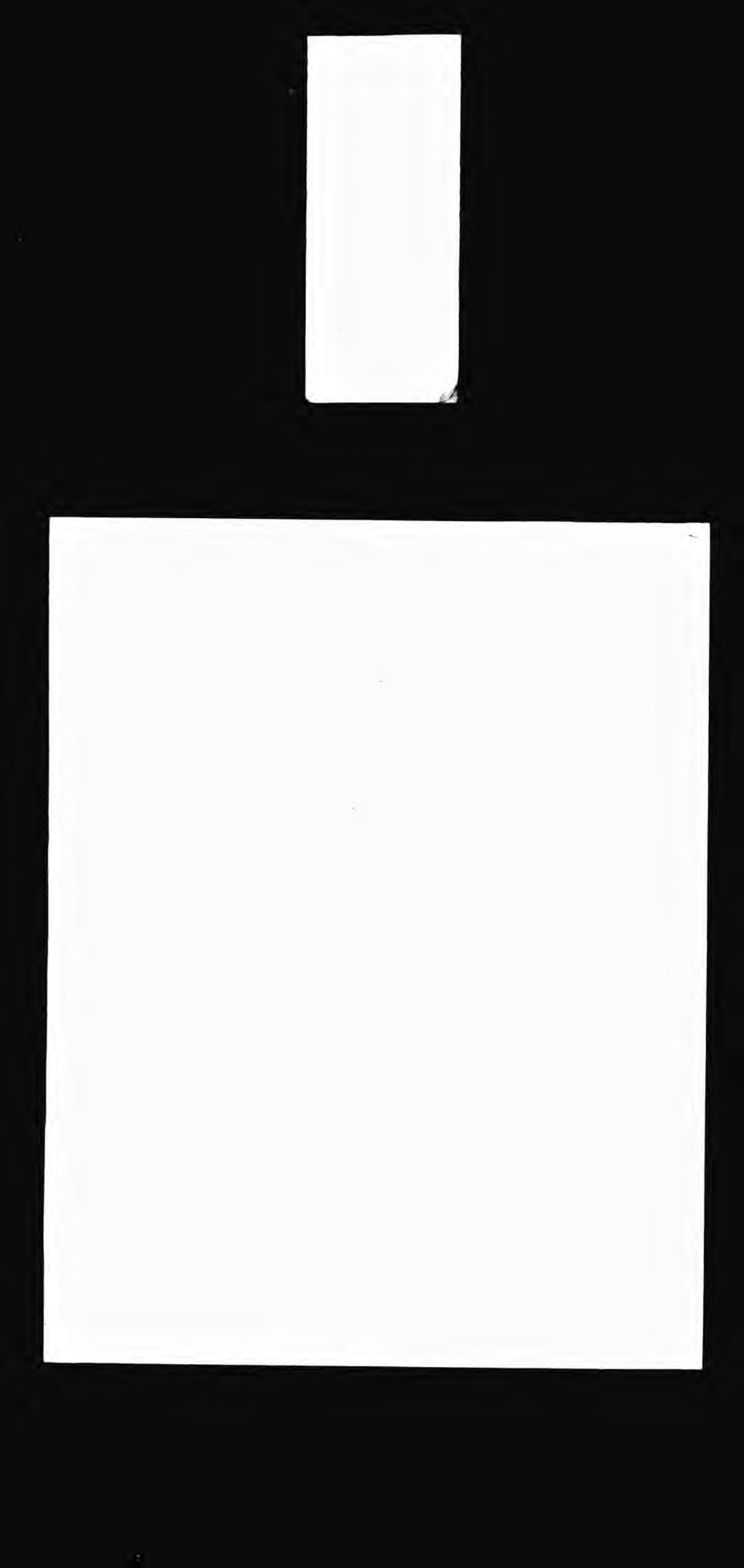

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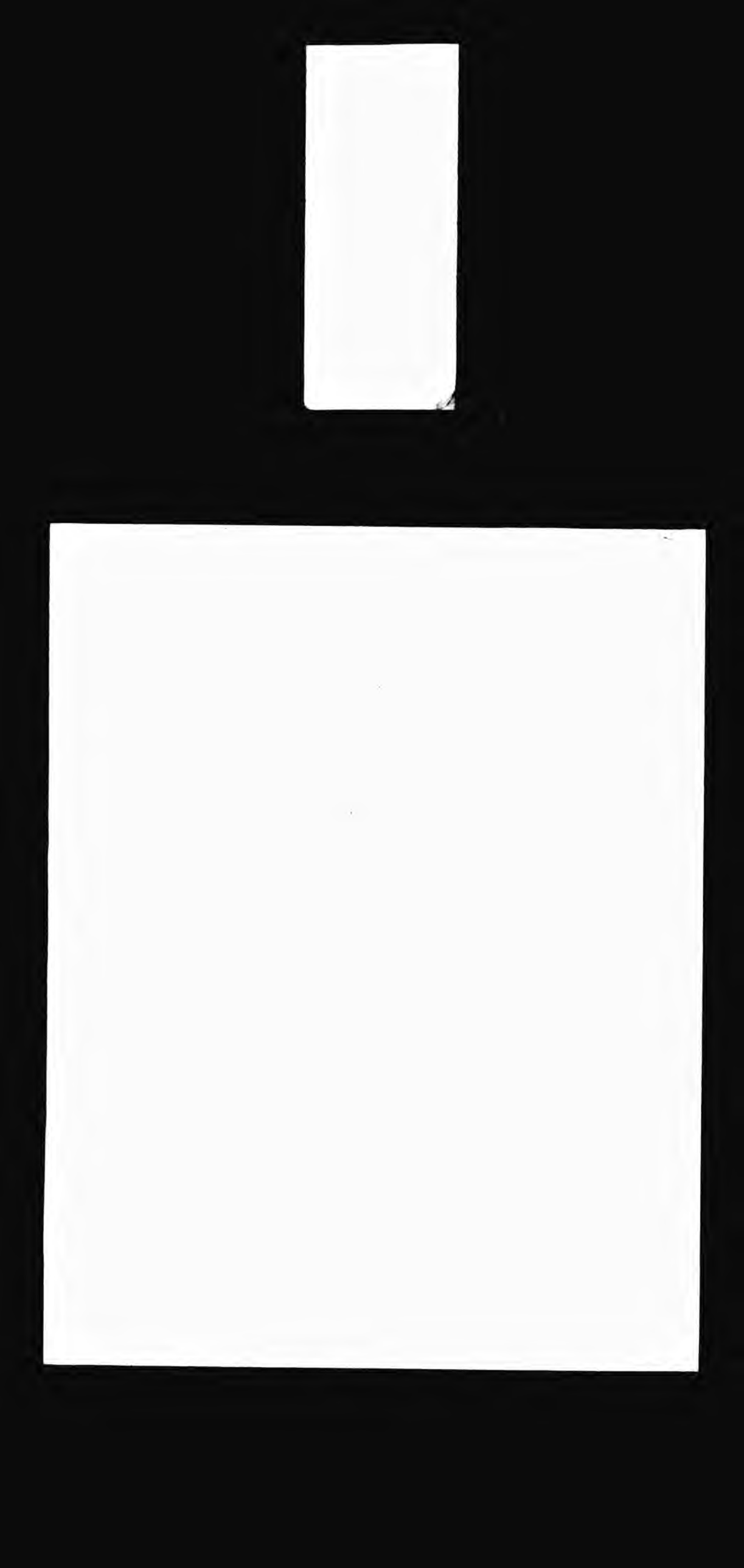

TITLE Synthesis and Biological Activities of α-aminoalkanephosphonic acids and α-aminoalkanephosphonous acids and their derivatives

AUTHOR Fatima Bawa

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The Polytechnic of North London in collaboration with Kenogard AB (Sweden)

Synthesis and Biological Activities of α-aminoalkanephosphonic acids and α-aminoalkanephosphonous acids and their derivatives

by

Fatima Bawa

A thesis submitted for the Degree of Doctor of Philosophy of the Council for National Academic Awards.

FOR MY CHILDREN

FAREED AND AYSHA

Synthesis and biological activities of α-aminoalkanephosphonic acids, α-aminoalkanephosphonous acids and their derivatives

F.BAWA

ABSTRACT

A study of preparation methods for α-aminoalkanephosphonic, α-aminoalkanephosphonous and α-aminoalkanephosphinic acids has been made, based on the combined use of an aldehyde, an amino compound, and a phosphorus reagent. Reported yields are frequently poor and the mechanisms of the reactions are unclear.

The synthesis of α-aminoalkanephosphonic acids has been systematically examined. Propanal was used as a model carbonyl compound in reaction with various combinations of the following:

1) $(PhO)_3P$, $(PhO)_2PH$, $(MeO)_3P$, $(EtO)_3P$, $(MeO)_2PHO$, $(EtO)_2PHO$, PCl_3, H_3PO_3.
2) H_2NCO_2Et, $H_2NCO_2CH_2Ph$, H_2NCH_2Ph, H_2NCHPh_2, H_2NCONH_2, $H_2NCONHPh$, NH_3.

The yields of various routes developed have ranged from 65% to 12%. The products have been fully characterised by melting point, elemental analysis, and nmr (^1H, ^{13}C, ^{31}P) spectroscopy.

Radiolabelled α-amino-1-[^{14}C]-propanephosphonic acid was prepared for toxicology studies. An interesting feature of this compound has been the formation of chemically identical. crystalline products whose melting points differ by 10 °C after repeated recrystallisation. The crystal structure of α-amino-1-[^{14}C]-propanephosphonic acid was determined in order to examine the possibility of different crystalline forms.

^{31}P nmr spectroscopy studies of "one-pot" syntheses of the α-aminopropanephosphonic acid have shown that low yields may be due to the formation of several phosphorus-containing by-products and not merely from the problems of isolation.

A range of α-aminoalkanephosphonous acids and their derivatives has been prepared and characterised by nmr (^1H, ^{13}C, ^{31}P) spectroscopy. These acids were also examined by FAB mass spectrometry and were found to give strong $[M+H]^+$ ions.

New derivatives of α-aminopropanephosphonic acid were prepared and characterised. Results of screening tests have been presented.

Preliminary tests against pathogenic fungi have shown that whereas the phosphonic acids are active the phosphonous analogues are inactive, indicating that *in vivo* oxidation does not occur.

DECLARATION

Whilst registered as a candidate for this degree I have not been registered as a candidate for any other award

In partial fulfilment of the requirements of the degree I have completed the M.Sc. lectures on Structural Methods. Additionally I have attended the 10th International Conference on Phosphorus Chemistry, Bonn (1986).

F.BAWA

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ABSTRACT

DECLARATION

ACKNOWLEDGMENTS

CHAPTER 5-BIOLOGICAL ACTIVITIES OF α–AMINOALKANE-PHOSPHONIC ACID DERIVATIVES AND α-AMINOALKANE-PHOSPHONOUS ACIDS AND THEIR DERIVATIVES

INTRODUCTION

A fungicide is an agent that kills or inhibits fungal spores or mycelia. Organic fungicides that were introduced before the mid-1960's were not systemic. These do not penetrate the plant cuticle and are not translocated within the plant. Consequently, such fungicides are effective as protectants but not highly effective in eradicating established infections. Application was by foliar spray, and since the protectant fungicides are not translocated in the plant complete coverage was necessary for protection. Furthermore, spraying had to be repeated to prevent new growth from becoming infected.

The presystemic fungicides usually interfere with energy-producing processes and so are strong inhibitors of cell respiration. In contrast, fungicides that are systemic in their action are absorbed by the plants and then are translocated within them. The essential features of a systemic fungicide are:

1) it should be either fungicidal, or be converted into an active fungitoxicant within the host plant;

2) it should be capable of being absorbed by the roots, seeds, or leaves of the plant, and then be translocated within the host plant;

3) it should have low phytotoxicity since the chemical is in close contact with the host plant.

Systemic fungicides interfere with biosynthetic processes and. generally exhibit a narrow and specific structure-activity relationship.

The development of purely organic fungicides with protectant

action began in 1934 with the discovery of fungicidal activity of dithiocarbamates and their derivatives.

Thiram or tetramethylthiuram disulphide was the first purely organic compound to be applied as a protectant broad-spectrum fungicide.[1] It is still used as a seed dressing against soil fungi causing damping off diseases.

Since then important advances have been made towards achieving greater selectivity of fungicidal action. This may depend upon differences between the cell structure of plants and of the fungi and their biochemistry.

In 1951, Kittleson[2,3] discovered that certain compounds containing the N-trichloromethylthio group exhibit powerful fungicidal activity on the surface of the substrate. Thus, N-(trichloromethylthio)-4-cyclohexene-1,2-dicarboximide (captan) is an effective and persistent fungicide, and was mainly used as a foliar spray. However, recent toxicological data based on administration of ^{35}S-labelled captan to mice have been published,[4] which suggest that captan may be a potent carcinogen.

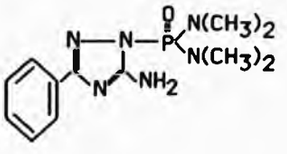
Although the past fifty years have seen rapid progress in the development of protectant fungicides, the search has continued for compounds with properties to offset some of the disadvantages of protectant fungicides.

Since Fleming's discovery of penicillin in 1929,[5] there has been much activity in the search for antibiotics to control plant diseases. Several antibiotics such as chloramphenicol, griseofulvin, cycloheximide, and streptomycin, are known to possess systemic activity. However, their widespread use has been limited by cost, phytotoxicity, or limited activity. Therefore, in

contrast with the commercial success in the control of human and animal diseases, there are few antibiotics of practical importance in plant protection. However, in Japan two antibiotics[6] have been developed for the control of paddy blast in rice, namely, kasugamycin and blasticidin S.

Systemic antifungal action has also been demonstrated in many other compounds[7,8] which have included sulphonamides, phenoxyalkanecarboxylic acids, 6-azauracil, and phenylthiourea. However, like antibiotics, their discovery has made little impact on the commercial control of fungal diseases.

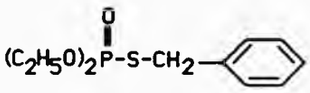
Wepsyn (1) has been claimed to be the first commercial systemic fungicide. It was introduced by Philips Duphar in 1960[3] for the control of powdery mildew in roses and in apple culture. This compound also exhibits insecticidal properties and high mammalian toxicity.



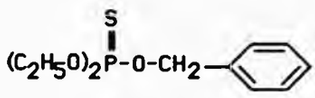
(1)

After 1960, a large number of successful systemic fungicides have appeared on the market. These belong to quite different chemical classes and are often very specific in their action. For example, Kitazin (2) O,O-diethyl S-benzyl phosphorothioate is a systemic fungicide used specifically for the control of *Piricularia oryzae* in rice. It inhibits mycelial growth in tissues. Kitazin also has weak insecticidal properties. However,

the isomeric O-benzyl ester (3) is virtually inactive as a fungicide.

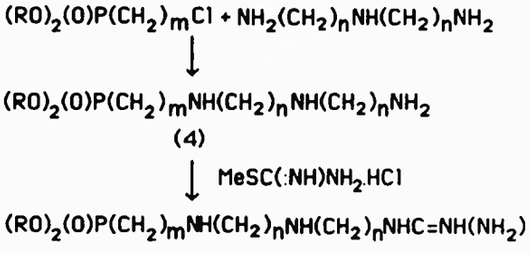


(2)



(3)

The first commercial non-systemic fungicide containing a guanidine group was dodine[9] introduced in 1956. Previous workers[10,11] in this laboratory sought a way to improve systemic activity and water solubility of dodine-related guanidine compounds. As a result, various guanidated aminophosphonic acids (5) were synthesised using a halogenoalkanephosphonic acid and an alkylene diamine. The intermediate aminoalkylaminophosphonic acids (4) were amidinated by S-alkylisothiouronium salt to yield the desired compound (5) (Reaction 1).[10,11]



(4)

(5)

R = H, alkyl; m = 1-3; n = 4-16

(Reaction 1)

Guazatine was first synthesised as the sesquisulphate by the reaction of 1,17-diamino-9-azaheptadecane with S-methylisothiouronium sulphate.[12] The fungicidal potential of the salt of guazatine was described in 1968.[13] KenoGard AB[14] later developed guazatine under the trade name of Panoctine. It is a mixture of the reaction products formed by the amidination of technical iminodi(octamethylene)diamine.[15]

Panoctine is an effective fungicide for cereal seed treatments against *Septoria nodorum*, *Tilletia caries*, and *Fusarium*.It is also used as a foliar spray against *Cercospora* spp. in peanuts, soya beans, and as a post-harvest treatment of citrus fruit against *Penicillium* spp.

The fungicidal activity of aminoalkanephosphonic acids has been the subject of a recent patent[16] and currently forms the subject of further studies. Of particular interest was the α-aminopropanephosphonic acid (6) which exhibited very good growth inhibition of *Drechslera sativa* (76-100%) in <u>vitro</u> and also of *D.teres* (99.7-100%) on barley in field tests. The seeds were treated in a laboratory seed-treatment machine with formulations containing 20% of active ingredient/Kg of seeds.

$CH_3CH_2CH(NH_2)P(O)(OH)_2$

(6)

The α-aminoalkanephosphonic acids are a relatively well known class of compounds. These are white crystalline zwitterionic solids with typical melting point generally above 250 °C.

Their biological activity[17,18] and chelating ability[19] have

also been documented. Some of them, for example the aminomethanephosphonic acid, are claimed to have herbicidal and plant growth retardant properties for grass and cereals.[20,21,22]

A recent report[23] claimed that 2-aminoethylphosphonic acid (7) had considerable activity as a herbicide against some lowland weeds.

$$H_2NCH_2CH_2P(O)(OH)_2$$

(7)

Synthesis of α-aminoalkanephosphonic acids (8) frequently gives poor yields and there is limited information on the reaction mechanisms involved.

$$H_2NCHRP(O)(OH)_2$$

(8)

R = alkyl

The aims of this project were:-

(a) to develop new routes with improved yield for the synthesis of α-aminoalkanephosphonic acids;

(b) to synthesise new derivatives of α-aminoalkanephosphonic acids, the analogous α-aminoalkanephosphinic acids and their derivatives, and to investigate their fungicidal activity with respect to their structure;

(c) to obtain information regarding the reaction mechanisms involved by using spectroscopic methods for the identification of components of the reaction mixtures and information on the by-products formed from the interaction of the reagents.

A review of the literature concerning the α-aminoalkanephosphonic acids and α-aminoalkanephosphonous acids

indicated that these acids have been charaterised mostly by means of infra-red, ^{1}H nmr, and elemental analysis. Although the latter may indicate purity, its use is limited if the compound can exist in various hydrated forms or is a mixture of isomers. Similarly, there is little reference to the ^{13}C and ^{31}P nmr spectroscopy of these acids. It was therefore decided to use ^{1}H, ^{13}C, and ^{31}P nmr spectroscopy in our studies . Fast Atom Bombardment (FAB) mass spectroscopy can be employed succesfully to reveal the $[M+H]^{+}$ ion of α-aminoalkanephosphonic acids as the base peak.[24] This technique has also been applied in the present studies to a range of zwitterionic derivatives.

CHAPTER 1

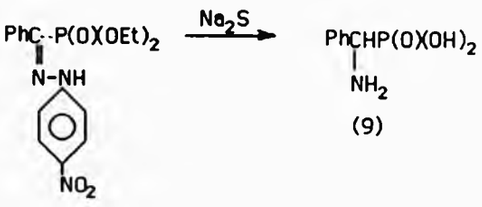
SYNTHESIS OF α-AMINOALKANEPHOSPHONIC ACIDS

1.1 SYNTHESIS OF α-AMINOALKANEPHOSPHONIC ACIDS

In this chapter, the established synthetic routes for the synthesis of the α-aminoalkanephosphonic acids (8) are reviewed. The results obtained using modifications of reported routes are also presented. Synthesis of these acids frequently gives poor yields and the products are often isolated as non-crystallizing hygroscopic syrups. For convenience, it was decided to concentrate upon the synthesis of α-aminopropanephosphonic acid (6) using propanal as a model aldehyde.

Numerous methods have been reported for the synthesis of α-aminoalkanephosphonic acids (8). Their complexity ranges from one stage[25] to multistage[26] reactions, but yields are frequently poor. Furthermore, the papers lack mechanistic evidence concerning the reactions involved.

The first major effort towards the synthesis of (8) can be attributed to Kosolapoff[26,27] who synthesised α-aminobenzylphosphonic acid (9). This involved the reduction of the p-nitrophenylhydrazone of diethyl benzoylphosphonate in the presence of sodium sulphide (Reaction 2).



(9)

(Reaction 2)

Subsequently, more methods have been reported which include:

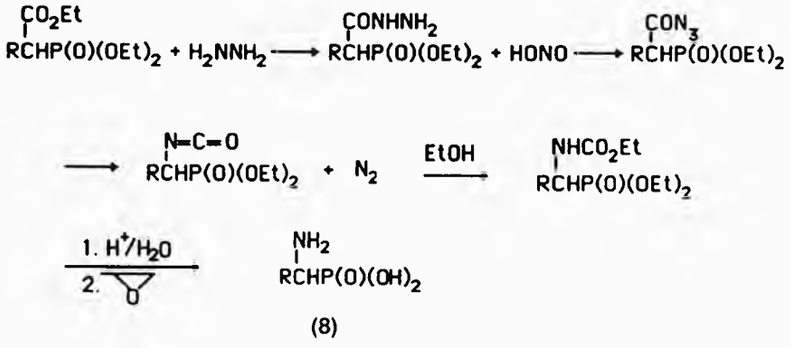
(i) the reaction between dialkyl phosphites, ammonia and carbonyl compounds; [28,29]

(ii) reductive amination involving various carbonyl derivatives such as acyl phosphonates; [30,31]

(iii) addition of phosphite esters to Schiff bases; [32,33,34]

(iv) Curtius rearrangement of substituted phosphonoacetic esters;[35]

Chambers and Isbell[35] first employed the Curtius reaction for the synthesis of (8). These workers concentrated mainly on the synthesis of analogues of naturally occurring amino acids. Their method involved condensation of hydrazine with a phosphonoacetic ester followed by degradation of the substituted diethyl phosphonohydrazides (Scheme1). The phosphonoacetic ester was synthesised from the reaction of an alkyl 2-bromopropionate and triethyl phosphite.[35]

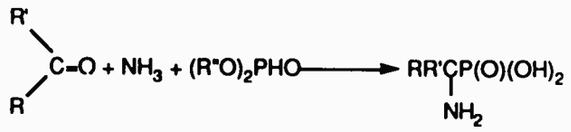


(8)

(Scheme1)

1.2 SYNTHESIS OF α-AMINOALKANEPHOSPHONIC ACIDS USING DIALKYL PHOSPHITES

Kabachnik and Medved[36] employed a general method for the synthesis of (8). This involved condensation of a carbonyl compound (aldehyde or ketone) with ammonia and a dialkyl phosphite, followed by hydrolysis of the resultant aminoalkane-phosphonate to give the free phosphonic acid (Reaction 3). However, their method gave poor overall yields of 10% or less.[35]



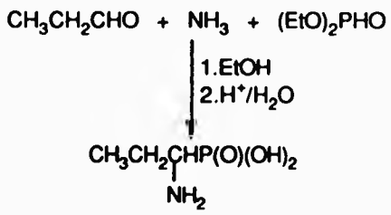
R, R'= Alkyl or H, R"= Alkyl

(Reaction 3)

An extension of the work by Kabachnik and Medved[36] was later reported by Chalmers and Kosolapoff[29] who synthesised a series of aminophosphonates, using ammonia, diethyl phosphite, and various aromatic and aliphatic aldehydes. These phosphonates were purified by distillation and subsequently hydrolysed to give the corresponding phosphonic acids. The authors[29] have claimed that the yields of the aminophosphonates could be substantially improved over those of Kabachnik and Medved[36] if anhydrous ammonia and the aldehyde were mixed in alcohol solution.

The method of Chalmers and Kosolapoff[29] for the synthesis of (6) appeared attractive, and was investigated further in the present work. Accordingly, freshly distilled propanal was mixed

with anhydrous ammonia in absolute ethanol before treatment with diethyl phosphite (Reaction 4).



(Reaction 4)

In an attempt to improve the yield, it was decided to hydrolyse the intermediate phosphonate without further purification. However, work-up of the hydrolysate yielded a brown oily residue whose ^{1}H nmr spectrum was extremely ill defined. The ^{31}P nmr spectrum showed 13 signals, ranging from 5.5 to 25.2 ppm which suggested that the oil was a multicomponent mixture of phosphorus-containing compounds.

The oil was dissolved in the minimum amount of methanol and left at 4 °C for several weeks. Although the white solid which precipitated was characterised as α-aminopropanephosphonic acid (6) the crude yield (9.1%) and purity were poor as determined by both its melting point (243-245 °C) (lit. 264-266 °C)[25] and elemental analysis.

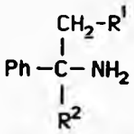
It was therefore decided to re-investigate the Chalmers and Kosolapoff[29] procedure exactly as reported in the literature. This involved purification of the intermediate diethyl α-aminopropanephosphonate and then subsequent hydrolysis to yield (6). The ^{31}P nmr spectrum of the crude mixture prior to distillation

showed four signals at δ 2.7, 23.4, 24.3, and 25.9 ppm. However, distillation of this mixture yielded a pungent liquid whose boiling point was considerably higher than that of diethyl α-amino-propanephosphonate. The ^{1}H nmr spectrum showed three signals [δ 1.1 (t), 1.9-2.1 (m), 4.0 (q)], whereas the ^{31}P nmr spectrum indicated the absence of a phosphorus group.

At this stage the work-up procedure was modified as follows; the brown residue from the above distillation was dissolved in concentrated hydrochloric acid and heated under reflux for eight hours. The resultant hydrolysate was extracted with toluene, concentrated in *vacuo*, and then treated with excess chloroform. A white solid (5.4%) gradually precipitated after several months, which was characterised as the required α-aminopropane-phosphonic acid (6) by ^{1}H nmr spectrum and melting point.

In general, the above results show that the Chalmers and Kosolapoff[29] route gives low yields and by-products (which were not characterised in the present work). Additionally, the melting point for α-aminopropanephosphonic acid (6) was reported[29] to be above 350 °C, a result which is in disagreement with the range from 259-266 °C reported[33-35] by other workers.

Lukszo and Tyka[34] reported another general method for the synthesis of α-aminoalkanephosphonic acids (8). This involved the addition of dialkyl phosphites to Schiff bases prepared from aldehydes and branched derivatives of benzylamine (10) having the amino group at a tertiary benzylic carbon atom (benzylic carbinamines).



R^1 = H, Alkyl; R^2 = Alkyl (10)

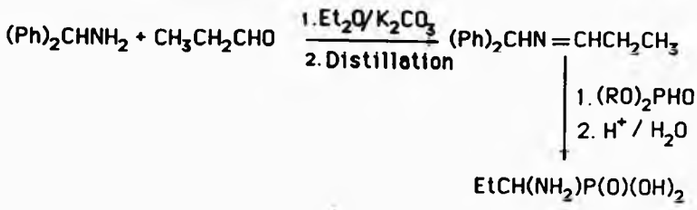
These workers[34] investigated the reaction in the absence of any solvent, and the intermediate phosphonates were hydrolysed with concentrated hydrochloric acid to yield the required phosphonic acids (Reaction 5).

$$(Ph)R^2C(CH_2R^1)N{=}CHR^3 + (EtO)_2PHO \xrightarrow{H^+ / H_2O} R^3CH(NH_2)P(O)(OH)_2$$

(Reaction 5)

The protecting group is acid labile and can therefore be easily hydrolysed because of the easy formation of a carbonium ion from a carbon atom which is both benzylic and tertiary.[34]

In the present work, the above synthetic method was modified by the use of N-propylidenediphenylmethylamine, derived from diphenylmethylamine and propanal. In this case, the acid labile group forms a carbonium ion from a secondary benzylic carbon atom. Reaction of the dialkyl phosphite (Me or Et) with the imine, followed by hydrolysis gave α-aminopropanephosphonic acid (6) as a crystalline white solid in 45-46% yield (Reaction 6).



