidines and thus lead to an understanding of the mechanisms operating in these systems.

CHAPTER II

RESULTS AND DISCUSSION

2.1 PRELIMINARY WORK

The project was started with the investigation of reaction 1 (see introduction and chapter 3.3), which was described by Schenkenberg and Williams[7] and which yields 1,3-dimethyl-2-methylamino-2-oxo-4,5-dihydroxy-1,3,2-diazaphospholidine monohydrate (**3**). Reaction 1 was interesting in that: (1) it introduced a method for the synthesis of new phospholidine species and (2) the product thereof **3** incorporated some of the characteristics of compounds **1** and **2**. Thus, it was hoped by Schenkenberg and williams[7] that such a compound would exhibit both the permanent press properties of **1** and the fire retarding properties of **2**. Therefore, an investigation into the stereochemistry of this compound and a study of the stereochemical course of reaction 1 was undertaken.

However, obtaining product **3** by reaction 1 proved more complex than described by Schenkenberg and Williams[7]. The crude product obtained by reaction 1 consisted of a mixture of compounds. this was verified by ^{1}H NMR analysis. TLC plates showed that there was no starting material in the mixture and the elemental analysis was non-conclusive. Thus, due to the difficulty encountered in isolating the wanted product (**3**), this reaction was not investigated any further.

As an alternative to reaction 1, reaction 2 (see chapter 3: reaction of $P(O)(NHMe)_3$ with glyoxal sodium bisulfite) was carried out. This was done in the hope that it would yield a single product. However, the ^{1}H NMR analysis of the products of reaction 2 showed clearly that no reaction had taken place between the two substrates.

Finally, reaction 3 was performed (see chapter 3: reaction of $PhOP(O)(NHMe)_2$ with glyoxal) under the same conditions as reaction 1. TLC plates showed that two separate products were obtained, the main product being the starting material. The ^{1}H NMR was non-conclusive and no further attempt was made at separating the two fractions.

The results of these experiments support Schenkenberg and Williams's claim[7] that when, in reaction 1, N,N',N"-trimethyl-phosphoric triamide is substituted by other phosphoramidates, no phospholidine structures are isolated. This was substantiated by the results of reaction 3, which

yielded mostly starting material. The failure to separate the components of the product mixture of reaction 1 may be attributable to the small quantities of substrates that were used (the method described by Schenkenberg and Williams[7] used two hundred times more starting material than was used here). In light of these results, it was decided to synthesise other types of phospholidines, with the aim to find a reaction which yielded a single compound as product.

Therefore, reaction 4 (see chapter 3: reaction of $P(O)(NHMe)_3$ with methanal) was carried out. Reaction 4 was performed with the aim to repeat the synthesis described by Heitsch[6], which yielded compound **2**. The ^1H NMR was very complex and difficult to interpret. However, the results obtained from mass spectrometry and elemental analysis indicated that the same compound (as a dihydrate) as that described by Heitsch[6] (**2**) had been obtained.

However, the main analytical tool used in this thesis is ^1H NMR. Since the ^1H NMR of compound **2** was very difficult to interpret, it was decided to further investigate the synthesis of other phospholidine type compounds. This was done with the aim to find a reaction which is relatively simple and which permits the synthesis of compounds which can be unambiguously identified using ^1H NMR. Thus, 1,3-dimethyl-2-methylamino-1,3,2-diazaphospholidine-2,4,5-trione (trimet, **24**), a compound similar to those already described by Mulliez[8], was synthesised.

2.2 TRIMET

2.2.1 GENERAL

Trimet (**24**) was synthesised with the aim to investigate its solvolytic and structural properties, and to compare the outcome of this study with Mulliez's work on similar compounds[8]. The reaction between phosphoric triamide and oxalyl chloride gave trimet (**24**) as the only product. We did not observe any formation of other products, as indicated in figure 1.

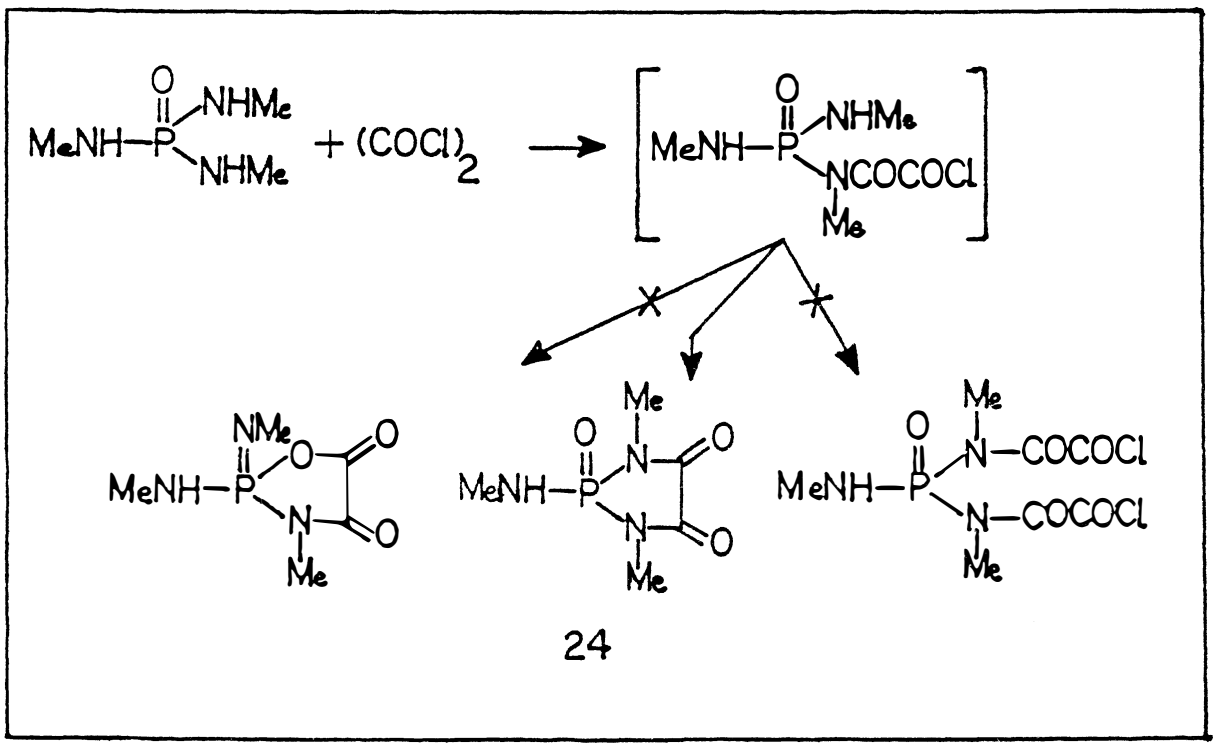
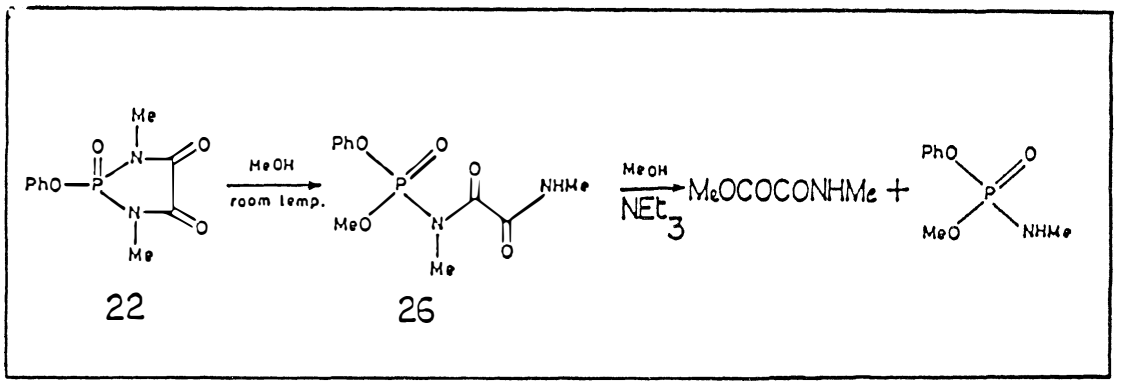


FIGURE 1: SYNTHESIS OF TRIMET

Trimet is a slightly hygroscopic compound which was soluble in the usual organic solvents. Once **24** had been unambiguously identified (by ^{1}H NMR, elemental analysis and mass spectrometry - see chapter 3.4.1) its reactivity and structure were studied.

2.2.2 METHANOLYSIS OF TRIMET

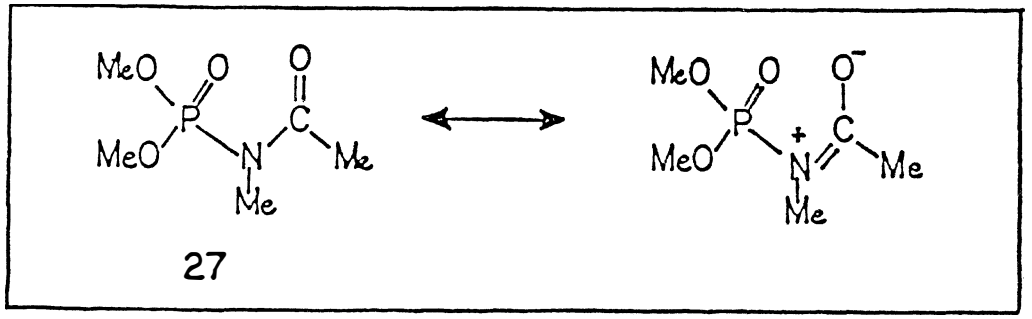
In his studies on the nucleophilic cleavage of the 1,3,2-diazaphospholidine system, Mulliez[8] found that 2-phenoxy, 2-ethoxy, and 2-phenyl derivatives undergo methanolysis with cleavage of only one P-N bond, yielding ring opened products which were relatively stable towards further solvolysis. This behaviour is illustrated in scheme 9, which shows the methanolysis of 1,3-dimethyl-2-phenoxy-1,3,2-diazaphospholidine-2,4,5-trione (PHENOXYDIMET, **22**).



SCHEME 9

Mulliez[8] proposed that the attack at the phosphoryl centre (see scheme 9) must be facilitated, at least in part, by the formation of a trigonal bipyramidal intermediate. This is accompanied by a relief of ring strain, which then acts as the driving force for the nucleophilic selectivity of MeOH at the phosphoryl centre[12].

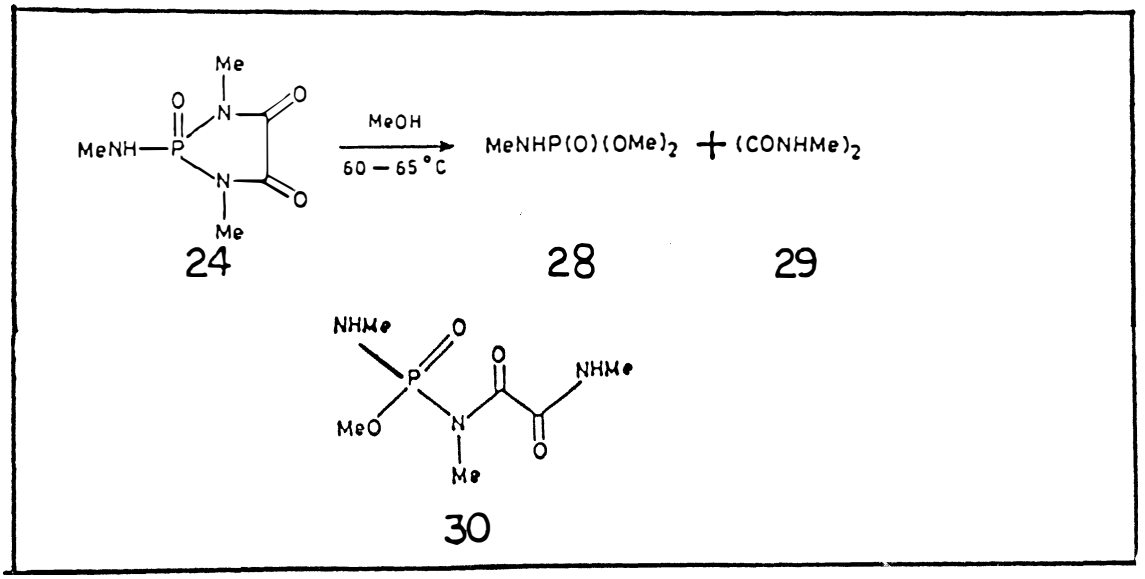
Only one P-N bond is cleaved, which indicates that the ring-opened product (**26**) is more stable to methanolysis than the cyclic compound (**22**). The reluctance of **26** to undergo further methanolysis is not suprising; work done in this lab on mixed phosphoric-carboxylic imides demonstrated the low reactivity of such compounds under solvolytic conditions[14]. For example, compound **27** (scheme 10) which may be considered an analogue to **26**, shows relatively slow P-N bond cleavage at 25°C ($t_{1/2}$ ca.100h)[14].



SCHEME 10

However, under neutral conditions, **27** undergoes nucleophilic attack by MeOH exclusively at the phosphoryl centre[14]. **26**, on the other hand, undergoes, under base-catalysed conditions, nucleophilic attack by MeOH at the carbonyl centre[8] (see scheme 9). It was proposed[14] that the regiospecificity of the nucleophilic attack by MeOH onto the phosphoryl centre in **27** resulted from the restrained carboxy-amide resonance effect in **27** which increases the electrophilic character of the phosphorus atom (see scheme 10). In **26**, the presence of the second electron-withdrawing carbonyl centre activates the carbonyl group closest to the phosphoryl group. This activation makes this carbonyl group more prone to nucleophilic attack than the phosphoryl group. This results in the cleavage of the C-N bond, as illustrated in scheme 9.

The study of the methanolysis of trimet (**24**) demonstrated that a change in the exocyclic P-substituent in a 1,3,2-diazaphospholidine can dramatically affect the relative reactivities of the two initially endocyclic P-N bonds. Trimet was found to be indefinitely stable in methanol at room temperature. This was supported by the ^{1}H NMR spectrum of trimet, which, when incubated in methanol at 25°C, did not show any noticeable change after 1430h. The solvolysis of trimet could be achieved at elevated temperature. However, such solvolysis invariably resulted in cleavage of both imide P-N bonds (see scheme 11). The product of cleavage of the first P-N bond of **24**, the ring-opened carboxylic phosphoric imide **30**, was never detected.



The absence of detection of **30** (analogue to **26**) indicates that the solvolysis of **30** is much faster than the initial solvolytic cleavage of the cyclic substrate **24**. The reasons for this difference in the solvolytic reactivity of the imide P-N bond in **30** and the endocyclic bond in **24** can be attributed to many factors. For example, phosphorus atom in **24**, substituted by three nitrogen atoms, is certainly less electrophilic than the phosphorus atom in the monoester derivative (**30**). However, it could be that the observed low reactivity of **24** stems at least partially from its molecular geometry. According to a generally accepted theory[12], which explains the abnormally high reactivity of phosphoric derivatives in which the phosphorus atom is constrained in a five-membered ring, significant release of strain is achieved when two endocyclic bonds of a substrate attain an apical-equatorial configuration in the intermediate bipyramidal structure. In a typical case of the conversion of a five-membered cyclic phosphate into the trigonal bipyramidal intermediate, the endocyclic O-P-O angle is reduced from ca.99 to ca.90°, with release of ca.3-6 kcal.mol^{-1} [25]. This stereoelectric effect on the rate of nucleophilic cleavage has been found to operate also in the base[17]- and acid[16]-catalysed hydrolysis of 1,3,2-oxazaphospholidines.

Therefore, to obtain more information about the geometry changes which could be involved in the association step of the solvolysis, it was decided that the molecular structure of **24** should be determined. In addition, since no molecular structure for 1,3,2-diazaphospholidine-2,4,5-triones have been reported, it was hoped that the x-ray diffraction study of **24** would provide insight into (the molecular parameters characteristic of this system.

2.2.3 CRYSTAL STRUCTURE OF TRIMET

Crystals of trimet were grown and its structure was determined. Details of the data collection and structural refinement are presented in table 1. Fractional atomic co-ordinates are given in table 2 and figures 2 and 3 are perspective views (and contain atom numbering) of the trimet molecule. Table 3 contains the relevant bond lengths (Å) and bond angles (°) with e.s.d.s in parentheses.

The most important feature of the molecular structure of trimet relevant to its solvolytic behaviour is the very small endocyclic N-P-N angle (92.3 + 0.1°). The small N-P-N angle in trimet, being close to 90°, could be responsible for the absence of the usual energy release upon formation of a trigonal bipyramidal intermediate. This low N-P-N angle could therefore account for part of the stability of trimet to nucleophilic attack. According to this interpretation, the N-P-N angle in **22** (phenoxydimet) should be significantly larger than in **24** (trimet). However, because of the high hygroscopic nature of this compound, all attempts to grow suitable crystals have failed. The molecular structure of **22** could therefore not be determined.

Another important feature of the molecular structure of trimet, relevant to its solvolytic behaviour, is the short exocyclic P-N distance (1.60 Å). This distance is significantly shorter than that typical (1.78 Å) of the "pure" single P-N bond[26], and is not far from the range (1.60-1.66 Å) observed for a variety of phosphoramidates[27] for which a certain amount of P-N π bonding must be considered. This, in turn, causes an increase in electron density around the phosphoryl centre, thereby reducing its electrophilicity. This could play a role in the high stability of trimet.

Also, the endocyclic P-N bond distance (1.67 Å) is longer than the exocyclic P-N bond distance. This indicates that the resonance donation of the amide N lone pair to the phosphoryl group is more effective than the resonance donation of the imide N to the same group. Thus, it could be speculated that, in reality, **30** resembles structure **30A** more than structure **30B** (scheme 12). This could partially explain the high sensitivity of (undetected) **30** to methanolysis, since this effect would weaken the P-N imide bond in **30**.

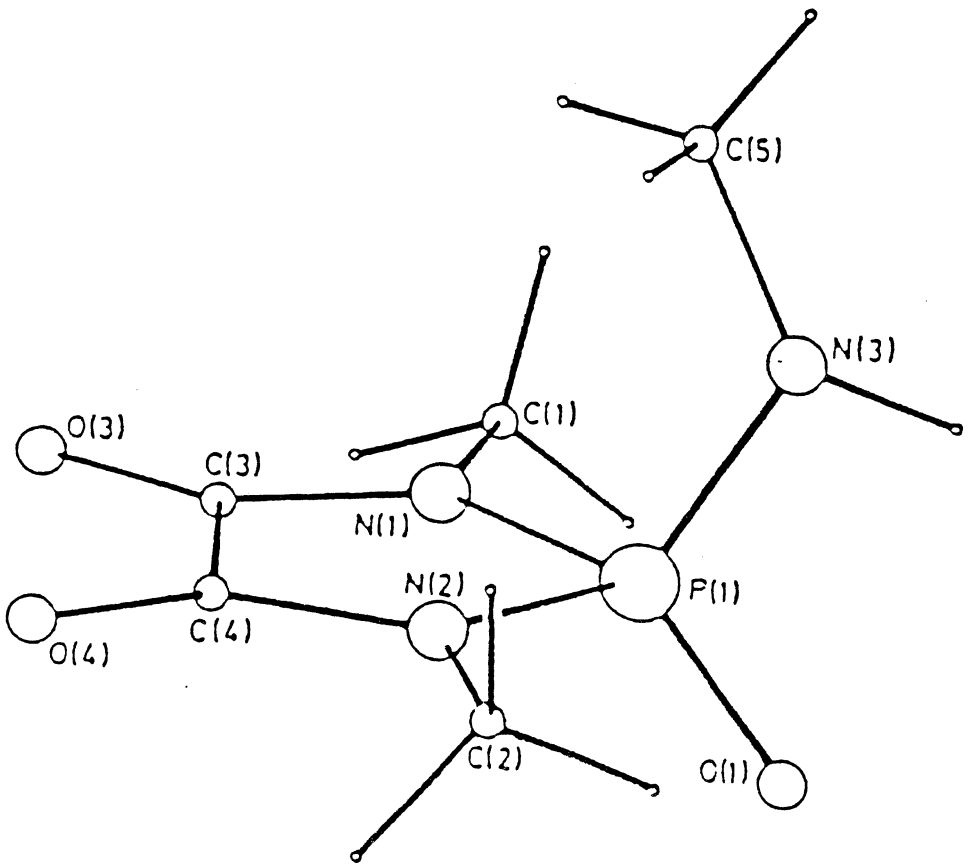


FIGURE 2 : PROSPECTIVE VIEW (AND ATOM NUMBERING) OF TRIMET

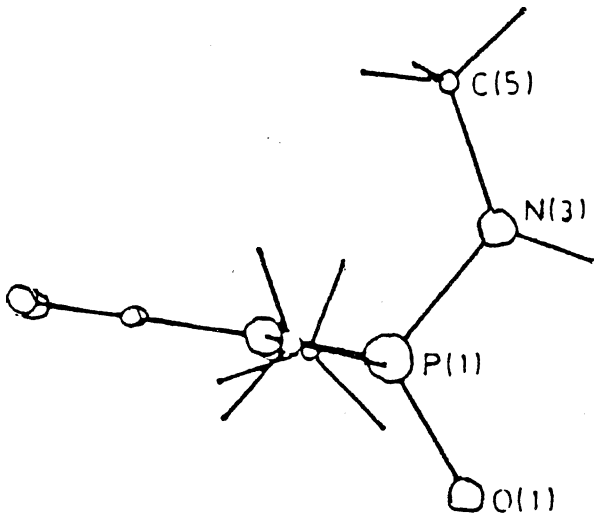


FIGURE 3 : PROSPECTIVE VIEW OF THE TRIMET MOLECULE ILLUSTRATING THE PLANARITY OF THE PHOSPHOLIDINE RING.

TABLE 2 : FRACTIONAL ATOMIC CO-ORDINATES (x 10^4) FOR THE NON-HYDROGEN ATOMS OF TRIMET.