(Reaction 6)

Synthesis of (6) by this route was also attempted using N-propylidenediphenylmethylamine and different phosphorous esters, viz. triphenyl phosphite, diphenyl phosphite, triethyl phosphite and trimethyl phosphite. In all cases, the ^{31}P nmr spectra of the reaction mixtures after hydrolysis, indicated the absence of any α-aminopropanephosphonic acid (11). Work-up of the hydrolysate yielded diphenylmethylammonium chloride in high yield (ca. 85-90%). The neutral conditions employed in these reactions may not therefore be favourable for this type of process. Dialkyl phosphite is presumably active because of its acidic proton. In the case of diphenyl phosphite, although a similar acidic proton is present, the phosphorus is much less nucleophilic because of the electron attracting phenoxy groups.

Repetition of the above reactions in the presence of acetic acid and using a longer reaction time led, after hydrolysis, to a high recovery of diphenylmethylammonium chloride; resulting from the hydrolysis of the unreacted imine. The ^{31}P nmr spectrum of the hydrolysate indicated the absence of any α-aminopropane-phosphonic acid (6).

1.3 SYNTHESIS OF α-PROPANEPHOSPHONIC ACID USING TRIPHENYL PHOSPHITE OR TRIALKYL PHOSPHITES

Oleksyszyn and Tyka[25] reported a "one pot" synthesis which gave (6) in 35% yield and similar results were obtained in the present work (Reaction 7).

$$(PhO)_3P + RCHO + H_2N.CO.OR' \xrightarrow[2.H^+/H_2O]{1.AcOH} \underset{\underset{NH_2}{|}}{RCHP(O)(OH)_2} + PhOH + R'OH$$

R = Et; R' = $PhCH_2$, Et (6)

(Reaction 7)

Previous studies in this laboratory[11] indicated that yields obtained with longer chain aliphatic aldehydes using the above scheme were either extremely low or failed to give the desired product. Thus, the reaction using octanal gave 5.2% yield, whilst decanal or dodecanal gave none. The above method is still convenient for the synthesis of (6) and other short chain α-aminoalkanephosphonic acids. However, phenol is produced as an undesirable by-product which requires several extractions by benzene or toluene for its removal. Therefore, the reaction was modified and attempted with triethyl phosphite (Reaction 8).

$$(EtO)_3P + RCHO + H_2N.CO.OR' \xrightarrow[2.H^+/H_2O]{1.AcOH} RCH(NH_2)P(O)(OH)_2$$

R = Et; R' = $PhCH_2$, Et

(Reaction 8)

The reaction product, after hydrolysis, yielded ammonium chloride in 62% yield, indicating that much of the benzyl carbamate had not reacted. In addition a white crystalline solid was obtained (17% yield) whose ^1H nmr spectrum was identical with that of α-aminopropanephosphonic acid (6). However, this solid was characterised as the α-hydroxypropanephosphonic acid (11) from its melting point (162-163 °C), elemental analysis, and ^{31}P nmr spectrum. Comparison of the I.R. spectrum with that of authentic α-hydroxypropanephosphonic acid further supported the above conclusion. The mechanism of formation for compound (11) will be discussed later.

$CH_3CH_2CH(OH)P(O)(OH)_2$

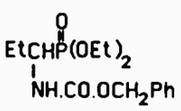
(11)

The above reaction was therefore re-examined by ^{31}P nmr spectroscopy in order to determine if any α-aminopropane-phosphonic acid (6) was being formed.

The ^{31}P nmr spectrum of the reaction mixture before hydrolysis gave three signals at δ 25.2 (major), 21.9 and 22.6 ppm. The major signal at 25.2 ppm was characterised as being due to

diethyl α-hydroxypropanephosphonate (see page 54-55 for further detail). This conclusion was supported by a comparative ^{31}P nmr spectrum of an authentic sample of diethyl α-hydroxypropane-phosphonate. The spectrum of the mixture after hydrolysis gave a major signal at 25.9 ppm and a minor signal at 6.3 ppm; indicating that no α-aminopropanephosphonic acid (6) was formed. The latter usually gives a ^{31}P nmr signal between 13 and 18 ppm depending on the pH of the solvent (see page 49 for further detail). The signal at 25.9 corresponds to the α-hydroxypropanephosphonic acid formed from the hydrolysis of the above ester.

One further modification to Reaction 8 involved the use of boron trifluoride-etherate instead of acetic acid. The initial reaction time was increased from 1 h to 5 h, and sodium dried toluene was used as the solvent. The ^{31}P nmr spectrum of the reaction mixture before hydrolysis gave three peaks at δ 25.3, 28.1, and 6.3 ppm. The signal at 28.1 may be the intermediate diethyl (N-benzyloxycarbonyl)-α-aminopropanephosphonate (12).

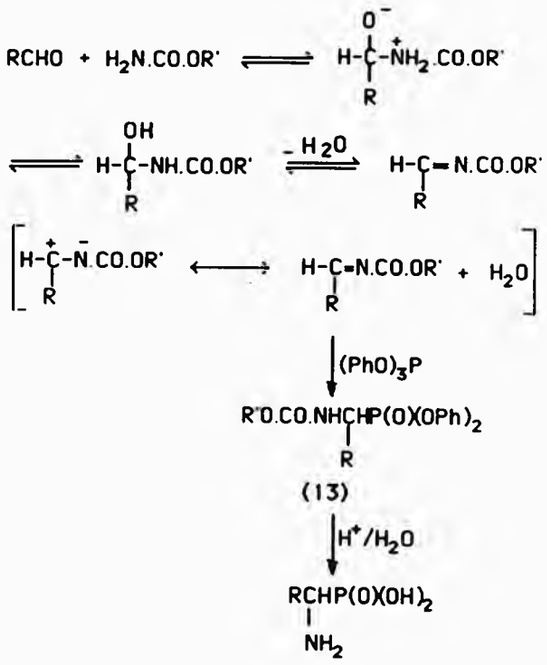


(12)

Hydrolysis yielded ammonium chloride (26.6%), and α-aminopropanephosphonic acid (6) in low yield (20.8%). The isolation of ammonium chloride signifies that benzyl carbamate reacts only partially.

The mechanism of the above type of reaction is uncertain, although it is thought that a Schiff base is formed as a reaction intermediate (Scheme 2) which subsequently undergoes

nucleophilic attack by triphenyl phosphite. In a later publication Oleksyszyn *et al.*[37] have reported the isolation of compounds of type (13) in (35-54%) yield.



R = Alkyl, R' = CH_2Ph

(Scheme 2)

It was thought that further evidence to support Scheme 2 may be obtained by isolating water from the initial condensation of propanal and benzyl carbamate in a Dean and Stark apparatus. Thus the reaction of these two reagents was attempted in a mixture of benzene and acetic acid in order to remove the water of reaction by azeotropic distillation. No water was, however, obtained in the distillate, as determined by ^1H nmr spectroscopy.

The only observable peaks were those due to the presence of benzene and acetic acid. Upon addition of triphenyl phosphite, a distillate was collected whose ^{1}H nmr spectrum gave some evidence for the formation of water. However, hydrolysis of the product yielded phosphorous acid rather than the required phosphonic acid. The formation of phosphorous acid was supported by the ^{31}P nmr spectrum δ 7.35 ($^{1}J_{PH}$ 680 Hz).

Scheme 2 was further investigated in an attempt to isolate the intermediate diphenyl (N-benzyloxycarbonyl)-α-aminoalkane-phosphonate (13). This was attempted using the method described by Oleksyszyn *et al.*[37] When acetaldehyde was used the required diphenyl (N-benzyloxycarbonyl)-α-aminoethanephosphonate (13, R=Me) was obtained in 49% yield. However, when propanal was used the reaction afforded a yellow viscous oil whose ^{31}P nmr spectrum indicated the presence of several phosphorus compounds (for further details see page 44). All attempts to purify this oil in order to isolate the required phosphonate failed.

Huber and Middlebrook[38] synthesised α-aminoalkane-phosphonic acids (8) by the reaction of phenylurea, triethyl phosphite and an aldehyde. These workers compared the effect of using 2-methylpropanal and benzaldehyde upon the yields of (8) and found that the yields obtained were comparable (41 and 46% respectively).

The authors proposed[38] that the reaction proceeds via the formation of phenylureidoalkanephosphonate intermediates. However, the intermediates were neither isolated nor characterised, but instead were hydrolysed directly to the α-aminoalkanephosphonic acids (8) in a "one pot" procedure.

The procedure of Huber and Middlebrook[38] was investigated further using propanal, triethyl phosphite and phenylurea. The mixture was heated in the presence of boron trifluoride-etherate in toluene to give a yellow syrup (Reaction 9).

$$(EtO)_3P + PhNHCONH_2 + CH_3CH_2CHO \xrightarrow[2.\ H^+/H_2O]{1.\ BF_3O(Et)_2/\text{toluene}} CH_3CH_2(NH_2)CHP(O)(OH)_2$$

(Reaction 9)

Attempted isolation of the intermediate in an analogous procedure to that described by Oleksyszyn *et al.*[37] failed to give the desired phenylureidoalkanephosphonate (14). However, hydrolysis of the syrup afforded α-aminopropanephosphonic acid (6) as a white crystalline solid in 29-32% yield.

$Et(PhNH.CO.NH)CHP(O)(OEt)_2$

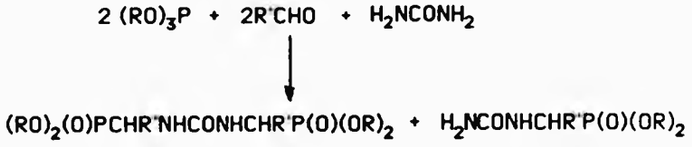
(14)

A similar result was obtained when the above reaction was examined with trimethyl phosphite when the yield of product (6) was 30%.

Birum[39] investigated the reaction of urea, substituted ureas, and their thio-analogues with aldehydes and certain esters of phosphorous acid in the absence of acetic acid. All the reactant combinations yielded α-ureidophosphonates and related products.

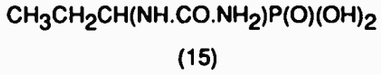
The results[39] indicated that the nature of the products obtained is largely dependent on the type of urea used. For example, mono- or di-substituted ureas only gave monophosphonates. In

contrast when urea was used, urylenediphosphonates as well as urylenemonophosphonates were obtained (Reaction10).



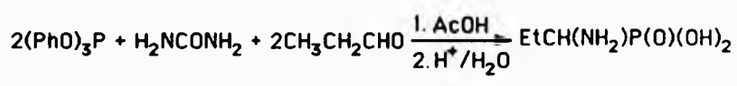
(Reaction 10)

According to Birum,[39] diphosphonates can be isolated in high yields (60%) whereas, the monophosphonates are usually difficult to isolate. The monophosphonates can be hydrolysed to the corresponding phosphonic acid more readily than the diphosphonates. The only phosphonic acid synthesised was α-ureidopropanephosphonic acid (15).



(15)

In the present work the reaction of triphenyl phosphite, propanal and urea in the molar ratio of 2:2:1 was investigated for the synthesis of α-aminopropanephosphonic acid (6). Glacial acetic acid was used as a catalyst with the aim of increasing the overall yield of (6) (Reaction 11).



(Reaction 11)

A yellow viscous liquid was obtained when the reaction

mixture was heated to 70-80 °C for 1 h. Examination of this liquid by ^{31}P nmr spectroscopy, before hydrolysis, indicated the presence of three different phosphorus compounds at δ 18.6 (major), 16.3 and 7.3 ppm. The first two peaks may correspond to di- and monophosphonate. Hydrolysis yielded α-aminopropanephosphonic acid (6) as a white solid in 36.4% yield; based on propanal and the phosphite.

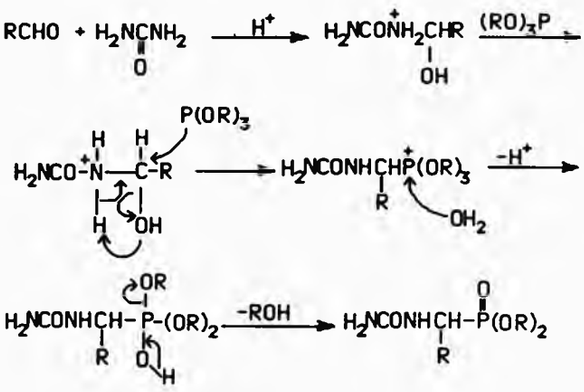
The above reaction was investigated further with the use of different molar ratios of reactants. Again, a yellow syrup was obtained which was hydrolysed. ^{31}P nmr examination of the hydrolysed mixture indicated the presence of three peaks at δ 22, 17 and 6.9 ppm respectively, the first being the major signal. ^{1}H nmr spectrum of the oil indicated all the relevant peaks attributable to (6), in addition to other peaks. However, all attempts to purify the oil, by washing with various solvents failed to give (6) in a satisfactory state of purity.

In an attempt to isolate pure α-aminopropanephosphonic acid (6) the above reaction was unsuccessfully repeated several times. Failure to isolate the desired product may be due to the possibility that the oil is a mixture of urylenediphosphonates, α-amino-propanephosphonic acid (signal at 17 ppm), phosphorous acid (signal at 6.9 ppm) and ammonium chloride. Phosphorous acid could originate from the hydrolysis of unreacted triphenyl phosphite (see Page 52). The presence of ammonium chloride may be due to the hydrolysis of unreacted urea.

Birum[39] also compared the reactivity of triphenyl phosphite with that of trialkyl phosphites in the synthesis of α-ureido-phosphonates and related products. The results obtained indicated a reversal of the normal order of reactivity of phosphite esters

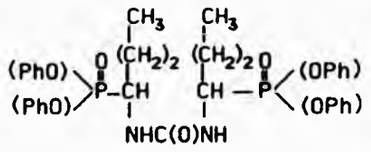
which was explained as being due to the differences in the basicity of the phosphites. The urea and aldehyde were said to undergo an acid-catalysed reaction. Trialkyl phosphites are basic enough to inhibit the first step (Scheme 3), whereas the less basic triphenyl phosphite would not lower the acidity below the level needed for the reaction between urea and aldehyde to occur.[39]

Thus, when triethyl phosphite was used there was no indication of any reaction, after 1 hour at 90-100 °C.



(Scheme 3)

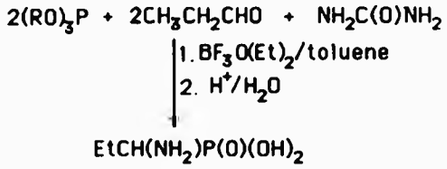
This difference was exemplified[39] by the formation of tetraphenyl (urylenedibutyl)-1,1-diphosphonate (16) from a mixture of triphenyl phosphite, n-butyraldehyde and urea (2:2:1) which was completed at 70 °C in less than 0.5 h, according to ^{31}P nmr measurements.



(16)

Birum claimed[39] that the addition of acetic acid or boron trifluoride-etherate to a mixture of triethyl phosphite, urea and butanal promoted the formation of urea phosphonates. However, the paper gave no indication regarding the extent of reaction, and no attempt was made to synthesise any phosphonates using triethyl phosphite.

In the present work the reaction of triethyl phosphite with urea and propanal was investigated with the use of boron trifluoride-etherate as a catalyst (Reaction 12).



(Reaction 12)

The reaction product was a white crystalline solid with a melting point of 205 °C. This solid was characterised as the ammonium salt of α-ureidopropanephosphonic acid (17) by nmr (^{1}H, ^{13}C, ^{31}P) spectra, elemental analysis, and fast atom bombardment (FAB) mass spectrometry.

$NH_2CONHCH(Et)P(O)(OH)(O^-NH_4^+)$

(17)

The ^1H nmr spectrum (D_2O) of (17) was similar to that of α-amino-propanephosphonic acid (6) but, with an additional doublet between 2.6 and 2.7 ppm, which disappeared over 0.5 h. The ^{31}P nmr spectrum gave a single signal at δ 23 ppm. In contrast, the ^{31}P nmr chemical shift for (6) was usually observed at δ 17 ppm. This difference reflects the presence of an electronegative group in close proximity to the phosphorus moiety which deshields the electron cloud around the phosphorus atom. Therefore the chemical shift of (17) is downfield with respect to (6).

Re-examination of the above reaction with prolonged hydrolysis (72 h), yielded the α-aminopropanephosphonic acid (6) in 29.9% yield identified by nmr (^1H, ^{31}P) spectra and melting point.

To determine the effect on the yield of (6) the above reaction was investigated using a 1:1:1 molar ratio of reactants. Prolonged hydrolysis (72 h) and work-up of the aqueous layer yielded a white oil which crystallised to give (6) in 26.9% yield.

A similar yield (29.7%) of α-aminopropanephosphonic acid (6) was obtained with trimethyl phosphite when an equimolar ratio of reactants was used.

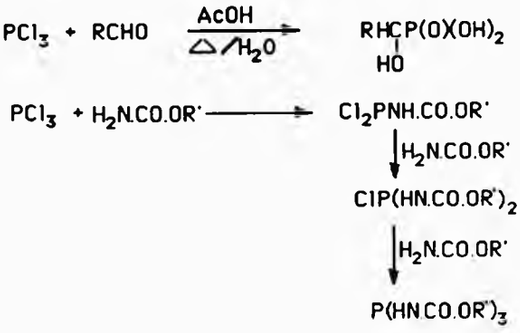
1.4 SYNTHESIS OF α-AMINOPROPANEPHOSPHONIC ACID FROM PHOSPHORUS TRICHLORIDE

The use of phosphorus trichloride for the synthesis of α-aminoalkanephosphonic acids (9) was reported by Oleksyszyn *et al.*[40] Phosphorus trichloride was allowed to react directly with

an alkyl carbamate, and a carbonyl compound (aldehyde or ketone) in the presence of glacial acetic acid. Yields were found to be comparable for both aliphatic and aromatic carbonyl compounds.

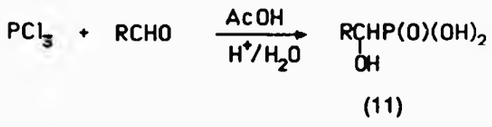
The procedure of Oleksyszyn *et al.*[40] was investigated using propanal, benzyl carbamate and phosphorus trichloride. The reaction afforded a brown oil which was washed with various solvents and recrystallised from methanol and acetone to give (6) in 12.3% yield. The ^{31}P nmr spectrum of the supernatant liquid showed signals at δ 24.9, 22.6,16.5, and 6.9 ppm, which indicated that a further quantity of (6) was present in addition to several other phosphorus containing compounds. The mother liquor was evaporated to dryness, washed with various solvents and a final recrystallisation was attempted. All attempts to collect a second crop of α-aminopropanephosphonic acid (6) failed.

The low yield of (6) may possibly be explained in terms of competing reactions between the aldehyde and phosphorus trichloride, and between carbamate and phosphorus trichloride (Scheme 4).



R=Et, R'=CH_2Ph, Et (Scheme 4)

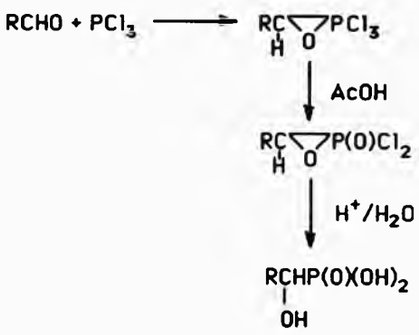
The reaction of an aldehyde with phosphorus trichloride, followed by hydrolysis for the synthesis of α-hyroxyalkane-phosphonic acids (Reaction 13), has been reported in the literature.[41,42]



(11)

(Reaction 13)

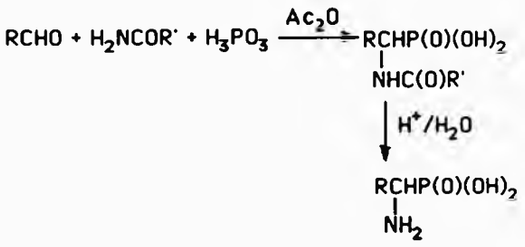
The mechanism for the formation of (11) is uncertain, although various proposals have been reported. For example, Connant *et al*[42] suggested the following scheme:



1.5 ATTEMPTED PREPARATION OF N-BENZYL α-AMINO-ALKANE PHOSPHONIC ACIDS FROM PHOSPHOROUS ACID

The use of phosphorous acid for the synthesis of α-aminoalkanephosphonic acids (8) has also been reported together with a possible mechanistic proposal. Oleksyszyn and Gruszecka[43] have proposed another type of mechanism for the reaction between

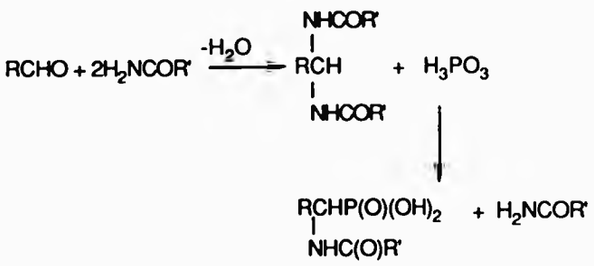
an amide, aldehyde and phosphorous acid (Reaction 14).



R' = Alkyl or Aryl

(Reaction 14)

It is thought that in this case the reaction involves the initial formation of N, N-alkylidene or N, N-arylidenebisamide, followed by its electrophilic attack on phosphorous acid[43] (Scheme 5).

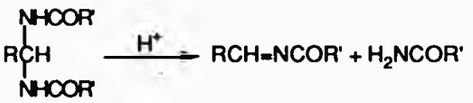


(Scheme 5)

The overall yields are low for aliphatic aldehydes compared to aromatic aldehydes.

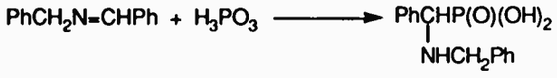
Oleksyszyn and Gruszecka[43] have shown that bisamides can be used as amidoalkylating agents for phosphorous acid. For example, the action of heat on a mixture of equimolar amounts of benzylidenebisacetamide and phosphorous acid in acetic acid

afforded N-acetyl-l-aminobenzylphosphonic acid in nearly quantitative yield. However, there is no direct evidence for the existence of the N, N- arylbisamide as the reaction intermediate. Furthermore, since the reaction is in acidic conditions the bisamide could form an imine with the loss of amide (Reaction 15) and the imine would be available to react with the phosphorous acid.



(Reaction 15)

The addition of phosphorous acid to imines, derived from benzylamine and aldehydes, has also been documented.[44] These reactions give N-benzyl α-aminoalkanephosphonic acids. Again, differences in yield have been observed between reactions involving aliphatic and aromatic aldehydes. For example, benzylidenebenzylamine with phosphorous acid afforded an almost quantitative yield of N-benzyl-α-aminobenzylphosphonic acid (18) (Reaction 16). In contrast, imines derived from aliphatic aldehydes gave only moderate yields of N-benzyl-α-aminoalkanephosphonic acids (19) (Reaction 17).[44]



(Reaction 16) (18)

$$PhCH_2N{=}CHCH_2CH_3 + H_3PO_3 \longrightarrow CH_3CH_2CHP(O)(OH)_2$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad NHCH_2Ph$$

(Reaction 17) (19)

The low yield of (19) has been rationalised in terms of competing reduction or addition reactions.[44]

Addition to the imine is said to be favoured in the presence of a strong acid (e.g. p-toluenesulphonic acid), and reduction to be favoured in the presence of a base (e.g. triethylamine) giving the corresponding amine.

The procedure of Redmore[44] was investigated in the present work using propylidenebenzylamine derived from propanal and benzylamine. Treatment with phosphorous acid as described afforded, after hydrolysis, mixtures of benzylammonium chloride and benzylammonium phosphite in high yield and none of the desired reaction had occurred. Examination of the reaction mixture by ^{31}P nmr spectroscopy did not indicate the presence of any N-benzyl-α-aminopropanephosphonic acid.

In order to facilitate the addition of phosphorous acid to the imine, the above reaction was re-examined in the presence of p-toluenesulphonic acid. However, the reaction again afforded only a mixture of benzylammonium chloride and benzylammonium phosphite. The reaction was also attempted in the presence of absolute ethanol as a solvent to reduce the viscosity of the reaction mixture but without success. These results are in accord with those previously obtained in this laboratory,[45] and in contrast with Redmore's. Attempts to duplicate Redmore's reaction involving isobutyraldehyde, benzylamine and phosphorous acid also

failed to give the required phosphonic acid.

1.6 SYNTHESIS OF α-AMINOPROPANEPHOSPHONIC ACID VIA DIMETHYL N-BENZYL-α-AMINOPROPANEPHOSPHONATE HYDROCHLORIDE

Primary and secondary amines were employed by Field[32] for the synthesis of various N-substituted α-aminoalkanephosphonates. However, hydrolysis of the phosphonate to give the corresponding N-substituted phosphonic acid generally led to the formation of a non-crystallising hygroscopic syrup (Reaction 18).

$$RR'C{=}O + (EtO)_2PHO + Et_2NH \longrightarrow Et_2NCRR'P(O)(OEt)_2 + H_2O$$

R = R'= H or alkyl

(Reaction18)

Field claimed[32] that primary amines frequently gave poor yields of the N-substituted α-aminoalkanephosphonates compared to secondary amines, a result which may be due to the side reaction shown (Reaction 19).

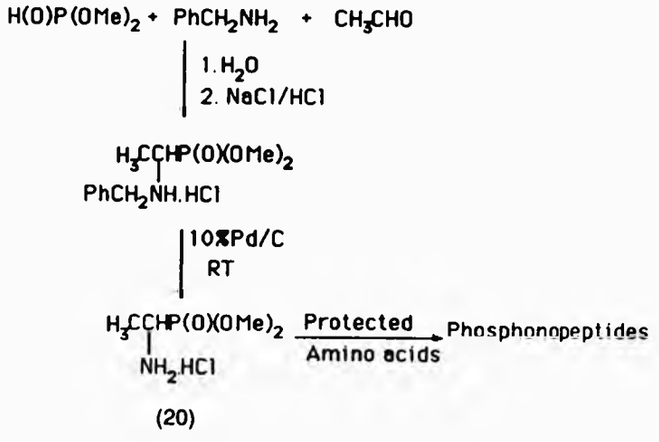
$$RCHO + (EtO)_2PHO + RNH_2 \longrightarrow R'CH(NHR)P(O)(OEt)_2 \xrightarrow{R'CHO/(EtO)_2PHO} RN-[(R')CHP(O)(OEt)_2]_2$$

(Reaction 19)

An extension of Field's work was later reported by Tyka[33]

who synthesised a series of N-substituted α-aminoalkanephosphonates and α-aminoalkanephosphinates. His method involved the addition of diethyl phosphite to benzylimines at 110-120 °C in the absence of any solvent. He claimed[33] that the hydrogenolysis of N-benzyl-α-aminoalkanephosphonic acids using Pd/C as a catalyst, provides another route for the synthesis of the corresponding α-aminoalkanephosphonic acids with a free amino group in good yield.

Atherton *et al.*[46] reported the synthesis of phosphonopeptides of α-aminomethanephosphonic acid and α-aminoethanephosphonic acid. These workers employed several different multistage methods. One route involved the preparation of the intermediate dimethyl N-benzyl-α-aminoethanephosphonate hydrochloride (20). The latter was debenzylated using 10% palladium on charcoal, and the resultant free dimethyl α-aminoethanephosphonate hydrochloride was coupled with various protected amino acids, to yield the required phosphonopeptides (Scheme 6).



(20)

(Scheme 6)

The yield of (20) was reported as 70%, after several lengthy steps of extractions and purification. The method is still very attractive requiring commercially available starting materials. The procedure of Atherton *et al.*[46] was investigated further by the use of propanal for the synthesis of α-aminopropanephosphonic acid (6). This three step reaction required the initial synthesis of dimethyl N-benzyl-α-aminopropanephosphonate hydrochloride (21) (Reaction 20).

$$(MeO)_2PHO + PhCH_2NH_2 + CH_3CH_2CHO \xrightarrow[2.NaCl/HCl]{1.\ H_2O} \underset{\displaystyle PhCH_2NH.HCl}{\overset{\displaystyle |}{EtCHP(O)(OMe)_2}}$$

(Reaction 20) (21)

A sample of the above reaction mixture in deuterated chloroform was examined by ^1H nmr spectroscopy and appeared to consist entirely of product (21). Work-up of the above solution was laborious and required several extractions, transfers, and further purifications. The product, dimethyl N-benzyl-α-aminopropane-phosphonate hydrochloride (21) was obtained as a white crystalline solid in 63% yield.

It was noted that compound (21) was unstable in air, turning to a non-crystalline hygroscopic syrup. This may be explained by the fact that (21) may be acid labile. The compound being a hydrochloride salt may, in the presence of moisture, lose one or more of the ester groups.

In order to support the above suggestion a sample of dimethyl N-benzyl-α-aminopropanephosphonate hydrochloride (21) was left

in the air for several days and the resultant syrup was re-examined by ^{31}P nmr spectroscopy. Three peaks at δ 24.3 (major), 14.8, and 14.7 (trace) ppm were observed. This indicates that the syrup is a mixture of the parent compound (21) δ 24.3, N-benzyl-α-aminopropanephosphonic acid hydrochloride δ 14.8 and possibly a trace amount of the monomethyl ester. The ^{1}H nmr spectrum of the syrup indicated numerous overlapping peaks which were too complex to be assigned.

Hydrogenolysis of dimethyl N-benzyl-α-aminopropanephosphonate hydrochloride (21) was attempted by a similar procedure to that of Atherton *et al.*[46] However, this failed to give the required dimethyl α-aminopropanephosphonate hydrochloride (22). Therefore, hydrogenolysis of compound (21) was re-examined using modified conditions, such as the use of ethanol instead of dichloromethane and varying the temperature and pressure (100 °C, 400 psi). After work-up, the required dimethyl α-aminopropanephosphonate hydrochloride (22) was obtained as a viscous yellow oil.

$$HCl.H_2NCH(Et)P(O)(OMe)_2$$

(22)

Compound (22) was then hydrolysed with no further purification. Work-up of the resultant hydrolysate yielded α-aminopropanephosphonic acid (6) as a white solid in 55% yield.

In an attempt to improve the yield of (6), the procedure of Atherton *et al.*[46] was further modified. The lengthy purification procedure for dimethyl N-benzyl-α-propanephosphonate hydrochloride (21) was omitted. Accordingly, the total crude mixture was used directly for hydrogenolysis without further

purification (Reaction 21). The use of hydrochloric acid was also eliminated since no preparation of the hydrochloride for the purpose of purification was involved.

$$(MeO)_2PHO + PhCH_2NH_2 + CH_3CH_2CHO \xrightarrow{H_2O} EtCHP(O)(OMe)_2 \quad (PhCH_2NH)$$

(Reaction 21) (23)

Prior to hydrogenolysis a sample of this solution was examined by ^1H nmr spectroscopy, and this appeared to consist entirely of dimethyl N-benzyl-α-aminopropanephosphonate (23). However, work-up of the hydrogenated mixture yielded a viscous oil whose ^1H nmr spectrum was very similar to that of the starting material indicating that no debenzylation occurred. The only difference in the ^1H nmr spectrum was that a marked decrease in the peak area of the methoxy protons was observed, which may have been the result of either hydrolysis or hydrogenolysis.

The ^{31}P nmr spectrum of this oil showed two signals at δ 26.8 (due to the reactant) and 14.8 ppm, which may correspond to the formation of N-benzyl-α-aminopropanephosphonic acid. It is possible that the formation of the latter may have poisoned the catalyst by chelation.

Further hydrogenations of crude dimethyl N-benzyl-α-aminopropanephosphonate (23), crude dimethyl N-benzyl-α-aminopropanephosphonate hydrochloride and the corresponding phosphonic acid were attempted (Table1 & 2). These involved various modifications such as the use of a different solvent, catalyst, temperature, pressure, and pretreatment of the reaction

product with catalyst prior to hydrogenolysis. However, all attempts failed to yield compound (22).

It appears that the catalyst in these attempts was not sufficiently active or that it was being poisoned by components of the reaction mixture.

Table 1: Attempted hydrogenation of crude $(PhCH_2NH)CH(Et)P(O)(OMe)_2$

Catalyst	Reaction Conditions (Solvent, T and P, Time)	Observation from ^1H nmr
5%Pd/C	H_2O, 50° C, 340 psi, 3 h	Sample - Partial loss of $PhCH_2$ group
	90° C, 420 psi, 5 h	Loss of MeO indicated
5% Pd/C	CH_2Cl_2 , 22 °C, 300 psi, 3 h	Sample - no apparent reaction
	100 °C, 440 psi, 4 h	Loss of MeO indicated
5% Pd/C	MeOH , 104 °C, 600 psi, 4 h	Sample - no apparent reaction
+ 5% Pd/C	100 °C, 650 psi, 15 h	Partial loss of $PhCH_2$ group
5% Pd/C	AcOH,100 °C, 500 psi, 6 h	Total loss of MeO group observed

Table 2 : Attempted hydrogenation of crude $(PhCH_2NH.HCl)CH(Et)P(O)(OR)_2$

R	Catalyst	Reaction Conditions (Solvent, Tand P, Time)	Observation from ^1H nmr
CH_3	5% Pd/C	CH_2Cl_2, 20 ° C, 535 psi, 3h	Sample -No apparent reaction
		100 °C, 595 psi, 3 h	Deliquescent solid. Loss of MeO group only.
CH_3	5% Pd/C	MeOH, 100 °C, 525 psi, 3 h	Loss of MeO group. No apparent change in benzyl peak
CH_3	Ni(Raney) + 5 cm^3 Ni	MeOH, 113 °C, 550 psi, 3 h 15 h	No apparent reaction Loss of MeO group.
H	5% Pd/C	MeOH 100 °C, 400 psi 3h,	No apparent reaction

One further modification to the procedure of Atherton *et al.*[46] involved replacing benzylamine with diphenylmethylamine (Reaction 22). This would eliminate the hydrogenolysis step and require only a simple acid hydrolysis to remove the protecting diphenylmethyl group.

$$(MeO)_2PHO + Ph_2CHNH_2 + CH_3CH_2CHO \xrightarrow[2.\,Conc.\,HCl]{1.\,H_2O} EtCH(NH_2)P(O)(OH)_2$$

(Reaction 22) (6)

The hydrolysed reaction mixture yielded a white crystalline

solid (46.9%) identified as diphenylmethylammonium chloride. Work-up of the mother liquor gave α-aminopropanephosphonic acid (6) in 28.8% yield.

The low yield of (6) may be due to a solubility problem that can arise from the bulky diphenylmethyl group. Water was used as the reaction medium which was too polar for the above system resulting in a non-homogeneous mixture. This suggests that reaction did not go to completion. Accordingly, reaction (22) was re-examined using methanol as the solvent. The resultant solution was hydrolysed to give diphenylmethyl-ammonium chloride (36.4%), and α-aminopropanephosphonic acid (47.1%).

CHAPTER 2

PROTON NMR SPECTROSCOPY OF α-AMINOALKANE-PHOSPHONIC ACIDS AND PHOSPHORUS ^{31}NMR SPECTRUM STUDIES OF "ONE-POT" SYNTHESIS FOR α-AMINOPROPANE-PHOSPHONIC ACID

2.1 PROTON NMR SPECTROSCOPY OF α-AMINOALKANE-PHOSPHONIC ACIDS

Although ^{1}H nmr spectroscopy was a useful tool to determine the success or failure of a new route for the synthesis of α-aminopropanephosphonic acid (6), this technique alone was insufficient for full characterisation of the compound because the by-product namely, α-hydroxypropanephosphonic acid, also showed an identical ^{1}H nmr spectrum to that of (6). Therefore, full characterisation of (6) was usually carried out by ^{1}H nmr spectroscopy coupled with melting point and either ^{31}P nmr spectroscopy or elemental analysis.

The ^{1}H nmr spectra of α-aminoalkanephosphonic acids have been reported.[47,48] These compounds show a fingerprint region mainly concentrated between 0.8 to 5 ppm. The spectrum of α-aminopropanephosphonic acid in D_2O shows generally the following signals: 1.05 (t, 3H, CH_3 $^{3}J_{HCCH}$ 7.8 Hz), 1.50-2.20 (m, 2H, CH_2), 2.80-3.42 (m, 1H, CH). The ^{1}H nmr spectrum of this compound was examined at 220 MHz by Cameron,[11] who found that the multiplet due to CH_2 consists of at least 20 peaks. This is in contrast to the expected sixteen peaks (2 x 2 x 4 =16) arising as a result of coupling to phosphorus, the methine and methyl protons. Additionally, the CH signal also consisted of 7 peaks instead of the expected 6, which is due to splitting by phosphorus and the CH_2 group.

The spectrum can be explained by the fact that the methylene protons are non-equivalent and consequently an AB pattern is observed. This non-equivalence arises as a result of the methylene

group being adjacent to a chiral centre, despite free rotation about the carbon-carbon bond.

In the present work it was found that as the length of the alkyl chain increased, the ^{1}H nmr spectrum became significantly second order. Whereas, a triplet and a multiplet could be observed due to CH_3 and CH protons, only a broad multiplet was observed due to overlap for all the CH_2 protons in the alkyl chain.

2.2 PHOSPHORUS 31 NMR SPECTRUM STUDIES OF "ONE-POT" SYNTHESIS FOR α-AMINOPROPANEPHOSPHONIC ACID

There have been several reports involving the "one-pot" syntheses of α-aminoalkanephosphonic acids. The majority of the procedures describe the use of three reactants, namely a trivalent phosphorus reagent, a carbonyl compound and an amino component. Typically these reactants are heated in the presence of glacial acetic acid, and the product is then hydrolysed to give the corresponding α-aminoalkanephosphonic acid. However, yields are frequently low and the reaction mechanisms involved are not fully understood.

A literature review revealed no previous references to the use of spectroscopy to monitor the "one-pot" synthesis of α-aminoalkanephosphonic acids. We investigated the "one-pot" reaction system procedure of Oleksyszyn and Tyka[23] by monitoring with ^{31}P nmr spectroscopy. The study was made in an attempt to explain the low yields and if possible, to obtain mechanistic information for the above type of reaction.

2.3 PHOSPHORUS 31 NMR SPECTRUM STUDIES OF "ONE-POT" SYNTHESIS FOR α-AMINOPROPANEPHOSPHONIC ACID INVOLVING TRIPHENYL PHOSPHITE

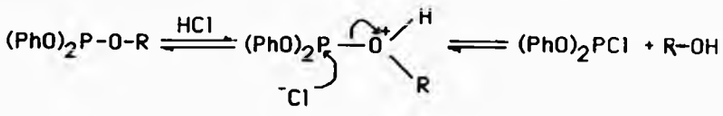
The first reaction studied was that between a mixture of benzyl carbamate, triphenyl phosphite, and propanal in acetic acid (Table 3).

The various reactant combinations were allowed to react under the 'normal' reaction conditions. Each combination was followed by ^{31}P nmr spectroscopy at various stages of the reaction. For example, the ^{31}P nmr spectrum of triphenyl phosphite in acetic acid, stirred at room temperature for 1 h, gave only a signal at 127.1 ppm which indicated that no reaction had occurred. However, upon heating the same mixture signals at 6.9 and 3.7 ppm were observed. The coupled spectrum indicated that each of these peaks gave rise to a doublet, with J values of 720 and 570 Hz respectively, which is indicative of P-H coupling.

Hudson and Roberts[49] have studied the reaction of hydrogen chloride with triphenyl phosphite and tri-n-butyl phosphite at low temperature. They reported the formation of a P-protonated intermediate $(RO)_3P^+H\ X^-$(X=Cl) in the case of the butyl ester, which was confirmed by ^{31}P nmr spectroscopy. It was shown that tri-n-butyl phosphite undergoes dealkylation upon raising the temperature. In contrast, the bulkier triphenyl phosphite undergoes phosphorus-oxygen cleavage to yield diphenyl phosphorochloridite, possibly via an O-protonated species (Scheme 7).[49a]

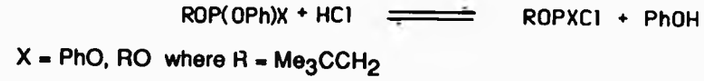
Table 3: ^{31}P nmr chemical shifts for the various reactant combinations for the "one pot" system

Reactant combinations	Reaction condition	δ(ppm)	Intensity
$(PhO)_3P$	RT,1 h	127.1	7654
$(PhO)_3P$ +AcOH	RT,1 h	127.1	8643
$(PhO)_3P$ +AcOH	80-85 ° C, 1 h	6.9	6673
		3.7	5203
$(PhO)_3P$ +CH_3CH_2CHO	RT,1 h	127.1	9237
$(PhO)_3P$ +CH_3CH_2CHO	80-85 ° C, 1 h	127.3	8863
$(PhO)_3P$ +CH_3CH_2CHO	RT, 1 h	127.6	8843
+AcOH		22.0	1026
		15 .4	3352
$(PhO)_3P$+CH_3CH_2CHO	80-85 ° C,1 h	3.9	4882
+AcOH		6.9	6614
		13	4294
		17	12825
		21.6	11925
		25.1	5958
$(PhO)_3P$ +$PhCH_2OCONH_2$	80-85 ° C, 1 h	4.1	28997
+AcOH		6.9	20074
$(PhO)_3P$ +$PhCH_2OCONH_2$+	RT, 1 h	127	11546
CH_3CH_2CHO+AcOH		22	3346
		15	2341
$(PhO)_3P$ +$PhCH_2OCONH_2$+	80-85 ° C, 1 h	-18	4849
CH_3CH_2CHO+AcOH		-10	3344
		12.4	7150
		17.9	22398
		18.8	20530
		127.7	27232
		129.9	5430
$(PhO)_3P$ +$PhCH_2OCONH_2$+	1. 80-85 ° C, 1 h	25.3	2352
CH_3CH_2CHO+AcOH	2. HCl/105 ° C, 8 h	17.4	5184
		6.4	2715



(Scheme 7)

Hudson *et al.*[49b] later reported the effects of temperature and different substituents at phosphorus on the above process. It was stated that phosphorus-oxygen fission also predominates in the reaction of mixed phenyl neopentylesters with hydrogen chloride (Scheme 8).

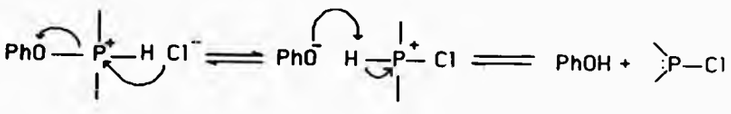


X = PhO, RO where R = Me_3CCH_2

(Scheme 8)

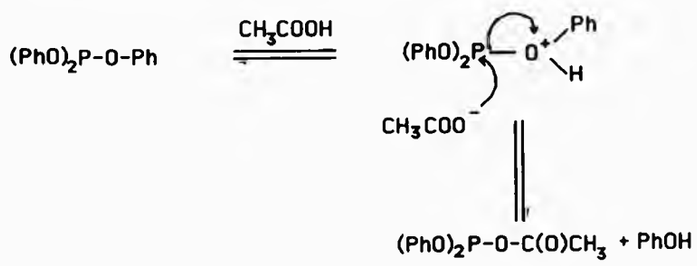
This preference for phosphorus-oxygen cleavage rather than P-protonation was explained in terms of lower electron density and with leaving ability of the phenoxide group.[49a]

Triphenyl phosphite has been shown[50] to give a P-protonated species in 100% sulphuric acid in which effective nucleophiles are absent. Therefore, Hudson *et al.*[49b] proposed an alternative to O-protonation as suggested previously. This cleavage by hydrogen chloride could occur by a nucleophilic attack of chloride ion on the phosphorus intermediate, with displacement of phenoxide (Scheme 9).



(Scheme 9)

An analogous possibility was considered for the reaction of triphenyl phosphite with acetic acid (Scheme 10).



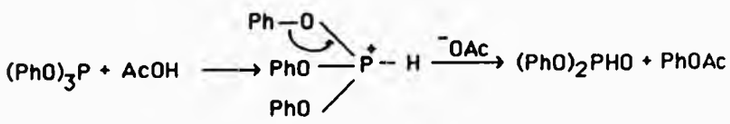
(Scheme 10) (26)

However, (26) was not formed in the above reaction as indicated by the following reasons:

1. the observed spectrum indicated the presence of large P-H coupling;

2. it is more likely that (26) will give a signal in the region of 140-160 ppm [cf. $(PhO)_2PCl$ (155 ppm)], but no signal in this region was observed.

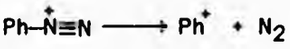
The ^{31}P nmr spectrum of diphenyl phosphite was recorded for comparison and gave a signal at 7.2 ppm, with a J value of 720 Hz. Two signals, at 7 and 4 ppm were observed when diphenyl phosphite was heated with acetic acid for 1 h. The former signal gave a doublet with similar J_{P-H} value to that observed above (710 Hz), whereas, the latter signal had J_{P-H} value of 570 Hz. These values are in reasonable agreement with those reported for di- and mono-phenyl phosphite.[51] Therefore, it was concluded that triphenyl phosphite reacts with acetic acid to give diphenyl phosphite and monophenyl phosphite, possibly via the formation of a P-protonated intermediate (Scheme 11).



(Scheme 11)

The next step probably involves an S_N1 attack by the weak acetate ion on the phenyl group to give phenyl acetate, although the latter was not investigated.

This S_N1 step is not common for aromatic systems but can occur with a very good leaving group e.g. N_2 in the case of aryldiazonium salts (Reaction 23).



(Reaction 23)

It may be that the positively charged quaternary phosphorus atom is itself strongly electrophilic, so that it may cause electron withdrawal from the Ph-O-P bond, causing an inherent tendency for dearylation. Additionally, the stability of the positively charged phenyl ion may be the second factor contributing towards S_N1 attack by the weak acetate ion.

A mixture of triphenyl phosphite with propanal stirred at room temperature for 1 h, showed no apparent reaction. Likewise, no reaction occurred when the mixture was heated under 'normal' reaction conditions (Table 3). However, addition of acetic acid to

the same mixture at room temperature, gave three signals around 127, 22 and 15 ppm. When the mixture was heated for 1 h, the observed ^{31}P nmr spectrum was extremely complex indicating the presence of six different phosphorus-containing compounds. Again, two signals at 3.9 and 6.9 ppm were indicative of monophenyl and diphenyl phosphite formation.

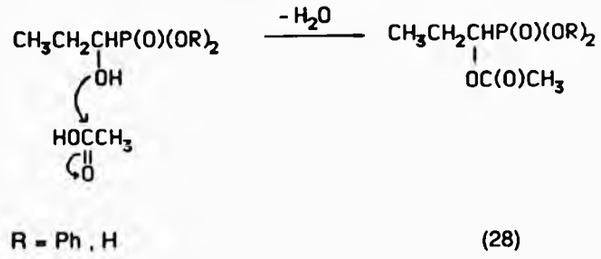
The reaction of phosphorus trichloride with propanal in the presence of acetic acid followed by hydrolysis gives α-hydroxypropanephosphonic acid.[52] It is possible that the reaction of propanal and triphenyl phosphite in the presence of acetic acid may follow a similar course (Reaction 24).

$$(PhO)_3P + CH_3CH_2CHO \xrightarrow{AcOH} CH_3CH_2\underset{\underset{OH}{|}}{CH}P(O)(OPh)_2$$

(27)

(Reaction 24)

Two signals were observed at 25.1 and 21.6 ppm in the above mixture, one possibly corresponding to the presence of (27), since phosphonates of this type usually give a signal in these regions. Two further signals (17 and 13 ppm) were not assigned, although various possibilities exist. For example, acetic acid may remove a phenoxy group from (27) to give the corresponding monophenyl α-hydroxypropanephosphonate. It is also possible that the α-hydroxy group may react with acetic acid to yield α-acetoxypropanephosphonate (diphenyl or monophenyl) or the corresponding acid (Reaction 25).



R = Ph , H (28)

(Reaction 25)

The above proposal was investigated using authentic α-hydroxypropanephosphonic acid. The ^{31}P nmr spectrum in D_2O gave a signal at 23 ppm (Table 4 & 5). Acetic acid was added to a quantity of α-hydroxypropanephosphonic acid and the mixture heated for 1 h, after which the ^{31}P nmr spectrum indicated two signals at 26 (major) and 21.3 ppm. This suggests the formation of two of the phosphorus containing compounds that were present in the system.

Table 4: ^{31}P signals of α- amino and α-hydroxypropane-phosphonic acids in different solvents

Solvent(s)	$EtCH(OH)P(O)(OH)_2$	$EtCH(NH_2)P(O)(OH)_2$
D_20	23.7	13.6
D_20/D_2SO_4	23.3	14.1
H_2O/H_2SO_4	26.0	17.5
AcOH/HCl	26.0	17.5
AcOH	26.0, 21.3	

Table:5 ^{31}P signals of diethyl esters of α-amino- and α-hydroxy-propanephosphonate in different solvents

Solvent	$EtCH(OH)P(O)(OEt)_2$	$EtCH(NH_2)P(O)(OEt)_2$
AcOH	25.2	28.3
$CDCl_3$	25.5	28.2

The signal at 26 ppm (Table 4) is due to α-hydroxypropane-phosphonic acid, and the minor peak at 21.3 ppm may arise from α-acetoxypropanephosphonic acid (28). This chemical shift compares well with one of the three unidentified peaks (21.6 ppm) in the above reaction mixture (Reaction 24). It appears therefore, that acetic acid may cause dearylation to the extent that the phosphonate was converted to the phosphonic acid.

The reaction of triphenyl phosphite with benzyl carbamate in the presence of acetic acid was also investigated. The mixture was heated for 1 h. The ^{31}P nmr spectrum gave two signals at 4.1 and 6.9 ppm corresponding to monophenyl and diphenyl phosphite formation only. This suggests that no reaction between triphenyl phosphite and benzyl carbamate has occurred.

In view of the above results, we monitored the total reaction mixture containing the phosphite, aldehyde and the carbamate in acetic acid. The ^{31}P nmr spectrum of the mixture at room temperature was similar to that observed for the combination of triphenyl phosphite, propanal and acetic acid at room temperature (page 44). This mixture was then heated for 1 h at 80-85 °C, and the ^{31}P nmr spectrum indicated seven signals ranging from -18 to 128 ppm. This suggests that the mixture is a multi-component system of phosphorus-containing compounds which could not be

fully assigned. The mixture was hydrolysed by boiling with concentrated hydrochloric acid for 8 h, and the 31P nmr spectrum of the hydrolysate revealed three signals (25.3, 17.4 and 6.4 ppm). No further change occured on boiling for a further 20 hours and it was concluded that the signal at 25.3 ppm must arise from α-hydroxypropanephosphonic acid. A comparative ^{31}P nmr of authentic α-hydroxypropanephosphonic acid gave a signal at 26 ppm in a mixture of acetic acid and concentrated hydrochloric acid (Table 4). The peak at 17.4 ppm arises from the presence of α-aminopropanephosphonic acid (6). Again, this was confirmed by ^{31}P nmr of an authentic sample of (6) in a mixture of acetic acid and hydrochloric acid. The signal at 6.4 ppm may arise from the hydrolysis of residual triphenyl phosphite, diphenyl or monophenyl phosphite to give phosphorous acid [δ H_3PO_3 (H_2O) 7.5 ppm].[51]

The results obtained from ^{31}P nmr studies on the "one pot" reaction of Oleksyszyn and Tyka[25] appear to explain satisfactorily the low yields obtained.

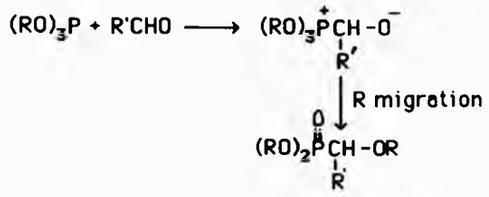
2.4 PHOSPHORUS 31 NMR SPECTRUM STUDIES OF "ONE-POT" SYNTHESIS FOR α-AMINOPROPANEPHOSPHONIC ACID INVOLVING TRIETHYL PHOSPHITE

Further studies were considered necessary to explain the failure of α-aminopropanephosphonic acid (6) to form when a mixture of triethyl phosphite, benzyl carbamate and propanal in acetic acid were allowed to react together. Yet, a similar reaction mixture in the pres ence of boron trifluoride-etherate afforded α-aminopropanephosphonic acid (6) in low yield (20.8%). The ^{31}P nmr

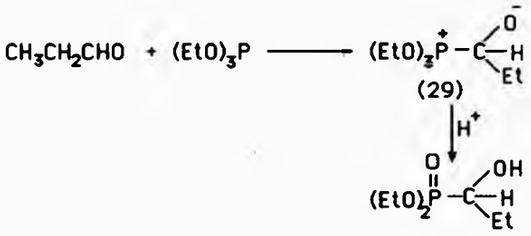
studies were conducted in a similar manner as above.

The observed ^{31}P nmr spectra for the various reactant combinations used were complex. For example, the spectrum of triethyl phosphite in acetic acid gave a sharp singlet at 8 ppm as a major signal, with two doublets around 20 and -2 ppm with J values of 32 Hz as minor signals. The chemical shift of the major peak and its J value (680 Hz) suggests formation of diethyl phosphite. The coupling constants and the chemical shifts for the latter two signals suggested a P-O-P linkage. The structure was unclear, but it was reasonable to suppose that it may contain the grouping (R') (EtO) (O) P-O-P (O) $(OEt)_2$, (where R' is not an ethoxy group).

A mixture of triethyl phosphite and propanal was stirred at room temperature and then heated for 1 h at 80-85 °C. The ^{31}P nmr spectrum was recorded before and after heating the mixture. In both cases, a major signal at 137 and a minor signal at 25 ppm were observed. The former signal arises from the presence of triethyl phosphite whereas, the latter is indicative of a phosphonate. The formation of phosphonates from aldehydes and phosphites has been reported[53] as shown below (Scheme 12). However, the formation of diethyl α-hydroxypropanephosphonate (30), a possible intermediate in the formation of α-amino-propanephosphonic acid (6), would require a protic solvent (Scheme 13).

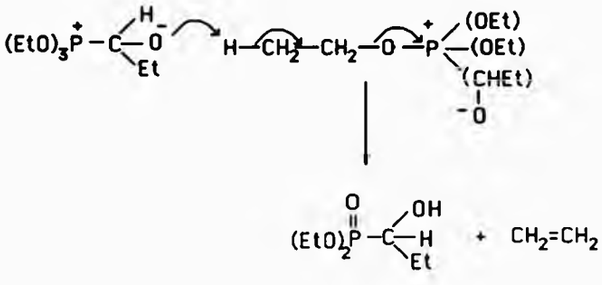


(Scheme 12)



(Scheme 13) (30)

Protons are one of the essential requirements for the formation of (30). In the above case, the reaction was carried out in the absence of any protic solvent. One possible explanation for the formation of (30) could be that the intermediate phosphonium ion (29) may itself act as a proton source, and consequently, attack another phosphonium ion to form (30) and ethene as a second product (Scheme 14).