	A			B		
	x	*y*	*z*	*x*	*y*	*z*
P(1)	7 755(2)	9·785(3)	1 451(5)	6 466(2)	8 901(3)	6 629(5)
O(1)	7 021(5)	8 909(7)	1 323(11)	7 316(5)	9 158(7)	6 214(11)
O(3)	8 274(5)	11 777(7)	5 777(13)	5 481(5)	9 752(7)	11 325(13)
O(4)	9 191(6)	10 357(7)	4 708(12)	5 194(5)	7 501(7)	10 245(12)
N(1)	7 705(6)	10 835(8)	3 186(14)	6 154(6)	9 736(8)	8 418(13)
N(2)	8 473(6)	9 630(8)	2.241(14)	6 001(6)	7 871(8)	7 601(14)
N(3)	8 082(6)	10·176(8)	−423(14)	6 046(6)	8 768(8)	4 886(15)
C(1)	7 147(8)	11 394(11)	3 378(20)	6 384(8)	10 882(10)	8 518(18)
C(2)	8 823(10)	8 786(13)	1 381(23)	6 051(9)	6 821(11)	6 761(20)
C(3)	8 231(8)	11 076(11)	4 383(20)	5 723(7)	9 295(10)	9 841(18)
C(4)	8 690(8)	10 320(10)	3 857(18)	5 610(8)	8 124(11)	9 341(19)
C(5)	8 780(9)	11 039(12)	−655(21)	5 190(8)	8 494(11)	4 980(19)

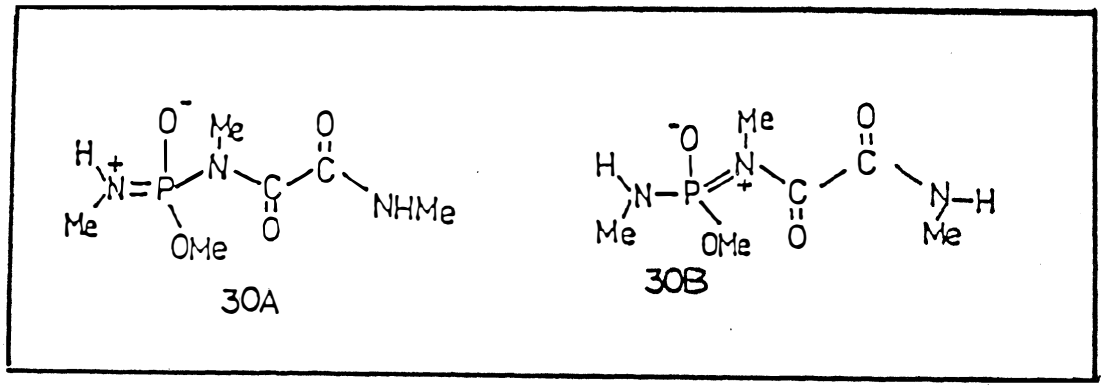
	C			D		
x	*y*	*z*	*x*	*y*	*z*	
2 758(2)	4 786(3)	573(5)	1 465(2)	3 902(3)	−4 191(5)	
2 028(5)	3 913(6)	570(11)	2 318(5)	4 154(7)	−4 365(11)	
3 275(5)	6 790(8)	−2 280(13)	482(5)	4 756(7)	−7 034(12)	
4 183(6)	5 353(7)	−3 543(13)	202(5)	2 495(7)	−7 939(13)	
2 705(6)	5 816(8)	−51(14)	1 157(6)	4 736(8)	−4 853(13)	
3 478(6)	4 630(8)	−1 111(13)	1 014(6)	2 874(8)	−5 752(13)	
3 078(6)	5 181(9)	2 522(15)	1 052(6)	3 778(8)	−2 188(14)	
2 148(8)	6 383(11)	878(19)	1 377(8)	5 883(10)	−4 040(18)	
3 810(9)	3 767(12)	−1 427(21)	1 035(9)	1 807(11)	−6 030(20)	
3 215(7)	6 073(10)	−1 545(18)	727(8)	4 275(11)	−6 280(18)	
3 704(8)	5 322(10)	−2 228(19)	601(8)	3 140(11)	−6 778(19)	
3 802(9)	6 042(12)	2 888(21)	205(8)	3 497(11)	−1 674(20)	

TABLE 1 : Bond lengths (Å) and bond angles (°), with e.s. d's in parentheses. The four crystalllographically independent molecules yielded structural parameters identical within their standard deviations. The bond lengths and angles reported here are therefore the average values for the four molecules.

Bond	
P=O	1.466(4)
P-N(amide)	1.601(10)
(amide)N-Me	1.461(15)
P-N(imide)	1.673(10)
(imide)N-Me	1.461(14)
N-C(O)	1.371(12)
C=O	1.218(14)
C(O)-C(O)	1.495(16)
Angle	
P-N-Me(amide)	123.1(6)
N-P=O(amide)	112.5(4)
N-P-N(exo)	109.5(5)
N-P=O(imide)	115.7(14)
N-P-N(endo)	92.3(1)
P-N-Me(imide)	123.1(8)
Me-N-C(O)	122.6(8)
N-C=O	125.7(8)
O=C-C(O)	124.7(11)
(O)C-C(O)-N	109.6(10)
(O)C-N-P	114.2(9)

TABLE 3 : Data pertaining to the crysallographic analysis of trimet.

Molecular formula	$C_5H_{10}N_3O_3P$
Space group	$P\bar{1}$
a/Å	18.365(9)
b/Å	13.877(7)
c/Å	7.653(4)
α/°	106.02(2)
β/°	77.99(2)
γ/°	110.17(2)
V/Å^3	1 746
Z	8
D_c/Mg m^{-3}	1.35
μ(Mo-K_α)/mm^{-1}	0.24
F(000)	800
Scan mode	$\omega-2\theta$
Scan width (θ/°)	1.2
Scan speed (° s^{-1})	0.048
θ range (°)	3—24
Stability of standard reflections (%)	1.5
Number of reflections collected	3 458
Number of reflections observed	1 990
Criterion for observed reflections	$I_{rel} > 2\sigma I_{rel}$
Number of parameters	263
$R = \Sigma\|\|F_o\| - \|F_c\|\|/\Sigma\|F_o\|$	0.084
$R_w = \Sigma w^{\frac{1}{2}}\|\|F_o\| - \|F_c\|\|/\Sigma w^{\frac{1}{2}}\|F_o\|$	0.069
Weighting scheme	$(\sigma^2 F)^{-1}$



SCHEME 12

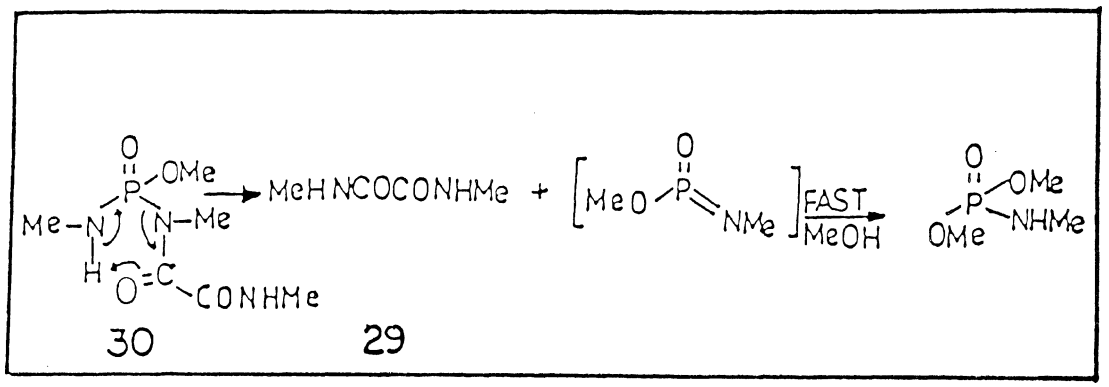
Additionally, the N-C(O) distance in trimet (1.37 Å) is significantly longer than the N-C(O) distance in the N,N'-dimethyl oxadiamide molecule (1.32 Å). This is due to the fact that when an N,N'-dimethyl oxadiamide unit is incorporated into a 1,3,2-diazaphospholidine system such as trimet, two major structural changes occur: first, the nitrogen atoms form a part of an imide and not an amide function; and second, the trans-orientation of the α-dicarbonyl linkage in the N,N'-dimethyl oxadiamide unit is changed to a cis-orientation. The amide-imide change in the chemical nature of the nitrogen atoms results in less effective resonance donation of the nitrogen lone pair to the carbonyl group and, hence, an increase in the N-C(O) distance. This decrease in resonance donation of the nitrogen lone pair to an acyl group, due to an amide-imide change in the chemical nature of the nitrogen atom, has been observed for acyclic mixed amides[15].

Upon the formation of the ring-opened carboxylic phosphoric imide (**30**), the N,N'-dimethyl oxadiamide function can regain the prefered trans-orientation. In this orientation more effective resonance donation of the nitrogen lone pair to the carbonyl group can occur. This, in turn, weakens the P-N imide bond by making the N,N'-dimethyl oxadiamide unit a good leaving group.

The two effects discussed above, i.e., the more effective resonance donation of the amide N to the phosphoryl group in **24**, and the better resonance donation of the N lone pair to the carbonyl groups in **30**, could be responsible, at least in part, for the increased susceptibility of **30** to nucleophilic attack.

However, there may be a third, more important factor which needs to be taken into consideration when analysing the high reactivity of **30** to solvolysis. Intramolecular proton transfer from

the NHMe group may take place towards the leaving group, via the six-membered transition state, as decribed in scheme 13. This would imply that solvolysis of **30** takes place via the unimolecular E1cB mechanism. This would explain the relative unreactivity of **26** towards further methanolysis.

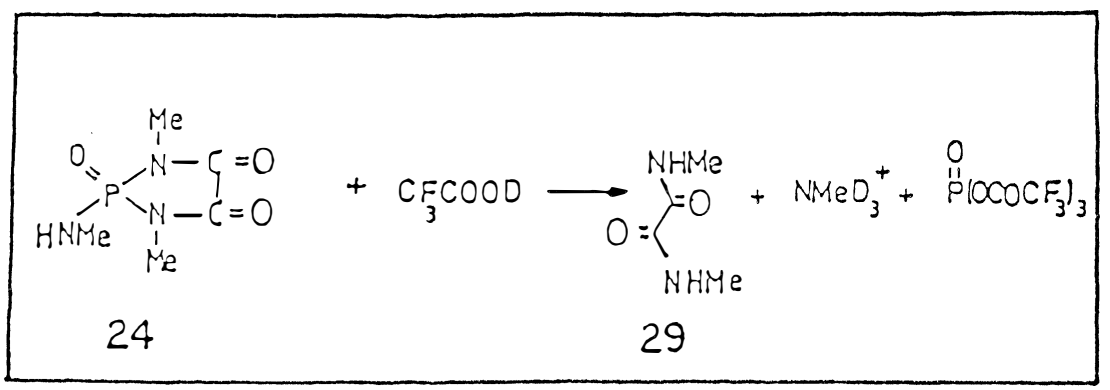


SCHEME 13

Such a proposal could be substantiated by the synthesis and consequent methanolysis of a compound similar to trimet, but within which the possibility of proton transfer does not exist. Such a compound was synthesised (TETRAMET, **25**) and its solvolytic behaviour was studied (see chapter 2.3).

2.2.4 ACIDOLYSIS OF TRIMET

The measurements of rate constants were not possible for the acidolysis of trimet in deuterated trifluoroacetic acid due to increased cloudiness of the sample in the ^1H NMR tube. However, $t_{1/2}$ can be estimated at about 40 hours. This estimation is based on the observation that after 45 hours ca. 67% of the original substrate showed signs of complete solvolysis of all P-N bonds. This was supported by the ^1H NMR spectrum of the reaction mixture, which showed a peak at δ 2.93 (integrating for 6H) for N,N'-dimethyl oxadiamide and another peak at δ 3.05 (integrating for 3H) for $MeND_3$ (see scheme 14).



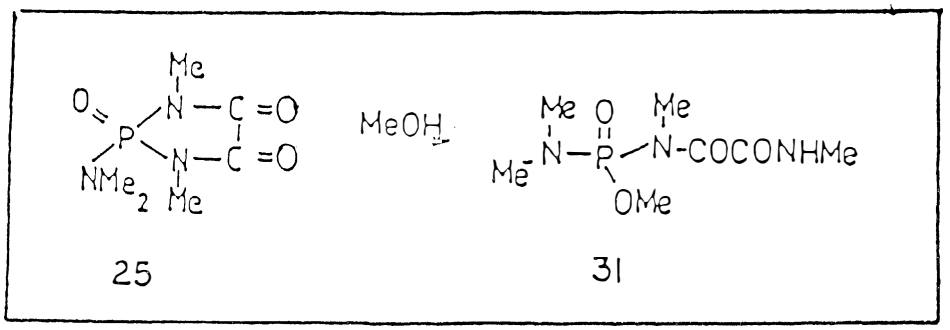
SCHEME 14

The acidolysis must involve a protonation step, followed by a P-N bond cleavage step. The results of this study indicated that protonation takes place at both the amide exocyclic and the imide (endocyclic) groups, without allowing us to postulate the order in which this protonation took place.

2.3 TETRAMET

2.3.1 GENERAL

In order to substantiate that the solvolysis of **30** takes place via the unimolecular E1cB mechanism (scheme 13), we synthesised and performed methanolysis of tetramet (**25**). Tetramet (**25**) is a compound in which the possibility of proton transfer does not exist (scheme 15) and, thus, this proposed catalytic mechanism can not take place. If the E1cB mechanism is responsible for the rapid cleavage of the second P-N (imide) bond in **30**, then it is reasonable to assume that the only product of the methanolysis of **25** will be **31**.



25 31

SCHEME 15

The synthesis of tetramet was performed following the general method described by Mulliez[8]. **25** was the only compound obtained. Once this new compound had unambiguously been identified (^{1}H NMR, elemental analysis and mass spectrometry, see chapter 3.5.1), its reactivity and structure were studied.

2.3.2 METHANOLYSIS OF TETRAMET

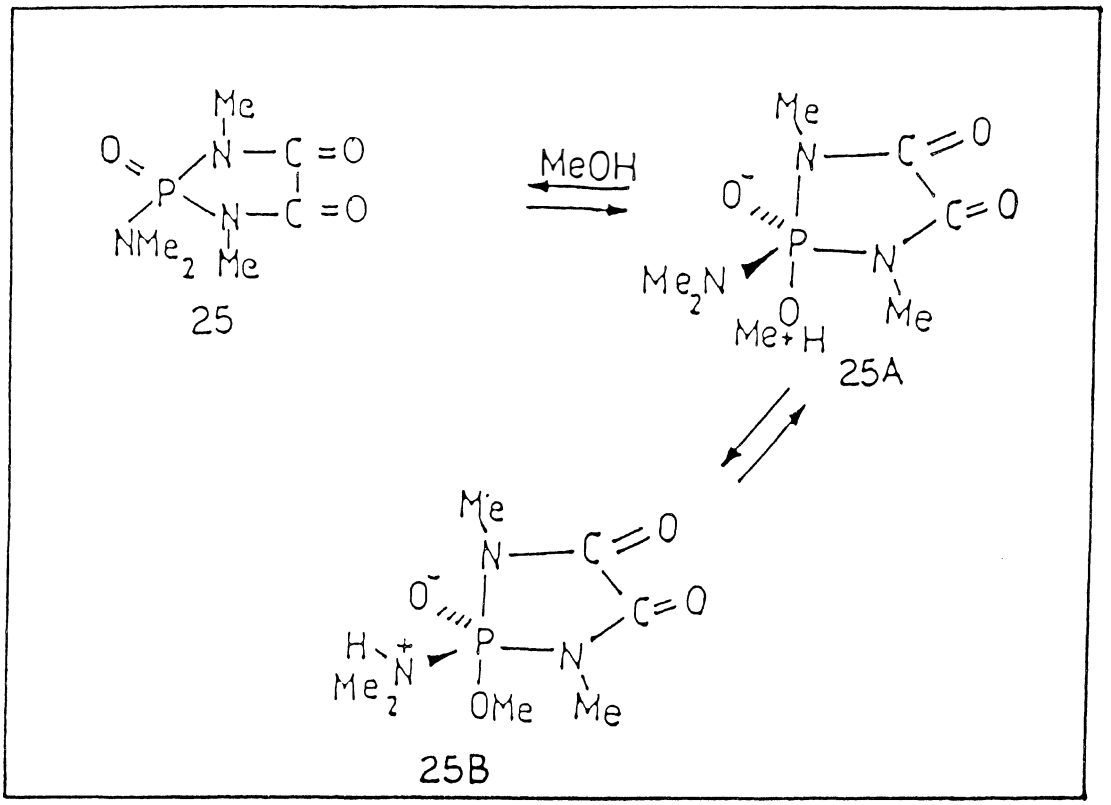
Tetramet was found to be practically indefinitely stable at room temperature in methanol, as no evidence of any bond cleavage was detected after 90 days (see chapter 3.5.2). When **25** was refluxed in rigorously dry methanol, evidence of bond cleavage was only detectable after 30 hours. Complete methanolysis was observed after 96 hours of continuous reflux. Finally, no evidence of methanolysis was observed after 6 hours of reflux under basic conditions. From these observations, it can be said that tetramet (**25**) is much less reactive to methanolysis than trimet (**24**).

The two main proposals for the apparent stability of trimet (**24**) to methanolysis: 1) the low N-P-N endocyclic angle; and 2) the decrease in the electrophilicity of the phosphoryl centre due to the short N-P exocyclic bond length, must also apply in the case of tetramet. The crystal structure determination, which will be discussed later (chapter 2.3.4), substantiated these claims. The much greater stability of tetramet in relation to trimet must, therefore, result from the replacement of the H atom in the exocyclic NHMe group by a methyl group.

It is generally accepted that the mechanism of nucleophilic attack onto a phosphorus atom constrained in a 5-membered ring is one of addition-elimination[12]. In a neutral environment, the nucleophilic attack at the phosphoryl centre results in the formation of a P^V intermediate. Deprotonation of the nucleophile is then followed by protonation of the P^V intermediate. This, in turn, may lead to bond cleavage either directly or after pseudorotation.

When a P^V intermediate is formed by nucleophilic attack onto tetramet, the exocyclic NMe_2 group is placed in the equatorial position (see scheme 16). This is a favoured position for this group, due to its bulkiness. Also, NMe_2 is a more basic group than NHMe, because of the é donating inductive effect of both methyl substituents. Therefore, protonation at the equatorial group will be more favoured in this P^V intermediate than in the trimet P^V intermediate. Moreover, the protonation of the exocyclic NMe_2 group is further favoured for steric reasons. This is because an exocyclic ammonium ion allows for P-N rotation, thereby minimizing the torsional strain at the tetrahedral ammonium nitrogen[16].

Therefore, ring opening by P-N cleavage is inhibited by two factors: 1) the low concentration of the N(endo) protonated form; and 2) the relative stability of the P^V intermediate. Under these conditions, the only pathway of decomposition for zwitterion **25A** (scheme 16) is retrogradation back to **25**. This would explain the low reactivity of tetramet to methanolysis.

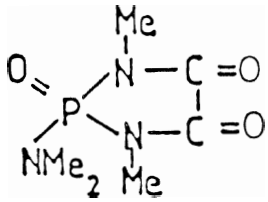


SCHEME 16

Figure 4 represents the ^1H NMR obtained after 30 hours of continuous reflux of a solution of tetramet in dry methanol. Most of the substrate is still intact. However, there is evidence of ring opening by nucleophilic attack onto the phosphoryl centre as a doublet at δ ($CDCl_3$) 3.76, J=11Hz, is seen to emerge. This doublet must belong to either one or two methoxy-methyl group(s) coupled to phosphorus. A doublet at δ ($CDCl_3$) 2.73, J=10Hz is also visible. $(MeO)_2P(O)NMe_2$ gives a doublet at the same place for its NMe_2 group. Thus, the doublet at δ ($CDCl_3$) 2.73, J=10 Hz is probably due to the NMe2 group that is still attached to the phosphorus atom.

It is not possible from this ^1H NMR spectrum to predict whether the products present in the reaction mixture result from only one or from multiple P-N bond cleavage. Signals for methoxy groups coupled onto P are obtained at very similar positions and with similar couplings. For example, $P(O)(OMe)_3$ gives a signal at δ 3.80 with a coupling constant of 11 Hz, while $(MeO)_2P(O)(NMe_2)$ gives a signal at δ 3.75 with the same coupling.

Figures 5 and 6 are ^1H NMR spectra obtained when the experiment was repeated in CD_3OD. The experiment was carried out in an ^1H NMR tube, immersed in a water bath at 70°C. Figure 5 is the spectrum at to, and figure 6 is the spectrum obtained after 100 hours at 70°C.



(25)