(Scheme 14)

In order to assign the signal at 25 ppm, the ^{31}P nmr spectrum of the authentic diethyl α-hydroxypropanephosphonate in acetic acid was recorded. A signal at 25.2 ppm was observed which compares well with the above value.

The effect on the ^{31}P nmr spectrum of the addition of acetic acid to a mixture of triethyl phosphite and propanal stirred at room temperature was pronounced. The spectrum of the mixture indicated a mixture of phosphorus-containing compounds. A major signal at 25.2 ppm suggests that the presence of acetic acid has promoted the formation of diethyl α-hydroxypropanephosphonate (Scheme 13). Two minor peaks at 137 and 8 ppm suggested the presence of triethyl phosphite and diethyl phosphite. Additionally, there were two unassigned peaks at 21.9 and 22.6 ppm.

The above mixture was heated under normal reaction conditions and the ^{31}P nmr spectrum recorded. Four peaks were observed at 25, 22.6, 21.9 and 8 ppm, no signal being observed for triethyl phosphite. The peak at 8 ppm which arises from diethyl phosphite increased with respect to the other signals which suggests that heating had promoted its formation.

A mixture of triethyl phosphite and benzyl carbamate in acetic acid was heated at 80-85 °C for 1 h, and then examined by ^{31}P nmr spectroscopy. A signal at 8 ppm was observed with J values around 690 Hz. Again, this suggested preferential formation of diethyl phosphite.

The ^{31}P nmr spectrum of the total reaction mixture containing triethyl phosphite, benzyl carbamate, propanal and acetic acid when heated for 1 h at 80-85 °C, indicated several phosphorus-containing compounds. The major signal at 25.2 ppm was characterised as being due to diethyl α-hydroxypropane-

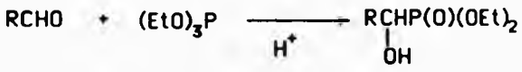
phosphonate. No signal was observed which could have arisen from diethyl (N-benzyloxycarbonyl)-α-aminopropanephosphonate a possible intermediate ester for which the expected signal is in the region of 28-29 ppm (by comparisor with diethyl α-amino-propanephosphonate).[54] Furthermore, two unassigned signals at 21.9 and 22.6 ppm were also observed .

Hydrolysis of the above mixture gave a major signal at 25.9 and a minor signal at 6.4 ppm. The former signal arises from the hydrolysis of the above ester to give the corresponding α-hydroxypropanephosphonic acid as previously confirmed. The above mixture was hydrolysed for an additional 24 h and then examined by ^{31}P nmr spectroscopy. In addition to the above two peaks, a third peak at around 16.9 ppm (trace) was also observed; this suggests the presence of α-aminopropanephosphonic acid (6).

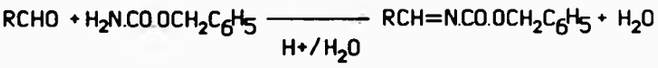
It is conceivable that the above hydrolysate contained a mixture of α-hydroxypropaneohosphonic acid and ammonium chloride which could have reacted to give the required compound (6). The ammonium chloride which had been isolated on various occasions may have originated from the hydrolysis of unreacted benzyl carbamate. In order to support the above proposal, a mixture of α-hydroxypropanephosphonic acid and excess ammonium chloride in acetic acid, was heated under reflux for 72 h. However, the ^{31}P nmr spectrum of the reaction mixture indicated the absence of any α-aminopropanephosphonic acid (6).

When the above reaction was investigated in the presence of boron trifluoride-etherate in toluene, the desired product (6) was obtained in poor yield (20.8%), and the purity of the product as determined by the melting point (245-246 °C) was low.

The preference for α-hydroxypropanephosphonate formation in the case of the reaction between triethyl phosphite and propanal, compared to triphenyl phosphite may be rationalised in terms of competing reactions (Reactions 26, 27).



(Reaction 26)



(Reaction 27)

The present studies indicated that no apparent reaction had occurred between triethyl phosphite and benzyl carbamate in the presence of acetic acid. In the case of triethyl phosphite the predominant reaction appears to be with propanal, to give the corresponding α-hydroxypropanephosphonic acid.

If the reaction proceeds <u>via</u> an imine intermediate its formation may be in equilibrium with the reactants. It is conceivable that the addition of triethyl phosphite to the imine may be slower than its addition to propanal, and therefore the required product (6) is not formed when acetic acid is used as a catalyst. However, when boron trifluoride-etherate in toluene is used as a catalyst instead of acetic acid, it may impede the addition reaction of propanal and triethyl phosphite. This is possibly due to complexation as shown in Scheme 15 which relates to complex formation between benzaldehyde and boron trifluoride-etherate.[55] Consequently, this may favour the addition of the

phosphite to the imine resulting in the formation of the α-aminopropanephosphonic acid (6) in low yield.

In contrast, the less basic triphenyl phosphite reacts with the intermediate imine in the presence of acetic acid to yield α-aminopropanephosphonic acid (6) in approximately 30% yield. Although the ^{31}P nmr spectrum suggested a higher yield in solution, this was not obtained, possibly due to isolation difficulties. The phosphite also reacts with propanal to yield the α-hydroxy product; acetolysis of triphenyl phosphite also occurs to give diphenyl phosphite as suggested by ^{31}P nmr spectrum.

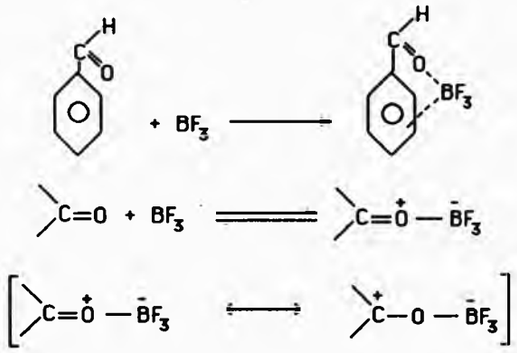
It is probable that formation of the products depends upon an addition reaction of the phosphite, which may show preference for attack at the electrophilic centre of either the carbonyl carbon or the carbon adjacent to the imine double bond.

The above triphenyl phosphite reaction was also investigated in the presence of boron trifluoride-etherate in toluene as catalyst, when the yield of (6) significantly increased to 65%. This result may be due to the absence of acetic acid which causes acetolysis of triphenyl phosphite and the formation of side-products such as diphenyl phosphite. The latter undergoes hydrolysis to give phosphorous acid, which may also cause isolation problems for the α-aminopropanephosphonic acid (6).

The ^{31}P nmr spectrum of the reaction mixture, before and after hydrolysis indicated only one peak in the desired region; suggesting that no major by-products such as the α-hydroxy compound had been formed.

Co-ordination of boron trifluoride with carbonyl compounds, such as benzaldehyde, has been reported in the literature (Scheme 15).[55] A similar interaction may occur between propanal and boron

trifluoride whereby the electrophilicity of the carbonyl C-atom is enhanced. Consequently, nucleophilic attack by benzyl carbamate instead of triphenyl phosphite may favour the formation of the imine and therefore the yield of product (6) increases significantly.



(Scheme 15)

Oleksyszyn and Tyka's[25] "one-pot" procedure using triphenyl phosphite, benzyl carbamate and propanal in glacial acetic acid (Reaction 7) was thus improved by the use of the following modifications:

(i) boron trifluoride-etherate was used as a catalyst with no acetic acid present;

(ii) the reaction time was increased from 1 h to 6 h;

(iii) treatment with propylene oxide in the isolation stage after hydrolysis involved a different procedure requiring only the theoretical amount of propylene oxide to give an immediate precipitation of (6). In contrast, the above workers[25] used a large excess of propylene oxide in order it was said to bring the pH of the solution to 6-7. In practice, a maximum pH of 5 was reached in

the present work, even when 15 X's theoretical amount of propylene oxide was used, and the result in general was to generate an oily precipitate rather than a crystalline material.

The ^{31}P nmr spectrum of the above reaction mixture was recorded before and after hydrolysis to the phosphonic acid; in both cases only one signal was observed at 18 and 17 ppm, respectively. The peak before hydrolysis at 18 ppm is indicative of diphenyl α-(N-benzyloxycarbonyl)-aminopropanephosphonate whilst, the peak after hydrolysis at 17 ppm is that of α-aminopropanephosphonic acid (6). The complete avoidance of the formation of any α-hydroxy compound is attributed to the absence of any proton donor such as acetic acid. Subsequent work-up of the reaction mixture afforded the required compound (6) in 65% yield. This suggests that isolation of α-aminopropanephosphonic acid (6) also presents a problem in the above reaction, as 35% was unaccounted for.

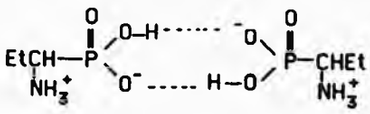
2.5 PREPARATION OF α-AMINO-1-[^{14}C]-PROPANEPHOSPHONIC ACID

The α-amino-1-[^{14}C]-propanephosphonic acid (6*) was synthesised in the present work using 1-[^{14}C]-propionaldehyde. The radio-labelled compound (6*) was required for various biological studies. It was imperative to minimise the loss of the very expensive starting material, 1-[^{14}C]-propionaldehyde, and to aim for the highest possible yield for (6*). Therefore, it was decided to use the above modification of the 'one-pot' method described by Oleksyszyn and Tyka,[25] with boron trifluoride-etherate in toluene used as catalyst. The product, α-amino-1-[^{14}C]-propane-

phosphonic acid (6*) was obtained in 59% crude yield (m.p 256-257 °C). Recrystallisation afforded a crystalline white solid whose melting point (275-276 °C) was however around 10 °C higher than that usually reported. Literature search revealed three additional references, each quoting a different melting point, viz. 350 °C,[29] 286 °C[56] and 271 °C.[57] The first of these can be discounted as being in error, although the other two suggest that a genuine variation in the melting point of the pure compound may occur, possibly because of different crystalline forms.

Although elemental analysis and nmr (^{13}C and ^{31}P) of (6*) were all in very good agreement with those expected for (6) , its ^{1}H nmr spectrum indicated some unusual features when taken immediately after the solution in D_2O was prepared. A sharp singlet around 5.2 ppm was an additional feature not observed previously. Furthermore, the methyl protons and methylene protons appear as though there are two overlapping triplets and overlapping multiplets, respectively. All these additional features disappeared over ten minutes and the final spectrum was identical with that obtained normally.

From the ^{1}H nmr spectrum, it was initially thought that the labelled α-aminopropanephosphonic acid (6*) may be in a hydrated form, but, microanalysis precluded this possibility. It may be possible that (6*) possesses a different crystalline form. For example, a hydrogen-bonded structure (e.g as in Figure1) may exist by some means of association of two or more molecules of (6*). Therefore, the crystal structure of (6*) was investigated by X-ray crystallography.



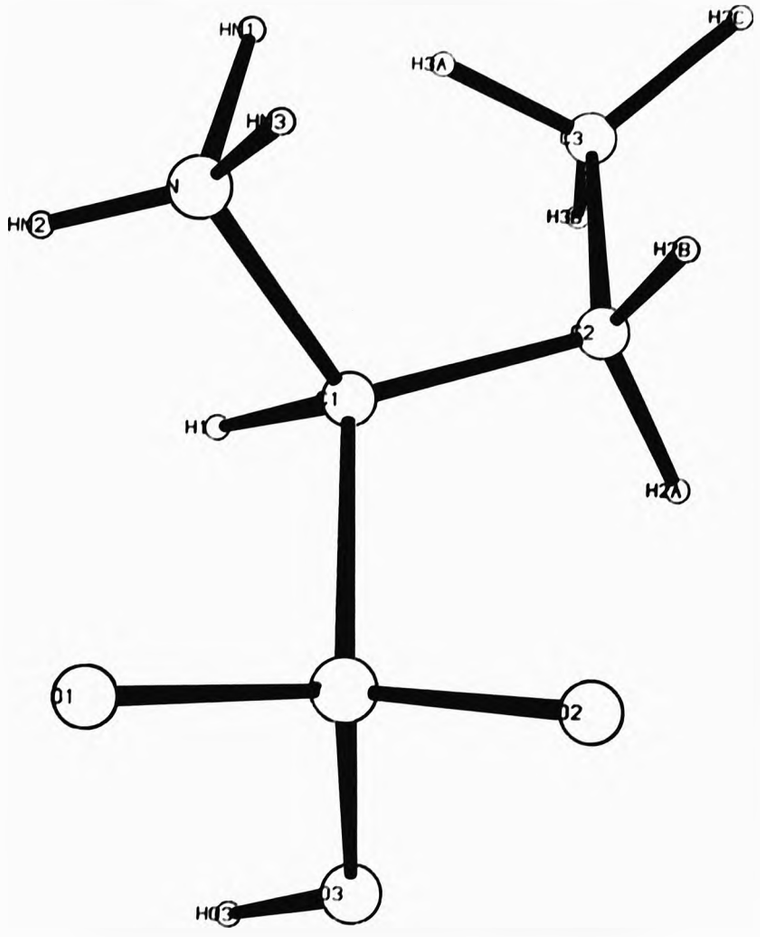
(Figure 1)

2.5.1 CRYSTAL STRUCTURE DETERMINATION OF 1-[^{14}C]-α-PROPANEPHOSPHONIC ACID INVOLVING A COMPARISON OF BOND LENGTHS MEASUREMENTS WITH SIMILAR COMPOUNDS

The reason for the examination was to determine whether the unusually high melting point is a consequence of a different crystal structure. The result obtained could then be compared with the crystal structure of α-aminopropanephosphonic acid (6) which was investigated simultaneously by Volckman *et al.*[8] in this laboratory.

The data of the crystal structure determination of radio-labelled α-aminopropanephosphonic acid (6*) were as follows: $C_3H_{10}O_3PN$, M = 139.09, monoclinic, a = 11.064 (2), b = 6.200 (2), c = 9.520 (2) A, = 107.31 (2) ∘, U = 622.94 Å^3, space group P2 1/c, Z = 4, Dc = 1.48 gcm^{-3}, F(OOO) = 296, u (Mo-K) = 2.95 cm^{-3}

The structure was solved using the direct method involving single crystal analysis. The result suggested that the compound is zwiterionic having a P=O, one P-OH, and a P-O$^-$ bond (Figure 2).



(Figure 2)

Table 6: Bond lengths (Å) about phosphorus in aminoalkanephosphonic acids, 1-guanidinopropane-phosphonic acid, and 1-[^{14}C]- α-aminopropanephosphonic acid.

Compound	P-C	P-OH	P-O	P-O	ref
XCH_2NH_2	1.82	1.51	1.51	1.49	59
$XCH_2CH_2NH_2$	1.80	1.51	1.51	1.50	60
$XCH_2CH_2CH_2NH_2$	1.81	1.53	1.53	1.51	61
$XCH_2NHCH_2CO_2H$	1.82	1.50	1.50	1.50	62
$XCH(Et)NHC(:NH)NH_2$	1.81	1.52	1.59	1.50	11
$XCH(Et)NH_2$ (6*)	1.83	1.55	1.49	1.49	

X= $P(O)(OH)_2$

A comparison of the above data for 1-[^{14}C]-α-amino-propanephosphonic acid (6*) with those obtained by Volkman *et al.*[58] for unlabelled α-aminopropanephosphonic acid (6) indicated an identical crystal structure. Additionally, the P-C and P-O bond lengths agreed reasonably well with those reported for various phosphonic acids (Table 6). The P-OH bond was slightly longer (1.55 Å) which is the crystal packing arrangements and the strong hydrogen bonding involving these bonds.

A literature search revealed only one reference which may provide a possible explanation for the differences in melting points for compound (6) and labelled compound (6*). Polymorphism has been demonstrated by Horiguchi and Kindatsu[63] for 2-aminoethylphosphonic acid (7, Chapter 1) which was shown to have two crystalline forms. A rhombic form, designated 'α' was most frequently obtained on rapid mixing of a hot, concentrated aqueous solution with an equal volume of hot ethanol. Needle crystals (the β

form) were obtained when a dilute solution of the compound was mixed slowly at room temperature with an equal volume of hot ethanol. The authors[63] claimed that the β form was the more stable form. Several different melting have been observed for 2-aminoethylphosphonic acid (7). These may be attributed in-part to polymorphism, but they also noted that the rate of heating had an effect on the melting point of compound (7). In addition, they observed that melting point was made difficult by preliminary sintering, darkening, and finally decomposition.

In the present studies, labelled α-aminopropanephosphonic acid (6*) was recrystallised with water and ethanol. The procedure involved rapid addition of hot ethanol to a hot concentrated aqueous solution of (6*) until a permanent faintness was observed. Crystallisation was rapid when the hot solution was allowed to cool down. The melting process involved sharp disintegration of crystals within a narrow range (275-276 °C). Upon cooling and re-melting the same crystals, the melting point decreased to 259-260 °C, suggesting a change in crystalline form.

It is possible that polymorphism may have been exhibited by (6*) and consequently, various changes were observed. One form may predominate initially and therefore, a higher melting point was observed. However, cooling may cause even crystallisation of both forms, and a decrease in subsequent melting point is observed.

Additionally the differences in ^{1}H nmr spectra may be explained using a similar proposal. If there are two forms of crystals, it is conceivable that one form may have stronger hydrogen bonding and therefore, the solvation time in deuterated water may differ, which may explain the gradual changes observed

in the ^{1}H nmr spectrum.

The X-ray crystallography in the present work and those of Volkman *et al.*[58] involved single crystal analysis. It is possible that on both occasions the same crystal form was analysed and consequently no apparent differences were observed.

CHAPTER 3

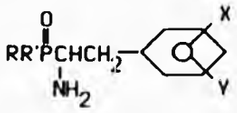
SYNTHESIS OF DERIVATIVES OF α-AMINOPROPANEPHOSPHONIC ACID

3.1 SYNTHESIS OF TETRAPHENYL N,N-THIOURYLENE-(1,1-DIPROPYL)-1,1-DIPHOSPHONATE

The synthetic programme so far conducted has been concerned with an investigation into different synthetic routes for α-aminopropanephosphonic acid (6, Chapter1). These studies involved the use of reported literature routes and various modifications of these procedures to provide alternative new routes. Detailed ^{31}P nmr studies of the two routes for the synthesis of α-aminopropanephosphonic acid were also conducted. These routes involved the reaction of benzyl carbamate and propanal with either an aryl phosphite or an alkyl phosphite in the presence of acetic acid. Further development of the ^{31}P nmr studies led to a modified route involving the use of boron trifluoride-etherate for the synthesis of the α-aminopropane-phosphonic acid (6) whereby the yield improved to 65%.

So far, few derivatives of α-aminopropanephosphonic acid (6) have been prepared, although some occur as reaction intermediates. Therefore, it was of interest to synthesise further derivatives of (6) in order to study both physical properties and fungicidal activity. The α-carbon chain length was kept constant whilst modifying various other groups, so that fungicidal activity could be compared directly with that of (6). Additionally, interest was directed towards the synthesis of various diphosphonic esters linked by a bridging ureido or thioureido group.

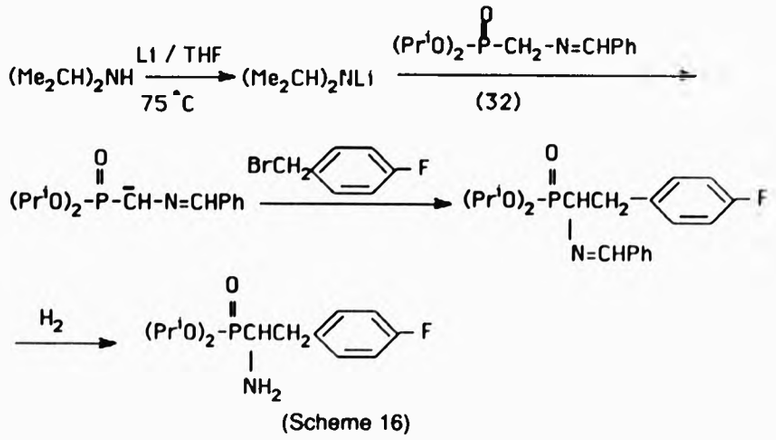
Maier[64] reported the synthesis of various substituted α-aminoethanephosphonic acids (31) and the corresponding phosphonates.



(31)

Where R R' = alkyl, alkoxy, OH; X= H, halo, alkyl, alkoxy, $CH_2CH(NH_2)P(O)RR'$ and other derivatives; Y= H, halo, alkyl, alkoxy and other derivatives.

The synthesis involved the interaction of di-isopropylamine, used as the lithium salt, with an imine (32). The resultant intermediate was allowed to react with a substituted benzyl bromide followed by reduction to yield the desired product (Scheme 16).[64]



(Scheme 16)

Maier reported[64] that many substituted benzyl bromides were used to synthesise compounds of type (31), several of which were effective seed dressings against *Fusarium nivale*.

Birum[39] reported the synthesis of various diphosphonates from the reaction of a phosphite, an aldehyde, and urea (Chapter 1). Hydrolyses of these phosphonates yielded the corresponding phosphonic acids. However, the only phosphonic acid reported by Birum[39] was α-ureidopropanephosphonic acid (33).

$(HO)_2P(O)CH(Et)NHC(:O)NH_2$

(33)

The ^1H nmr spectrum of this compound was recorded in DMSO-d_6 and appeared to provide the only literature reference[39] to the observation of the $P(OH)_2$ and NH protons of an amino-alkanephosphonic acid. It was reported that the NH group gave a broad signal at 6.2 whilst the $P(OH)_2$ and the NH_2 protons were revealed as a broad signal at 8.5 ppm.

In the present work the ammonium salt of α-ureido-propanephosphonic acid (17, Chapter1) was obtained unexpectedly when triethyl phosphite was allowed to react with propanal and urea. The ^1H nmr in DMSO-d_6 of this compound revealed a slightly different pattern to that of (6). In addition to the protons of the alkyl chain, the NH signal appeared as a sharp doublet at δ 7.3 ($^3J_{PCNH}$ 8 Hz). Furthermore, the NH signal was observed around 3.79-3.95 as a doublet, which exchanged over 0.5 h when the spectrum was run in D_2O.

Using the method described by Birum[39] various novel derivatives of α-aminopropanephosphonic acid (6) were synthesised, although work-up procedure and isolation of these derivatives required several modifications.

Initially, the procedure of Birum[39] was extended for the synthesis of tetraphenyl N,N-thiourylene-(1,1-dipropyl)-1,1-

diphosphonate (34) from the reaction of triphenyl phosphite, thiourea, and propanal in the absence of a catalyst (Reaction 28).

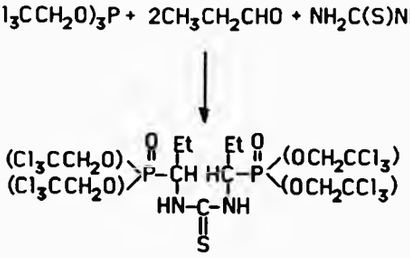
$$2(PhO)_3P + NH_2C(S)NH_2 + 2CH_3CH_2CHO \longrightarrow [(PhO)_2(O)PCH(Et)NH]_2C=S$$

(34) (Reaction 28)

The procedure used was similar to that reported by Birum[39] for the synthesis of the butyl analogue of (34). The final product was recrystallised from dichloromethane instead of acetonitrile to yield the novel tetraphenyl N,N-thiourylene-(1,1-dipropyl)-1,1-diphosphonate (34) as a crystalline white solid in good yield (58%). This compound was fully characterised by elemental analysis, nmr (^1H, ^{13}C, ^{31}P) and mass spectroscopy.

3.2 SYNTHESIS OF DIPHOSPHONATES USING TRIS(2,2,2,-TRIHALOETHYL) PHOSPHITES, PROPANAL, UREA OR THIOUREA

Further derivatives were synthesised using different phosphites such as tris-2,2,2-trichloroethyl phosphite and tris-2,2,2-trifluoroethyl phosphite. The former was synthesised from phosphorus trichloride and 2,2,2-trichloroethanol in the presence of pyridine. Distillation under high vacuum yielded pure tris-2,2,2-trichloroethyl phosphite,[65] which was then allowed to react with thiourea and propanal (Reaction 29) in an analogous procedure to that used for the synthesis of (34).



(35) (Reaction 29)

On this occasion a longer reaction time was employed. However, the ^{31}P nmr spectrum gave two signals at δ 24.9 (major) and 137.6 ppm, the latter of which indicated the presence of the parent phosphite.

The slower reaction in this case may probably be due to the lower nucleophilicity and basicity[66] of tris-2,2,2-trichloroethyl phosphite, when compared to the corresponding triphenyl phosphite. The -I effect of the trichloroethyl groups causes a lower electron density on the phosphorus atom, causing it to be a poorer nucleophile.

The work-up procedure involved three recrystallisations: twice from acetone and once from acetonitrile. Tetrakis(2,2,2-trichloroethyl) N,N-thiourylene-(1,1-dipropyl)-1,1-diphosphonate (35) was obtained as a crystalline white solid. It was fully characterised by elemental analysis, and nmr (^{1}H, ^{13}C, ^{31}P) spectroscopy. Mass spectrometry of this compound revealed some unusual features which will be discussed further on page 72.

When urea was substituted for thiourea the novel tetrakis(2,2,2-trichloroethyl) N,N-urylene-(1,1-dipropyl)-1,1-diphosphonate (36) was obtained (Reaction 30).

$$2(Cl_3CCH_2O)_3P + 2CH_3CH_2CHO + H_2NC(O)NH_2 \rightarrow [(Cl_3CCH_2O)_2(O)PCH(Et)NH]_2C{=}O$$

(36) (Reaction 30)

Compound (36) was characterised similarly; mass spectrometry of this compound again revealed some unusual features.

In the mass spectra of (35) and (36) the ions of highest m/e value were one unit more than the expected molecular ions. Thus, the expected molecular ion for compound (35) was 840 instead of the observed 841, calculated on the relative atomic mass of chlorine 35. The observed molecular ion for (36) was 825 instead of 824. Such a phenomenon which displays the presence of a protonated molecular ion, instead of a molecular ion, has been reported[67] for a small number of compounds (approximately 10 out of 1400) under electron ionisation mass spectroscopy. The authors claimed that the common features in all the compounds were that they all contained carbonyl groups and hydrocarbon portions.

Chlorine exists as two isotopes having different atomic masses, 35 and 37, the relative abundances being 3:1 respectively. Therefore, in mass spectrometry a compound containing a single chlorine atom gives two molecular ions separated by two mass units in a ratio of 3:1. Compounds containing higher numbers of chlorine atoms give correspondingly more complex spectra. In the case of compound (35) and (36), both of which contain 12 chlorine atoms, the spectra are extremely complex and difficult to

interpret.

Tris-2,2,2-trifluoroethyl phosphite was allowed to react with propanal and urea or thiourea (Reactions 31 and 32).

$$2(F_3CCH_2O)_3P + 2CH_3CH_2CHO + NH_2C(O)NH_2 \rightarrow [(F_3CCH_2O)_2(O)PCH(Et)NH]_2C=O$$

(37) (Reaction 31)

$$2(F_3CCH_2O)_3P + 2CH_3CH_2CHO + NH_2C(S)NH_2 \rightarrow [(F_3CCH_2O)_2(O)PCH(Et)NH]_2C=S$$

(38) (Reaction 32)

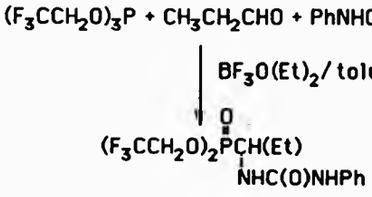
These products were isclated as white crystalline solids, but with considerably lower melting points than those of the chloro analogues.