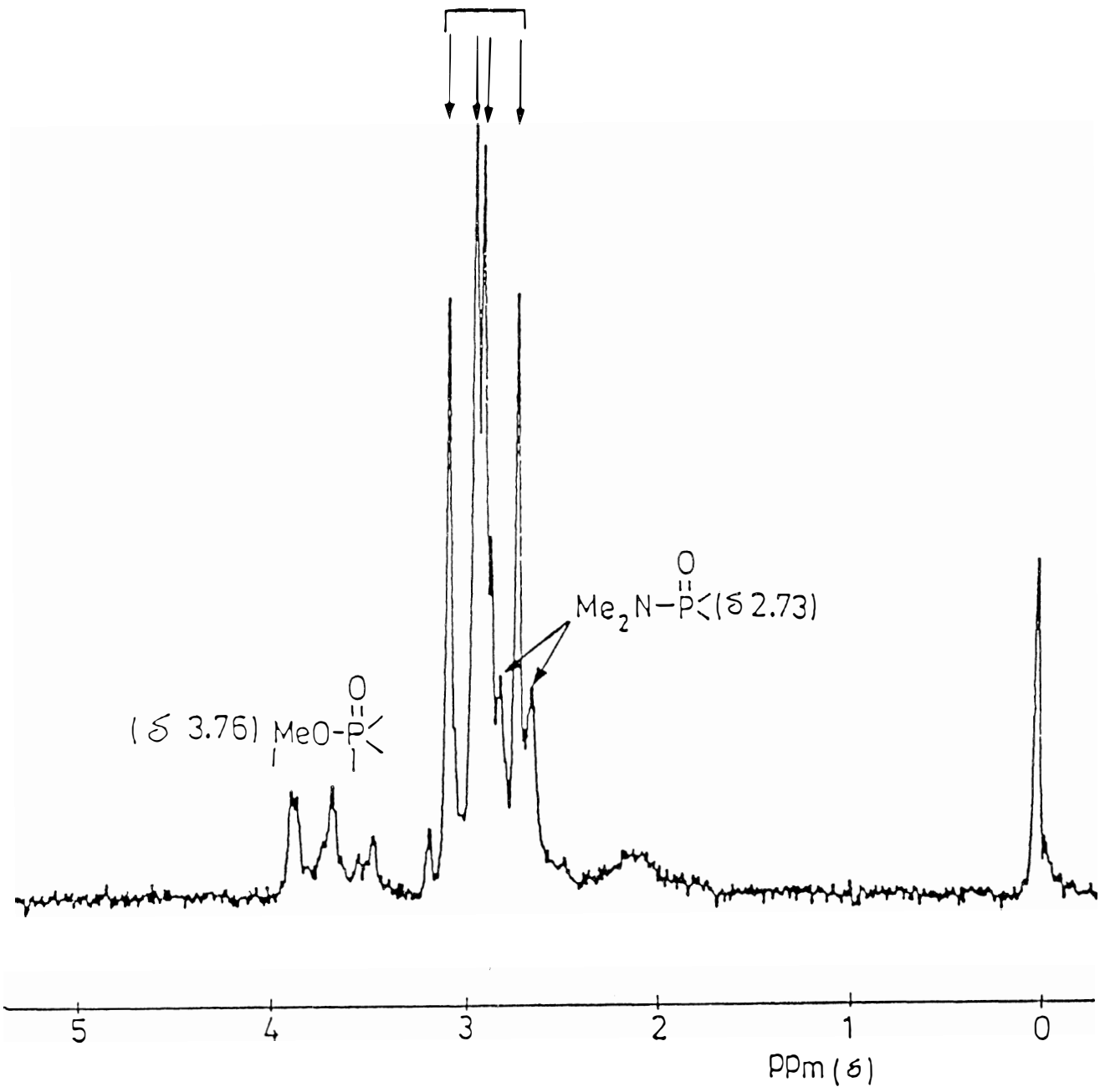


FIGURE 4 : ^{1}H NMR ($CDCl_3$) OF TETRAMET

AFTER 30 HOURS OF CONTINUOUS REFLUX IN DRY METHANOL

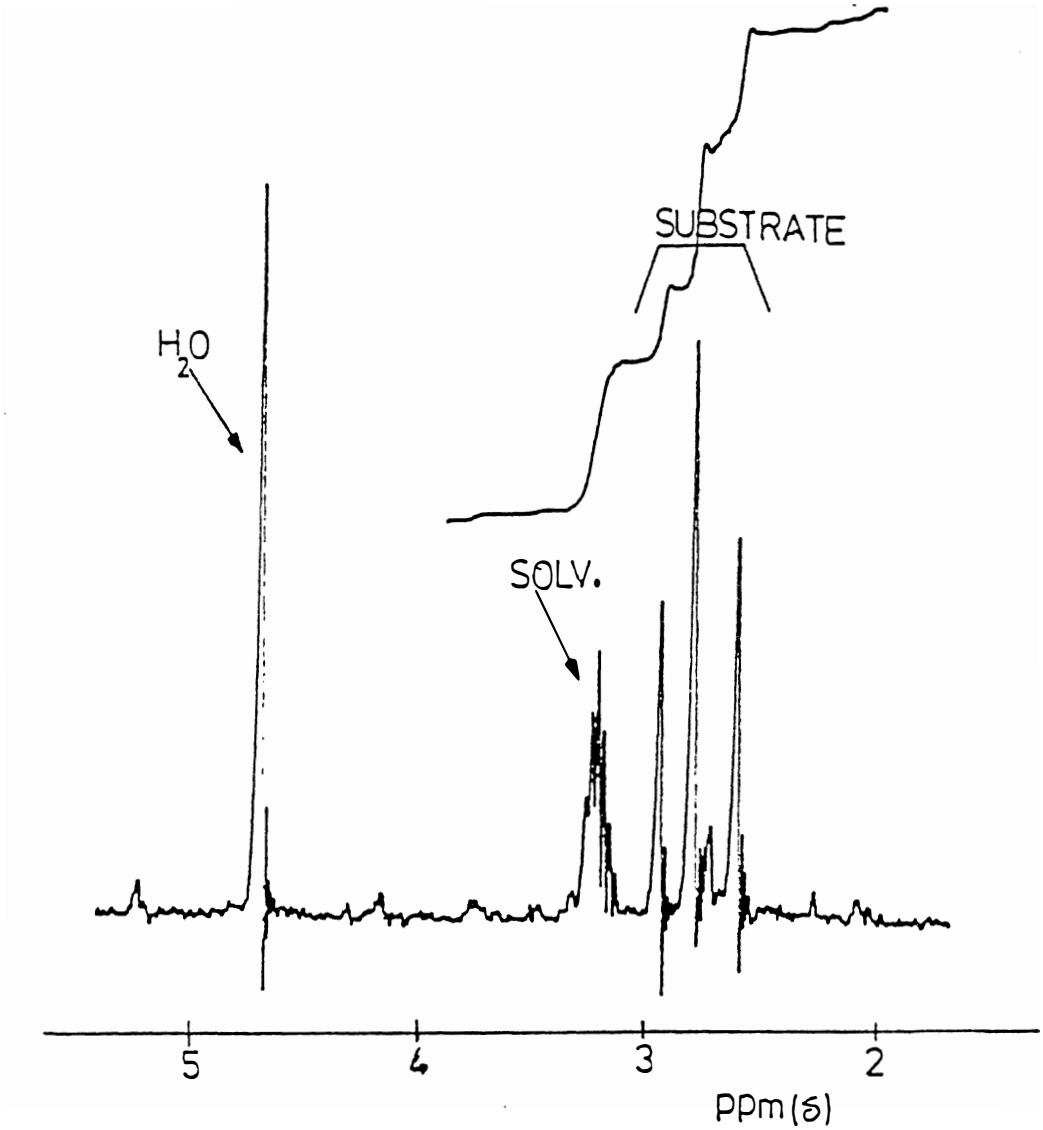


FIGURE 5 : ^1H NMR OF TETRAMET IN CD_3OD AT t_o.

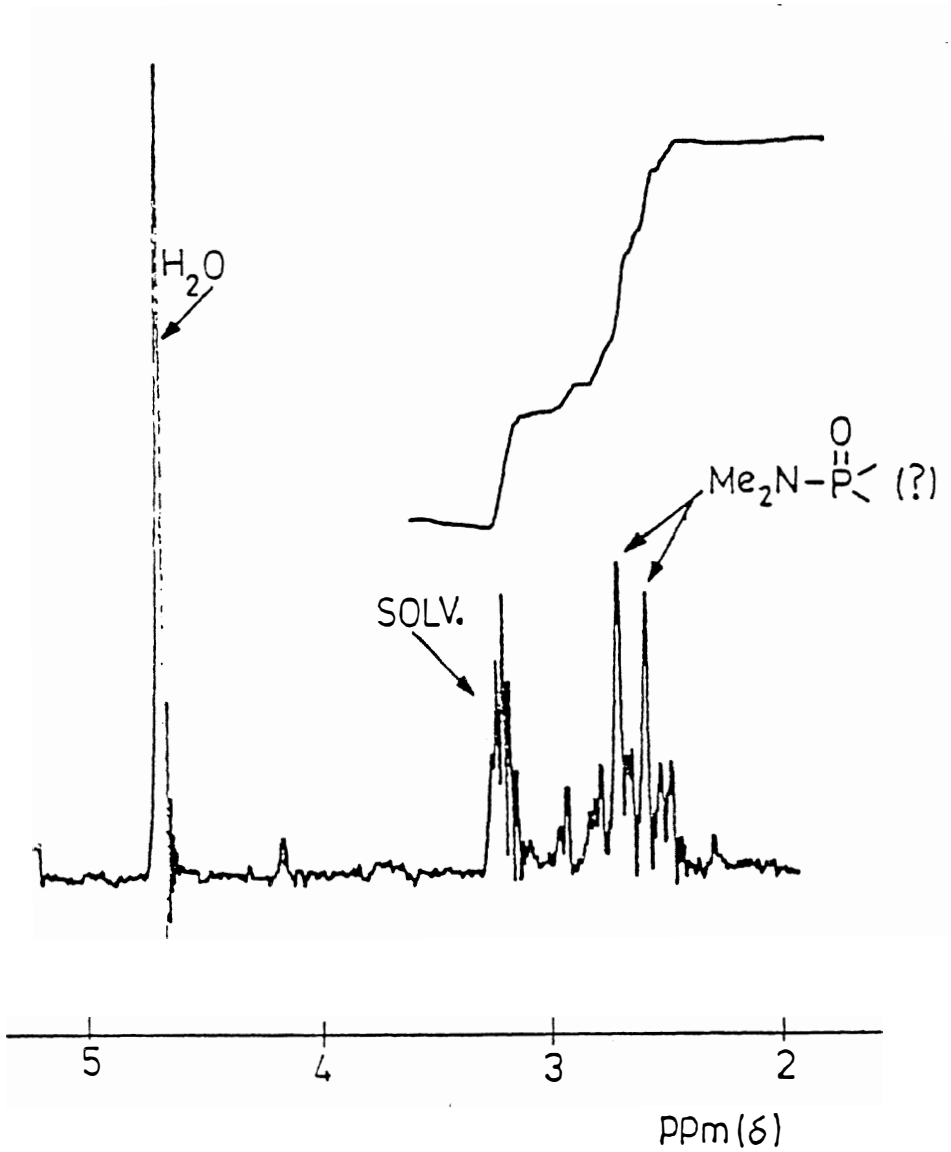
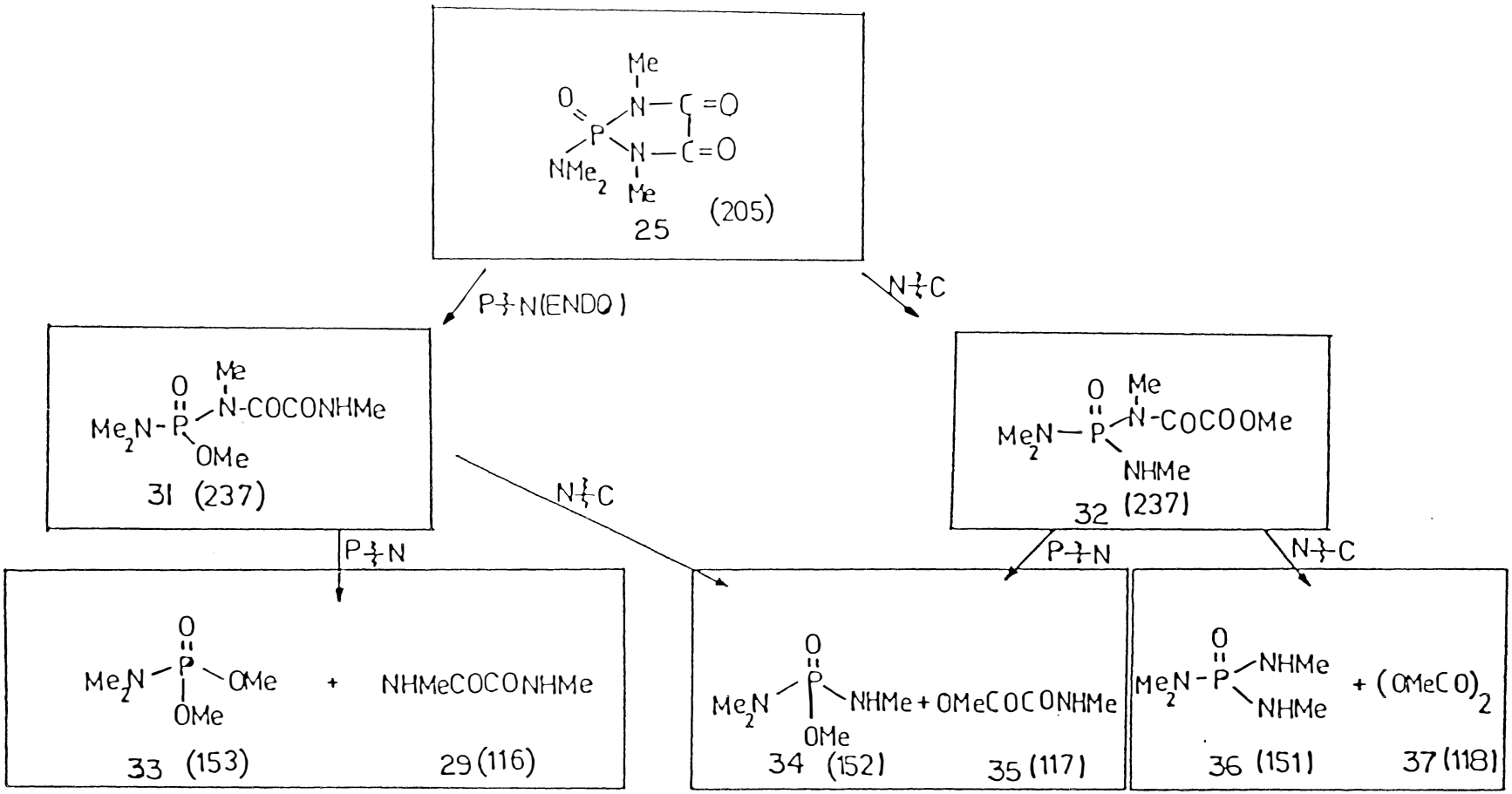


FIGURE 6 : ^{1}H NMR OF TETRAMET IN CD_3OD AFTER 100 HOURS AT 70°C.


Me
O
N—C=O
P
N—C=O
NMe2
Me
25 (205)
P⇢N(ENDO)
N⇢C
Me
O
N-COCONHMe
Me2N-P
OMe
31 (237)
Me
O
N-COCOOMe
Me2N-P
NHMe
32 (237)
P⇢N
N⇢C
P⇢N
N⇢C
O
Me2N-P
OMe
OMe
33 (153)
+
NHMeCOCONHMe
29 (116)
O
Me2N-P
NHMe + OMeCOCONHMe
OMe
34 (152)
35 (117)
O
Me2N-P
NHMe
NHMe
+ (OMeCO)2
36 (151)
37 (118)

SCHEME 17

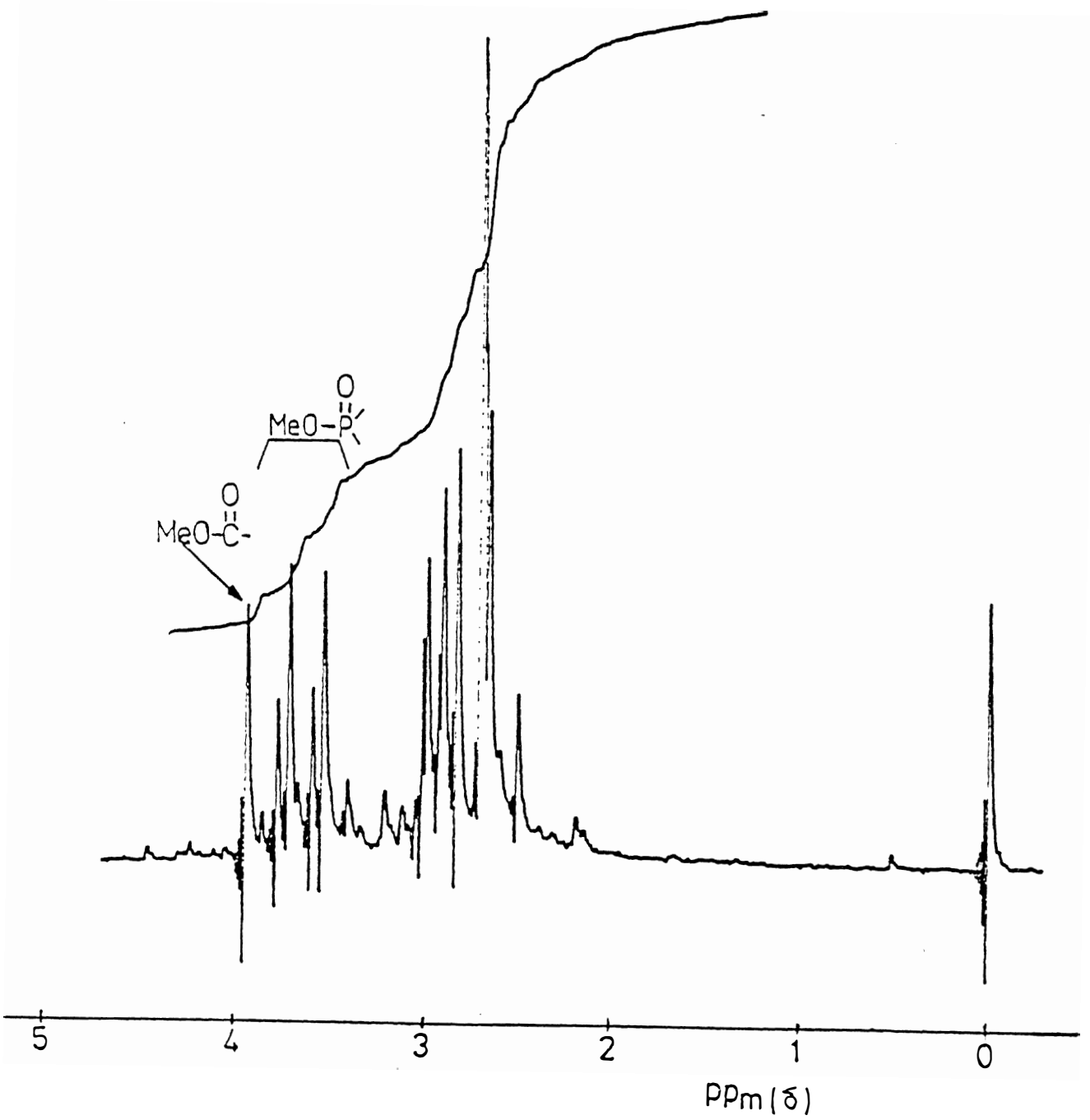


FIGURE 7 : ^{1}H NMR ($CDCl_3$) OF TETRAMET

AFTER 100 HOURS OF CONTINUOUS REFLUX IN DRY METHANOL

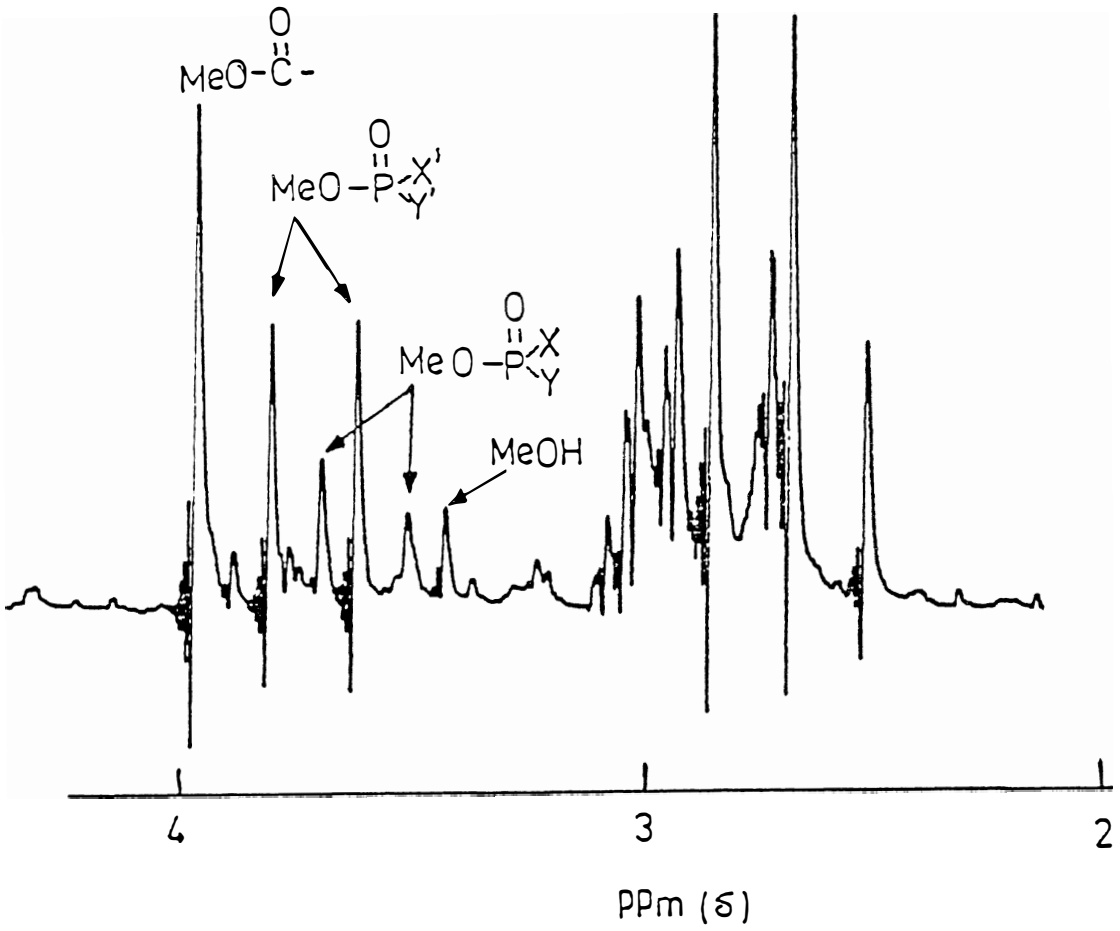


FIGURE 8 : D_2O WASH OF SPECTRUM PRESENTED IN FIG. 7

All that can be said is that there is very little substrate left. The rest of the spectrum in figure 6 is too ambiguous to be interpreted. Scheme 17 represents the possible pathways for nucleophilic attack of methanol either at the phosphoryl or at the carbonyl centres, with the expected products and their molecular weights.

The last methanolysis experiment involved complete methanolysis of **25** in undeuterated methanol. This was accomplished after 95 hours of constant refluxing. Figure 7 and 8 are the ^1H NMR obtained in $CDCl_3$ of the products obtained (figure 8 is a D_2O wash). Again, the spectra are too ambiguous to interpret. However, the following observations should be noted: A) After 100 hours of constant reflux, most of the substrate has been cleaved, i.e. methanolysis is completed; B) there is evidence of nucleophilic attack onto both the P(O) centre and the C(O) centre, as the doublets in the region of δ 3.7-3.8 (MeO-P(O)) and the singlet at δ 4 ($CDCl_3$) indicate (figures 7 and 8).

The products obtained from the methanolysis experiment in undeuterated dry methanol were submitted for mass spec and G.C/mass spec.

Compounds **29**,**34** and **35** (scheme 17) were unambiguously identified. *However, it is quite possible that some fragments are not sufficiently stable to give recognisable peaks. Therefore, conclusions as to which acyl centre is prefered for nucleophilic attack by MeOH cannot be drawn on the basis of these results.

Base-catalysed methanolysis was not observed after 6 hours of continuous reflux of tetramet in methanol in the presence of pyridine. Base-catalysis is achieved by facilitating the deprotonation of the nucleophile, thereby effectively increasing its nucleophilicity. This result indicates that the deprotonation of the nucleophile does not play a decisive role in the formation of the P^V intermediate during nucleophilic attack at the phosphoryl centre.

* Footnote : see page 36

* **Footnote :**

Fragmentation patterns:

Fraction 1: M^+ 140, trimethyl phosphate, $P(O)(OMe)_3$ (40)

Peaks of m/e 110 (base peak); 109; 80 and 79 were present and resulted from losses of either OCH_2 (30) or/and $OCH_3]^\bullet$ (31). A spectrum of pure trimethyl phosphate was also used to substantiate the identity of this fration.

Fraction 2: M^+ 117, N-methyl-methoxy oxamide, $NHMeC(O)C(O)OMe]^{+\bullet}$ (35)

$-CO$ (28) : $NHMeC(O)OMe]^{+\bullet}$ m/e 89

$-C(O)OMe]^\bullet$ (58) : $NHMeC(O)]^+$ m/e 58 (base peak)

A peak at m/e 30 is also present for $CH_2{=}NH_2]^+$

Fraction 3: M^+ 152, N,N-dimethyl-N'methyl-methoxy phosphate, (34)

$N(Me)_2P(O)(NHMe)(OMe)]^{+\bullet}$

$-NHMe]^\bullet$ (30) : $NMe_2P(O)OMe]^+$ m/e 122

$-NMe_2]^\bullet$ (44) : $NHMeP(O)OMe]^+$ m/e 108

$-NHMeP(O)OMe]^\bullet$ (108) : $Me_2N]^+$ m/e 44 (base peak)

$-Me_2NP(O)OMe]^\bullet$ (122) : $MeNH]^+$ m/e 30

Fraction 4: M^+ 116, N,N'-dimethyl oxadiamide, $NHMeC(O)C(O)NHMe]^{+\bullet}$ (29)

$-CO$ (28) : $NHMeCONHMe]^{+\bullet}$ m/e 88

$-NHMeCO]^\bullet$ (58) : $NHMeCO]^+$ m/e 58 (base peak)

Peaks at m/e 44 and m/e 30 were also present for the ions $CH_2{=}NHMe]^+$ and $CH_2{=}NH_2]^+$

2.3.3 ACIDOLYSIS OF TETRAMET

Tetramet was found to be completely unreactive in $CF_3C(O)OD$. If the unreactivity of tetramet in neutral methanol is partially due to the high basicity of the NMe_2 group, which could effectively reduce the concentration of N-Me (imide) protonated form, then the protonation step should be facilitated under acidic conditions and the reaction should be catalysed.

However, TFA^- is a weaker nucleophile than MeOH, which implies that the formation of the P^V intermediate will be slower. Therefore, the result of this acidolysis indicates that the formation of the P^V intermediate, in the nucleophilic addition-elimination reaction of tetramet, is a more important step than the protonation step.

2.3.4 CRYSTAL STRUCTURE OF TETRAMET

Crystals of tetramet were grown in a benzene:acetone system (2:1) and the structure was determined. Details of the data collection and structural refinement are presented in table 4. figures 9 and 10 are perspective views (and contain atom numbering) of the tetramet molecule. Table 5 contains the relevant bond lengths (Å) and bond angles (°) with e.s.d.s in parentheses.

Tetramet has a very similar structure to trimet. The N-P-N bond angle of 91.9° (0.1) and the relatively short exocyclic P-N bond length of 1.61 Å support the proposed hypotheses for the stability of tetramet. Therefore, it can be said that the big difference in reactivity between trimet and tetramet does not lie in their structural differences but rather in the electronic change brought about by the substitution of a methyl group onto the exocyclic nitrogen.

FIGURE 9 : Perspective view of the tetramet molecule illustrating the planarity of the phospholidine ring.

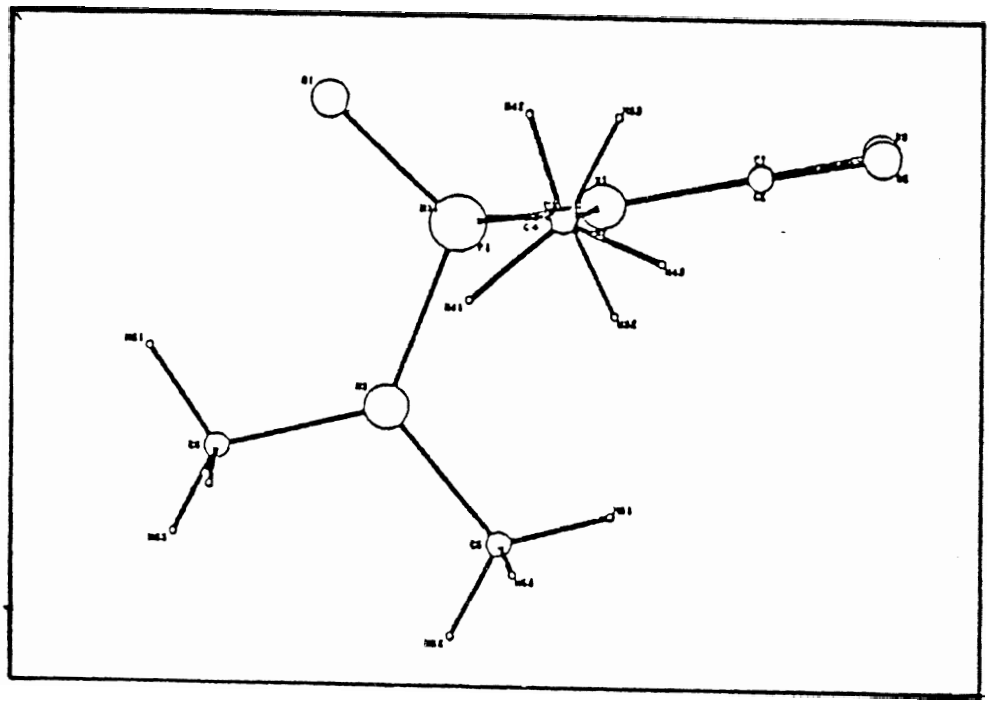


FIGURE 10 : Perpective view (and atom numbering) of tetramet.

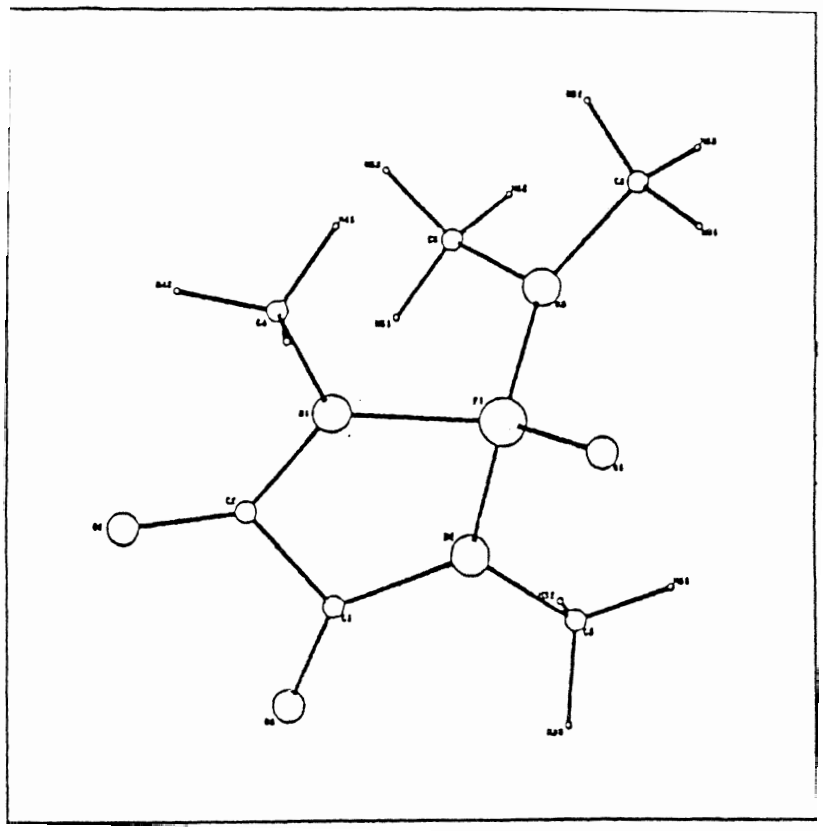


TABLE 4 : DATA PERTAINING TO THE CRYSTALLOGRAPHIC ANALYSIS OF TETRAMET

Molecular formula	$C_6 H_{12} N_3 O_3 P$
Molecular weight ($gr.mol^{-1}$)	205
Space group	Pbca (n^{o} 61)
a/Å	9.546(6)
b/Å	10.811(2)
c/Å	18.500(7)
V/A^3	1909.2
Z	8
Dc ($mg.m^{-3}$)	1.426
μ(Mo -K) (mm^{-1})	0.22
F(000)	864
Scan mode	ω-2θ
Scan width in ω(^{o})	(0.83 + 0.35 tanθ)
Aperture width (mm)	(1.09 + 1.05 tanθ)
θ range (^{o})	1-25
Stability of standard reflections (%)	<1.5
Number of reflections collected	1439
Number of reflections observed	1071
Criterion for observed reflections	$I_{rel} > 2\sigma_{rel}$
Number of parameters	131
$R = \Sigma \left\| \|F_o\| - \|F_c\| \right\| / \Sigma \|F_o\|$	0.048
$R_w = \Sigma w^{1/2} \left\| \|F_o\| - \|F_c\| \right\| / \Sigma w^{1/2} \|F_o\|$	0.051
Weighting scheme	$(\sigma^2 F + 0.002F^2)^{-1}$

TABLE 5 : BOND LENGTHS(Å) AND BOND ANGLES (°)

WITH E.S.D'S IN PARENTHESES FOR TETRAMET

BONDS

P = O	1.456(3)
P-N(amide)	1.612(3)
(Amide) N-Me	
N3 -C5	1.463(5)
N3 -C6	1.470(5)
P-N(imide)	
N1 -P1	1.686(3)
N2 -P1	1.679(3)
(imide) N-Me	
C6 -N3	1.470(5)
C5 -N3	1.463(5)
N -C(O)	
N2 -C1	1.371(5)
N1 -C2	1.358(5)
C = O	
C2 -O2	1.210(4)
C1 -O3	1.206(4)
C(O) -C(O)	1.206(4)

ANGLES

P-N-Me(amide)	
P1 -N3 -C5	121.0(0.2)
P1 -N3 -C6	121.8(0.3)
N - P =O(amide)	
N1 - P1 -O1	115.6(0.2)
N2 - P1 -O1	116.2(0.1)
N-P-N (exo)	
N2-P1-N3	108.0 (0.2)
N1-P1-N3	109.5(0.1)
N - P-N(amide)	
N2- P1 -N1	91.9(0.1)
P - N - Me(imide)	
P1 - N1 -C4	123.0(0.3)
P1 - N2 -C3	124.2(0.2)
Me - N -C(O)	
C3 - N2 -C1	121.0(0.3)
C4 - N1 -C2	121.8(0.3)
N - C = O	
N1 - C2 -O2	127.1(0.4)
N2 - C1 -O3	125.8(0.4)
O = C - (O)	
O3 - C1 -C2	125.2(0.3)
O2 - C2 -C1	124.0(0.4)
(O)C - C(O) - N	
C2 -C1 - N2	109.0(0.3)
C1 -C2 - N1	109.0(0.3)
(O)C - N -P	
C2 - N1 -P1	115.2(0.2)
C1 - N2 -P1	114.8(0.2)

2.3.5 CONCLUSION

Due to the high unreactivity of tetramet, few observations may be made on its solvolytic behaviour. However, there is evidence of both P(O)-N and N-C(O) bond cleavage during methanolysis. Trimet, on the other hand, under the same conditions exhibited only P(O)-N bond cleavage. finally, the results obtained in the methanolysis study of tetramet do not allow us to substantiate the proposal that the solvolysis of **30** takes place via the unimolecular E1cB mechanism.

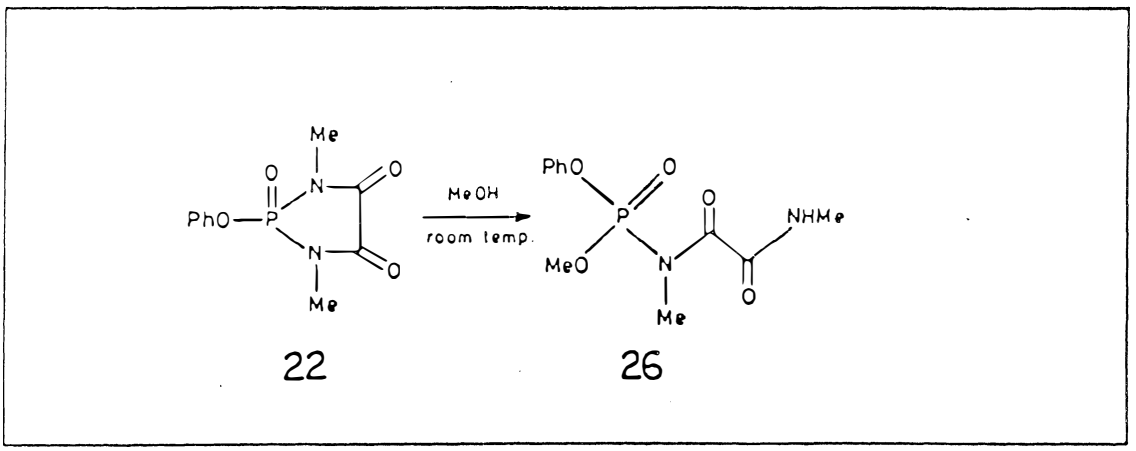
2.4 PHENOXYDIMET

2.4.1 GENERAL

Mulliez[8] showed that phenoxydimet (22) undergoes methanolysis by nucleophilic attack onto the phosphoryl centre. This attack results in the cleavage of a single P(O)-N bond, to yield the ring-opened carboxylic phosphoric imide **26** (see scheme 9). Under base-catalysed methanolysis, further cleavage took place at the N-C(O) bond (see scheme 9). As a means of comparison with the work done on trimet and tetramet, it was decided to investigate, under neutral conditions, the complete methanolysis of phenoxydimet.

Phenoxydimet (22) was synthesised according to the method described by Mulliez[8]. Although attempts were made at growing crystals to determine its structure, phenoxydimet was too sensitive to atmospheric moisture and decomposed upon standing. The only crystalline material isolated proved to be the hydrolysis product **29** (scheme 11). **22** was therefore used as soon as it was prepared.

2.4.2 METHANOLYSIS OF PHENOXYDIMET



22 26

The methanolysis of phenoxydimet in CD_3OD was monitored by ^1H NMR spectroscopy. The doublet at δ 3.20 (J=9 Hz) for the N-Me groups of phenoxydimet (**22**) disappeared as a new one, slightly higher field (δ 3.16, J=8 Hz) appeared for the P(O)NMeC(O) group of the ring-opened product (**26**). The reaction was completed after 30 minutes.

Compound **26** was unambiguously identified when the reaction was repeated and the product isolated. The ester **26** was stable in methanol at room temperature over a period of 24 hours, which indicated that the ring-opened product **26** was relatively more stable than the cyclic compound **22.** This was in accordance with Mulliez's results[8]. However, under reflux conditions, a solution of compound **26** with excess methanol yielded products which indicated that the nucleophilic attack by methanol took place ewclusively at the level of the phosphoryl centre. This was substantiated by ^1H NMR and G.C/mass spectrometry (scheme 18).

It was observed that the doublet at $\delta(CDCl_3)$ 3.95 (J=12 Hz) for the O-Me group of **26** (see figure 11) was being replaced by a new doublet shifted upfield to $\delta(CDCl_3)$ 3.80 (J=11 Hz) (see figure 12). At the same time, we noted the disappearance of the doublet at $\delta(CDCl_3)$ 3.16 (J=8 Hz) for the P(O)-N-Me-C(O) imide group and the enlargementof the doublet at $\delta(CDCl_3)$ 2.9 (J=5 Hz) for the formation of N,N'-dimethyl oxadiamide (figures 12 and 13). Moreover, we noted the liberation of phenol, which produced a new multiplet slightly higher field to the phenoxy group of ester **26** (figures 12 and 13). The new doublet which appeared at $\delta(CDCl_3)$ 3.80 (J=11 Hz) could be due to the formation of either $P(O)(OMe)_3$ or/and $PhOP(O)(OMe)_2$. The reaction mixture was submitted to G.C/mass spectroscopy in order to identify each of the products formed. Four distinct products were separated, as illustrated in table 6.

The products identified by G.C/mass spec as well as the ^1H NMR evidence indicated that no nucleophilic attack took place at the level of the carbonyl centre. Mulliez's results of nucleophilic attack at the level of the carbonyl centre in **26** (scheme 9) under base-catalysed conditions contrast with these results.

Methanolysis of trimet at elevated temperature (scheme 11, chapter 2.2.2) invariably resulted in the cleavage of both imide bonds. The product of cleavage of the first P-N bond of trimet, **30**, was never detected. It was proposed that (chapter 2.2.3) the lability of the imide P-N bond in **30** was caused, at least in parts, by the increase in resonance donation of the N lone pair to the carbonyl group of the N,N'-dimethyl oxadiamide unit.

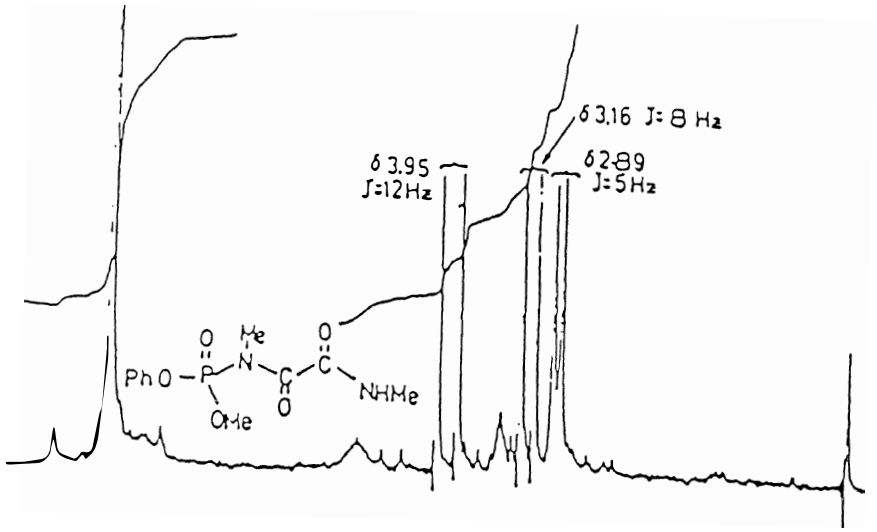


FIGURE 11

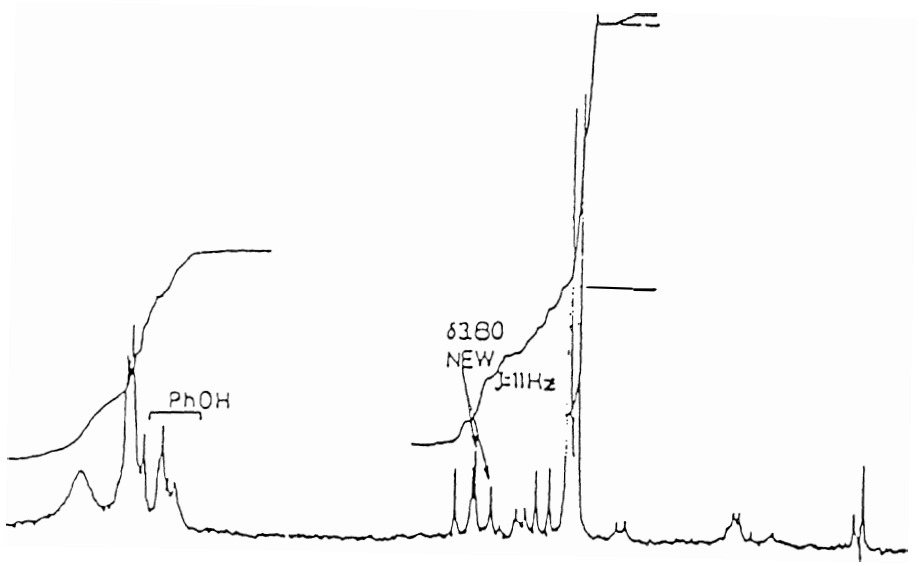


FIGURE 12

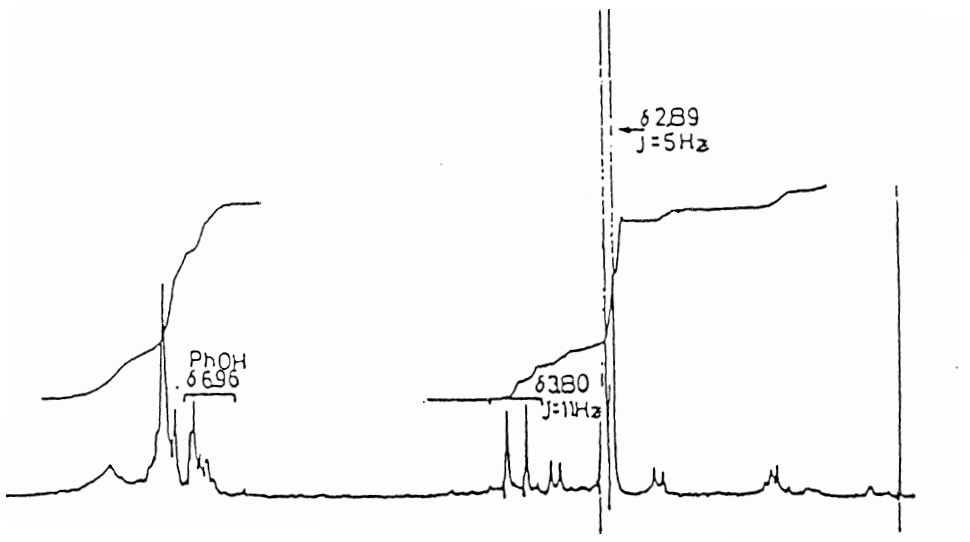


FIGURE 13

TABLE 6 : GAS CHROMATOGRAPHY AND MASS SPECTROSCOPY RESULTS FOR THE ANALYSIS OF METHANOLYSIS RESULTS OF COMPOUND 26

Compound	Retention time(min)	$M^{+(*)}$
Phenol	11	94
N,N'-dimethyl oxadiamide	16,20	116
Trimethyl phosphate	18	140
Dimethyl phenyl phosphate	23	202

* Footnote:

Fragmentation patterns:

Fraction 1: M^{+} = 94 , phenol, $C_6H_6O]^{+\cdot}$ (39)

-CO (28) = $C_5H_6]^{+\cdot}$ m/e 66

-CHO] (29) = $C_5H_5]^{+}$ m/e 65

$-C_2H_2$ (14) = $C_3H_3]^{+}$ m/e 39

Fraction 2: M^{+} = 116, N,N'-dimethyloxadiamide, $NHMeC(O)C(O)NHMe]^{+\cdot}$ (29)

-CO (28) = $NHMeC(O)NHMe]^{+\cdot}$ m/e 88

-NHMeC(O)] (58) = $NHMeC(O)]^{+}$ m/e 58 (cleavage)

Also present was a peak at m/e 44 for $CH_2{=}NH{-}CH_3]^{+}$ and a peak at m/e 30 for $CH_2{=}NH_2]^{+}$

Fraction 3: M^{+} = 140 , trimethylphosphate, $P(O)(OMe)_3]^{+\cdot}$ (40)

peaks at m/e 110, 109, 79, 80 were observed for losses of either 30 (OCH_2) or/and 31 (OCH_3)

Fraction 4: M^{+} 202 , dimethyl-phenyl phosphate, $PhOP(O)(OMe)_2]^{+\cdot}$ (38)

-PhO] (93) = $P(O)(OMe)_2]^{+}$ m/e 109

$-OCH_2$ (30) = $HP(O)(OMe)]^{+}$ m/e 79

peaks at m/e 77,65,51 were present for the benzene fragments of $PhOH]^{+\cdot}$ m/e (94).The base peak was at m/e 90.