The ^{1}H and ^{13}C nmr of compounds (37 and 38) indicated some interesting features, whereas the mass spectra gave the expected molecular ion peaks at m/z 632 for (37) and 648 for (38).

3.3 SYNTHESIS OF MONOPHOSPHONATE USING TRIS(2,2,2,-TRIFLUOROETHYL) PHOSPHITE, PROPANAL AND PHENYLUREA

A further derivative was prepared, involving the use of 2,2,2-trifluoroethyl phosphite, propanal and phenylurea in the

presence of boron trifluoride etherate (Reaction 33).



(39) (Reaction 33)

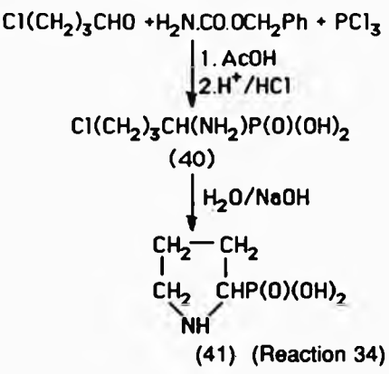
Reaction 33 was initially investigated using a similar procedure to that of Birum.[39] However, this proved to be very slow, as indicated by the ^{31}P nmr of the reaction mixture after 1 h. A large peak at δ 137.9, corresponded to the presence of the parent phosphite whilst a second smaller peak at δ 26.1 corresponded to the product. Boron trifluoride-etherate in toluene was therefore added to this mixture and the reaction time increased. A white solid, which precipitated gradually over several weeks, was filtered off, washed with ethyl acetate, and dried to yield the desired bis(2,2,2-trifluroethyl)-α-phenylureidopropanephosphonate (39) as a pale pink solid. At this stage, the work-up procedure was modified from that reported in the literature,[39] in order to isolate further crops from the mother liquor. The mother liquor was concentrated *in vacuo* to give a brown residue which was dissolved in ethyl acetate and then treated with light petroleum ether. The resultant mixture was stored at 4 °C for several weeks. A second crop of the product which crystallised after several weeks was filtered off, washed with ethyl acetate and dried in a vacuum oven at 50 °C. The above procedure was repeated to give a further crop. The combined crops were recrystallised from water

and ethanol to yield bis(2,2,2-trifluoroethyl)-α-phenylureido-propanephophonate (39) as a crystalline white solid in 48.6% yield.

The compound was fully characterised by elemental analysis, nmr (^{1}H, ^{13}C, ^{31}P) and mass spectrometry. The nmr spectra (^{1}H and ^{13}C) of this compound showed similar features to those of the other fluoro derivatives synthesised in the present work.

3.4 SYNTHESIS OF TETRA(PHENYL) N,N-THIOURYLENE1,1-DI(3-METHYLSULPHENYL)PROPYL-1,1-DIPHOSPHONATE AND TETRAKIS(2,2,2-TRIFLUOROETHYL) N,N-URYLENE-1,1-DI(3-METHYLSULPHENYL)PROPYL-1,1-DIPHOSPHONATE

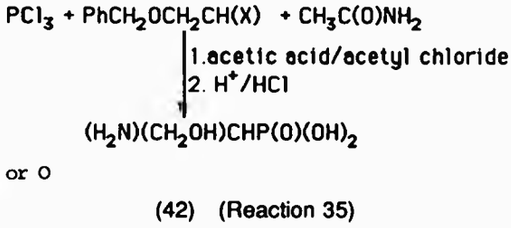
Further α-aminoalkanephosphonic acid (8) derivatives were synthesised whereby interest was directed towards different substituents at the end of the carbon chain. Possible substituents which have been reported in a few cases for these acids (8) include halogen, hydroxy and methylsulphenyl groups. Subotkowski *et al.*[68] reported the synthesis of the phosphonic analogue of proline (41), which required the synthesis of the intermediate ω-chloro-α-aminobutanephosphonic acid (40). The latter was cyclised in alkaline medium to give (41) in 38% yield (Reaction 34).



(41) (Reaction 34)

Compound (40) is one of the few reported aminophosphonic acids substituted at both the α-and ω- position.

An extension of the above work was later reported by Lejczak *et al.*[69] for the synthesis of the phosphonic acid analogue of serine (42). These workers caused phosphorus trichloride to react with acetamide and benzyloxyacetaldehyde or its diethyl acetal for the synthesis of compound (42) (Reaction 35).



X = $(OC_2H_5)_2$ or O

(42) (Reaction 35)

The authors also claimed[69] that when triphenyl phosphite, benzyl carbamate and benzyloxyacetaldehyde were used for the above reaction, the corresponding diphenylester was obtained in 51% yield (43). The latter was deprotected and subsequently used for peptide synthesis.

$(PhCH_2O.OC.)NH(PhCH_2O_2CH_2)CHP(O)(OPh)_2$

(43)

So far, however, there have been no reports concerning the studies of fungicidal activity of above types of ω-substituted α-aminoalkanephosphonic acids or the corresponding esters.

It seemed desirable therefore, to prepare similar compounds to the above, for fungicidal studies. Thus, the synthesis of (44) may possibly be achieved by using β-chloropropanal with a phosphite and urea.

$[(RO)_2P(O)CH(NH)CH_2CH_2Cl]_2C=O$

(44)

Subsequent hydrolysis of (44) with concentrated hydrochloric acid would then be expected to yield the novel ω-chloro-α-aminopropanephosphonic acid (45).

$ClCH_2CH_2CH(NH_2)P(O)(OH)_2$

(45)

There are various reports[70,71] concerning the synthesis of the required β-chloropropanal involving the interaction of acrolein with dry hydrogen chloride at -10 °C. The procedure of Shriner *et. al.*[70] was re-investigated but, only a brown polymer was obtained.

The above result is not entirely unexpected as the results of these workers[70] indicated the instability of the desired compound; they reported that the aldehyde should be distilled quickly in a stream of dry nitrogen and must be used immediately. Although these precautions were followed in the present work, no distillable product was obtained.

Acrolein does not undergo an aldol condensation[72] and therefore, polymerisation may be the result of an initial 1,2 addition followed by elimination of hydrogen chloride.

A subsequent literature search yielded a further reference[73] suggesting the instability of β-chloropropanal and its rapid polymerising ability. Repetition of the above reaction at lower temperature (-35 °C) again failed to yield the required compound and therefore, this route for the synthesis of β-chloropropanal was abandoned, as was the preparation of compound (45) by this route.

Tam *et al.*[74] reported the synthesis of phosphonic analogues of methionine, ethionine and related compounds. These workers synthesised phosphonomethionine (46) and various intermediates from commercially available 3-methylsulphenylpropanal, triphenyl phosphite and phenylthiourea in acetic acid (Reaction 36). The reactants were mixed and stirred at room temperature, and the intermediate ester was isolated.[74]

$$CH_3SCH_2CH_2CHO + (PhO)_3P + PhNHC(S)NH_2$$

$$\downarrow AcOH$$

$$CH_3S(CH_2)_2CHP(O)(OPh)_2$$
$$PhNHC(S)NH$$

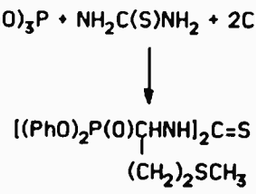
$$\downarrow H^+/HCl$$

$$CH_3S(CH_2)_2CH(NH_2)P(O)(OH)_2$$

(46) (Reaction 36)

The procedure of Tam *et. al.*[74] was modified in the present work, for the synthesis of tetraphenyl N,N-thiourylene-1,1-di(3-

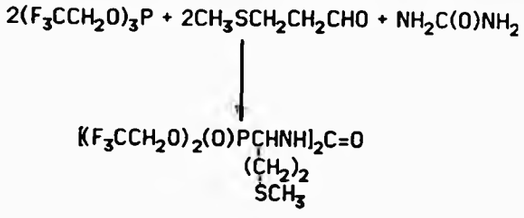
methylsulphenyl)propyl-1,1-diphosphonate (47) (Reaction 37).



(47) (Reaction 37)

The reaction was investigated in the absence of acetic acid, as our previous studies had indicated that acetic acid reacts with triphenyl phosphite to yield di-and mono-phenyl phosphite (Chapter 2). Sodium-dried toluene was used as the solvent to give a homogeneous solution and the resultant mixture was heated for 1 h. A feathery white solid crystallised after several months when the reaction mixture was left at room temperature. After recrystallisation, the product (47) was fully characterised by elemental analysis, nmr (^{1}H, ^{13}C, ^{31}P) and mass spectrometry which gave a peak at m/z 716 consistent with the parent ion.

By combining and modifying the procedures of Birum[39] and Tam *et al.*[74] further derivatives were synthesised including tetrakis (2,2,2-trifluoroethyl) N',N' -urylene- 1, 1 -di (3-methyl-sulphenyl)-propyl-1,1-diphosphonate (48) which was obtained by the reaction of 2,2,2-trifluoroethyl phosphite, urea and 3-methylsulphenylpropanal (Reaction 38).



(48) (Reaction 38)

Boron trifluoride-etherate was used as a catalyst, since present studies have indicated the low reactivity of (2,2,2-trifluoroethyl) phosphite, compared with that of triphenyl phosphite.

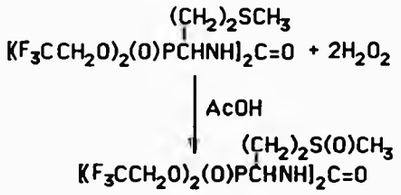
The compound was isolated as crystalline white needles, having complex nmr spectra (^{1}H, ^{13}C) compared with those of the analogous fluoro derivatives synthesised in the present work. In addition, a single signal at 27.1 ppm was observed in the ^{31}P nmr spectrum, whilst the mass spectrum gave a peak at m/z 740 consistent with the parent ion.

3.5 OXIDATION OF TETRAKIS(2,2,2-TRIFLUOROETHYL) N,N-URYLENE-1,1-DI(3-METHYLSULPHENYL)PROPYL-1,1-DIPHOSPHONATE

T a m *et al.*[74] also reported the oxidation of phosphomethionine to the corresponding sulphoxide or sulphone. This was achieved using hydrogen peroxide in glacial acetic acid; the nature of the product was dependent on the molar ratio of hydrogen peroxide used.

In order to obtain the sulphoxide, tetrakis(2,2,2-

trifluoroethyl) N,N-urylene-1,1-di(3-methylsulphenyl)propyl-1,1-diphosphonate (48), was treated with a solution of hydrogen peroxide in glacial acetic acid in 1:2 molar ratio (Reaction 39).



(49) (Reaction 39)

The aim of the synthesis of (49) was not only to obtain a new derivative for fungicidal studies but, to provide a possible precursor for the synthesis of the corresponding ω-chloro analogue (50) (see page.82).

$$[(F_3CCH_2O)_2(O)PCH(NH)CH_2CH_2Cl]_2C{=}O$$

(50)

According to Tam *et al.*[74] the oxidation product of phosphonomethionine was isolated as a white solid, when the residue from the reaction mixture was dissolved in a mixture of water and methanol and then the warm solution was treated with acetone.

In the present study the final residue was treated according to the reported procedure which gave an oil. Crystallisation of this oil over several weeks yielded the required tetrakis(2,2,2-trifluoroethyl) N,N-urylene-1,1-di(3-methylsulphinyl)propyl-1,1-diphosphonate (49) as a white solid.

The ^{1}H and ^{31}P nmr spectra of compound (49) gave little

information since the chemical shifts were similar to those of the parent compound (48). However, the melting point (151 °C) of this solid was higher than that of compound (48), and the mass spectrum gave a definite signal at m/z 756 in agreement with the parent ion. The ^{13}C nmr spectrum indicated the characteristic shift for the methylene group adjacent to the sulphoxide group. The chemical shift at δ 35.9 ppm was at a higher field than for the methylene group of the parent compound (48), indicating the additional deshielding effect on the carbon atom which arose from the presence of the oxygen. Surprisingly, the deshielding of the methyl carbon was very small.

It was of interest to synthesise tetrakis(2,2,2-trifluoroethyl) N,N-urylene-1,1-di(-3-chloropropyl)-1,1-diphosphonate (50) In addition to being a new derivative for fungicidal studies, compound (50) may provide an alternative route for the synthesis of the much desired novel derivative, the ω-chloro-α-aminopropanephosphonic acid (45).

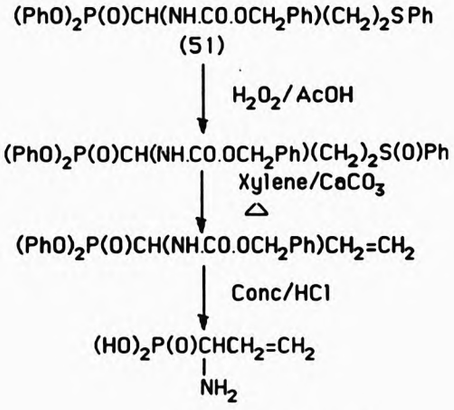
$$ClCH_2CH_2(NH_2)CHP(O)(OH)_2$$

(45)

A possible route for the synthesis of (50) involved the initial introduction of a double bond at the end of the alkyl carbon chain by sulphoxide elimination from compound (49). Treatment with hydrogen chloride of the alkene would give the corresponding ω-chloro analogue (50). Subsequent hydrolysis of (50) with concentrated hydrochloric acid would be expected to yield ω-chloro-α-aminopropanephosphonic acid (45).

Sulphoxide eliminations[75,76] have become widely used for

the introduction of a double bond into a molecule, an example being the synthesis of α-aminoalkenephosphonate by sulphoxide elimination from α-sulfinylated alkylphosphonates.[77] Vo-Quang *et al.*[78] reported the synthesis of 1-amino-2-propenylphosphonic acid (52) through sequential oxidation, sulphoxide elimination and deprotection of diphenyl 1-(N-benzyloxycarbonyl)-amino-3-[(phenylthio)propyl]phosphonate (51) (Reaction 40).



(52) (Reaction 40)

Calcium carbonate was used as a sulphinic acid trapping agent,[79] when the intermediate sulphoxide was thermolysed in refluxing xylene.

It was decided to apply a similar procedure for the thermolysis of tetrakis(2,2,2-trifluoroethyl) N',N'-urylene-1,1-di(3-methylsulphinyl)propyl-1,1-diphosphonate (49), in-order to obtain the corresponding propenyl analogue (53).

$[(F_3CCH_2O)_2(O)PCH(CH{=}CH_2)NH]_2C{=}O$

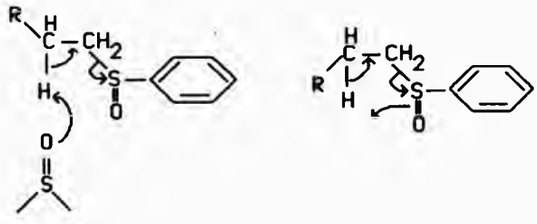
(53)

This reaction was attempted according to the procedure of Vo-Quang *et al.*[78] After cooling, the mixture was filtered, and the solution was concentrated to give an oily residue. This residue in methanol did not crystallise, even after several months when stored at 4 °C. Furthermore, in addition to all the other signals, the ^1H nmr of this oil gave a peak at δ 1.9 corresponding to the methyl signal adjacent to the sulphoxide group suggesting the presence of the parent compound. Additionally, the chemical shifts of the γ and β-methylene protons were identical with those of the parent compound, indicating the absence of alkene protons which would have been expected at lower field.

The failure of compound (49) to undergo elimination of the sulphoxide group may have been due to two factors. The solubility of (49) in xylene was poor, even when the mixture was refluxed for 24 h; this immiscibility may have prevented thermolysis. Secondly, in the present studies 3-methylthiopropanal was used instead of 3-phenylthiopropanal as used by the above workers.[78] Consequently, a less stable methyl sulphinyl ion ($MeSO^-$) may have been formed as a result of thermolysis. This is less favourable compared to the formation of the phenyl sulphinyl ion ($PhSO^-$), which would be stabilised by resonance and is a better leaving group (Scheme 17).

(Scheme 17)

The mechanism of the sulphoxide elimination may involve a β- proton elimination by inter or intra molecular reaction (Scheme 18).



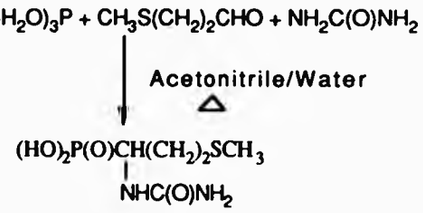
(Scheme 18)

At this stage, our investigation of the synthesis of tetrakis-(2,2,2-trifluoroethyl)N,N-urylene-1,1-di(-3-chloro-propyl)-1,1-diphosphonate (50) was stopped, due to the difficulties experienced in the synthesis of the propenyl precursor (53).

3.6 PREPARATION OF α-UREIDO-3-(S-METHYLSULPHENYL) PROPANE PHOSPHONIC ACID

Interest was also directed towards the synthesis of a new type of phosphonic acid. This was achieved using a modification of the method of Birum[39] for the synthesis of α-ureidopropane-phosphonic acid. It was decided to synthesise the analogous α-

ureido-3-(S-methylsulphenyl)propanephosphonic acid (54) from 3-methylsulphenylpropanal, tris-2,2,2-trichloroethyl phosphite and urea (Reaction 41).



(54) (Reaction 41)

In order to isolate product (54), the residue from the reaction mixture was treated with a mixture of acetonitrile and water, according to the reported[39] procedure. However, no precipitation was observed, so the work-up procedure was modified by concentrating the residue *in vacuo*, followed by the addition of ethyl acetate to the concentrate. The resultant yellow residue was stored at 4 °C for several weeks during which a white solid gradually precipitated. This solid was filtered, washed with ether and dried to yield the new α-ureido-3-(S-methyl-sulphenyl)-propanephosphonic acid (54) in low yield (15.6 %). The low yield of (54) is probably due to the low nucleophilicity and therefore basicity of tris-2,2,2-trichloroethyl phosphite. The low nucleophilicity is the result of the -I effect due to chlorine atoms which withdraws the lone pair electron density from phosphorus. Compound (54) was fully characterised by elemental analysis and nmr spectroscopy (^{1}H, ^{13}C, ^{31}P). The ^{1}H spectrum in $CDCl_3$ was complex but revealed a similar pattern to that observed by Birum[39]

for the analogous α-ureidopropanephosphonic acid (33). The main differences were an additional singlet observed at δ1.85 for the ω-methyl group, and a triplet for the γ-methylene protons. The ^1H nmr spectrum of (54) in D_2O indicated an absence of the NH signal; this was in contrast to the earlier observation for the ammonium salt of α-ureidopropanephosphonic acid (17, Chapter 1), in which the NH proton was replaced only slowly by deuterium.

3.7 CARBON 13 NMR SPECTROSCOPY OF COMPOUNDS OF TYPE $[(RO)_2P(O)CH(R')(NH)]_2C=X$ WHERE R = ALKYL or PHENYL; R' = Et OR CH_3CH_2SMe; X = O OR S

An examination of the spectral characteristics of these compounds (Table 7 & 8) showed a number of general trends. It was found that derivatives with fluorine groups had more complicated spectra, especially in the case of ^{13}C nmr spectra.

Table 7:

Compound	Solvent	$^1J_{PC}$	$^2J_{PCC}$	$^3J_{PCCC}$	$^3J_{PCNC}$	$^2J_{POC}$
$[(RO)_2P(O)CH(NH)CHCH_2R']_2C=X$						
R = Ph, R' = CH_3, X = S	$CDCl_3$	152.6	-	12.8	8.6	
R = Ph, R' = CH_2-S-CH_3, X = S	$CDCl_3$	151.4	3.1	16.8	7.9	
R = Cl_3CCH_2, R' = CH_3, X = S	$CDCl_3$	147.6	-	11.8	8.9	6.7, 6.1
R = CCl_3CH_2, R' = CH_3, X = O	$CDCl_3$	146.9	-	11.7	9.3	6.7, 6.2
R = CF_3CH_2, R' = CH_3, X = S	$CDCl_3$	155.0	3.0	13.4	-	6.7, 6.2
R = CF_3CH_2, R' = CH_3, X = O	$CDCl_3$	155.3	3.1	13.3	-	6.7, 6.2
R = CF_3CH_2, R' = CH_2SCH_3, X = O	MeOD	160.8	3.1	16.3	-	7.0, 7.2
R = CF_3CH_2, R' = $CH_2S(O)CH_3$, X = O	MeOD	160.2	3.1	16.1	-	7.1, 7.0

Table 8: Carbon 13 nmr spectroscopy of compounds of type $(RO)_2P(O)CH(NHX)CHCH_2R'$

Compound	Solvent	$^1J_{PC}$	$^2J_{PCC}$	$^3J_{PCCC}$	$^3J_{PCNC}$
$(RO)_2P(O)CH(NHX)CHCH_2R'$					
R = CF_3CH_2, R' = CH_3, X = CONHPh	MeOD	154.3	2.9	13.6	
R = H, R' = CH_2-S(O)CH_3, X = $C(O)NH_2$	D_2O	161.3	1.6	15.8	10.3

From the above ^{13}C nmr spectral data it can be seen that on average the $^{1}J_{PC}$ values range from 147 to 161 Hz, with fluoro derivatives generally showing higher coupling constants than the chloro analogues.

Cameron *et al.*[80] reported the synthesis, and nmr studies of N-(ω-guanidinoalkyl)aminoalkanephosphonic acids (55) and their aminophosphonic acid precursors. A study of the ^{13}C nmr spectroscopy of these compounds by the above workers indicated that, upon protonation, a marked increase in the $^{1}J_{PC}$ values was observed.

$(NH_2)(NH:)CNH(CH_2)_nNHCH_2P(O)(OH)_2$

(55)

Similar increases in $^{1}J_{PC}$ values have been reported by Appleton *et al.*[81] during the two stages of protonation of α-aminomethanephosphonic acid (56) (X to Z).

$NH_3^+CH_2P(O)(O^-)(O^-)$ $NH_3^+CH_2P(O)(O^-)(OH)$ $NH_3^+CH_2P(O)(OH)(OH)$

(X) (Y) (Z)

A possible explanation for the increase in $^{1}J_{PC}$ values is that upon protonation the phosphorus becomes more deshielded by the oxygen (since there is a net reduction of negative charge around oxygen); and therefore the coupling between phosphorus and the α-carbon increases.

The above reasoning may also account for the differences observed in $^{1}J_{PC}$ values for the chloro and fluoro analogues in the present studies (Table 8). Fluorine being more electronegative than chlorine deshields the phosphorus more, and as a result larger $^{1}J_{PC}$

values were observed.

The $^{2}J_{PCC}$ values were found to be either zero or very small. In general, for all the fluoro analogues small $^{2}J_{PCC}$ values (~ 3.1 Hz) were observed whereas, for α-ureido-3-(S-methylsulphenyl)-propanephosphonic acid (54) this value was 1.6 Hz. In the latter case phosphorus to β-carbon coupling was unexpected since, so far, in the present studies similar phosphonic acids had $^{2}J_{PCC}$ values of zero.

The $^{3}J_{PCCC}$ values are similar (11-16 Hz) and unaffected by varying the substituents. However, an interesting feature was that the $^{3}J_{PCNC}$ values were zero for all the fluoro analogues whereas a value of 8-10 Hz wac observed for all the other derivatives.

It was also observed that the chemical shift for the ureido carbon was in general around 158-160 ppm, whereas the thioureido carbon gave a signal around 185 ppm. The electronegativity of oxygen is higher than that of sulphur. Therefore, oxygen would deshield the carbon to a greater extent than the sulphur; and consequently it would be expected that the ureido carbon should be at a lower field than the corresponding thioureido carbon. However, the observed spectra showed a reversal in field positions, the thioureido group appearing at lower field than the ureido carbon. Although similar results have been observed for other urea and thiourea derivatives, no explanation can be offered for these results.

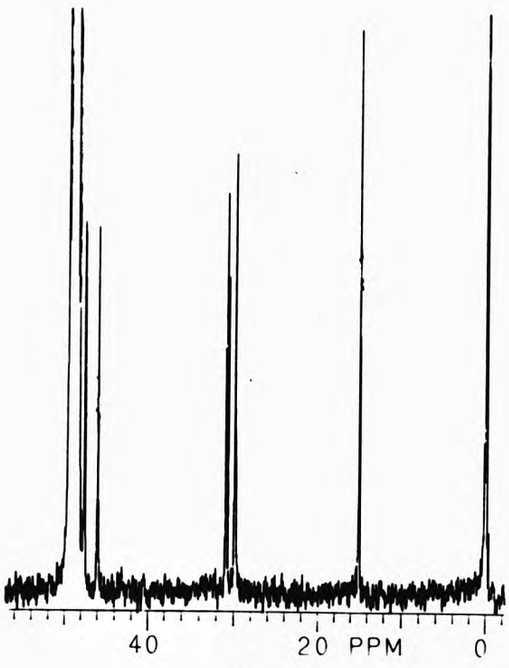
3.7.1 CARBON-13 NMR SPECTROSCOPY OF TETRAKIS(2,2,2-TRIFLUOROETHYL)N,N-URYLENE-1,1-DI(3-METHYL SULPHENYL)PROPYL-1,1-DIPHOSPHONATE

The ^{13}C nmr spectra of this type of compound were interesting and complex. It was noticed that the 80 MHz spectrum although useful for the initial characterisation of these compounds, appeared to be insufficient for detailed information on various couplings. In order to study the spectrum complexity the ^{13}C nmr of a typical example was examined at high field. Accordingly, the spectrum of tetrakis(2,2,2-trifluoroethyl) N, N-urylene-1,1-di(3-methylsulphenyl)propyl-1,1-diphosphonate (48) was determined at 400 MHz.

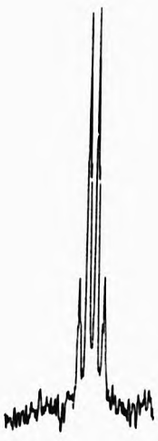
It was observed that in addition to phosphorus-carbon couplings, other couplings such as between carbon and fluorine, and possibly phosphorus and fluorine were observed as a fine pattern.

In general the ^{13}C nmr spectra of compounds of this type have characteristic patterns for the alkyl chain carbon atoms ranging from 12 to 50 ppm. This was also observed for the above compound (48) (Figure 3).

An interesting feature observed was the appearance of the signals due to the CH_2OP group. These would have been expected to give a doublet as a result of phosphorus coupling to the carbon via the oxygen. However, initial examination of the spectrum indicated the signal to be quartet. This arises as a result of carbon coupling with fluorine with a $^2J_{CCF}$ value of 114 Hz. Closer examination of this quartet when expanded, indicated that each line from the quartet appears to split further in to a triplet (Figure 4).



(Figure 3)



(Figure 4)

This may be due to the fact that the CH_2OP groups are non-equivalent and as such, individual couplings with phosphorus may occur to give two doublets ($^2J_{POC}$ 7.0, 7.1 Hz), which then overlap to give the appearance of a triplet. This non-equivalence may be due to the CH_2OP group being adjacent to a chiral α-CH group, although there is free rotation about the carbon-phosphorus bond.

In addition to coupling with phosphorus it appears that the methylene carbon couples with fluorine to give a quartet, in an analogous way to hydrogen. This result is not unexpected since, like hydrogen, fluorine has a spin of one half. The net result of all these couplings appears to be a quartet of multiplets for the CH_2OP group.