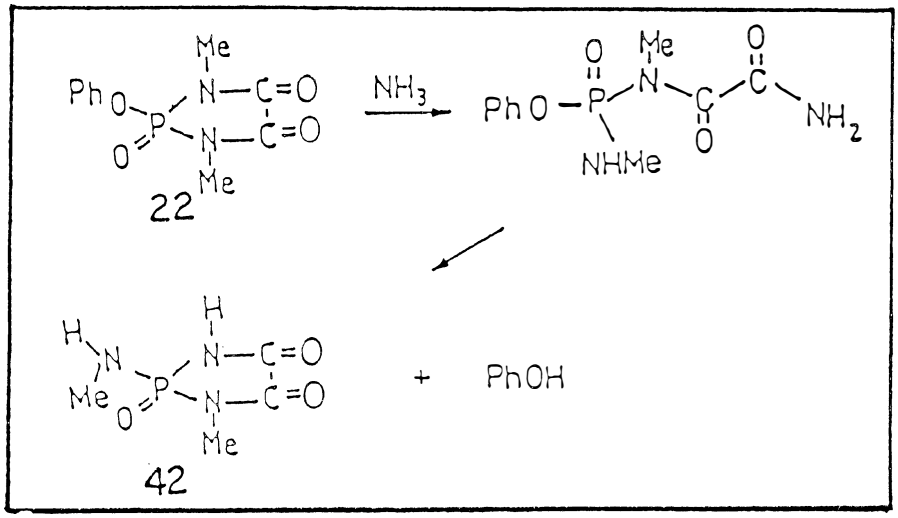
This argumentation can also be applied to **26**. Moreover, in **26**, the phosphoryl centre is substituted by 3 electron withdrawing groups (PhO, Ome, O). These increase the electrophilicity of this acyl centre. Therefore, the combination of both these factors (increased electrophilicity of the P(O) centre and the increased lability of the P-N (imide) bond) makes the phosphoryl centre in **26** a prime target for nucleophilic attack.

It should be noted that even though the phosphoryl centre in **26** may be considered more electrophilic than the one in **30** (due to the substitution by 3 electron withdrawing groups on the P(O) centre of **26** in comparison to only 2 on the P(O) centre of **30**), **26** is relatively more stable to methanolysis than **30**, since **30** is never detected. This implies that there must be an additional mechanism which intervenes in the catalysis of the P-N (imide) bond cleavage of **30**. As was proposed earlier (see chapter 2.2.3), this catalysis may be achieved via the unimolecular E1cB mechanism.

2.4.3 AMINOLYSIS OF PHENOXYDIMET WITH AMMONIA

Mullez[8] showed that aminolysis of phenoxydimet (**22**) with a series of amines (NH_2R": R"=Me, Me_2CH, $CHMe_2CH_2$, Bzl) resulted in nucleophilic attack at the level of the carbonyl centre. Furthermore, he demonstrated that, if the exocyclic group attached onto the phosphorus atom was a good leaving group (e.g. PhO), then ring closure took place, expelling PhOH (see scheme 4).

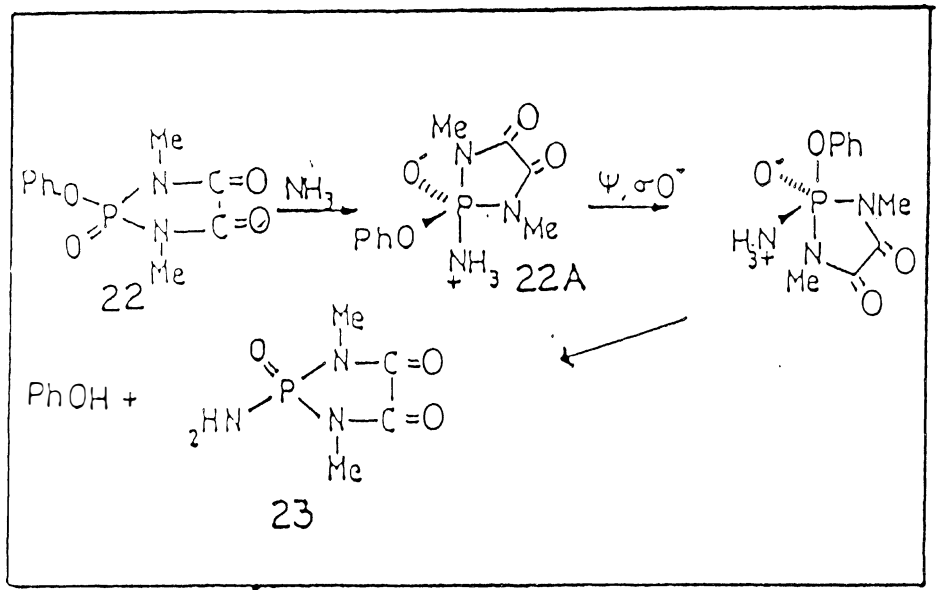
We decided to perform the aminolysis of **22** with ammonia, an amine that Mulliez had not tried. If ammonia (NH_3) behaved like all the other amines used by Mulliez[8] in the aminolysis of **22**, then compound **42** (scheme 19) was expected to be obtained.



SCHEME 19

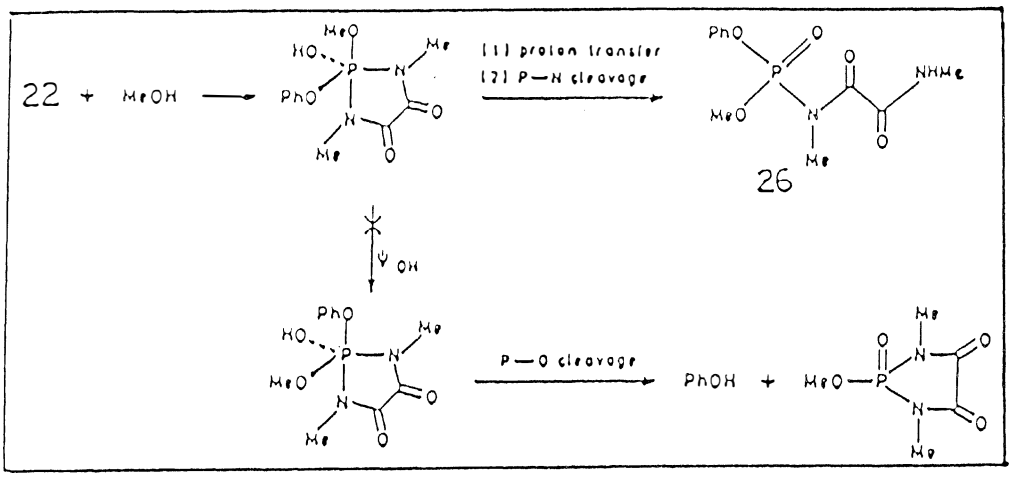
However, **42** was not obtained. Instead, the product which resulted from the reaction of **22** with NH_3 indicated that nucleophilic attack by NH_3 took place at the level of the phosphoryl centre, and not, as was expected, at the level of the carbonyl centre (see scheme 20). 2-amino-1,3-dimethyl-1,3,2-diazaphospholidine-2,4,5-trione (dimet, **23**) could only have been formed if the mechanism described in scheme 20 took place. That is, a P^V intermediate was formed following the nucleophilic attack of NH_3 onto the phosphoryl centre of **22**. This P^V intermediate then pseudorotated to place the phenoxy group in the apical position, from which it subsequently departed (see scheme 20). Dimet (**23**) was obtained in sufficiently high yields (91%) to exclude this mechanism as a side reaction (see chapter 3.6.4).

Dimet was unambiguously identified by ^1H NMR, which showed a signal at δ ($(CD_3)_2SO$) 2.88 (6H, d, J=9 Hz) for the two endocyclic NMe groups, and a signal at δ ($(CD_3)_2SO$) 7.70 (2H, br s) for the exocyclic NH_2 group.



SCHEME 20

These results contrast sharply with the aminolysis of 22 reported by Mullier[8]. It seems that the pseudorotation of 22A (scheme 20) is much faster than endocyclic bond cleavage, since only the displacement of the PhO group is observed. On the other hand, the methanolysis of 22 (see chapter 2.4.2) only yielded the ring opened product 26. This product 26 is the result of the addition-elimination mechanism of solvolysis, in which the endocyclic P-N bond cleavage is faster than pseudorotation (see scheme 21). In this sense, reactions of 22 with methanol (scheme 21) and with ammonia (scheme 20) represent the two extreme cases of nucleophilic displacement at the 1,3,2-diazaphospholidine system.

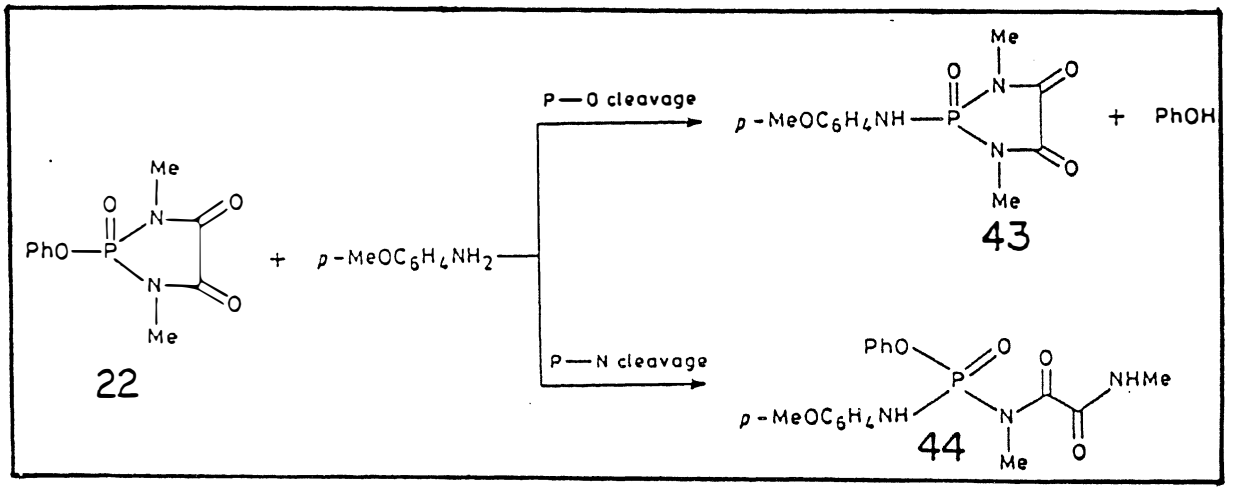


SCHEME 21

Many factors are involved in the selectivity of the acyl centre during nucleophilic attack. Mulliez's methanolysis studies were carried out with alkylamines, which are slightly stronger bases than NH_3 ($Kb=1.8x10^{-4}$). Thus, it seems that the basicity of the nucleophile might play an important role in the selectivity of the acyl centre during nucleophilic attack. Therefore, it was decided to investigate the aminolysis of **22** with other amines, such as p-anisidine ($Kb=15x10^{-10}$) which is a much weaker base than NH_3.

2.4.4 AMINOLYSIS OF PHENOXYDIMET WITH p-ANISIDINE AND BENZYLAMINE

The aminolysis of phenoxydimet (**22**) with p-anisidine (p-$MeOC_6H_4NH_2$) at room temperature proceeded with the displacement of the PhO group, resulting in the formation of 2-(p-anisidino)-1,3,2-dimethyl-1,3,2-diazaphospholidine-2,4,5-trione (anidimet, **43**) in high yield. The ring-opened product, **44**, was also isolated from the reaction mixture (scheme 22).



SCHEME 22

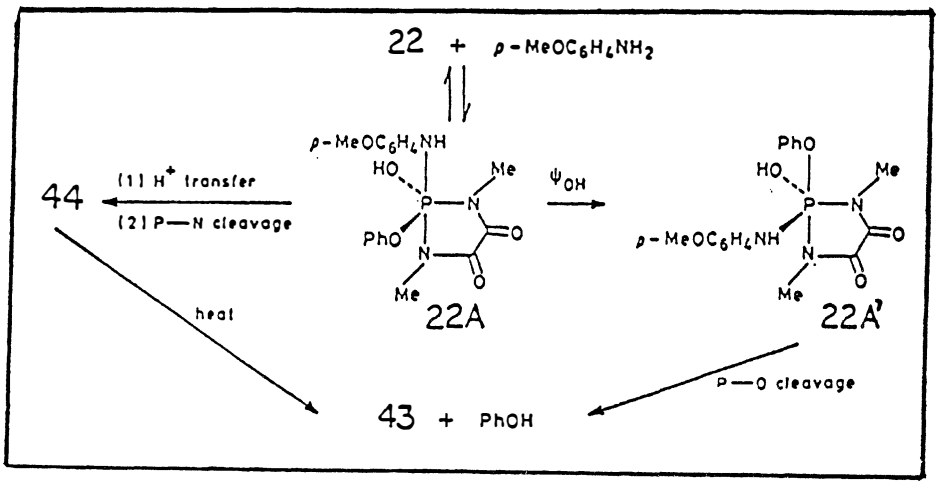
No products resulting from N-C bond cleavage of **22** were detected. The formation of **43** is accompanied by the release of phenol, which might have subsequently reacted with **43** to produce **44**. This possibility was tested and **43** was found to be unaffected by phenol over a long period. It was also found that under refluxing in THF **44** can be converted into **43**, presumably via intramolecular displacement of phenol by the NHMe group.

However, we do not believe that the ring closure, from **44** to **43** in scheme 22, can be responsible for the bulk of **43** formed in the reaction of **22** with anisidine. The product **43** separates from the THF-toluene solution of the substrates almost immediately after mixing, while the ring closure of **44** requires reflux for at least 0.5 hours.

The mechanism which takes place in this reaction involves nucleophilic attack onto the phosphoryl centre. The P^V intermediate formed (**22A**, scheme 23) as the result of the attack can either :

(1) pseudorotate and place the phenoxy group in the apical position (**22A'**, scheme 23), from which it can depart, forming product **43** or

(2) proton transfer might take place to the N-Me group of the ring in the apical position which will then be followed by P-N bond cleavage, to produce **44** (scheme 23).



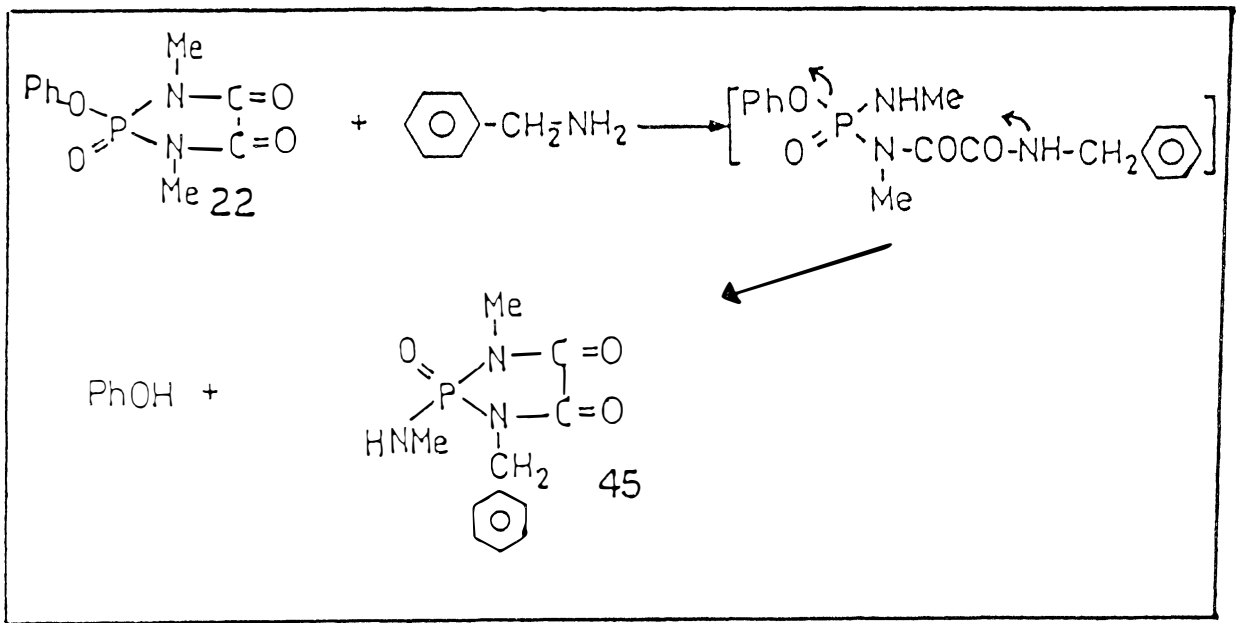
SCHEME 23

In the case of aminolysis with ammonia, we noticed that pseudorotation took place. With p-anisidine, products resulting from pseudorotation (**43**, schme 22) and from direct P(O)-N cleavage (**44**, scheme 22) were obtained. This indicates that NH_3 is less apicophilic in relation to the phenoxy group than p-anisidine.

The phenoxy group is apicophilic due to its electronegativity[12]. Also, it is a good leaving group. Therefore, pseudorotation will be favoured, in order to place this group in the apical position, provided that the attacking nucleophile is not too apicophilic. Pseudorotation of the P^V intermediate formed (**22A**, scheme 23) is therefore a direct result of the relative apicophilicity of the nucleophile in relation to the phenoxy group. These results seem to agree with the proposed hypothesis that weaker bases prefer nucleophilic addition-elimination reactions at the level of the phosphoryl centre.

However, basicity is only one of the factors which plays a role in the selectivity of the acyl centre. Mulliez[8] showed that the steric bulk of the attacking nucleophile also plays a role, as bulkier amines, such as t-butyl or dialkyl amines (Kb's in the range of 10^{-4}) were found to be unreactive towards phenoxydimet. Thus, This bulk factor may be the determinant factor in the selectivity of the acyl group during aminolysis of **22** with benzylamine.

Benzylamine has a basicity comparable to ammonia ($Kb=0.23x10^{-4}$). Therefore, benzylamine might be expected to favour the phosphoryl centre as the site for nucleophilic attack. Instead, we observed that benzylamine attacks at the level of the carbonyl centre, as Mulliez[8] had previously



SCHEME 24

These aminolysis results of **22**, combined with Mulliez's observations[8], allow us to draw two broad conclusions:

(1) The selectivity of the acyl centre depends on the nature of the nucleophile involved.

Two factors were found to play an important role :

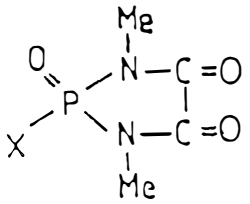
(I) the basicity and

(II) the steric effects of the attacking nucleophile.

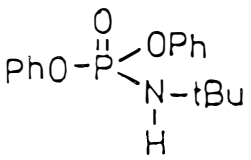
(2) The electrophilicities of both acyl centres are comparable, since both were found to be involved in nucleophilic addition-elimination ,

2.5 ACIDOLYSIS IN ANHYDROUS TFA

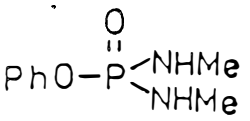
The acidolysis of compounds of type **S** was carried out in anhydrous TFA at 25°C. As a means of comparison, we have included the results of acidolysis in TFA for compound **K** and for compound **T**[28]. These results are summarised in table 7.



(S)



(T)



(K)

Table 7: Solvolysis in anhydrous TFA

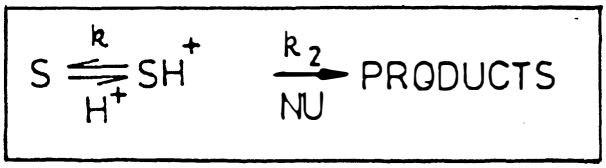
Group X	10^3xk (h^{-1}) (r)*		(°C)
(1) PhO- (22)	2321.00	(0.994)	25
(2) MeO-Ph-NH- (43)	2.77	(0.987)	25
(3) H_2N- (23)	5.00	(0.996)	25
(4) MeNH- (24)	24**		25
(5) Me_2N- (25)	0.05***		25
(6) T[28]	400		34
(7) K[28]	5.47****		25

Footnote:

1) The rate constants were obtained by monitoring the increase in size of the integral signal of N,N'-dimethyl oxadiamide, which forms a singlet at δ(CF3COOD) 2.9, and the decrease in size of the integral signal for the doublets of the N-Me (endo) groups of (1)-(5). 2)* (r) Is the linearity coefficient of the results obtained for the measurements of rate constants. 3)** The rate constant given for (4) was obtained from one reading at ca. 67% conversion, which involved cleavage of all three P-N bonds.

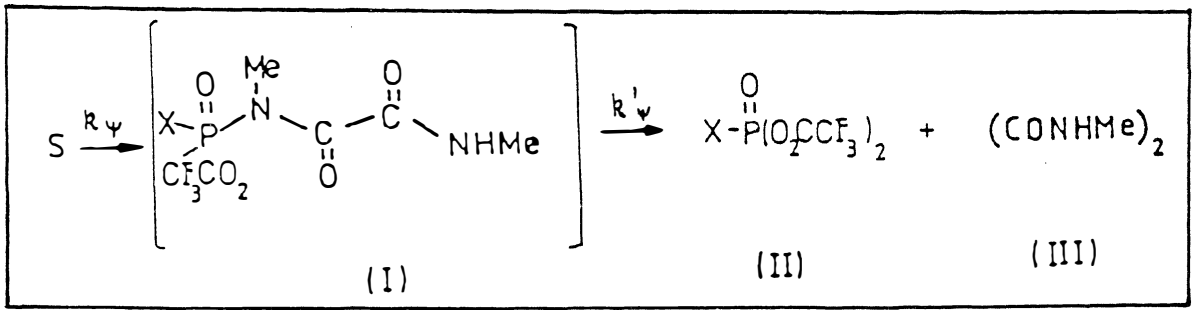
4)*** The rate constant given for (5) is a maximum value calculated on the assumption that less than 5% conversion could have taken place, as determined by ^1H NMR, since tetramet was completely unreactive in CF3COOD over a period of 92 days. 5)**** The rate constant given for (7) was obtained from one reading at ca. 56% conversion.

A general scheme for the solvolysis of compound **S** in acidic conditions is represented in scheme 25.



SCHEME 25

In all cases, the reaction involved the cleavage of both (endo) P-N bonds as evidence for the formation of **I** (scheme 26) was never found. There is therefore no accumulation of product **I** which implies that its decomposition by the cleavage of the second P-N (imide) bond is very fast (k'ψ) while its formation (kψ) by the cleavage of the first (endo) P-N bond is very slow (k'ψ>>kψ).



SCHEME 26

Three main observations may be deduced from these results :

(1) Even though compound **S** is a much stronger base than compound **I**, the phosphorus atom in **I** is more electrophilic than in S (due to the strong electron withdrawing group attached to it). Since k'ψ>>kψ we can say that the electrophilicity of the phosphorus atom is the most important factor in determining the reaction rate.

(2) The ratio of kψ (**22**)/kψ(**S**), where group X= MeO-Ph-NH-(2), H_2N- (3), MeNH- (4), is equal to ca. 260. This krel 260 is a measure of the effect of the PhO group (relative to the R_2N groups) in **S** on the electrophilicity of the phosphorus atom. These results support our proposals for the stability of cyclic compounds (**S**) where X=NMeH, NMe_2, NH_2. It was proposed that the relative unreactivity of trimet (**24**), tetramet (**25**) and dimet (**23**) in relation to methanol (when compared to the reactivity of phenoxydimet (**22**) in methanol) was due in part to the decrease in electrophilicity of the phosphorus atom. This decrease is caused by the extensive resonance effect which exists between the phosphoryl centre and the exocyclic amide (and imide) group. This resonance effect was substantiated by crystal structure determinations which yielded (exo) P-N bond length much shorter than would be expected.

(3) The ratio of kψ (**22**)/kψ(**T**) is greater than 7 despite the fact that **22** has only one electron withdrawing PhO group and two nitrogen atoms at the phosphorus centre, while (**T**) has two PhO groups and one nitrogen atom, which would cause **T** to have a more electrophilic phosphorus atom than **22**. This krel>7 can therefore be taken as a possible measure of the reactivity enhancement of **22** due to ring strain[12]. This is supported by the results obtained from the acidolysis of the compound **K** in TFA at 25°C. kψ(**22**)/kψ(**K**) is equal to ca. 420, which indicates that cyclic compound **22** is much less stable than the acyclic analogue **K**. This krel 420 is a measure of the release of ring strain brought about by the formation of a P^V intermediate involved during the nucleophilic attack of TFA^- onto the phosphoryl centre of **22**. This supports our proposal that the relatively high susceptibility of **22** to nucleophilic attack, when compared to that of our phosphoroamide diimides, was due to an increase in ring strain in **22** caused by a large N-P-N endocyclic angle.

As was mentioned earlier, we were not able to obtain suitable crystals of **22** but the determination of the crystal structures of both trimet (**24**) and tetramet (**25**) indicated that the endocyclic N-P-N angle was relatively small (92.3° for **24** and 91.9° for **25**). We proposed that the small N-P-N bond angle played a major role in reducing the usual energy release brought about by the formation of a trigonal bipyramidal intermediate, thereby reducing the reactivity of compounds **43**, **23**, **24** and **25** to nucleophilic attack.

We can therefore conclude that two main factors are responsible for the unusual unreactivity towards nucleophilic attack of cyclic phosphoroamide diimides **43**, **23**, **24** and **25** when compared to **22** :

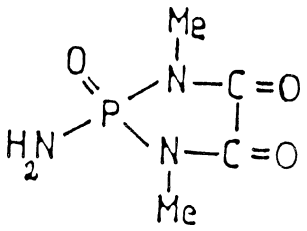
(1) **The lowered electrophilicity of the phosphorous atom due to extensive resonance occurring between the phosphoryl centre and the exocyclic amido group;**

(2) **The increase in stability of the cyclic compounds brought about by the low endocyclic N-P-N bond angle.**

2.6 THE REACTIONS OF THE AMINOLYSIS PRODUCTS OF PHENOXYDIMET

2.6.1 DIMET

2-Amino-1,3-dimethyl-1,3,2-diazaphospholidine-2,4,5-trione (dimet, **23**) was obtained as a product of aminolysis of phenoxydimet (**22**) with dimet.



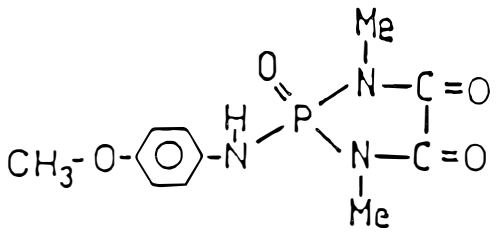
(23)

No hydrolysis in D2O of **23** was noticed after 190 hours at 25°C. It is indefinitely stable in methanol at room temperature, and no change was observed after 3 hours of refluxing in methanol. Its solvolytic behaviour is therefore very similar to **24** and **25** in that **23** exhibits the unexpected high unreactivity to nucleophilic attack.

However, these results indicate that within our series of phosphoroamide diimides, **23** seems to be less reactive than 24 and more reactive than **25**. This reflected in its acidolysis in TFA which yielded a $k= 5x10^{-3}\ h^{-1}$, while **24** had a $k= 24x10^{-3}\ h^{-1}$ and 25 had a $k< 0.05x10^{-3}\ h^{-1}$. We do not expect the structure of **23** to be very different to that of either **24** or **25**, and its N-P-N bond angle is probably very similar. An attempt was made at growing crystals, but was unsuccessful.

2.6.2 ANIDIMET

2-p-Anisidino-1,3-dimethyl-1,3,2-diazaphospholidine-2,4,5-trione (anidimet, **43**), was obtained as a product of the aminolysis of phenoxydimet with p-anisidine.



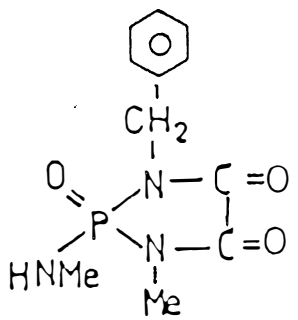
(43)

Both the hydrolysis and the methanolysis of **43** were not achieved after 60 hours at 25°C, as no sign of any P-N bond cleavage was observed. Its solvolytic behaviour is therefore comparable to that of **23**. This is reflected in its acidolysis in TFA. The acidolysis of **43** in TFA yielded a pseudo first order rate constant, k, equal to 2.77×10^{-3} h^{-1}, which is very close to that obtained for **23** (k= 5×10^{-3} h^{-1}).

2.6.3 BENZ-DIMET

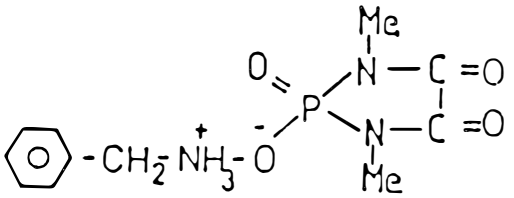
The aminolysis of 22 with benzylamine yielded two products:

A) 1-benzyl-3-methyl-2-methylamino-1,3,2-diazaphospholidine-2,4,5-trione (**45**):



(45)

B) Salt (46), which was very hygroscopic. Its acidolysis in TFA followed the same pathway as that described for the other compounds in our study, as the only product detected was N,N'-dimethyl oxadiamide, resulting from both endocyclic P-N bond cleavage. A rate constant of $k = 798 \times 10^{-3}\ h^{-1}$ was estimated from one ^1H NMR reading. This value is in the range expected for cyclic phosphordiamidates of the phenoxydimet type.

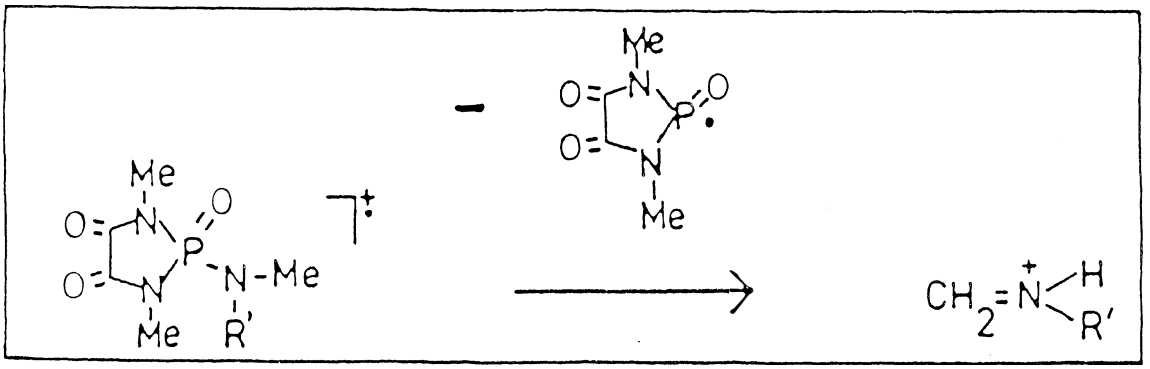


(46)

2.7 MASS SPECTROMETRY OF 2-AMINO-1,3-DIMETHYL-2-OXO-1,3,2-DIAZAPHOSPHOLIDINE-4,5-TRIONES

The relative reactivity of the three diazaphospholidine systems **23**, **24** and **25** was also studied by comparing the behaviour of these substrates under conditions of electron-impact induced fragmentation. We were particularly interested in the relative importance of fragmentations involving the cleavage of the endocyclic and the exocyclic P-N bonds.

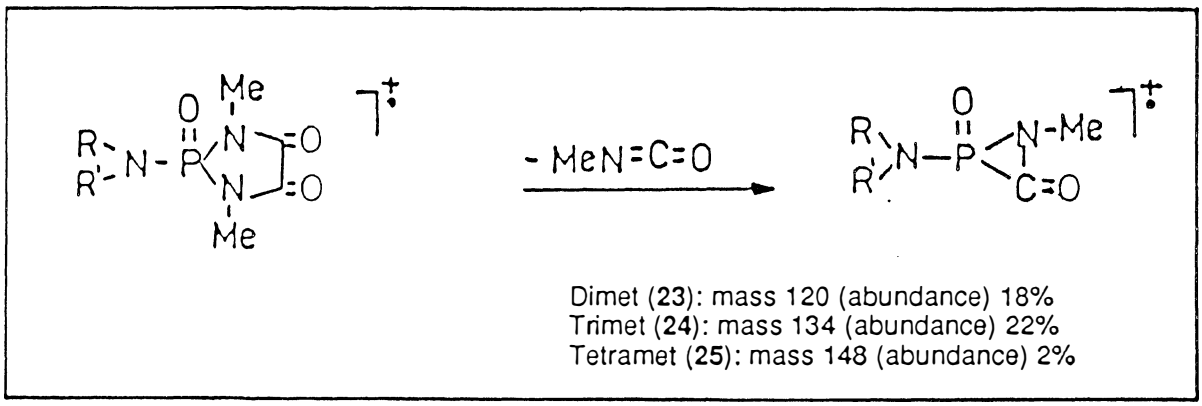
All three substrates form stable molecular ions with the relative abundance of 80% (for **23**), 97% (for **24**) and 30% (for **25**). The general fragmentation pattern for the compounds studied is summarized in scheme 28. It can be seen (scheme 29) that the substrates differ greatly with respect to the initial fragmentation of the molecular ion. Exocyclic P-N bond cleavage is the major pathway for the mono- and the dimethylamino derivatives (**24** and **25**, figures 15 and 16). This cleavage involves expulsion of the common phosphoryl radical and the formation (via proton migration) of the protonated iminium ion (as described in scheme 27).



SCHEME 27

Such a fragmentation is not available to **23**, and for this compound the major reaction involves ring contraction achieved by the expulsion of a CO molecule (figure 14). The same fragmentation is also important for **24** (figure 15) but almost negligible for **25** (figure 16). The loss of neutral CO is also a main feature of the N,N'-dimethyl oxadiamide mass spectrum (figure 17; abundance of the M^+-28 fragment = 20%). The loss of CO in **23** and **24** may indicate that the bonds in the ring of those compounds are more labile than those of **25**. This was observed in the solvolysis study, which showed that **25** was much more stable towards nucleophilic attack than **23** and **24**.

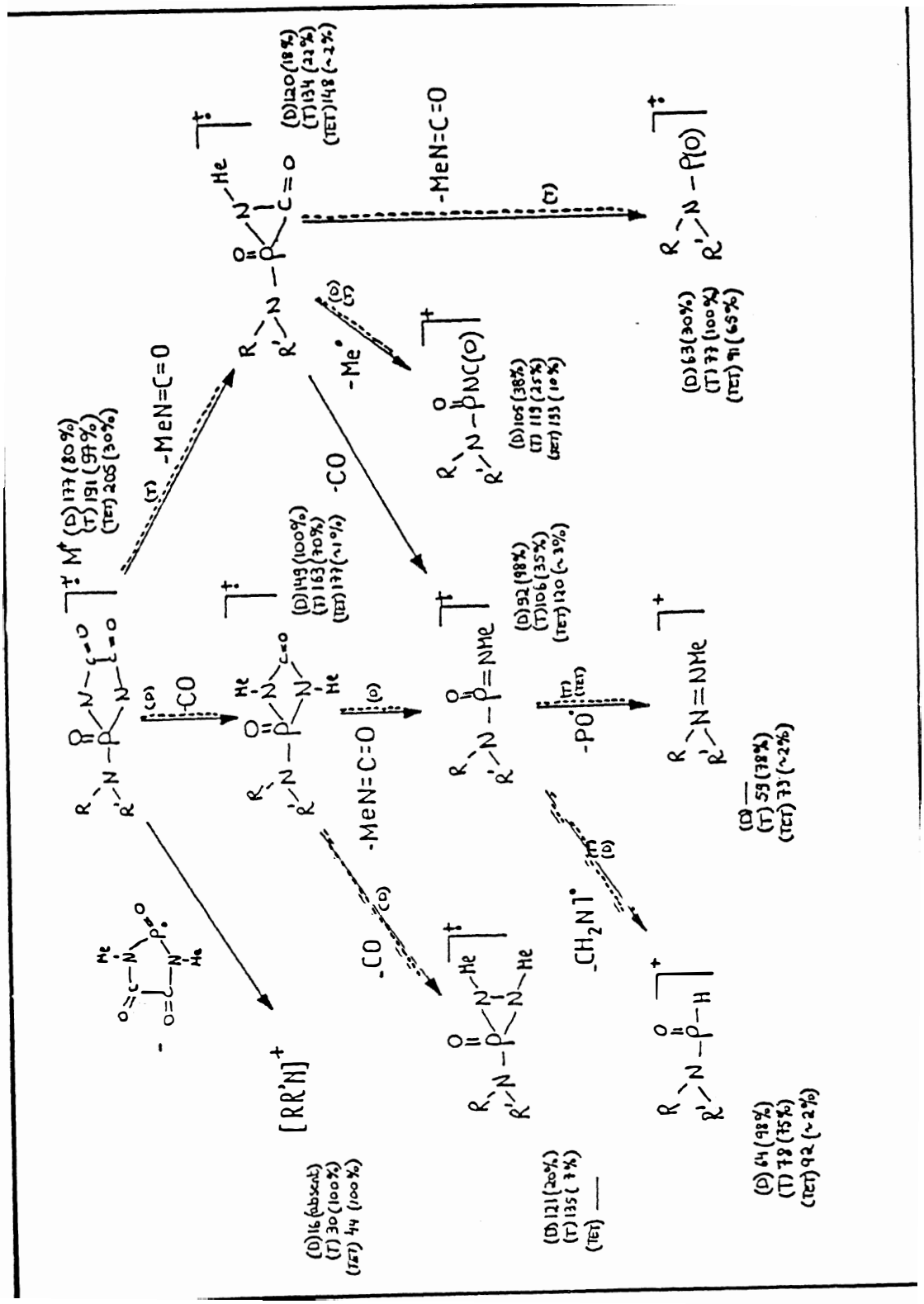
An interesting fragmentation of the molecular ions of all three substrates is the loss of N-methyl-carboimide involving significant ring contraction (scheme 28) :



SCHEME 28

The subsequent fragmentations of the primary products derived from the molecular ions proceed as expected. The most typical are presented in the general scheme 29.

Another important feature of this study was the high abundance of fragments containing an intact P-N exocyclic bond. This may indicate that this bond is more stable than the P-N endocyclic one, which preferentially cleaves. This interpretation is supported by the structural study, carried out on **24** and 25, which indicated that extensive resonance was taking place between the N(exocyclic) and the P atoms, thereby strengthening the P-N exocyclic bond.



SCHEME 29

(1) D = dimet; T = trimet; TET = tetramet.
(2) The fragments illustrated had their accurate masses determined.
(3) The dotted line indicates that metastable peaks support this particular pathway. In ( ) next to it is the initial for the compound for which the metastable was obtained.
(4) The relative abundances in % of each of the fragment ion is indicated in ( ) next to its mass.

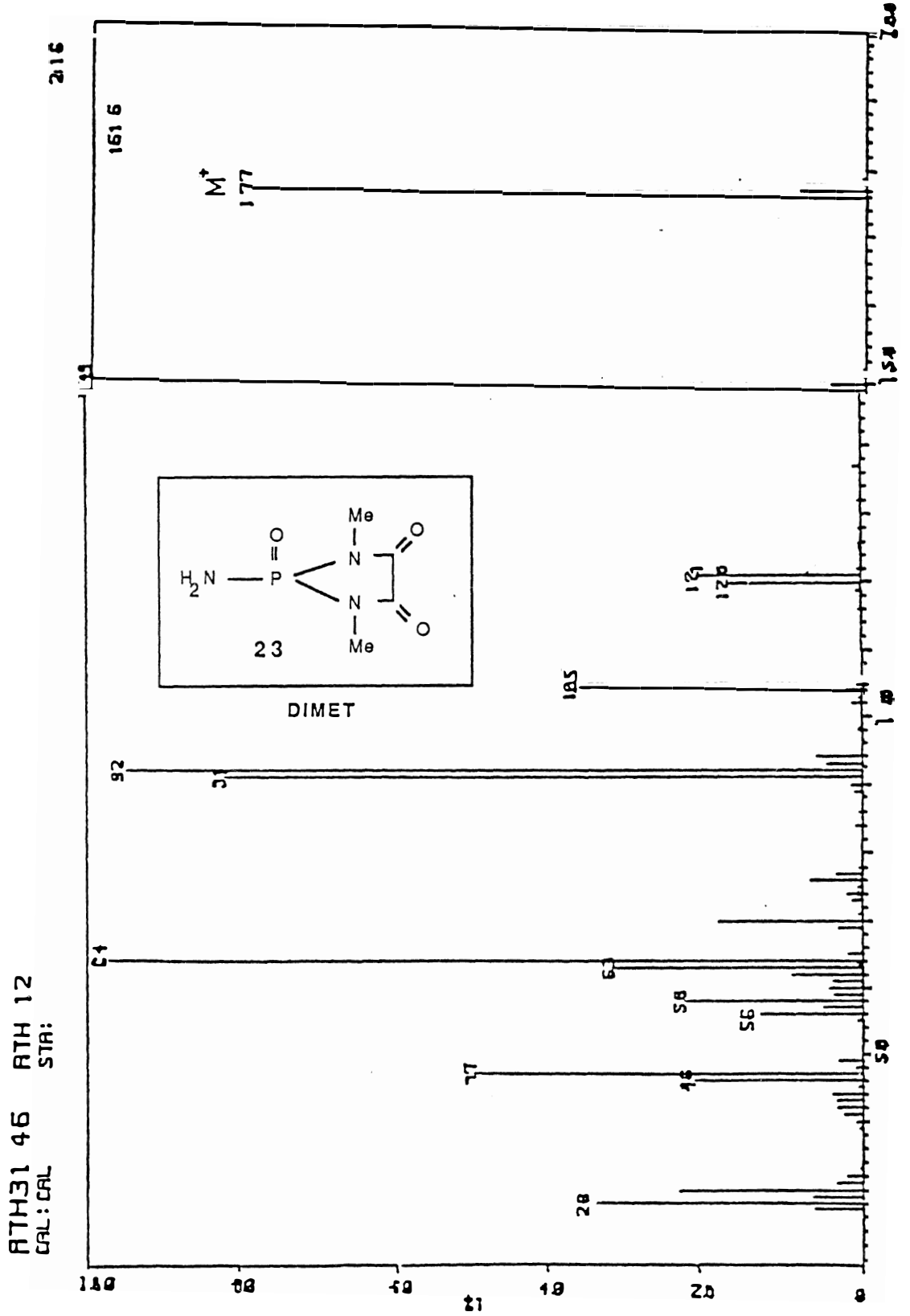


FIGURE 14 : Mass spectrum of dimet (23)

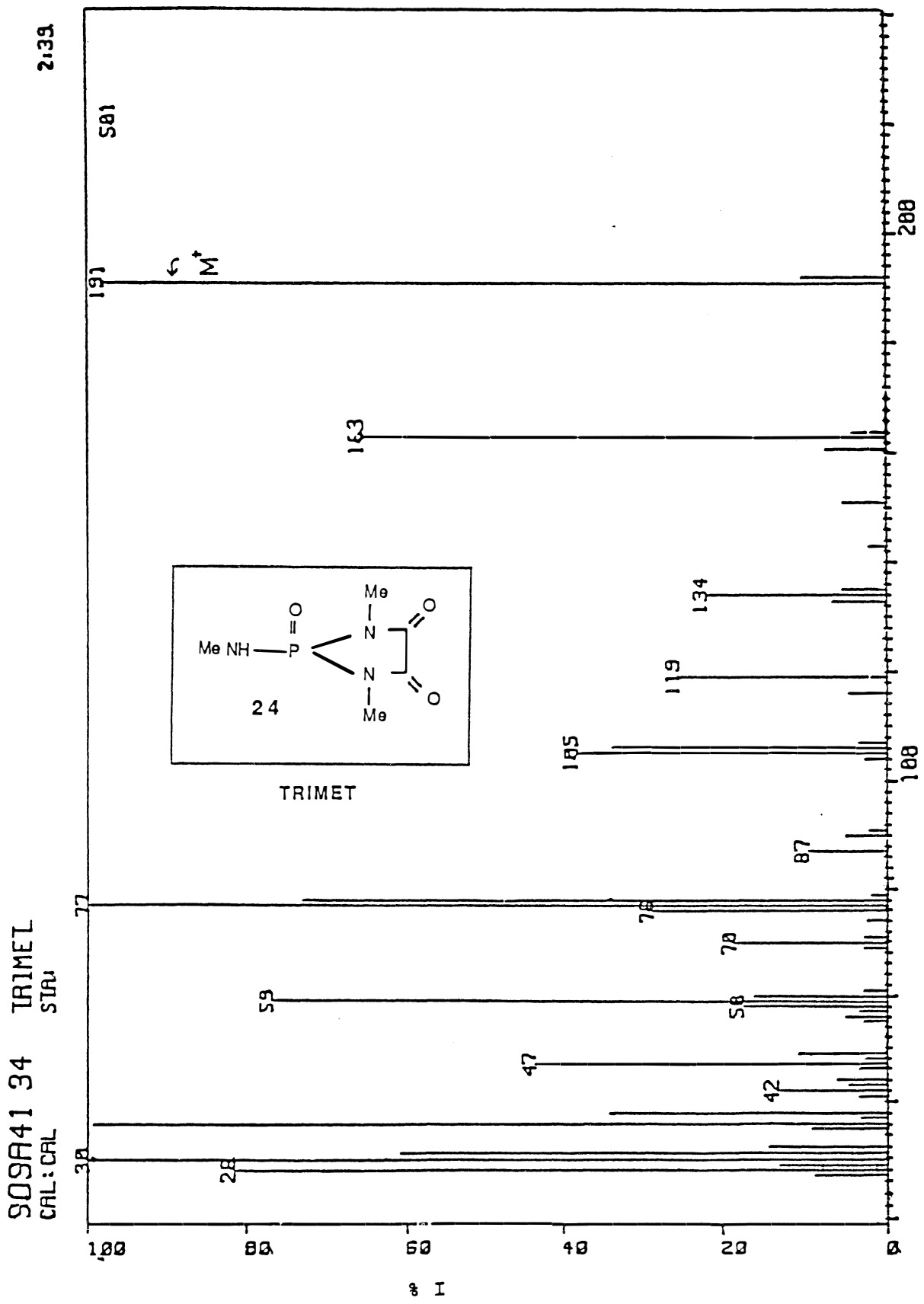


FIGURE 15 : Mass spectrum of trimet (24)