The coupling for the CF_3 group was the largest (~260 Hz), giving rise to a quartet as would be expected. Again when this signal was expanded each line of the quartet appeared to be more complicated, as indicated by the presence of "shoulders". This is probably the result of further coupling from phosphorus, for which a small value of $^3J_{POCC}$ (6.8 Hz) was observed. Similar coupling $^3J_{POCC}$ (5.3 Hz) of this type has been observed for diethyl α-aminopropanephosphonate (56) in the present studies.

$(EtO)_2P(O)CH(NH_2)CH_2CH_3$

(56)

3.7.2 PROTON NMR OF $(R'O)_2P(O)CH(R)NHC(:X)NHCH(R)P(O)(OR')_2$ WHERE R'= ALKYL OR PHENYL; R = Et OR CH_3CH_2SMe; X = O OR S

$(R'O)_2(O)PCH\ (R)NHC(:X)NHCH(R)P(O)(OR')_2$

R'= Ph; R = Et, X = S or O

R'= Cl_3CCH_2; R = Et, X = S or O

R'= F_3CCH_2; R = Et, $CH_3S(CH_2)_2$ or $CH_3S(O)(CH_2)_2$; X = S or O

^1H nmr spectroscopy was a useful tool for the initial identification of these compounds and for the determination of the success or failure of a reaction. Like α-aminoalkanephosphonic acids, the above compounds showed a fingerprint region between 0.8 to 5.5 ppm, which is characteristic of the alkyl chain carbon atoms (R). In general, when R = Et these compounds gave a triplet, with two complex multiplets arising as a result of couplings of the CH_3, CH_2, and CH groups, as described in the case of the α-amino-propanephosphonic acid (6) (page 41). However, when R' was either (Cl_3CCH_2) or (F_3CCH_2) the chemical shifts of the multiplets were at lower field than that observed for (6). This is attributed to the high electronegativity of the halo groups which deshields the methylene and methine protons.

The complexity of the spectra increased with the nature of the substituents on the ester group. Thus, the 80 MHz ^1H nmr spectrum of tetrakis(2,2,2-trichloroethyl) N,N-urylene-1,1-dipropyl-1,1-diphosphonate (36) in $CDCl_3$ revealed the following signals; 1.03 (t, 3H, $C\underline{H}_3$ $^3J_{HCCH}$ 6.9 Hz), 4.40 (br m, $C\underline{H}_2$) 4.50-4.95 (complex m, consisting of 11 lines, 8H, $POC\underline{H}_2$), 5.0-5.55 (m, 1H,

CH), 7.65 (d, NH $^3J_{PCNH}$ 10.0 Hz exchanged with D_2O within 5 min).

The complex multiplet at 4.50-4.95 consisted of a total of 11 lines and arises as a result from coupling between phosphorus and the OCH_2 protons.

The spectra were further complicated when the alkyl chain carbon was a 3-methylsulphenylpropyl group as exemplified by the 80 MHz ^1H nmr spectrum of tetrakis(2,2,2-trifluoroethyl) N,N-urylene-1,1-di(3-methylsulphenyl)propyl-1,1-diphosphonate (43) as follows; ^1H (MeOD) 1.50-2.30 (m, 2H, CH_2CH), 2.08 (s, 3H, CH_3), 2.65 (t, 2H, CH_2-S $^3J_{HCCH}$ 7.1 Hz), 4.31-4.80 (complex m, CF_3CH_2O), 5.0-5.55 (m, 1H, CH), 6.49 (br d, PCNH $^3J_{PCNH}$ 9.5 Hz, exchanged with D_2O within 5 min).

It was observed that the multiplet which resulted from coupling between the β-CH_2 protons and phosphorus was broad and diffuse which may be due to the overlapping signal that arose from the methyl group. The multiplet due to the ester group was extremely complex as a result of possible coupling between fluorine and the CH_2O protons, in addition to coupling between the CH_2O protons and phosphorus.

3.8 FAB MASS SPECTROMETRY OF α-UREIDO-3-(S-METHYLSULPHENYL)PROPANEPHOSPHONIC ACID AND AMMONIUM SALT OF α-UREIDOPROPANEPHOSPHONIC ACID

Fast atom bombardment (FAB) was discovered by Barber *et al.*[82,83] in 1980 as a new ion source. This technique uses an ion source which produces argon or xenon atoms with about 5 Kev energy, which are directed on to a sample mixed with glycerol. Both negative and positive ions characteristic of the molecule are emitted, and mass analysed by the spectrometer in the normal way.

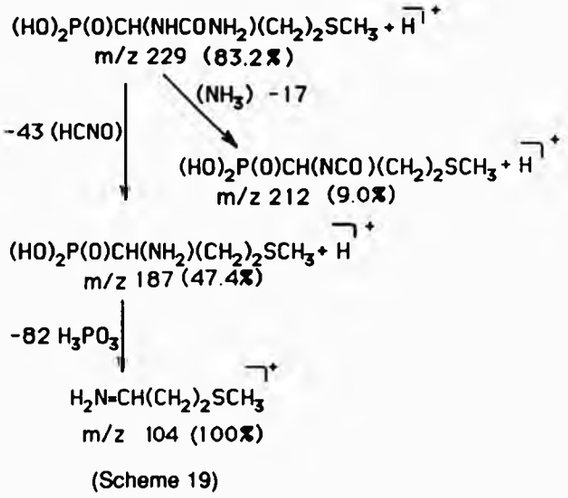
FAB spectrometry has been applied to a wide range of ionic and zwitterionic compounds such as potassium iodide[84] and polypeptides[85] which were previously difficult, or impossible, to study directly. This is attributed to their low volatility and hence it is impossible to record the mass spectra using standard methods. Several reports have been documented on FAB studies of various thermally labile organophosphorus co mpounds.[86,87,88,89]

The α-aminoalkanephosphonic acids are zwitterionic and high melting solids and therefore are not amenable to electron-impact mass spectrometry. Previous workers[24] in this laboratory investigated the FAB mass spectra of these phosphonic acids and have shown that they give a very strong $[M+1]^+$ ion which is usually the base peak.

In the present work, the FAB mass spectra of two phosphonic acids namely, α-ureido-3-(S-methylsulphenyl)propanephosphonic acid (54) and the ammonium salt of α-ureidopropanephosphonic acid (17, Chapter1) were studied in order to determine the

fragmentation patterns and to provide additional characterisation of the compounds.

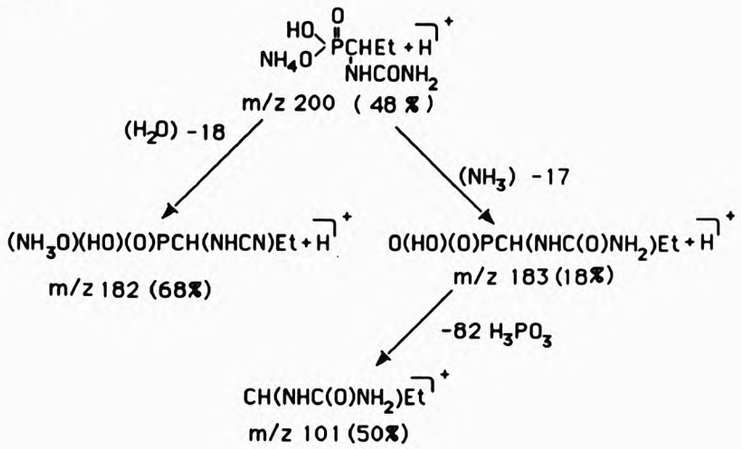
The FAB mass spectrum of α-ureido-3-(S-methylsulphenyl)propanephosphonic acid (54) gave a strong $[M+1]^+$ ion which is generally characteristic of α-aminoalkanephosphonic acids.[24] In addition, adduct ions such as $[2M+1]^+$ and $[M+glycerol+1]^+$ were also observed. The fragmentation of (54) was simple, involving the initial loss of the carbamyl group (Scheme 19). There was loss of ammonia also to a minor extent from $[M+1]^+$. A major fragment resulted from the loss of the phosphonic acid group leading to the formation of $CH_3S(CH)_2CHNH_2^+$ which was also the base peak.



(Scheme 19)

Similarly, the fragmentation of ammonium salt of α-ureidopropanephosphonic acid (17) gave a strong $[M+1]^+$ ion

(Scheme 20). Initial loss appears to be water and ammonia to a small extent. The major fragmentation in the compound is represented by the loss of the phosphonic acid group as observed above.



(Scheme 20)

CHAPTER 4

SYNTHESIS OF α-AMINOALKANEPHOSPHONOUS ACIDS AND α-AMINOALKANEPHOSPHINIC ACIDS

4.0 SYNTHESIS OF α-AMINOALKANEPHOSPHONOUS ACIDS AND α-AMINOALKANEPHOSPHINIC ACIDS

$RCH(NH_2)P(O)(OH)(R^1)$

R= alkyl

(57)

The α–aminoalkanephosphonous acids (57) (R^1= H), and the α–aminoalkanephosphinic acids (57) (R^1= alkyl, aryl) are white crystalline solids with high melting points. Several phosphorus-carbon containing compounds, most of which contain nitrogen have been detected in nature and isolated since 1959. The first compound of this kind was 2-aminoethylphosphonic acid isolated from ciliated protozoa, by Horiguchi and Kandtsu.[18] Also the aminophosphinic acid (58) has been detected in nature and isolated from cultures of *Streptomyces viridochromogenes*,[90] as the tripeptide phosphinothricyl-L-alanyl-L-alanine.

$HO_2CCH(NH_2)CH_2CH_2P(O)(OH)CH_3$

(58)

In this chapter, various routes for the synthesis of α–aminoalkanephosphonous acids, α–aminoalkanephosphinic acids, and their derivatives are investigated. Additionally, the spectroscopic studies (^1H, ^{13}C, ^{31}P nmr, and FAB mass spectrometry) of these compounds will be discussed. The present studies were undertaken to investigate whether these acids possess fungicidal activity similar to that shown by the analogous α–aminoalkanephosphonic acids (8, Chapter 1).

4.1 SYNTHESIS OF α-AMINOALKANEPHOSPHONOUS ACIDS

One of the first reports of the synthesis of a phosphonous acid was presented by Raudnitz,[91] who prepared p-N,N-dimethylaminophenylphosphonous acid by the reaction of dimethylaniline with phosphorus trichloride followed by hydrolysis (Reaction 42).

$$Me_2NPh + PCl_3 \xrightarrow{H^+/H_2O} (Me)_2NC_6H_4P(O)(OH)H$$

(Reaction 42)

In general, many of the types of method which have been described for the preparation of α–aminoalkanephosphonic acids are also suitable for the synthesis of α–aminoalkane-phosphonous acids[92] and -phosphinic acids.

Thus, a general procedure for the synthesis of α–aminoalkanephosphonous acids, involves the addition of a phosphonous moiety to an imine. Early studies by Quin[94] indicated that O-ethyl phenylphosphonite added readily to benzylidene-phenylimine in the presence of an alkoxide as a catalyst to yield an N-substituted phenyl(α–aminoalkane)phosphinate (Reaction 43).

$$PhCH{=}NPh + (EtO)(O)PH(Ph) \longrightarrow PhNHCH(Ph)P(O)(OEt)(Ph)$$

(Reaction 43)

Similarly, an extension of the above work was later reported by Tyka[33] who obtained α-aminoalkanephosphonous acids more conveniently and in good yield from the hydrogenolysis of N-

benzyl-α-aminoalkanephosphonous acids using H_2 in the presence of Pd/C as a catalyst.

Baylis *et al.*[95] attempted hydrogenolysis of N-benzyl-α-aminoalkanephosphonous acids using the same procedure as that reported by Tyka.[33] However, these workers found that hydrogenolysis failed due to catalyst poisoning, and under higher catalyst loadings carbon-phosphorus bond cleavage occurred.

The authors[95] employed diphenylmethylamine for the synthesis of α-aminoalkanephosphonous acids (57). Addition of 100% hypophosphorous acid to an N-diphenylmethylimine in ethanol yielded N-diphenylmethyl-α-aminoalkanephosphonous acids (59) (Reaction 44).

$$Ph_2CHN{=}CHR + H_3PO_2 \longrightarrow Ph_2CHNHCH(R)P(O)(OH)H$$

(Reaction 44) (59)

The diphenylmethylamine acted as an acid-labile protecting group, which could be cleaved under a variety of conditions. These included the use of 49% hydrobromic acid and refluxing the mixture for 45 minutes. The free aminophosphonous acid was obtained by treatment of the hydrobromide salt with propylene oxide. Alternatively, a mixture of trifluoroacetic acid and anisole was used for hydrolysis.

The authors[95] also used the reaction of the diphenylmethylamine salt of hypophosphorous acid with aldehydes, in refluxing ethanol or dioxane, to give product (59).

The procedure of Baylis *et al.*[95] using diphenylmethylamine hydrochloride was investigated for the synthesis of N-diphenylmethyl-α-aminoalkanephosphonous acids (59) from a

series of aldehydes (C_2-C_6). (Reaction 45).

$$Ph_2CHNH_2.HCl + H_3PO_2 + RCHO \longrightarrow Ph_2CHNHCH(R)P(O)(OH)H$$

(Reaction 45) (59)

Addition of the aldehyde to a refluxing solution of diphenylmethylamine hydrochloride and hypophosphorous acid in water yielded an immediate precipitation of (59) in very good yield (44-86%). The yield of (59) decreased as the alkyl chain length increased, an observation which is in agreement with that made by Baylis *et al.*[95] This may be attributed to the fact that water was used as the solvent, and the solubility of the longer chain aldehyde decreased due to decrease in polarity.

The N-diphenylmethyl-α-aminoalkanephosphonous acids (59) were easily hydrolysed with hydrochloric or hydrobromic acid to give the corresponding α-aminoalkanephosphonous acids (60) in good yield (Reaction 46).

$$Ph_2CHNHCH(R)P(O)(OH)H + HX \longrightarrow RCH(NH_2)P(O)(OH)H + Ph_2CHX$$

X = Cl, Br (Reaction 46) (60)

The resultant compound (60) were readily oxidised according to the reported procedure[95] with saturated bromine water to yield α-aminoalkanephosphonic acids (8, Chapter 1), and were also found to be easily oxidised by chlorine and hydrogen peroxide.

4.2 SYNTHESIS OF METHYL(α-AMINOPROPANE)PHOPHINIC ACID AND PHENYL(α-AMINOPROPANE)PHOPHINIC ACID

Oleksyszyn *et al* [40] have reported the synthesis of phenyl (α-aminopropane) phosphinic acid from phenyl dichlorophosphines, propanal and an alkyl carbamates. It was claimed that the reaction proceeds readily when the reagents are heated in glacial acetic acid. Hydrolysis of the resultant mixture, and subsequent work-up affords the corresponding phosphinic acids as crystalline white solids in moderate yields (30-55%).

In the present work methyl (α-aminopropane)phosphinic acid was synthesised using the procedure of Oleksyszyn *et al.* [40] . The precursor, methyl dichlorophosphine was prepared using a modified method employed by Sobramanien[96] from the reported literature route.[97,98] This involved the initial interaction of chloromethane, phosphorus trichloride, and aluminium trichloride (Reaction 47).

$$AlCl_3 + PCl_3 + CH_3Cl$$

$$\downarrow$$

$$[CH_3PCl_3]^+[AlCl_4]^-$$

(61)

$$\downarrow \text{ dibutyl phthalate}$$

$$CH_3PCl_4$$

$$\downarrow \text{ powdered antimony}$$

$$CH_3PCl_2$$

(Reaction 47)

The intermediate complex (61) was decomposed with dibutyl

phthalate and subsequently reduced with powdered antimony. The latter was used instead of the reported dry sulphur dioxide, in order to ensure that the reduction goes to completion. This also eliminates the need to separate volatile by-products such as thionyl chloride by distillation. The crude methyl dichlorophosphine was distilled under vacuum, and then condensed with propanal and benzyl carbamate in glacial acetic acid according to the procedure of Oleksyszyn *et al.*[40] (Reaction 48).

$$CH_3PCl_2 + PhCH_2O.CO.NH_2 + CH_3CH_2CHO \xrightarrow[2.\ H^+/H_2O]{1.\ AcOH} CH_3CH_2CH(NH_2)P(O)(OH)(CH_3)$$

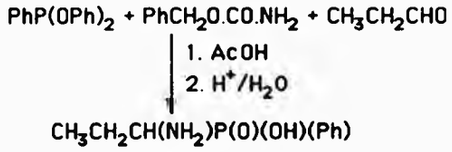
(62) (Reaction 48)

In the present work treatment with propylene oxide yielded a brown oil, which was then washed with various solvents and finally crystallised with methanol and water. A white solid crystallised slowly over several months, and was fully characterised as the novel methyl(α-aminopropane)phosphinic acid (62) by nmr (^1H, ^{13}C and ^{31}P) spectra, elemental analysis, and FAB mass spectrometry.

An attempt to prepare the analogous phenyl(α-aminopropane)phosphinic acid (63) from phenyldichlorophosphine according to the procedure of Oleksyszyn *et al.*[40] failed.

The above procedure was therefore modified using the phosphonous ester which was synthesised by the reaction of phenyldichlorophosphine and phenol in anhydrous ether. The

resultant distilled product was allowed to react with benzyl carbamate and propanal according to the procedure of Oleksyszyn *et al.*[40] (Reaction 49).



(63) (Reaction 49)

Work-up after hydrolysis yielded phenyl(α-aminopropane)-phosphinic acid (63) as a crystalline white solid. The yield (43.5%) of (63) compared well with the reported yield (41%). The compound was fully characterised by melting point, elemental analysis, FAB and nmr (^{1}H, ^{13}C and ^{31}P) spectroscopy.

4.3 SYNTHESIS OF THE DERIVATIVES OF α-AMINOPROPANE-PHOSPHONOUS ACID

Two examples of N-substituted derivatives of α-amino-propanephosphonous acid were prepared viz N-benzyl-oxycarbonyl-α-aminopropanephosphonous acid and N-(2,2,2-trichloro-carboethoxy)-α-aminopropanephosphonous acid.

Gilmore and McBride[99] reported the synthesis of N-benzyl-oxycarbonyl-α-aminoalkanephosphonic acids using benzyl chloroformate and the appropriate phosphonic acid in the presence of a base. This procedure was used for the synthesis of the corresponding N-benzyloxycarbonyl-α-aminopropanephosphonous acid (64) (Reaction 50).

$$PhCH_2O.CO.Cl + CH_3CH_2CH(NH_2)P(O)(OH)H \xrightarrow{NaOH} CH_3CH_2CH(NH.CO.OCH_2Ph)P(O)(OH)H$$

(64) (Reaction 50)

Benzyl chloroformate was added at low temperature to α-aminopropanephosphonous acid in the presence of a base. The reaction afforded (64) in good yield (87%) as a crystalline white solid which was characterised by nmr (^1H and ^{31}P) spectra, elemental analysis, and melting point. Similarly, N-(2,2,2-trichlorocarboethoxy)-α-aminopropanephosphonous acid was prepared using tris 2,2,2-trichloroethyl chloroformate.

The protected N-benzyloxycarbonyl-α-aminopropane-phosphonous acid (64) was subsequently used for the esterification to give methyl α-aminopropanephosphinate. It was hoped that the phosphinate could be used for peptide synthesise at a later stage.

There have been many reports on the synthesis of phosphonic and phosphonous esters.[100,101,102] The direct monoesterification of phosphonic acids requires forcing reaction conditions such as the use of a large excess of the alcohol, or a condensing agent like dicyclohexylcarbodiimide (DCC) which forms undesirable by-product. Furthermore, the esterification was usually unsuccessful with bulky alcohols due to steric hindrance.

In order to prevent the formation of by-products, Wasielewski *et al.*[103] reported monoesterification of various N-benzyloxycarbonyl-α-aminopropanephosphonic acids using the desired alcohol in the presence of a base and trichloroacetonitrile. It was decided to use the same procedure for the synthesis of

methyl N-benzyloxycarbonyl-α-aminopropanephosphinate (65) (Reaction 51).

$$CH_3CH_2CH(NH.CO.OCH_2Ph)P(O)(OH)H + CH_3OH \xrightarrow{Cl_3CCN/Pyridine} CH_3CH_2CH(NH.CO.OCH_2Ph)P(O)(OCH_3)H$$

(65) (Reaction 51)

The product was initially isolated in an oil form which was crystallised, to yield the required product (65) in good yield (67.3%).

In order to remove the protective N-benzyloxycarbonyl group, the ester (65) was treated with 45% hydrobromic acid and glacial acetic acid, at room temperature. However, a viscous oil was yielded which was washed successively with various solvents and recrystallised several times but, the oil failed to crystallise to give the required methyl α-aminopropanephosphinate. The ^{31}P nmr spectrum of the reaction product gave two signals (δ 24.9, 20.1) corresponding to the parent compound (65) and its hydrolysis product N-benzyloxycarbonyl-α-aminopropanephophonous acid (64). This suggests that under these conditions partial hydrolysis of the methylester group was in progress. The observed result was in agreement with those obtained by Wasielewski *et al.*[103] for the synthesis of monoalkyl α-aminoalkanephophinates from the corresponding N-benzyloxycarbonyl derivatives.

The authors also reported[103] the synthesis of various monoesters of α-aminoalkanephosphonic acids from the corresponding N-benzyloxycarbonyl derivatives. They claimed that

the protected N-benzyloxycarbonyl group can be removed by catalytic hydrogenolysis using 10% Pd/C without the loss of the ester group. In addition, hydrogenolysis of aliphatic esters required a shorter reaction time than the corresponding aromatic analogues.

The hydrogenolysis of monomethyl N-benzyloxycarbonyl-(α-aminopropane)phosphinate (65) was investigated according to the procedure of Wasielewski *et al.*[103] However, similar results were obtained as above. The loss of methyl group may have occured as a result of dehydrogenation or hydrolysis possibly initiated by the presence of traces of water. It is also conceivable that the catalyst may have been poisoned by complexation. At this stage further attempt to synthesise the free monomethyl-(α-aminopropane)phosphinate (65) were abandoned.

4.3.1 ATTEMPTED AMIDINATION OF α-AMINOPROPANE-PHOSPHONOUS ACID

Because of the interest in guanidinophosphonic acids as potential fungicides, the amidination of α-aminopropane-phosphonous acid was attempted using S-methylisothiouronium hydrochloride (Scheme 21).

Although free methanethiol was liberated as a by-product which was collected in a potassium permanganate trap, no guanidinophosphonous acid was formed. The unreacted parent compound was recovered in 92% yield.

$CH_3CH_2CH(NH_2)P(O)(OH)H$ + $2MeSC(:NH)NH_2.HCl$ + $3KOH$

↓

$CH_3CH_2CH(NH_2)P(O)(OK)H$ + $2MeSC(:NH)NH_2$ + KCl + $3H_2O$

↓ - MeSH

$(NH_2C(:NH)NH)CH(Et)P(O)(OK)H$

↓ HCl

$HCl.(NH_2C(:NH)NH)CH(Et)P(O)(OH)H$

↓ Propylene Oxide

$(NH_2C(:NH)NH)CH(Et)P(O)(OH)H$

(71) (Scheme 21)

It was therefore decided to use an alternative guanidating agent. Cyanamide was chosen as it is a stronger guanidating agent and is non-specific randomly converting both primary and secondary amino groups to guanidine.[104]

This was attempted by dissolving α-aminopropane-phosphonous acid in the minimal volume of water required followed by the addition of cyanamide. Concentrated ammonia solution was added so that a pH of 12 was obtained for the solution, and the mixture was left for several weeks. Subsequent work-up of the reaction mixture yielded a crystalline white solid with a significantly higher melting point (267 °C) than that of the parent compound (225 °C). The ^{13}C nmr spectrum of this solid indicated a doublet ($^3J_{PCNC}$ 3.5 Hz) at 159.8 ppm; this being consistent with a guanidine carbon. However, the remaining part of the spectrum indicated numerous overlapping peaks consistent with those

arising from the presence of the parent compound. Additionally, the ^{31}P nmr spectrum showed two signals (δ 21.3, 20.6), indicating that the white solid was a mixture of unreacted parent compound (major) and the desired guanidine product.

It is possible that the high pH used in the reaction system hydrolysed the cyanamide to urea and subsequently to ammonia and carbon dioxide. Alternatively, side reactions such as the formation of dicyandiamide may have taken place.

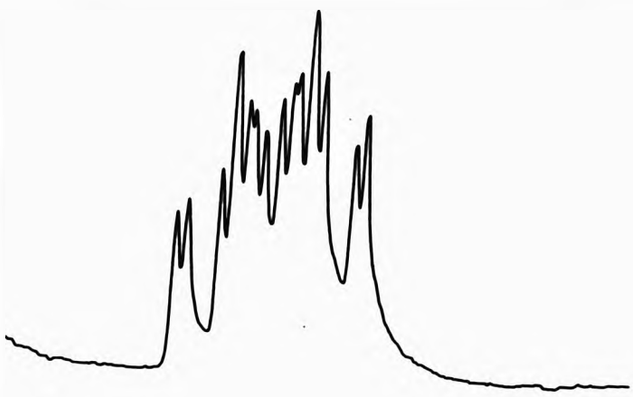
$$2CNNH_2 \longrightarrow (NH_2)_2C{=}NCN$$

Re-investigation of the above reaction under lower pH (9) and the use of excess cyanamide failed to give the desired guanidino product.

4.4 PROTON NMR SPECTROSCOPY OF THE α-AMINOALKANE PHOSPHONOUS ACIDS

The ^1H nmr of α-aminoalkanephosphonous acids have been reported in the literature[95] and have been recorded in the present work. The spectra are very similar to those of α-amino-alkanephosphonic acids, with an additional signal due to P-H coupling (J_{PH} 500-560 Hz) centered about 6.5-7.4 ppm. Thus, the ^1H nmr spectrum of α-aminopropanephosphonous acid in D_2O shows the following signals 1.15 (3H, t, CH_3, $^3J_{HCCH}$ 6 Hz), 1.45-2.25 (2H, br m, CH_2), 2.75-3.30 (1H, m, CH). At 80 MHz the multiplets appeared as overlapping signals and did not reveal the fine patterns that arise as a result of couplings. Therefore, the spectrum of this compound was recorded at 200 MHz.

Like the spectrum of the corresponding phosphonic acid the spectrum of the phosphonous analogue was found to be complicated. The multiplet due to CH_2 consisted of ca. 38 separate peaks, whereas a maximum of sixty four would be expected as a result of coupling to phosphorus, P-H, CH and to the CH_3 protons (i.e. 2 x 2 x 2 x 4 = 32). Similarly, the signal due to CH hydrogen consisted of 14 peaks (Figure 5), instead of the expected sixteen as a result of spliting due to phosphorus, CH_2 and P-H protons.



(Figure 5)

The ^{1}H nmr spectra of the longer chain series were similar and again, indicated a similar pattern to those of the α-aminoalkanephosphonic acids.

4.4.1 CARBON 13 NMR SPECTROSCOPY OF THE α-AMINO-ALKANEPHOSPHONOUS ACIDS

A consideration of phosphorus-carbon coupling values (Tables 9 &10) for α-aminoalkanephosphonous acids revealed some interesting features.

The methine carbon directly bonded to the phosphorus atom exhibits a $^{1}J_{PC}$ coupling value of between 89-94 Hz. In contrast, $^{1}J_{PC}$ coupling values for the corresponding α-aminoalkane-phosphonic acids lie between 150-162 Hz. Similarly, no couplings were observed between phosphorus and the methylene carbon throughout the series, thus $^{2}J_{PCC}$ was zero, whilst $^{2}J_{PCC}$ have been observed in the higher series of α-aminoalkanephosphonic acids. For example, $^{2}J_{PCC}$ for α-aminobutanephosphonic acid was around 4.4 Hz, $^{3}J_{PCCC}$ for α-aminoalkanephosphonous acids (n =1-3) was around 8.6-9.5 Hz, and zero for n=4. Interestingly, the latter acid also exhibits four-bond P-C coupling with $^{4}J_{PCCCC}$ = 8.5 Hz.