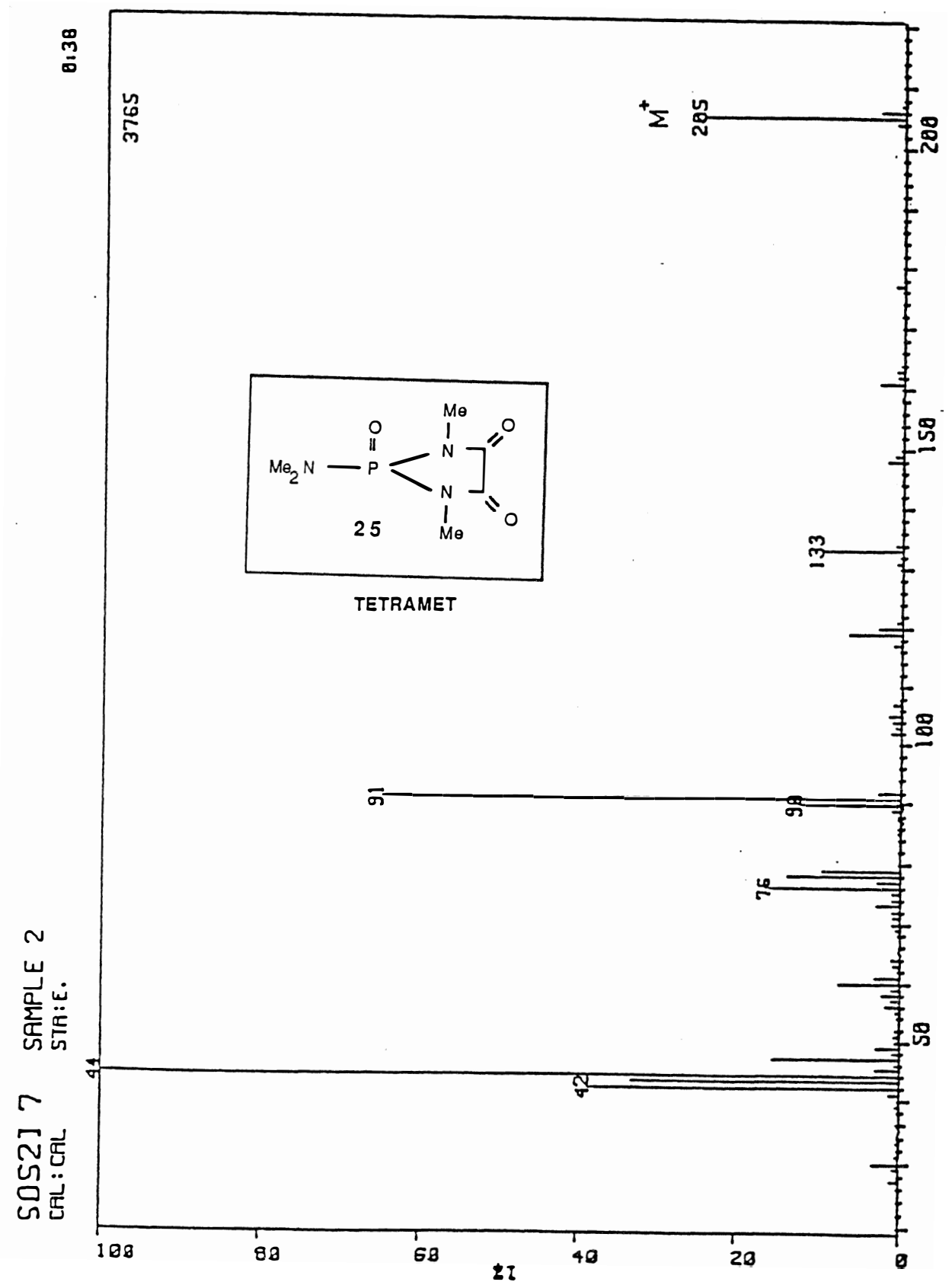


FIGURE 16 : Mass spectrum of tetramet (25)

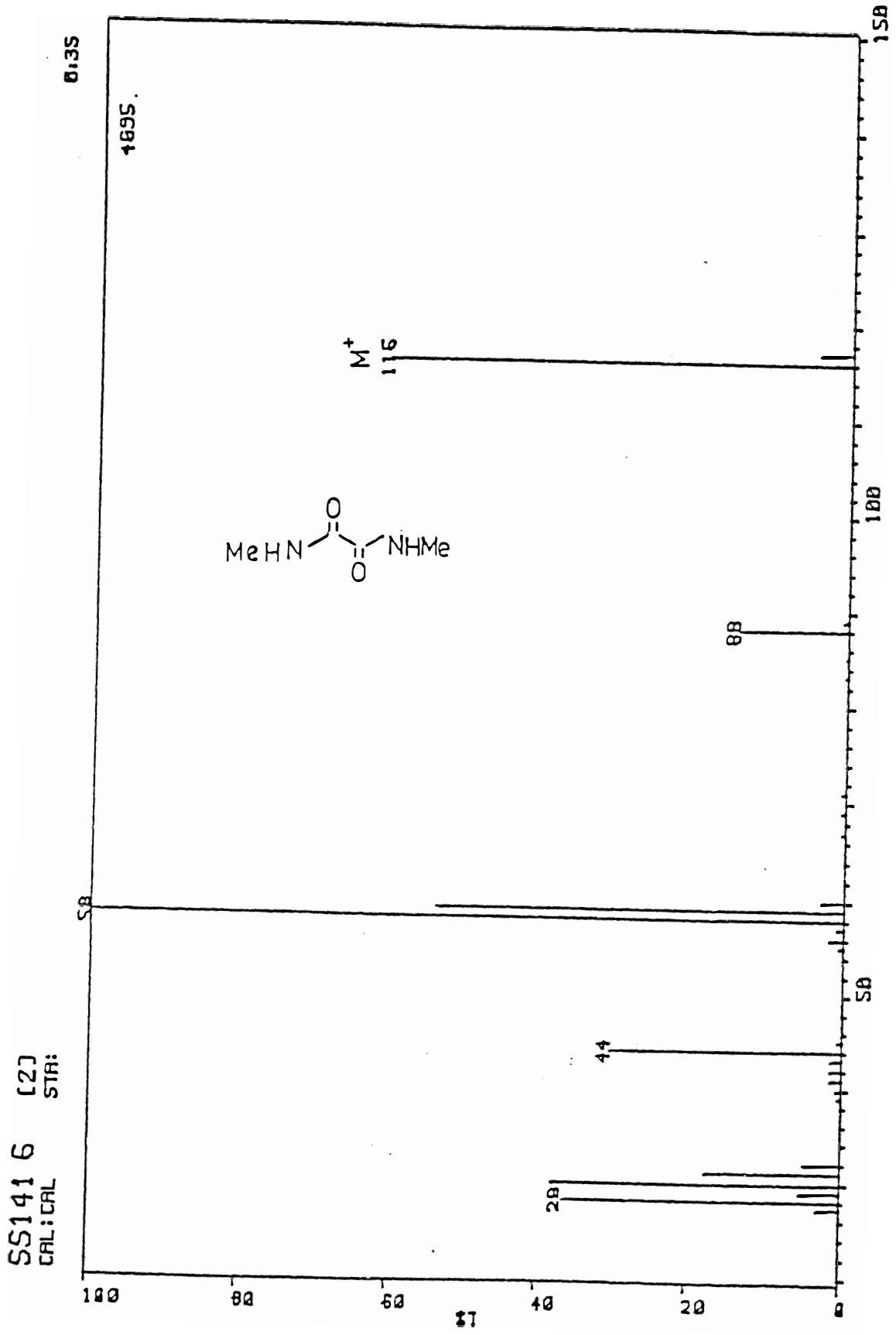


FIGURE 17 : Mass spectrum of N,N' - dimethyl oxadiamide

2.8 CONCLUSION

The 1,2,3-trisubstituted derivatives of 1,3,2-diazaphospholidine-2,4,5-trione represent a versatile system which can undergo nucleophilic cleavage according to different mechanistic patterns. Nucleophilic attack can take place at either one of the two acyl centres (phosphoryl and carbonyl), depending on the nature of the nucleophile. Furthermore, substitution at phosphorus can occur with either ring-opening P-N bond cleavage or with expulsion of the exocyclic substituent, depending on the nature of the exocyclic substituent. The crystal structures of **24** and **25** yielded very similar structures and the low reactivity of these compounds towards solvolysis can partially be explained by their low endocyclic N-P-N angle. The reduced electrophilicity of the phosphorus atom in the 2-amino (**23**), 2-methylamino (**24**), 2-dimethylamino (**25**) and 2-p-anisidino (**43**) derivatives also plays a role in the stability of these compounds towards solvolysis.

CHAPTER III

EXPERIMENTAL

3.1 GENERAL

When benzene and toluene were used as reaction media, they were distilled over metallic sodium and stored over sodium wire. Diethyl ether was distilled as required and stored over molecular sieves (4Å). Other solvents were purified in the conventional manner.

The gases used were rigorously dried by first passing them through cotton wool and then over KOH pellets before entering the reaction mixture.

Aluminium-backed silica gel plates (Merck, Kieselgel-60F_{254}, Art. 554) were used for thin layer chromatography (TLC).

The ^{1}H NMR spectra were recorded on a 60 MHZ Varian EM360 and 100 MHZ Varian XL100 spectrometer with tetramethyl silane (TMS) as internal reference.

Mass spectra were recorded on a VG Micromass 16F spectrometer operating on an ion source temperature of 200°C. GC/MS was carried out using a Carlo Erba gas chromatograph coupled to the mass spec. The separation was achieved using a 2m long column containing 3% OV101 on chromosorb W/HP (100/120 mesh).

Melting points were recorded on a Fisher-Johns m.p.apparatus. Solvents were removed under reduced pressure using a Buchi rotary evaporator, equipped with a Kotterman water bath.

All precautions were taken to ensure complete anhydrous conditions in all reactions.

All analyses for C, H and N were carried out at the University of Cape Town by Mr. W.R.T. Hemsted.

3.2. PREPARATION OF SUBSTRATES

1. N, N', N'' - TRIMETHYL PHOSPHORIC TRIAMIDE[18] $P(O)(NHMe)_3$

$P(O)Cl_3 + 6\ MeNH_2 \rightarrow P(O)(NHMe)_3 + 3\ MeNH_3^+\ Cl^-$

Dried methylamine gas was bubbled from a 40% aqueous solution into 150cm^3 of chloroform, placed in an acetone dry ice bath (temperature = -65°C to -70°C).

Once the solution was saturated, phosphoric oxychloride (100mmd) was added, slowly dropwise, as the reaction was highly exothermic. The resulting mixture was allowed to stir for 0.5h before the reaction flask was removed from the acetone dry ice bath, and allowed to equilibrate to room temperature.

The white precipitate of methylammonium chloride was removed by filtration. The solvent was then removed under reduced pressure. Once the solvent was removed, N, N', N" - trimethyl phosphoric triamide was isolated.

N, N', N" - trimethyl phosphoric triamide was then recrystallized from hot benzene. Hygroscopic white crystals were obtained.

Yield : 94%

M.Pt : 94°C - 96°C [lit.,[18] 102°C -104°C]

^1H NMR : δ ($CDCl_3$) 2.60 (9 H, d, J1 2 Hz ,3 NCH_3)

3.43 (3H, brs, 3 NH)

Analysis calculated for $C_3H_{12}N_3\ O\ P$: C,26.30 ; H 8.76 ; N,30.60%

Found: C,25.80 ; H,8.60 ; N,29.30%

2. PHENYL - N, N' - DIMETHYL PHOSPHORODIAMIDATE[8]

$PhOP(O)Cl_2 + 4\ MeNH_2 \rightarrow PhOP(O)(NHMe)_2 + 2\ MeNH_3^+Cl^-$

Phenyl-dichloro-phosphate (20 mmol) was dissolved in 150cm^3 dry tetrahydrofuran (THF). The reaction flask was then immersed in a $CHCl_3$/ dry ice bath (temperature ca.-54°C). The mixture was then stirred. Dried methylamine gas was bubbled from a 40% aqueous solution into the stirring mixture until the mixture was saturated. The reaction mixture was then allowed to equilibrate to room temperature. The white precipitate of methylammonium chloride, which had formed almost immediately, was removed by filtration.

Phenyl- N, N'- dimethylphosphorodiamidate was isolated once the THF solution was evaporated to dryness. The product may be recrystallized from hot toluene.

Some product was trapped in the salt and was recovered by dissolving the salt in a minimum volume of water and then adding $CHCl_3$ to extract the product.

Yield : 84%

M.pt : 102°C - 104°C [lit.[8] 103°C - 104°C]

^1H NMR : δ ($CDCl_3$) 2.71 (6H, d, J13Hz, 2 NCH_3)
3.06 (2 H, br s, 2 NH)
7.3 (5 H, s, Ph)

Analysis caculated for $C_8H_{13}N_2O_2P$: C, 48.00 ; H, 6.50 ; N, 14.00%

Found : C, 47.50 ; H, 6.30 ; N, 13.90%

MS : m/e 200 (M^+).

3. N, N - DIMETHYL PHOSPHOROAMIDODICHLORIDATE. $^{19}(NMe_2)\ P(O)Cl_2$

$P(O)Cl_3 + 2\ Me_2NH \rightarrow (NMe_2)\ P(O)Cl_2 + Me_2NH_2^+Cl^-$

A round bottom flask, containing 240 ml of ether was weighed. Dried Me_2NH gas was generated from an aqueous solution and bubbled into the ether, with cooling in a dry ice/MeOH bath. After 45 minutes, the bubbling was stopped and the flask reweighed. 65g (1.44 mol) of Me_2NH gas was found to have dissolved. A stoichiometric amount (1:2) of $P(O)Cl_3$(0.72 mol) was dissolved in 240 ml of ether, and the mixture was added dropwise to the amine solution over 4 hours.

After stirring overnight, the white precipitate was filtered off and washed well with ether.

The ether was evaporated under reduced pressure and the product was distilled on the high vac.

Yield : 87%

B.pt. : 29°C/0.1 mm Hg

^1H NMR : δ ($CDCl_3$) 2.92 (d, J 16Hz, NMe_2)

Analysis calculated for $C_2H_6Cl_2NOP$: C, 14.8; H,3.7 ; N, 8.6%

Found : C, 14.80 ; H,3.75 ; N, 8.60%.

3. N, N - DIMETHYL PHOSPHOROAMIDODICHLORIDATE. $^{19}(NMe_2)\ P(O)Cl_2$

$P(O)Cl_3 + 2\ Me_2NH \rightarrow (NMe_2)\ P(O)Cl_2 + Me_2NH_2^+Cl^-$

A round bottom flask, containing 240 ml of ether was weighed. Dried Me_2NH gas was generated from an aqueous solution and bubbled into the ether, with cooling in a dry ice/MeOH bath. After 45 minutes, the bubbling was stopped and the flask reweighed. 65g (1.44 mol) of Me_2NH gas was found to have dissolved. A stoichiometric amount (1:2) of $P(O)Cl_3$(0.72 mol) was dissolved in 240 ml of ether, and the mixture was added dropwise to the amine solution over 4 hours.

After stirring overnight, the white precipitate was filtered off and washed well with ether.

The ether was evaporated under reduced pressure and the product was distilled on the high vac.

Yield : 87%

B.pt. : 29°C/0.1 mm Hg

^1H NMR : δ ($CDCl_3$) 2.92 (d, J 16HZ, NMe_2)

Analysis calculated for $C_2H_6NOCl_2P$: C, 14.8; H,3.7 ; N, 8.6%

Found : C, 14.80 ; H,3.75 ; N, 8.60%.

4. N,N,N',N''-TETRAMETHYLPHOSPHOROTRIAMIDATE[13].$(Me_2N)P(O)(NHMe)_2$

$Me_2NP(O)Cl_2 + 4\ MeNH_2 \rightarrow Me_2N - P(O)(NHMe)_2 + MeNH_3^+Cl^-$

N, N - Dimethyl phosphoroamidodichloridate (20 mmol) was dissolved in 150cm^3 ether and the reaction flask was immersed in an acetone/dry ice bath.

Dried methylamine gas was bubbled into the stirring solution from a 33% ethanoic solution until the mixture was saturated.

The reaction mixture was then allowed to equilibrate to room temperature and the white precipitate of methylammonium chloride was removed by filtration. The ether solution was evaporated to dryness and a yelow oil was collected. This product was used without further purification.

Yield : 81%

^1H NMR : δ ($CDCl_3$) 2.7 (6 H, d, J 10Hz, $N(Me)_2$), 2.6 (8 H, m, 2 NHMe)

(D_2O) 2.5 (6 H, d, J 11.1Hz, 2 NDMe)

(D_2O) 2.6 (6 H, d, J 10Hz, $N(Me)_2$)

MS : m/e 151(M^+) $C_4H_{14}N_3OP$

5. PHENYL PHOSPHORODIAMIDATE. $PhOP(O)(NH_2)_2$

$$PhOP(O)Cl_2 + 4\ NH_3 \rightarrow PhOP(O)(NH_2)_2 + 2\ NH_3^+Cl^-$$

Phenyldichlorophosphate (200 mmol) was dissolved in $20cm^3$ 25% NH_3 aqueous solution, to allow for a large excess of NH_3. The mixture was stirred at room temperature, and a white precipitate was collected by filtration.

Yield : 12%

M.Pt. : 175 -180°C [lit., 185 -190°C]

Analysis calculated for $C_6H_9N_2O_2P$: C,41.86 ; H, 5.23 ; N,16.28%

Found : C, 41.9 ; H, 5.2 ; N,16.0%

3.3. PRELIMINARY WORK

1. Reaction of $P(O)(NHMe)_3$ with Glyoxal[7]

The reaction was carried out independently at pH 11 and at pH 8.0. In both cases, at 65°C. 1.07 gr of a 30% aqueous glyoxal solution (0.0055 moles) was placed in a 5 ml round bottom flask, and the pH of the solution was adjusted to 7 with 50% (NaOH solution. $P(O)(NHMe)_3$ (5.5 mmol) was then added to the glyoxal solution, and the mixture was left to stir for 5 minutes. The pH of the mixture changed to pH 11 when $P(O)(NHMe)_3$ was added. The second time the reaction was carried out, the pH was immediately adjusted to 8.5. The reaction mixture was then placed in ice for quenching and a yellow oil separated, which later solidified. The product, which was soluble in $CHCl_3$ was analysed by TLC, ^1H NMR, elemental analysis and its melting point was measured.

M.Pt. : 185 -200°C [lit.,[7] 106 -115°C]

2. Reaction of $P(O)(NHMe)_3$ with glyoxal sodium bisulfite

An aqueous solution of 0,0055 moles $P(O)(NHMe)_3$ with 0.0055 moles of glyoxal sodium bisulfite was brought to reflux under neutral conditions for 20 min. The solution was then evaporated and the product analysed by ^1H NMR.

3. Reaction of $PhOP(O)(NHMe)_2$ with glyoxal

The reaction was carried out at 65°C and at pH 8.5 in a similar manner as reaction 1, but the reaction was left to stir for 20 minutes. No product separated out upon cooling. The solvent was then evaporated and the product obtained was analysed by TLC and by ^1H NMR.

4. Reaction of $P(O)(NHMe)_3$ with a ca.40% aqueous solution of methanal

0.01 moles of methanal in aqueous solution were mixed with 0.0073 moles of $P(O)(NHMe)_3$. The solution was adjusted to pH 7 with a 20% NaOH solution and the solution was stirred at room temperature for 2 hours.

The reaction mixture was then refrigerated overnight. The solution was then evaporated and white crystals were obtained. These were analysed by ^1H NMR, mass spec and elemental analysis.

Analysis calculated for $C_9H_{24}N_6O_2P_2$. 2 H_2O : C, 31.21 ; H, 8.09 ; N, 24.27%

Found : C, 31.0 ; H.8.0 ; N, 24.9%

Mass spec : m/e 310(M^+)

3.4. SYNTHESIS AND REACTIONS OF TRIMET[8,24]

3.4.1. Synthesis of NHMeP(O)NMeCOCONMe

$1\ P(O)(NHMe)_3 + 1.1\ (ClCO)_2 + 2\ Et_3N \rightarrow trimet + 2\ Et_3NH^+Cl^-$

N, N', N" - trimethylphosphoric triamide (20 mmol) was dissolved in 150 cm^3 dry benzene with a Et_3N (44 mmol). The solution was brought to reflux and a solution of oxalyl chloride (22 mmol) in 10 cm^3 of benzene was added slowly, in a dropwise manner, to the refluxing solution. Each addition of oxalyl chloride provoked a vigorous exothermic reaction and HCl gas was seen to evolve almost instantly. Once all of the oxalyl chloride solution had been added, the reaction mixture was left to reflux for a further 3 hours. Triethylammonium chloride was filtered off and washed with hot benzene, and the combined benzene solutions were evaporated under reduced pressure. The crude 1,3-dimethyl-2-methylamino-1,3,2-diazaphospholidine-2,4,5-trione was recrystlallized from toluene-acetone (2:1).

Yield : 60%

Melting point : 205 - 207°C

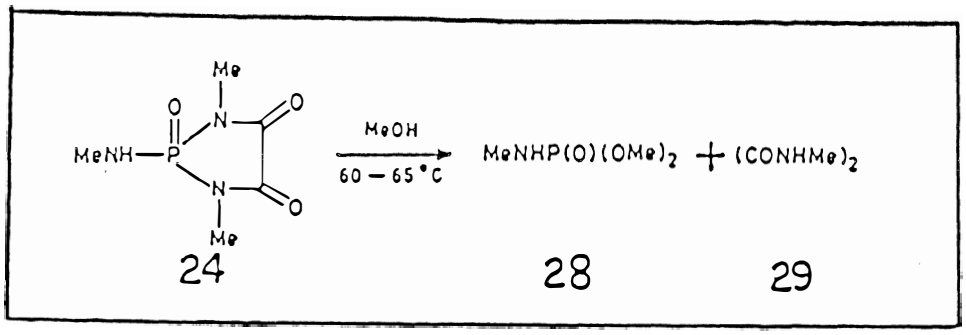
Mass spec. : m/e 191 (M^+)

^1H NMR $\delta(CDCl_3)$: 2.58 (3 H, d of d, J 14 and 5.5 Hz exocyclic NCH_3),
2.9 (1 H, br s, NH),
3.03 (6 H, d, J 9Hz, 2 endocyclic NCH_3).

Analysis calculated for $C_5H_{10}N_3O_3P$: C, 31.4 ; H,.5.3 ; N, 20.0 %

Found : C, 31.9 ; H, 5.5 ; N , 20.9 % .

3.4.2. Methanolysis of NHMeP(O)NMeCOCONMe



Trimet (20 mmol) was dissolved in 50 cm^3 of rigorously dry methanol and stored at room temperature. Samples were withdrawn and evaporated and the residues dissolved in $CDCl_3$; the ^1H NMR spectra were then recorded.

No change in the spectrum of trimet was observed after 1430h. When the same experiments were carried out in methanol under reflux, the ^1H NMR spectra of the reaction samples showed the presence of increasing amounts of products 28 and 29. There was no indication of the formation of any other products. Under reflux conditions, methanolysis was complete after ca. 30 min. After cooling, the crystalline product was filtered, washed with cold methanol and dried to give the oxamide 29.