Table 9: Carbon-Phosphorus coupling constants (Hz) for $CH_3(CH_2)_nCH(NH_2)P(0)(OH)H$ compounds

Solvent: water

n	$^{1}J_{PC}$	$^{2}J_{PCC}$	$^{3}J_{PCCC}$	$^{4}J_{PCCCC}$
0	93.5	-	-	-
1	89.0	-	8.6	-
2	93.0	-	9.5	-
3	93.0	-	9.0	-
4	92.1	-	-	8.5

Table 10: Number of signals observed in the ^{13}C nmr of the phosphonous acids $CH_3(CH_2)_nCH(NH_2)P(O)(OH)H$

n.	No. of C atoms	No. of signals	δ (ppm)
0	2	3	14.1(s), 49.1 (d)
1	3	5	12.6 (d), 22.7 (s), 54.3 (d)
2	4	6	15.7 (s), 21.4 (d),31.0 (s), 53.3 (d)
3	5	7	15.7 (s), 24.4 .(s), 30.0 (d), 36.2 (s),54.0 (d)
4	6	8	16.1 (s), 24.4 (s), 27.5 (d), 29.1(s), 33.4 (s), 53.6 (d)

4.4.2: PHOSPHORUS-31 NMR SPECTROSCOPY OF α-AMINO-ALKANEPHOSPHONOUS ACIDS

Table 11: ^{31}P phosphorus-hydrogen coupling (Hz) for $CH_3(CH_2)_nCH(NH_2)P(O)(OH)H$

Reference: 85% H_3PO_4

Solvent: D_2O

No of Carbon (n)	δ (ppm)	$^1J_{PH}$ (Hz)	$^2J_{PCH}$ (Hz)
0	21.4	531	15.7
1	20.5	528	31.0
2	20.6	532	32.0
3	20.9	532	32.0
4	20.7	534	34.0

Spectra of phosphonous acids are a good indication of the phosphorus purity of a sample. A signal was usually observed at about 20-22 ppm with characteristic values for $^1J_{PH}$ and $^2J_{HCP}$. The latter increased with increase in alkyl chain length. The values for $^3J_{HCCP}$ however, were not clear; with an increase in alkyl chain length a broad signal is observed from which no useful information can be obtained.

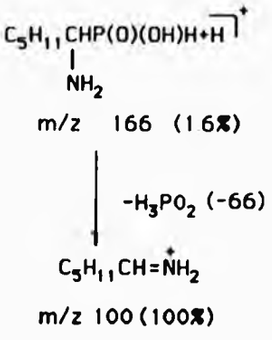
4.5 FAB MASS SPECTROMETRY OF α-AMINOALKANE-PHOSPHONOUS ACIDS AND α-AMINOALKANEPHOSPHINIC ACIDS

Like the phosphonic acids, the α-aminoalkanephosphonous acids and the α-aminoalkanephosphinic acids are zwitterionic and high melting solids and therefore are not amenable to electron-impact mass spectrometry. Therefore, these acids were studied by FAB in order to determine the fragmentation patterns and characterisation of the compounds.

In general, it was found that these acids gave strong $[M+H]^+$ and $[2M+H]^+$ ions, with the base peak apparently resulting from the elimination of HPO_3 from a dimeric structure as seen in the fragmentation pattern of the α-aminopropanephosphonous acid (Scheme 22).

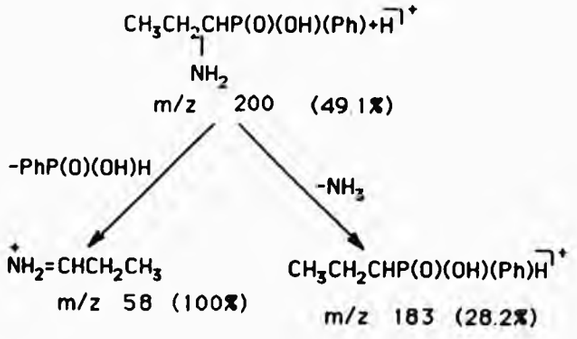
Higher members of the series do not show the prominent $[2M+H]^+$ and $[2M+H-66]^+$ ions and the base peak appears to be $[M+H-H_3PO_2]^+$. In addition, a few adduct ions were observed as seen in α-aminohexanephosphonous acid (Scheme 23).

An additional peak at m/z 184 (12.6%) was assumed to be due to the ion $[M+H+H_2O]^+$, formed possibly from a trace of water in the glycerol matrix.



(Scheme 23)

Similarly, the α-aminoalkanephosphinic acids were found to give $[M+H]^+$ and $[2M+H]^+$ ions with the base peak arising from the loss of methyl or phenyl phosphonous acid from $[M+H]^+$. Loss of ammonia was also seen as in the case of phenyl(α-amino-propane)phosphinic acid (Scheme 24).



(Scheme 24)

CHAPTER 5

BIOLOGICAL ACTIVITIES OF α-AMINOALKANEPHOSPHONIC ACIDS DERIVATIVES AND α-AMINOALKANEPHOSPHONOUS ACIDS AND THEIR DERIVATIVES

5.0 Biological Activity

α-Aminopropanephosphonous acid, its N-diphenylmethyl derivative, and α-amino (methyl)propylphosphinic acid were tested for activity against Drechslera teres by the "osmos tests". In this, infected barley seeds of the variety *Tellus* were treated with aqueous formulations containing 20% w/v of the test compound for 10 minutes in a laboratory seed treatment machine, at a dosage rate of 2 ml solution per kg of seed. The dressed seeds were placed on filter papers moistened with buffered sugar solution. The filter papers were then placed in transparent plastic dishes and maintained at 22 °C in a growth chamber with alternating periods of light (12 h) and darkness (12 h). After one week the seeds with living fungi were identified by a colour test. Results presented below (Table 12) are expressed as percent control of the disease and are compared to results for α-aminopropanephosphonic acid (6) under similar conditions.

Table 12

COMPOUNDS	% ACTIVITY	% ACTIVITY OF $Et(NH_2)CHP(O)(OH)_2$
$Et(NH_2)CHP(O)(OH)H$ (72)	3%	47
$Et(Ph_2CHNH)CHP(O)(OH)H$ (73)	0%	49
$Et(NH_2)CHP(O)(OH)Me$ (62)	0%	58

It is clear that the α-aminopropanephosphonous acid (72) is much less effective than the α-aminopropanephosphonic acid (6). Although one might have expected the possibility of activation of (72) by *in vivo* oxidation to (6) but clearly this does not occur. The

derivative having the substituent in N (73) or the methyl group on the phosphonous (62) were totally inactive.

5.1 Foliar Sprays and Systemic Soil Tests

Further tests of compounds as foliar sprays were carried out in the present work. Formulations were prepared at 1000 ppm of active ingredient with 400 ppm etoxylated fatty alcohol. For systemic soil tests, the compounds were watered down on the soil as 500 ppm solution. Results are given below (Table. 13).

Table 13

COMPOUNDS	E.G.	P.R.	S.N.	P.I.	F.C.
$Et(NH_2)CHP(O)(OH)H$	1 *	1	2 (1*)		2
$CH_3(NH_2)CHP(O)(OH)H$	2		1		
$Et(NH_2)CHP(O)(OH)Me$		1			
$Et(NH_2)CHP(O)(OH)Ph$		1			
$Et(NH_2CONH)CHP(O)(OH)(ONH_4)$		1			

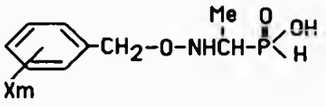
E.G. = Erysiphe graminis
P.R. = Puccinia recondita
S.N. = Septoria nodorum
P.I. = Phytophthora infestans
F.C. = Fusarium culmorum

(*) = systemic soil test
1 = 50-75% control
2 = 75-100% control

It is interesting that although α-aminopropanephosphonous acid (72) had given very low activity in the seed treatment test, it gave up to 75-100% control against PI and FC as a foliar spray.

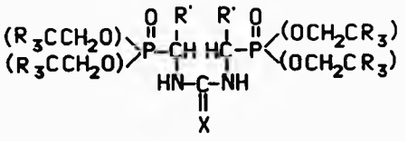
Also the ethyl analogue of phosphonous acid gave good activity against E.G. Activity of the methyl- and -phenyl(α-aminopropane)-phosphinic acid was however only moderate and against P.R. only. Longer chain α-aminoalkanephosphonous acids (C4 to C6) showed no activity.

It is of interest in this context to note that fungicidal activity against Plasmopara viticola has recently been claimed for N-benzyloxyaminoethylphosphinic acid derivatives.[105]



X = H, halogeno, lower alkyl, phenoxy, and (5-trifluoromethyl-3-chloropyrid-2-yl)oxy; m =1 or 2

The 2,2,2-trihaloethyl esters of the ureido or thioureido-bisphosphonic acids (74) showed no activity indicating that compounds of these types do not act as profungicides for α-amino-propanephosphonic acid (6) by undergoing *in vivo* hydrolysis.



(74)

R' = Et, $CH_3S(CH_2)_2CH$, $CH_3SO(CH_2)_2CH$; X = O OR S; R = Cl OR F

List of experiments

phosphite, propanal and urea using boron trifluoride-etherate in toluene

7.3 Preparation of α-aminopropanephosphonic acid from triethyl phosphite and urea in the presence of boron trifluoride-etherate and toluene

7.4 Attempted preparation of α-aminopropanephosphonic acid by the addition of diphenyl phosphite to N-propylidene-diphenylmethylamine

7.5 Preparation of α-aminopropanephosphonic acid from phosphorus trichloride, propanal and benzyl carbamate

7.6 Preparation of N-propylidenebenzylamine

7.7 Attempted preparation of N-benzyl α-aminopropanephosphonic acid from phosphorous acid and N-propylidenebenzylamine

7.8 Preparation of α-aminopropanephosphonic acid from diethyl phosphite, propanal and ammonia

7.9 Preparation of dimethyl N-benzyl-α-aminopropane-phosphonate hydrochloride

8.0 Preparation of dimethyl α-aminopropanephosphonate hydrochloride

8.1 Preparation of α-aminopropanephosphonic acid from dimethyl α-aminopropanephosphonate hydrochloride

8.2 Modified preparation of N-benzyl-α-aminopropanephosphonic acid hydrochloride

8.3 Preparation of α-aminopropanephosphonic acid from dimethyl N-diphenylmethyl-α-aminopropanephosphonate

8.4 Repeat preparation of α-aminopropanephosphonic acid from dimethyl N-diphenylmethyl-α-aminopropanephosphonate

8.5 Attempted hydrogenolysis of N-benzyl-α–aminopropane–

phosphonic acid hydrochloride for the synthesis of α-aminopropanephosphonic acid

8.6 Preparation of crude dimethyl N-benzyl-α-aminopropane phosphonate and its attempted hydrogenolysis

8.7 Attempted hydrogenolysis of the crude dimethyl N-benzyl-α-aminopropanephosphonate in water

8.8 Attempted hydrogenolysis of crude dimethyl N-benzyl-α-aminopropanephosphonate in dichloromethane

8.9 Attempted hydrogenolysis of crude dimethyl N-benzyl-α-aminopropanephosphonate in methanol

9.0 Attempted hydrogenation of crude dimethyl N-benzyl-α-aminopropanephosphonate in acetic acid

9.1 A modified preparation of crude dimethyl N-benzyl-α-aminopropanephosphonate hydrochloride

9.2 Attempted hydrogenolysis of the above crude dimethyl N-benzyl-α-aminopropanephosphonate hydrochloride in dichloromethane

9.3 Preparation of tetrakis(2,2,2-trichloroethyl) N,N-thiourylene (-1,1-dipropyl)-1,1-diphosphonate

9.4 Preparation of tetrakis(2,2,2-trichloroethyl) N,N-urylene (-1,1-dipropyl)-1,1-diphosphonate

9.5 Preparation of tetrakis(2,2,2-trifluoroethyl)N,N-thiourylene (-1,1-dipropyl)-1,1-diphosphonate

9.6 Preparation of tetrakis(2,2,2-trifluoroethyl) N,N-urylene (-1,1-dipropyl)-1,1-diphosphonate

9.7 Preparation of tetrakis(2,2,2-trifluoroethyl) N,N-urylene di(-3-methylsulphenyl-1,1-dipropyl)-1,1-diphosphonate

9.8 Oxidation of tetrakis(2,2,2-trifluoroethyl) N,N-urylene (-3-methylsulphenyl-1,1-dipropyl)-1,1-diphosphonate

11.5 Synthesis of phenyl(α-aminopropane)phosphonous acid

11.6 Synthesis of N-benzyloxycarbonyl-α–aminopropane-phosphonous acid

11.7 Synthesis of monomethyl (N-benzyloxycarbonyl)-α-amino-propanephosphinate

11.8 Synthesis of N-(2,2,2-trichloroethoxycarbonyl)-α-amino-propanephosphonous acid

11.9 General method for the oxidation of α-aminoalkane-phosphonous acids to α-aminoalkanephosphonic acids

12.0 Synthesis of α-aminoethanephosphonic acid

12.1 Synthesis of α-aminopropanephosphonic acid

12.2 Synthesis of α-aminobutanephosphonic acid

12.3 Synthesis of α-aminopentanephosphonic acid

12.4 Synthesis of α-aminohexanephosphonic acid

12.5 Oxidation of α-aminopropanephosphonous acid to α-amino-propanephosphonic acid with hydrogen peroxide

12.6 Attempted synthesis of α-guanidinopropanephosphonous acid

12.7 Preparation of methylphosphonous dichloride

12.8 Preparation of tris(2,2,2-trichloroethyl) phosphite

6.1 Preparation of α-aminopropanephosphonic acid from triphenyl phosphite, propanal and ethyl carbamate in the presence of acetic acid

Ethyl carbamate (4.45 g, 0.05 mol), triphenyl phosphite (15.5 g, 0.05 mol), and propanal (3.48 g, 0.06 mol) were heated under reflux for 1 h with glacial acetic acid (10 cm^3). Concentrated hydrochloric acid (50 cm^3) was added and the mixture was refluxed for a further 6 h. The cooled solution was extracted with toluene (2 x 15 cm^3) and the aqueous phase evaporated to dryness under reduced pressure (15 mm Hg, 70 °C). The resultant yellow residue was dissolved in methanol (30 cm^3) and treated with propylene oxide until maximum precipitation had occurred. The solid product was filtered, washed with acetone (2 x 10 cm^3) and recrystallised with water/methanol. After drying in a vacuum oven at 50 °C α-aminopropanephosphonic acid (6) (2.11 g, 25.3%) was obtained as a crystalline white solid, m.p. 261-262 °C (lit. m.p. 264-266 °C),[33] (Found: C, 25.2; H, 7.0; N, 9.8. Calc. for $C_3H_{10}NO_3P$: C, 25.9; H, 7.2; N, 10.1%); ^1H NMR (D_2O/D_2SO_4) δ1.15 (3H, t, $C\underline{H}_3$ $^3J_{HCCH}$ 7.4 Hz), 1.30-2.0 (2H, br m, $C\underline{H}_2$), 2.75-3.30 (1H, m, $C\underline{H}$); ^{13}C NMR (D_2O/D_2SO_4) δ 12.9 (d, $\underline{C}H_3$, $^3J_{PCCC}$ 8.7 Hz), 24.5 (s, $\underline{C}H_2$), 52.5 (d, CH, $^1J_{PC}$ 152.8 Hz); ^{31}P NMR (D_20/D_2SO_4) δ 17.2 (br s).

6.2 Preparation of α-aminopropanephosphonic acid from triphenyl phosphite, propanal and ethyl carbamate in the presence of boron trifluoride-etherate

Redistilled triphenyl phosphite (26.7 g, 0.086 mol), ethyl carbamate (7.60 g, 0.086 mol), and propanal (5.0 g, 0.086 mol) were mixed in sodium-dried toluene (80 cm^3), and boron trifluoride-

etherate (2.5 cm^3), in toluene (50 cm^3), was added dropwise with stirring at room temperature (15 min). The mixture was heated at 85-90 °C under reflux (5 h) after which toluene was removed under reduced pressure, to yield a pale-yellow oil having ^{31}P nmr signals at 18.3 and 22.8 (trace) ppm. Concentrated hydrochloric acid (120 cm^3) was added to the residue and the mixture was heated at 105 °C under reflux (8 h). Phenol and other by-products were removed by extraction with toluene (3 x 15 cm^3) and the aqueous layer was evaporated *in vacuo* to yield a yellowish oil which was dissolved in methanol (15 cm^3). The methanol solution was warmed under reflux and propylene oxide (10 cm^3) was added to give an immediate precipitate which was filtered off, washed with acetone (15 cm^3) and dried in a vacuum oven at 60 °C to give the crude α-aminopropanephosphonic acid (5.06 g, 42.3%), m.p. 256-258 °C. Recrystallisation from hot water/ethanol yielded α-amino-propanephosphonic acid (6) (4.39 g, 36.7%) as a crystalline white solid, m.p. 259-260 °C (lit. m.p. 264-266 °C),[33] ^1H NMR (D_2O) δ 1.12 (t, 3H, CH_3, $^3J_{HCCH}$ 6.1 Hz), 1.38-2.20 (br m, 2H, CH_2), 2.84-3.39 (m, 1H, CH).

6.3 Preparation of α-aminopropanephosphonic acid from triphenyl phosphite, propanal and benzyl carbamate

Redistilled triphenyl phosphite (26.7 g, 0.086 mol), benzyl carbamate (13.0 g, 0.086 mol), and propanal (5.0 g, 0.086 mol) were mixed in sodium-dried toluene (80 cm^3), and boron trifluoride-etherate (2.5 cm^3), in toluene (50 cm^3), was added dropwise with stirring at room temperature (15 min). The mixture was heated at 85-90 °C under reflux (5 h), after which toluene was removed under reduced pressure to yield a pale-yellow oil which showed a

^{31}P signal at 18.3 ppm. Concentrated hydrochloric acid (120 cm^3) was added to the residue and the mixture was heated at 105 °C under reflux (8 h). Phenol and other by-products were removed by extraction with toluene (3 x 20 cm^3) and the aqueous layer was evaporated *in vacuo* to yield a yellowish oil which was dissolved in methanol (15 cm^3). The methanol solution was warmed under reflux and propylene oxide (10 cm^3) was added to give an immediate precipitate which was filtered off, washed with acetone (15 cm^3) and dried in a vacuum oven at 60 °C to give crude α-aminopropanephosphonic acid (6) (7.88 g, 65.8%), m.p. 259-260 °C. Recrystallisation from hot water/ethanol yielded α-amino-propanephosphonic acid (6.83 g, 57.1%) as a crystalline white solid, m.p. 261-262 °C (lit. m.p. 264-266 °C),[33] ^1H NMR (D_2O) δ 1.11 (t, 3H, CH_3, $^3J_{HCCH}$ 6.0 Hz), 1.39-2.20 (br m, 2H, CH_2), 2.85-3.40 (m, 1H, CH).

6.4 Preparation of 1-[^{14}C]-α-aminopropanephosphonic acid

Redistilled triphenyl phosphite (26.7 g, 0.086 mol), benzyl carbamate (13.0 g, 0.086 mol), and 1-[^{14}C]-propanal (5.0 g, 0.086 mol, 22.5 mCi, >95% radiochemical purity, obtained from Amersham International) were mixed in sodium-dried toluene (80 cm^3), and boron trifluoride-etherate (2.5 cm^3), in toluene (50 cm^3) was added dropwise with stirring at room temperature (15 min). The mixture was heated at 85-90 °C under reflux (5 h) after which toluene was removed under reduced pressure. Concentrated hydrochloric acid (120 cm^3) was added to the residue and the mixture was heated at 105 °C under reflux (8 h). Phenol and other by-products were removed by extraction with toluene (3 x 20 cm^3) and the aqueous

layer was evaporated *in vacuo* to yield a yellowish oil which was dissolved in methanol (15 cm^3). The methanol solution was warmed under reflux and propylene oxide (10 cm^3) was added to give an immediate precipitate which was filtered off, washed with acetone, and dried in a vacuum oven at 60 °C to give crude 1-[^{14}C]-α-aminopropanephosphonic acid (7.10 g, 59.0%), m.p. 255-258 °C. Recrystallisation from hot water/ethanol yielded two crops of white crystalline product (5.53 g, 46% combined yield), which were dried initially in an oven at 80-90 °C and than under vacuum at 50 °C. The first crop (3.72 g, 31%), had a slightly higher melting point (275-276 °C) then that of the second crop (274-275 °C) (lit. m.p. 264-266 °C).[33] All analytical data were obtained from the first crop. (Found: C, 25.3; H, 7.2; N, 10.2. Calc. for $C_3H_{10}NO_3P$: C, 25.9; H, 7.2; N, 10.1%); ^{1}H NMR (D_2O) δ 1.05 (t, 3H, C$\underline{H}_3$, $^3J_{HCCH}$ 7 Hz), 1.45-2.15 (m, 2H, C$\underline{H}_2$), 2.85-3.45 (m,1H, C$\underline{H}$); ^{13}C NMR (D_2O) δ 13.06 (d, $\underline{C}H_3$, $^3J_{PCCC}$ 9.2 Hz), 24.71 (d, $\underline{C}H_2$, $^2J_{PCC}$ 1.8 Hz) 53.66 (d, $\underline{C}H$, $^1J_{PC}$ 142.8 Hz); ^{31}P NMR (D_2O) δ 13.5 (s).

Specific activity; 1.736 μCi/mg (calculated activity; 1.784 μCi/mg, based on the propanal used assuming 95% radiochemical purity).

6.5 Preparation of α-aminopropanephosphonic acid from triphenyl phosphite, propanal and urea

Triphenyl phosphite (4.96 g, 0.016 mol), propanal (0.92 g, 0.016 mol), and urea (0.48 g, 0.016 mol) were heated under reflux (1 h) with glacial acetic acid (3.20 cm^3). The resultant yellow oil ^{31}P NMR ($CDCl_3$) δ 18.6 (major), 16.3 and 7.3 ppm was treated with concentrated hydrochloric acid (15 cm^3) and the mixture was

heated under reflux (8 h). The cool aqueous phase was separated, washed with toluene (3 x 5 cm^3), and the volatile components distilled off on a rotary evaporator. The residue was dissolved in methanol (5 cm^3), and treated with propylene oxide until maximum precipitation was formed. The solid was filtered, washed with acetone (5 cm^3) and dried in a vacuum oven at 60 °C to yield α-aminopropanephosphonic acid (1.20 g) as a fine white solid, m.p. 257-258 °C. The volatile components from the combined mother liquor and the washings were distilled off on a rotary evaporator to give a yellow oil, which crystallised from water/ethanol. White crystals were formed after several weeks at 4 °C to yield a second crop of α-aminopropanephosphonic acid (0.7 g), m.p. 256-257 °C. The combined solids were recrystallised from water/ethanol to give α-aminopropanephosphonic acid (1.6 g, 36.4% based on propanal and the phosphite) as a crystalline white solid, m.p. 261-262 °C (lit. m.p. 264-265 °C), [33] ^1H NMR (D_2O) δ1.11 (t, $C\underline{H}_3$, $^3J_{HCCH}$ 6.0 Hz), 1.39-2.20 (br m, 2H, $C\underline{H}_2$), 2.85-3.40 (m, 1H, C<u>H</u>); ^{31}P NMR (D_2O) δ 13.8 (s).

6.6 Preparation of N-propylidenediphenylmethylamine

Freshly distilled propanal (5.8 g, 0.1 mol), was added dropwise to a cooled solution of diphenylmethylamine (18.3 g, 0.1 mol) in ether (30 cm^3), and anhydrous potassium carbonate (<u>ca.</u> 5 g). The mixture was stirred at room temperature for 1 h. Potassium carbonate was filtered off, and the volatile components were distilled off on a rotary evaporator to give the crude imine as a viscous pale yellow liquid (18.9 g, 85.1%). Distillation under reduced pressure gave <u>N</u>-propylidenediphenylmethylamine (16.5 g, 74.3%), b.p. 60-63 °C at 0.5 mm Hg as a clear free running liquid. ^1H

NMR ($CDCl_3$) δ 1.30 (3H, t, C<u>H</u>$_3$, $^3J_{HCCH}$ 7.1 Hz), 1.95-2.30 (2H, br m, C<u>H</u>$_2$), 5.16 (1H, s, Ph_2C<u>H</u>), 7.1 (10H, br s, <u>aromatic</u>). 7.64 (t, CH_2C<u>H</u>=N, $^3J_{HCCH}$ 5.6 Hz).

6.7 Preparation of α-aminopropanephosphonic acid by the addition of diethyl phosphite to N-propylidenediphenylmethylamine

Distilled <u>N</u>-propylidenediphenylmethylamine (13.8 g, 0.05 mol), and diethyl phosphite (6.90 g, 0.05 mol), were heated at 120-140 °C for 0.5 h. Concentrated hydrochloric acid (80 cm^3) was added, and the resultant orange solution was heated under reflux for 3 h. The reaction mixture was extracted with toluene (3 x 15 cm^3). The aqueous phase was separated and the volatile components were distilled off *in vacuo* (70 °C, 15 mm Hg) to give a viscous yellow residue. Methanol (<u>ca.</u> 30 cm^3) was added, and the resultant solution treated with propylene oxide until maximum precipitation was formed. The solid product was filtered, washed with acetone (10 cm^3) and ethanol (5 cm^3) and dried in a vacuum oven at 40 °C to give α-aminopropanephosphonic acid (3.25 g, 46.8%) as a fine white solid, m.p. 259-260 °C (lit. m.p. 264-266 °C),[33] ^{1}H NMR ($D_2$0) δ 1.10 (t, C<u>H</u>$_3$, $^3J_{HCCH}$ 6.1 Hz),1.40-2.20 (br m, 2H, C<u>H</u>$_2$), 2.85-3.41 (m, 1H, C<u>H</u>).

Re-investigation of the above reaction using dimethyl phosphite (0.55 g, 0.005 mol) with <u>N</u>-propylidenediphenylmethylamine (13.8 g, 0.05 mol), yielded α-aminopropanephosphonic acid (0.32 g, 45.9%) as a white crystalline solid, m.p. 259-261 °C (lit. m.p. 264-266 °C),[33] ^{1}H NMR ($D_2$0) δ 1.11 (t, C<u>H</u>$_3$, $^3J_{HCCH}$ 6.1 Hz), 1.41-2.22 (br m, 2H, C<u>H</u>$_2$), 2.86-3.45 (m, 1H, C<u>H</u>).

6.8 Preparation of α-aminopropanephosphonic acid from triethyl phosphite, propanal and phenylurea

A mixture containing, sodium-dried toluene (50 cm^3), redistilled triethyl phosphite (5.0 g, 0.03 mol), phenylurea (4.08 g, 0.03 mol), and propanal (1.74 g, 0.03 mol) was stirred at room temperature. Boron trifluoride-etherate (0.5 cm^3), in sodium-dried toluene (5 cm^3), was then added dropwise (15 min). The resultant white suspension was heated at 90-110 °C for 1.5 h to give a homogeneous solution. The volatile components were distilled off on a rotary evaporator and the yellow residue was treated with concentrated hydrochloric acid (125 cm^3). The solution was heated under reflux for 72 h, cooled, and the hydrolysate was washed with dichloromethane (3 x 12 cm^3). The aqueous phase was separated and the volatile components were distilled off from the aqueous phase on a rotary evaporator tc give a yellow suspension. Ethanol (25 cm^3) was added, and the solution was treated with propylene oxide until maximum precipitation was formed. The white solid was filtered, washed from acetone (10 cm^3) and recrystallised from water/ethanol to yield α-aminopropane-phosphonic acid (1.57 g, 36.9%) as a crystalline white solid, m.p. 262-263 °C (lit. m.p. 264-266 °C),[33] ^{1}H NMR (D_2O) δ 1.12 (t, C$\underline{H}_3$, $^3J_{HCCH}$ 6.1 Hz), 1.41-2.22 (br m, 2H, C$\underline{H}_2$), 2.87-3.40 (m, 1H, C$\underline{H}$).