Yield : 82%

Melting point : (sealed tube) 212° [lit.,[20] 217°C].

^1H NMR : δ ($CDCl_3$) 2.92 (6 H, d, J 5Hz, 2 NCH_3),

7.57 (2 H, brs, 2 NH).

Elemental analysis calculated for $C_4H_8N_2O_2$: C, 41.4 ; H, 6.9 ; N, 24.1 %

Found : C, 41.3 ; H ,6.9 ; N ,24.1 % .

The methanolic solution was evaporated under reduced pressure and the residual oil was purified by distillation to give the phosphoramidate **28**.

Phosphoramidate 28

Yield : 63 %

Boiling point : 95 - 96°C at 0.5 mmHg [lit.,[21] 81°C at 1 mmHg]

Mass. spec. : m/e 139 (M^+)

^{1}H NMR : δ ($CDCl_3$) 2.55 (3 H, dd, J 11 Hz and 5 Hz, NCH_3),
3.23 (1 H, brs, NH) and
3.68 (6 H, d, J 11 Hz, 2 OCH_3).

Elemental analysis calculated for $C_3H_{10}NO_3P$: C, 25.9 ; H, 7.2 ; N, 10.1 %

Found : C, 25.45 ; H, 7.5 ; N, 9,95 %

3.4.3. Acidolysis of NHMeP(O)NMeCOCONMe

A small sample of NHMeP(O)NMeCOCONMe was dissolved in deuterated trifluoracetic acid and stored at room temperature. ^{1}H NMR spectra were recorded at several intervals.

After 45 hours ca. 33 % of the substrate remained and ca. 67 % of the original substrate showed signs of complete solvolysis of all P-N bonds as a peak at δ 2.93 indicated the presence of N, N'-dimethyloxadiamide, integrating for 6 H in comparaison to a peak at δ 3.05 for $MeND_3^+$, integrating for 3 H.

3.4.4. Crystal structure of NHMeP(O)NMeCOCONMe

Accurate unit cell parameters and a set of X-ray data were obtained from a single crystal (0.20 x 0.20 x 0.33 mm) using a Philips PW 1100 fourcircle diffractometer and Mo-K_α radiation (0.7107 Å).

The intensities of three reference reflections were periodically monitored to ascertain crystal stability : data were corrected for Lorentz-polarization but not for absorption.

The structure was solved using a preliminary version of the direct method package of SHELX-84[22], which yielded all non-hydrogen atoms in an E-map. Refinement was carried out using SHELX-76[23]. The phosphorus atoms were treated anisotropically and all others isotropically. Methyl groups were treated as rigid, with a single temperature factor for all their hydrogen atoms. The amide hydrogen atoms were constrained at 1.00 (5) Å from their parent nitrogen atom, again with a unique temperature factor. In the final refinement, a weighting scheme $(\sigma^2 F)^{-1}$ was employed.

3.5. SYNTHESIS AND REACTIONS OF TETRAMET

3.5.1. Synthesis of $NMe_2P(O)NMeC(O)C(O)NMe$ (tetramet)

$N(Me)_2P(O)(NHMe)_2 + 1.1\ (ClC(O))_2 + 2.2\ Et_3N \rightarrow$ tetramet + 2 $Et_3NH^+Cl^-$

N, N, N', N" - tetramethylphosphorotriamidate (33mmol) and Et_3N (73 mmol) were dissolved in 150 cm^3 of dry benzene. The solution was stirred at room temperature, and a mixture of oxalyl chloride (36.3 mmol) in 10 cm^3 of benzene was added dropwise. Once all the oxalyl chloride had been added, the solution was brought to reflux, for 2h.

The white precipitate of triethylammonium chloride was filtered off and washed with benzene and the combined benzene solutions were evaporated under reduced pressure. The product obtained was contaminated with $Et_3NH^+Cl^-$ salt and was purified by extraction. The mixture was dissolved in $CHCl_3$ and the salt was extracted 3 times with H_2O. The $CHCl_3$ solution was then evaporated under reduced pressure and the crude 1,3-dimethyl-2-dimethylamino-1,3,2-diazaphospholidine-2,4,5-trione was recrystallized from hot benzene.

Yield : 81 %

Melting point : 75 - 80°C

Mass spec. : m/e 205 (M^+)

^1H NMR : δ ($CDCl_3$) 2.74 (6 H, d, J 11 Hz, NMe_2(exocyclic)),

2.94 (6 H, d, J 9 Hz, 2 NMe(endocyclic)).

Analysis calculated for $C_6H_{12}N_3O_3P$: C, 35.12 ; H, 5.85 ; N, 20.48 %

Found : C, 35.35 ; H, 5.65; N, 20.25 %.

3.5.2. Methanolysis of tetramet.

A. Methanolysis at room temperature, in tetradeuterated dry methanol :

A small sample of tetramet was dissolved in dry methanol (CD_3OD) and stored at room temperature. The ^1H NMR spectra were recorded at various intervals and no change in the spectrum of tetramet was observed after 90 days.

B. Methanolysis under reflux conditions, in undeuterated and deuterated methanol :

(i) A small sample of tetramet was dissolved in dry, deuterated methanol and the tube was placed in a 70°C water bath. The ^1H NMR spectra were recorded at various intervals over a period of 100 hours, after which time most of the substrate had reacted.

(ii) Tetramet (20 mmol) was dissolved in 50 cm^3 of rigorously dry methanol and brought to reflux. Samples were withdrawn and evaporated at various intervals and the residues dissolved in $CDCl_3$. The ^1H NMR spectra were then recorded.

After 30 hours, some change in the ^1H NMR was observed, although most of the substrate was still intact. After 96 hours, none of the original substrate was detected by the ^1H NMR and G.C/mass spec was then used to analyse the products.

The following MS data were obtained :

FRACTION 1 (**40**)

m/e 140 ; 110 ; 109 ; 80 ; 79

FRACTION 2 (**35**)

m/e 117 ; 89 ; 58

FRACTION 3 (**34**)

m/e 152 ; 122 ; 108 ; 44 ; 30

FRACTION 4 (**29**)

m/e 116 ; 88 ; 58 ; 44 ; 30

C. Base catalysed methanolysis:

Tetramet (20 mmol) was dissolved in 50 cm^3 of rigorously dry methanol, to which pyridine (22 mmol) was added. The solution was brought to reflux for a period of 6h. Samples were withdrawn and evaporated and then dissolved in $CDCl_3$. The ^1H NMR spectra were then recorded. No change in the spectrum of tetramet was observed after 6 hours of reflux in methanol with a slight excess (1:1.1) of pyridine.

3.5.3. Acidolysis of tetramet

A small sample of $NMe_2P(O)NMeCOCONMe$ was dissolved in deuterated trifluoroacetic acid and stored at room temperature. ^1H NMR spectra were recorded over a period of 92 days, during which no change was observed.

3.5.4. Crystal structure of tetramet

Accurate unit cell parameters and a set of x-ray data were obtained from a single crystal (dimensions : 0.09 x 0.28 x 0.31 mm) using a CAD 4 Diffractometer and Mo-K_α radiation (λ = 0.7107 Å). Crystal stability was monitored and the crystal decay involved was less than 1 %. Data was corrected for Lorentz- polarization but not for absorption. The structure was solved using the Patterson heavy atom method of SHELX-76[23] which yielded the position of the phosphorus atom. Subsequent difference maps, obtained using SHELX-76[23] enabled the location of all other non-hydrogen atoms. These were treated anisotropically. Methyl groups were treated as rigid, with a single temperature factor for all their hydrogen atoms. In the final refinement, all non-hydrogen atoms were treated anisotropically and a weighting scheme of $(\sigma^2F + 0.002F^2)^{-1}$ was employed.

3.6. SYNTHESIS AND REACTIONS OF PHENOXYDIMET[8]

3.6.1 Synthesis of phenoxydimet.

N, N'-dimethyl phenyl phosphate (7.5 mmol) was dissolved in 100 cm^3 of dry warm toluene and the mixture was brought to reflux. Oxalyl chloride (7.5 mmol) was mixed in 3 cm^3 of dry toluene and added dropwise to the stirring and refluxing mixture. Hydrogen chloride gas was released immediately and the mixture was left to reflux for 2 hours.

Upon cooling, the unreacted N, N'-dimethyl phenyl phosphate precipitated and was filtrated off. The solvent was removed under reduced pressure and the highly hygroscopic 1, 3-dimethyl-2-phenoxy-1, 3, 2-diazaphospholidine-2, 4, 5-trione (phenoxydimet) product was collected.

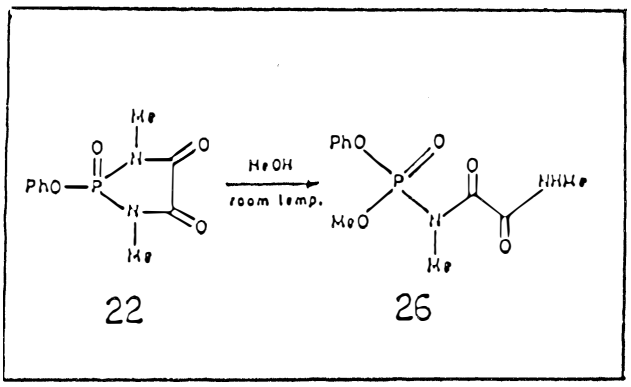
Yield : 87%

Melting point : 102 - 104°C [lit.,[8] 103°- 104°C]

^1H NMR: δ ($CDCl_3$) 3.20 (6 H, d, J 9 Hz, 2 NCH_3)

6.9 - 7.6 (5 H, m, Ph)

3.6.2. Methanolysis of phenoxydimet



22 26

A. Methanolysis was carried out in tetra-deuterated methanol, in a sealed NMR tube and followed by NMR by recording a spectrum every minute over a period of 30 minutes, after which time no more change in the ^1H NMR spectra was observed.

The reaction mixture was then left to stand for 24 hours at room temperature, after which time a ^1H NMR spectrum was recorded. This spectrum was identical to the one obtained after 30 minutes.

B. Phenoxydimet (2 mmol) was also dissolved at room temperature in 10 cm^3 of undeuterated methanol and left to stir for 30 minutes. The solution was then evaporated to dryness and a white crystalline compound was collected. This compound was identified as the ester **26**.

Melting point : 84 - 86°C [lit.,[8] 86 - 88°C]

^1H NMR: δ ($CDCl_3$) 2.89 (3 H, d, J 5 Hz, NHMe),
3.16 (3 H, d, J 8 Hz, NMeCO),
3.95 (3 H, d, J 12 Hz, OCH_3),
7.33 (5 H, br *s*, Ph).

C. A sample of the ester **26** (1mmol) was dissolved in 5 cm^3 of chloroform with an excess of dry methanol. The solution was immersed in a 70°C water bath and samples were withdrawn at various intervals over a period of 4 hours. These were evaporated to dryness, redissolved in $CDCl_3$ and their
^1H NMR spectra were then recorded. A sample of the solution was then submitted for G.C/mass spec for analysis. The following MS data were obtained :

FRACTION 1 (39)

m/e 94 (base peak) ; 66; 65; 39

FRACTION 2 AND 5 (**29**)

m/e 116 ; 88 ; 58 ; (base peak) ; 44,30

FRACTION 3 (**40**)

m/e 140 ; 110 (base peak) ;109 ; 80 ;79

FRACTION 4 (**38**)

m/e 202 ; 109 ; 94 ; 90 (base peak) ; 77 ; 65 ; 51;39

3.6.3. Acidolysis of phenoxydimet

A sample of phenoxydimet was dissolved in deuterated TFA and placed in an NMR tube, at room temperature. The reaction was monitored by ^1H NMR, by measuring the integration of the product formed (N, N'-dimethyl oxadiamide, singlet at δ(TFA) 2.9) versus the integration of the disappearing substrate doublet δ(TFA) 3.20, J = 9 HZ.

Ten spectra were collected over a period of 40 minutes, after which time 82 % conversion of the substrate was achieved. The reaction was treated as a first order reaction and a rate constant of k = 2.3218 h^{-1} (R = 0.994) was obtained.

3.6.4. Aminolysis of phenoxydimet with NH_3

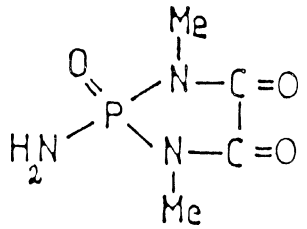
Two different techniques were used to carry out the aminolysis.

The first technique consisted of preparing a NH_3 solution in THF by bubbling dry NH_3 gas from a 40 % aqueous solution into dry THF at room temperature. The concentration of the NH_3 solution in the THF was determined to be 0.5 M by tritration of 1 cm^3 of the solution with 0.05 M HCl aqueous

solution, using Methyl Red indicator Phenoxydimet (20 mmol) was dissolved in 150 cm^3 of dry toluene and 60 cm^3 of the prepared NH_3 THF solution was then added (60 mmol NH_3) to the stirring mixture. Almost instantaneously, a white precipitate formed and the solution turned milky.

The reaction mixture was left to stir at room temperature overnight and the precipitate was collected by filtration (fraction 1). The product was analysed by ^1H NMR, microanalysis and mass spec. The toluene/THF filtrate was shown (TLC) to contain large amounts of phenol. The toluene/THF solution was then evaporated to dryness and the product, fraction 2, was analysed by ^1H NMR.

FRACTION 1



(23)

2-amino-1, 3-dimethyl-1, 3, 2-diazaphospholidine-2, 4, 5-trione (dimet).

Yield : 70 %

Melting point : 223 - 227°C

^1H NMR : δ [$(CD_3)_2SO$] 2.88 (6 H, d, J 9 Hz, 2 NCH_3),
3.43 (2 H, br s, NH_2).

Analysis calculated for $C_4H_8N_3O_3P$: C, 27.1 ; H, 4.6 ; N, 23.7 %

Found : C, 26.8 ; H, 4.8 ; N, 23.6%.

Mass spec.: m/e 177 (M^+)

FRACTION 2 (THF soluble)

i) phenoxydimet ; ii) phenol.

^{1}H NMR : i) δ ($CDCl_3$) 3.2 (d, J 9 Hz, NCH_3)

(ii) δ ($CDCl_3$) 7.0 - 7.5 (m,ph)

The second technique involved bubbling dry NH_3 gas at room temperature directly into a chloroform solution of phenoxydimet (20 mmol) for ca. 30 seconds. Then, the solution was left to stir at room temperature for 30 minutes. The white precipitate was filtered off and washed with chloroform and identified as fraction 1 described above.

Yield : 91%.

The filtrate was shown (TLC) to contain large quantities of phenol.

3.6.5. Reactions of dimet.

A. Methanolysis

Dimet (20 mmol) was dissolved in 50 cm^3 of rigorously dry methanol and stored at room temperature. Samples were withdrawn and evaporated and the residues dissolved in $CDCl_3$. The ^{1}H NMR spectra were then recorded. No change in the spectrum of dimet was observed after 720 hours. The same experiment was repeated for 3 hours under refluxing conditions, after which time still no change was observed in the ^{1}H NMR spectrum.

B. Hydrolysis

A solution of a small sample of dimet in D_2O was placed in an NMR tube. ^{1}H NMR spectra were recorded at various intervals over a period of 190 hours at 25°C. No change in the spectrum of dimet was observed.

C. Acidolysis

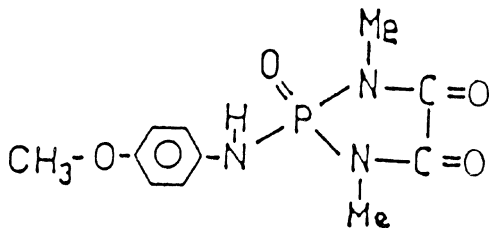
A sample of dimet was dissolved in deuterated TFA, placed in an NMR tube and stored at 25°C. The ^1H NMR spectra were recorded at various intervals over a period of 13 days after which time 74 % conversion of the original substrate was achieved. The ^1H NMR spectra were monitored by measuring the decrease in integration for the doublet at δ(TFA) 2.88 (J = 9 HZ) for the imido groups of dimet versus the increase in integration for the singlet growing at δ 2.9 for N, N'-dimethyl oxadiamide. The reaction was treated as a first order reaction and a rate constant of $k = 5 \times 10^{-3}\ h^{-1}$ was obtained (r = 0.996).

3.6.6. Aminolysis of phenoxydimet with p-anisidine.

P-anisidine was prepared by dissolving 5 gr of P-anisidinium chloride salt (31.3 mmol) in 20 cm^3 of H_2O. Aqueous NaOH ws then added, until pH = 14. Dry benzene was added to the mixture to extract p-anisidine. This was repeated 3 times, with 20 cm^3 of benzene each time. The benzene fraction was then dried with $MgSO_4$. Once the $MgSO_4$ had been filtrated out, the benzene solution was evaporated under reduced pressure and anisidine was collected.

Yield : 51 %

P-anisidine (7.5 mmol) was added dropwise at room temperature to a THF-toluene solution of an equimolar quantity of phenoxydimet with stirring and exclusion of moisture. The solution was left at room temperature and examined periodically by TLC (chloroform-acetone, 4 :1). After 24 hours, no substrate was detected and the crystalline product had precipitated. It was filtered off and recrystallized from acetone to give 2-p-anisidino-1, 3-dimethyl-1, 3, 2-diazaphospholidine- 2, 4, 5 trione (anidimet) :



(43)

Yield : 60 %

Melting point : 183 -185°C

^{1}H NMR : δ [$(CD_3)_2SO$] 2.80 (6 H, d, J 7 Hz, 2 NCH_3),

3.81 (3 H, s, OCH_3),

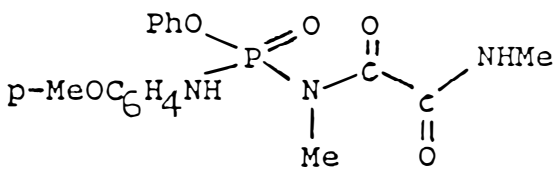
7.06 (2 H, d, J 9 Hz, 2 and 6-H),

7.32 (2H, d, J 9 Hz, 3 and 5-H).

Analysis calculated for $C_{11}H_{14}N_3O_5P.H_2O$: C, 43.8 ; H, 5.3 ; N, 13.9 %

Found : C, 43.3 ; H, 5.3 ; N, 13.8 %.

A TLC. plate of the filtrate showed the presence of two products, one of which was identified as phenol by comparison with an authentic sample. The second product precipitated out when the partially evaporated solution was left at room temperature for 60 hours to give N-[p-anisodino (phenoxy) phosphonoyl]-N, N'-dimethyl oxamide :



(44)

Yield : 18 %

Melting point : 129 -132°C

^{1}H NMR : δ [$(CD_3)_2SO$] 2.56 (3 H, d, J 5 Hz, amide NCH_3),

2.79 (3 H, d, J 7 Hz, imide NCH_3),

3.77 (3 H, s, OCH_3),

6.99 (2 H, d, J 9 Hz, 2- and 6-H),

7.10-7.40 (8 H, m , 3 and 5-H and Ph, and imide NH),

7.87 (1H, q, J 5 Hz, amide NH).

Analysis calculated for $C_{17}H_{20}N_3O_5P.H_2O$: C, 51.5 ; H, 5.6 ; N, 10.5 %

Found : C, 51.6 ; H, 5.6 ; N, 10.6 %.

When a sample of N-[p-anisodino(phenoxy)phosphonoyl]-N, N'-dimethyl oxamide was heated in THF under reflux for 30 minutes and left at room temperature overnight, the ring-closed product anidimet precipitated out.

Yield : 90 %

Melting point : 182 -184°C

Analysis Found : C, 43.7 ; H, 5.3 ; N, 13.5%

3.6.7. Reactions of anidimet

A. Methanolysis of anidimet

Anidimet was dissolved in deuterated methanol and placed in an NMR tube at room temperature. The tube was left to stand for 65 hours, after which time no change was noticed.

B. Reaction of anidimet with phenol

A sample of anidimet (0.5 mmol) was placed in 5 cm^3 $CHCl_3$ with an excess of phenol and left to stir at room temperature over a period of 120 hours. The solution was then evaporated to dryness and the residues dissolved in $CDCl_3$ for ^1H NMR analysis. No change in the spectrum of anidimet was observed.

C. Acidolysis of anidimet

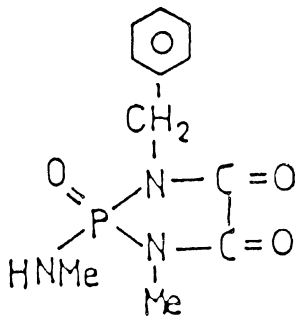
A sample of anidimet was dissolved in deuterated TFA, placed in an NMR tube and stored at 25°C. ^1H NMR spectra were recorded at various intervals over a period of 14 days, after which time complete conversion of the original substrate was obtained.

The ^1H NMR spectra were monitored by measuring the decrease in integration for the doublet at δ (TFA) 2.80 (J 7 HZ) for the imido groups of anidimet versus the increase integration for the singlet growing at δ 2.9 for N, N'-dimethyl oxadiamide.

The reaction was treated as a first order reaction and a rate constant of $k = 2.77 \times 10^{-3}$ ($r = 0.987$) was obtained.

3.6.8. Aminolysis of phenoxydimet with benzylamine[8]

A solution of benzylamine (20 mmol) in dry toluene was added to a solution of an equimolar amount (20 mmol) of phenoxydimet in toluene at room temperature and the mixture was stirred overnight. The precipitate was filtered off, washed with toluene and dried to give 1-benzyl-3-methyl-2-methylamino-1, 3, 2-diazaphospholidine-2, 4, 5-trione :



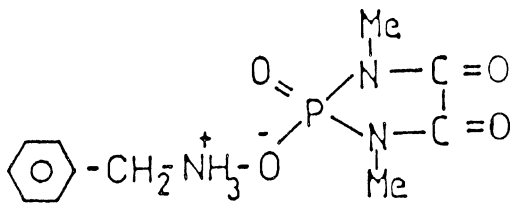
(45)

Yield : 30 %

Melting point : 120 -124°C [lit.,[8] 127 -130°C]

^{1}H NMR : δ [$(CD_3)_2SO$] 2.28 (3 H, dd, J 15 and 6 Hz, amide NCH_3),
2.93 (3 H, d, J 9 Hz, imide NCH_3),
4.67 (2 H, J 11.5 Hz, CH_2Ph), 5.83 (1H, m, NH),
7.50 (5H, s, Ph).

Upon standing, the filtrate yielded another precipitate. It was filtered off, washed with toluene and dried to give N-benzylammonium salt of 1, 3-dimethyl-2, 2-dioxo-1, 3, 2-diazaphospholidine-4, 5-dione :



(46)

Melting point : 187 -193°C

^{1}H NMR : δ [$(CD_3)_2SO$] 2.82 (6 H, d, J 8 Hz, imide NCH_3),

4.09 (2 H, br s, CH_2

7.5 (5 H, s, Ph).

A sample of the salt was used for acidolysis study. It was dissolved in deuterated trifluoacetic acid and placed in an NMR tube and stored at room temperature. 3 spectra were recorded over a period of 18 hours, at the end of which there was no more sign of the original product.

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