Re-investigation of the above reaction on the same scale but using trimethyl phosphite (3.72 g, 0.03 mol), yielded α-aminopropanephosphonic acid (1.45 g, 35.0%) as a white crystalline solid, m.p. 259-260 °C (lit. m.p. 264-266 °C),[33] ^{1}H NMR (D_2O) δ 1.11 (t, C$\underline{H}_3$, $^3J_{HCCH}$ 6.0 Hz), 1.39-2.20 (br m, 2H, C$\underline{H}_2$), 2.85-3.40 (m, 1H, C$\underline{H}$).

6.9 Attempted preparation of α-aminopropanephosphonic acid from triethyl phosphite, propanal and benzyl carbamate using glacial acetic acid

Benzyl carbamate (3.47 g, 0.023 mol), triethyl phosphite (3.81 g, 0.023 mol), and propanal (1.45 g, 0.025 mol) were heated under reflux (1.5 h) with glacial acetic acid (5 cm^3). Concentrated hydrochloric acid (20 cm^3) was added and the mixture was heated under reflux for a further 6 h. The pale yellow solution was cooled, and extracted with toluene (2 x 10 cm^3). The aqueous phase was separated, the volatile components were distilled off on a rotary evaporator to give a pale yellow residue. Methanol (10 cm^3) was added to yield a whito solid whose I.R spectrum was identical to an authentic sample of ammonium chloride. This solid was filtered, washed with methanol (4 cm^3), and dried to give ammonium chloride (0.74 g, 62%), m.p. > 180 °C (subl.). The combined washings and the mother liquor were treated with propylene oxide to give a pale yellow oil. The mother liquor was decanted, and the oil was crystallised from water/ethanol to yield α-hydroxypropane-phosphonic acid (0.54 g, 17.0%) as a crystalline white solid, m.p. 162-163 °C (lit. m.p. 165 °C)[106], (Found: C, 25.4; H, 6.2; Calc. for $C_3H_9O_4P$: C, 25.7; H, 6.4%); ^1H NMR (D_20) δ 1.20 (t, 3H, CH_3, $^3J_{HCCH}$ 6.2 Hz), 1.45-2.25 (br m, 2H, CH_2), 2.85-3.45 (m, 1H, CH); ^{31}P (D_20) 23.9 (s).

7.0 Preparation of α-aminopropanephosphonic acid from triethyl phosphite, propanal and benzyl carbamate using boron trifluoride-etherate in toluene

A mixture of benzyl carbamate (3.47 g, 0.032 mol), triethyl

phosphite (3.81 g, 0.023 mol), and propanal (1.45 g, 0.025 mol) in dry toluene (25 cm^3) was vigorously stirred, whilst a solution of boron trifluoride-etherate (0.5 cm^3) in dry toluene (5 cm^3) was added dropwise over 20 min. The mixture was heated under reflux for 5 h and the volatile components were distilled off on a rotary evaporator to give a mobile oil having ^{31}P nmr signals at δ 25.3, 28.1, and 6.3 ppm. Concentrated hydrochloric acid (125 cm^3) was added and the solution was heated under reflux for 8 h. The cooled solution was washed with dichloromethane (2 x 10 cm^3) and ether (2 x 10 cm^3). The aqueous phase was separated, boiled with charcoal (1.0 g), filtered, and finally concentrated *in vacuo*. Methanol (10 cm^3) was added to yield a white solid which was filtered, washed with methanol (4 cm^3), and dried to yield ammonium chloride (0.32 g, 26.6%), m.p. > 180 °C (subl.). The I.R spectrum of the white solid was identical to an authentic sample of ammonium chloride. The combined mother liquor and the washings were treated with propylene oxide to give a sticky white precipitate. The mother liquor was decanted, and methanol (5 cm^3) was added to the semi-solid. Crystallisation was completed on leaving the mixture at -15 °C for several hours. The solid product was filtered, washed with acetone (5 cm^3), and dried in a vacuum oven at 60 °C to yield α-aminopropanephosphonic acid (0.52 g, 20.8%) as a white solid, m.p. 249-250 °C (lit. m.p. 264-266 °C),[33] (Found: C, 24.3; H, 7.1; N, 9.4; Calc. for $C_3H_{10}NO_3P$: C, 25.9; H, 7.2; N, 10.1%); ^{31}P NMR (D_2O) δ 23.9 (trace) 16.3 (major). The mother liquor from the final filtration was concentrated *in vacuo* and the oil examined by ^{31}P nmr which showed signals at δ 24.1(major), 16.5 and 6.5 (trace). However, crystallisation from

water/ethanol failed to give a further crop of α-aminopropane-phosphonic acid.

7.1 Preparation of ammonium salt of α-ureidopropane-phosphonic acid

A mixture of urea (1.92 g, 0.032 mol), triethyl phosphite (5.31 g, 0.032 mol), and propanal (1.85 g, 0.032 mol) in dry toluene (25 cm^3) was vigorously stirred, whilst a solution of boron trifluoride etherate (0.9 cm^3) in dry toluene (10 cm^3) was added dropwise over 20 min. The mixture was heated under reflux for 2 h, and the volatile components were distilled *in vacuo* to give a yellow oil. Concentrated hydrochloric acid (100 cm^3) was added and the solution was heated under reflux for 8 h. The aqueous phase was separated, washed with dichloromethane (2 x 10 cm^3), boiled with charcoal (1.1 g), filtered, and concentrated *in vacuo* to give a solid residue. Methanol (10 cm^3) was added and the resultant solution was treated with propylene oxide until maximum precipitation was obtained. The solid product was filtered, washed with acetone (5 cm^3), and recrystallised with ethanol/water to give a white solid, which was characterised as the *ammonium salt of α-ureidopropanephosphonic acid* (17) (1.97 g, 31.3%), m.p. 205 °C, (Found: C, 23.9; H, 6.4; N, 20.8 $C_4H_{13}N_3O_4P$ requires: C, 24.2; H, 6.5; N, 21.2%); ^{1}H NMR (D_2O) δ 1.15 (t, 3H, CH_3 $^3J_{HCCH}$ 7 Hz), 1.30-1.95 (br m, 2H, CH_2), 2.59-2.71 (d, 1H, NH, $^3J_{PCNH}$ 8 Hz, exchanged after 0.5 h), 3.38- 4.15 (m, 1H, CH); ^{13}C NMR (D_2O) δ 12.9 (d, CH_3, $^3J_{PCCC}$ 14 Hz), 25.7 (d, CH_2, $^2J_{PCC}$ 3 Hz), 53.3 (d, CH, $^1J_{PC}$ 154.9 Hz), 159.1 (d, NHC(:O)NH2, $^3J_{PCNC}$ 6.1 Hz); ^{31}P NMR (D_20) δ 23.3 (s); m/z (FAB, %) 200 (M+1, 48), 182 ((M+H-H_2O, 68), 183 (M+H-NH_3,18), 166 (18.9), 165 (23.3),

101 (50), 140 (59.3), 110 (50.1), 58 (100).

7.2 Preparation of α-aminopropanephosphonic acid from triethyl phosphite, propanal and urea using boron trifluoride-etherate in toluene

A mixture of urea (1.92 g, 0.032 mol), triethyl phosphite (5.31 g, 0.032 mol), and propanal (1.85 g, 0.032 mol) in dry toluene (25 cm^3) was vigorously stirred, whilst a solution of boron trifluoride-etherate (0.9 cm^3) in dry toluene (10 cm^3) was added dropwise (20 min). The mixture was heated under reflux for 2 h and the volatile components were distilled off on a rotary evaporator to give a yellow oil. Concentrated hydrochloric acid (100 cm^3) was added and the mixture was heated under reflux for 72 h. The solution was cooled and washed with dichloromethane (2 x 10 cm^3). The aqueous phase was separated, boiled with charcoal (1.0 g), filtered, and concentrated *in vacuo*. Methanol (10 cm^3) was added and the resultant yellow solution was treated with propylene oxide to give an oil. The mother liquor was decanted, and the oil was allowed to crystallise from ethanol/water to yield α-aminopropanephosphonic acid (1.19 g, 26.9%) as a crystalline white solid, m.p. 258-259 °C (lit. m.p. 264-266 °C),[33] ^{1}H NMR (D_2O) δ 1.11 (t, C$\underline{H}_3$, $^3J_{HCCH}$ 6.0 Hz), 1.39-2.20 (br m, 2H, C$\underline{H}_2$), 2.85-3.40 (m, 1H, C$\underline{H}$); ^{31}P NMR (D_2O) δ14.8 (s).

When the above preparation was repeated on the same scale however, using non-equivalent molar ratio of urea (0.96 g, 0.016 mol), the required α-aminopropanephosphonic acid (1.33 g, 59.9% based on urea, 29.9% based on propanal) was obtained as a crystalline white solid, m.p. 256-258 °C (lit. m.p. 264-266 °C),[33]

^{1}H NMR (D_2O) δ 1.11 (t, C$\underline{H}_3$, $^3J_{HCCH}$ 6.0 Hz), 1.39-2.20 (br m, 2H, C$\underline{H}_2$), 2.85-3.40 (m, 1H, C$\underline{H}$); ^{31}P NMR (D_2O) 13.8 (s).

7.3 Preparation of α-aminopropanephosphonic acid from trimethyl phosphite and urea in the presence of boron trifluoride-etherate and toluene

Redistilled trimethyl phosphite (3.96 g, 0.032 mol), urea (1.96 g, 0.032 mol), and freshly distilled propanal (1.85 g, 0.032 mol) in dry toluene (25 cm^3) were vigorously stirred, whilst a solution of boron trifluoride etherate (0.9 cm^3) in dry toluene (10 cm^3) was added dropwise (20 min). The mixture was heated under reflux for 4 h, and the volatile components were distilled off from the reaction mixture under reduced pressure to leave a clear yellow oil. Concentrated hydrochloric acid (100 cm^3) was added and the solution was heated under reflux for 72 h. The pale-yellow solution was cooled, and washed with dichloromethane (3 x 10 cm^3). The aqueous phase was separated, boiled with charcoal (1 g), filtered, and concentrated *in vacuo* to give a yellow solid residue. Methanol (10 cm^3) was added and the solution was treated with propylene oxide to give a sticky white precipitate. The mother liquor was decanted, and the white mass was allowed to crystallise from ethanol/water to yield α-aminopropane-phosphonic acid (1.32 g, 29.7% based on propanal) as a crystalline white solid, m.p. 257-258 °C (lit. m.p. 264-266 °C),[33] (Found: C, 25.2; H, 7.0; N, 9.8. Calc. for $C_3H_{10}NO_3P$: C, 25.9; H, 7.2; N, 10.1%); ^{1}H NMR (D_2O) δ 1.11 (t, 3H, C$\underline{H}_3$, $^3J_{HCCH}$ 6.0 Hz), 1.39-2.20 (br m, 2H, C$\underline{H}_2$), 2.85-3.40 (m, 1H, C$\underline{H}$); ^{31}P NMR (D_20/D_2SO_4) δ 17.9 (br s).

7.4 Attempted preparation of α-aminopropanephosphonic acid by the addition of diphenyl phosphite to N-propylidenediphenylmethylamine

Distilled N-propylidenediphenylmethylamine (6.90 g, 0.025 mol), was stirred and heated with diphenyl phosphite (5.8 g, 0.025 mol), at 120-140 °C for 0.5 h. Concentrated hydrochloric acid (40 cm^3) was added and the solution heated under reflux for 4 h. The reaction mixture was cooled. The resultant white needles were filtered, and washed with ether (50 cm^3) and toluene (15 cm^3). After drying in a vacuum oven at 50 °C diphenylmethylamine hydrochloride (5.92 g, 87.2%) was obtained as a crystalline solid, m.p. 295-296 °C (lit. m.p. 297-298 °C),[107] ^1H NMR (NaOD) δ 5.10 (s, 1H, CH), 7.3 (br m, 10H, aromatic). The mother liquor was extracted with ether (3 x 15 cm^3) and the aqueous phase was evaporated to dryness under reduced pressure (15 mm Hg, 70 °C) to give a brown oil which consisted of phosphorous acid as determined by ^{31}P nmr; ^{31}P NMR (D_2O) δ 7.3 (s, $^1J_{PH}$ 710 Hz).

7.5 Preparation of α-aminopropanephosphonic acid from phosphorus trichloride, propanal and benzyl carbamate

Freshly distilled propanal (1.6 g, 0.029 mol), was added dropwise at room temperature to a stirred solution of benzyl carbamate (3.02 g, 0.02 mol), phosphorus trichloride (2.75 g, 0.02 mol), and glacial acetic acid (5 cm^3). The mixture was heated under reflux for 40 min, treated with 4 M hydrochloric acid (25 cm^3) and refluxed further for 1 h. After cooling, the solution was extracted with dichloromethane (3 x 10 cm^3), ether (2 x 10 cm^3), and toluene (10 cm^3). The aqueous phase was separated, boiled with charcoal (1 g), filtered, and concentrated under reduced pressure (15 mm Hg,

70 °C). The resultant pale-brown residue was dissolved in methanol (10 cm^3) and treated with propylene oxide to yield a mobile oil, ^{31}P (D_2O) 24.9, 22.6,16.5, and 6.9 ppm. The mother liquor was decanted and the oil was allowed to crystallise from water/ethanol. A white solid which precipitated after several months at -4 °C, was filtered off, and dried to give α-amino-propanephosphonic acid (0.34 g, 12.3%), m.p 251-252 °C (lit. m.p. 264-266 °C),[33] ^1H NMR (D_2O) δ 1.20 (t, 3H, CH_3, $^3J_{HCCH}$ 5.8 Hz), 1.38-2.20 (br m, 2H, CH_2), 2.85-3.30 (m, 1H, CH).

7.6 Preparation of N-propylidenebenzylamine

Propanal (5.8 g, 0.1 mol), was added dropwise to a stirred solution of benzylamine (10.7 g, 0.1 mol) in ether (30 cm^3) at 0 °C. The solution was stirred for 1 h at room temperature in the presence of anhydrous potassium carbonate (ca. 3.1 g). The mixture was filtered, and excess ether was distilled off on a rotary evaporator to yield crude N-propylidenebenzylamine as a pale-yellow oil (13.1 g, 89.5%). Distillation under reduced pressure yielded pure N-propylidenebenzylamine (10.5 g, 71.6%) as a clear free running liquid, b.p. 48-51 °C at 1 mm Hg, ^1H NMR ($CDCl_3$) δ 1.40 (3H, t, CH_3, $^3J_{HCCH}$ 7.2 Hz), 1.90-2.40 (m, 2H, CH_2CH_3), 4.41(s, 2H, CH_2), 7.18 (br s, 5H, aromatic), 7.61 (t, 1H, CH, $^3J_{HCCH}$ 5.9 Hz); ^{13}C ($CDCl_3$) 10.1 (s, CH_3), 29.1 (s, CH_2CH_3), 64.9 (s, CH_2Ph), 125.6 (s, ortho C, aromatic), 127.9 (s, meta C, aromatic), 129.9 (s, para C, aromatic), 167.0 (s, N=CH)

7.7 Attempted preparation of N-benzyl α-aminopropane-phosphonic acid from phosphorous acid and N-propylidenebenzylamine

A mixture of N-propylidenebenzylamine (3.6 g, 0.025 mol), and phosphorous acid (2.05 g, 0.025 mol) was stirred with a mechanical stirrer and slowly heated to 75-80 °C, where-upon the reactants gave an orange sticky semi-solid. Further heating to 100-120 °C brought about a significant viscosity increase and an internal temperature of 140-160 °C. The reaction mass was cooled to 85 °C and dissolved in water (10 cm^3). Concentrated hydrochloric acid (5 cm^3) was added and the solution was heated under reflux for 30 min. Shiny white plates were formed on cooling the reaction mixture. These were filtered, washed with ethanol (18 cm^3), and dried in a vacuum oven at 80 °C to yield benzyl-ammonium chloride (1.20 g, 34.2%), m.p. 250-251 °C (lit. m.p. 254-255 °C).[46] The I.R spectrum of the white solid was identical to an authentic sample of benzylammonium chloride. The aqueous phase was reduced *in vacuo*, to yield a brown residue which showed a ^{31}P nmr signal at 6.5 ppm. The residue was extracted with anhydrous ethanol to yield benzylammonium phosphite (2.02 g, 46 .7%) as a shiny white solid, m.p. (123 °C), (Found: C, 39.1; H, 6.3; N, 7.1 Calc. for $C_6H_{12}NO_3P$: C, 38.1; H, 6.3; N, 7.4%) ^1H NMR (D_2O) δ 4.2 (s, 2H, CH_2), 7.5 (s, 5H, aromatic).

7.8 Preparation of α-aminopropanephosphonic acid from diethyl phosphite, propanal and ammonia

A solution of propanal (11.6 g, 0.20 mol) in absolute ethanol (100 cm^3) was cooled to 0 °C and stirred whilst dry ammonia was

passed into the solution until the latter was saturated (3 h). The resultant cold solution was added slowly to diethyl phosphite (27.6 g, 0.20 mol), contained in a steel autoclave, precooled to approximately 0 °C. The solution was heated for 8 h (100 °C, 75 psi) , cooled, and concentrated *in vacuo* to yield a yellow oil. The ^{31}P nmr spectrum (MeOD) of the oil indicated 4 different signals (2.7, 23.4, 24.3, 25.9). Concentrated hydrochloric acid (200 cm^3) was added and the mixture was heated under reflux for 8 h. The reaction mixture, a dark-brown solution, was cooled, extracted with toluene (3 x 20 cm^3) and dichloromethane (3 x 10 cm^3). The aqueous phase was separated and concentrated *in vacuo*, to yield a brown residue. Methanol (80 cm^3) was added to dissolve the residue. Treatment with propylene oxide (ca. 60 cm^3) yielded a brown oil. The mother liquor was decanted and the oil (8.51 g) was dissolved in a minimal amount of methanol (60 cm^3) and left at 4 °C for several weeks. A white solid was formed, which was filtered, washed with acetone (2 x 8 cm^3) and dried in a vacuum oven at 70 °C to yield α–aminopropanephosphonic acid (2.52 g, 9.1 %) as a fine white solid, m.p. 255-256 °C (lit. m.p. 264-266 °C),[33] ^1H NMR (D_2O) δ 1.11 (t, CH_3, $^3J_{HCCH}$ 6.0 Hz), 1.39-2.20 (br m, 2H, CH_2), 2.85-3.40 (m, 1H, CH). The combined filtrate and the washings were concentrated *in vacuo*, to give a brown oil (6.1 g) for which ^{31}P (D_20) showed 13 signals, as follows: 5.57, 7.4, 9.9, 11.4, 13.7, 17.4, 18.8, 19.7, 20.5, 21.2, 22.6, 23.7, 25.2.

The above procedure was repeated using a longer period of heating in the autoclave (18 h, 100 °C, 100 psi). Thereafter, the procedure was as follows. The resultant yellow viscous oil was distilled *in vacuo*, yielding a colourless liquid (13.5 g) with a

pungent smell, b.p. 72-74 °C at 2.5 mm Hg, n_D^{20} 1.4030, ^{1}H NMR ($CDCl_3$) δ 1.20 (t, J 6.5 Hz), 2.20-2.90 (m), 3.68 (q, J 8 Hz); no ^{31}P signal was registered.

The brown residue (18.6 g), ^{31}P nmr ($CDCl_3$) (5 signals, 2.2, 5.0, 20.0, 22.7 and 27.2 ppm) was dissolved in hydrochloric acid (200 cm^3) and heated under reflux for 8h. The cooled brown solution was extracted with toluene (3 x 15 cm^3), ether (2 x 10 cm^3) and concentrated *in vacuo* to yield a viscous pale brown oil. This oil was treated with chloroform (100 cm^3) and left for several months at room temperature. During this period a white solid was formed, which was filtered, washed with ethanol (2 x 3 cm^3) and dried in a vacuum oven at 60 °C to yield α-amino-propanephosphonic acid (2.50 g, 5.4 %) as a fine white solid, m.p. 251-254 °C (lit. m.p. 264-266 °C),[33] ^{1}H NMR (D_2O) δ 1.10 (t, CH_3, $^3J_{HCCH}$ 6.0 Hz), 1.39-2.18 (br m, 2H, CH_2), 2.84-3.38 (m, 1H, CH).

7.9 Preparation of dimethyl N-benzyl-α-aminopropane-phosphonate hydrochloride

Propanal (14.5 g, 0.25 mol), was added to a stirred solution of benzylamine (29.9 g, 0.28 mol), in water (30 cm^3) cooled at 0 °C. Dimethyl phosphite (32.0 g 0.29 mol), precooled to -5 °C was added dropwise (0.5 h), and the resultant cloudy mixture was stirred initially at 0 °C (8 h) and then at room temperature overnight. Sodium chloride (10.6 g) was added, and the pH of the solution was adjusted to 2-3 by the addition of concentrated hydrochloric acid (13.8 cm^3). Dichloromethane (36 cm^3) was added and the mixture was stirred for 15 min. The two phases were separated and the aqueous layer was re-extracted with dichloromethane (3 x 17 cm^3). The combined organic phases were dried (Na_2SO_4) and the volume

reduced *in vacuo* to ca. 40 cm^3 to yield a colourless liquid. Ethyl acetate (15 cm^3) was added and the volume was again reduced to 45 cm^3 *in vacuo*. This ethyl acetate procedure was repeated five times to remove most of the dichloromethane. Acetone (125 cm^3) was added and the crystallisation was completed by storage at 4 °C overnight. The white solid was filtered, washed with acetone (2 x 20 cm^3) and dried in an oven at 60 °C to yield crude ***dimethyl N-benzyl-α-aminopropanephosphonate hydrochloride*** (21) (46.2 g, 63.2 %). ^1H nmr of the crude product showed that it contained approximately 7% benzylammonium chloride. The product was purified by dissolving the crude solid in dichloromethane (95 cm^3); and the resultant benzylammonium chloride (1.39 g), m.p. 254-255 °C (lit. m.p. 254-255 °C)[46] was filtered off, washed with dichloromethane (2 x 5 cm^3) and dried in an oven at 60 °C, ^1H NMR (D_2O) δ 5.15 (s, 2H, CH_2), 7.50 (s, 5H, aromatic). The filtrate was reduced to approximately half its volume (45 cm^3) and concentrated with two separate portions of ethyl acetate (2 x 35 cm^3). Acetone (95 cm^3) was added and the mixture was stored at 4 °C overnight. A white solid was formed which was filtered, and washed with acetone (2 x 12 cm^3) to give ***dimethyl N-benzyl-α-aminopropanephosphonate hydrochloride*** (21) (39.4 g, 53.7%) as a crystalline white solid, m.p. 112-113 °C dec, (Found: C, 48.1; H, 6.9; N, 4.5; $C_{12}H_{21}ClNO_3P$ requires: C, 48.9; H, 7.1; N, 4.7%), ^1H NMR (D_2O) δ 0.93 (t, 3H, CH_3, $^3J_{HCCH}$ 7.5 Hz), 1.50-2.35 (m, 2H, CH_2), 3.25-3.98 (m, 1H, CH), 3.70, 3.90 (two d, 6H, $POCH_3$, $^3J_{POCH}$ 12 Hz), 4.33 (s, CH_2Ph), 7.45 (s, 5H, aromatic); ^{13}C NMR ($CDCl_3$) δ 10.9 (d, CH_3, $^3J_{PCCC}$ 6 Hz), 21.3 (s, CH_2CH_3), 49.9 (s, CH_2Ph), 51.9 (d, $POCH_3$, $^2J_{POC}$ 6 Hz), 53.2 (d, $POCH_3$, $^2J_{POC}$ 6 Hz), 53.5 (d, CH,

$^{1}J_{PC}$ 153.3 Hz), 131.6 (s, ortho C, aromatic), 132.3 (s, meta C, aromatic), 132.9 (s, para C, aromatic), 133.7 (s, $\underline{C}CH_2NH$, aromatic); ^{31}P NMR ($CDCl_3$) δ 24.4 (s).

The original mother liquor (from 46.2 g of crude dimethyl N-benzyl-α-aminopropanephosphonate) and the washings, were combined and evaporated *in vacuo* to give a pale yellow gum (33.2 g). This was partitioned between potassium carbonate (15.8 g) in water (35 cm^3) and toluene (23 cm^3). The organic phase was separated and dried (Na_2SO_4). Treatment with a solution of 8 M methanolic hydrochloric acid (35 cm^3) and then acetone (35 cm^3) yielded a further crop of crude phosphonate (10.1 g). Purification as above gave a further crop of (21) (9.1 g, 12.3%) as a crystalline white solid, m.p. 112-113 °C dec; total yield (48.5 g, 66.2%).

8.0 Preparation of dimethyl α-aminopropanephosphonate hydrochloride

Dimethyl N-benzyl-α-aminopropanephosphonate hydrochloride (5.0 g, 0.017 mol), in ethanol (100 cm^3), and 5% palladium on charcoal (1.0 g) were introduced into a steel autoclave and the mixture was treated with hydrogen for 3 h (100 °C, 400 psi). The reaction mixture was cooled and the catalyst was filtered. The resultant pale yellow liquid was concentrated *in vacuo* to give dimethyl α-aminopropanephosphonate hydrochloride (22) as a viscous oil (2.98 g, 86.1%). ^{1}H NMR (D_2O) δ 0.93 (t, 3H, CH_3, $^{3}J_{HCCH}$ 7.5 Hz), 1.50-2.35 (m, 2H, CH_2), 3.25-3.98 (m, 1H, CH), 3.70,3.90 (two d, 6H, $POCH_3$, $^{3}J_{POCH}$ 12 Hz). ^{13}C NMR (D_2O) δ 10.9 (d, $\underline{C}H_3$, $^{3}J_{PCCC}$ 6 Hz), 21.3 (s, $\underline{C}H_2CH_3$), 51.9 (d, $PO\underline{C}H_3$, $^{3}J_{POCH}$ 6 Hz), 53.2 (d, $PO\underline{C}H_3$, $^{3}J_{POCH}$ 6 Hz), 53.5 (d, $\underline{C}H$, $^{1}J_{PC}$ 153.3 Hz). ^{31}P NMR

(D_2O) δ 23.9 (s).

8.1 Preparation of α-aminopropanephosphonic acid from dimethyl α-aminopropanephosphonate hydrochloride

Dimethyl α-aminopropanephosphonate hydrochloride (2.90 g, 0.014 mol), from the above hydrogenation, and concentrated hydrochloric acid (25 cm^3) were heated under reflux (8 h). After cooling, the mixture was extracted with toluene (2 x 10 cm^3) and the aqueous phase was separated. The resultant solution was boiled with charcoal (1.0 g), filtered, and concentrated *in vacuo* to give a viscous residue. Methanol (8.0 cm^3) was added and the solution was treated with propylene oxide to give a sticky white precipitate. The mother liquor was decanted and the product allowed to crystallise from water/ethanol to yield α-aminopropane-phosphonic acid (1.35 g, 57.2%) as a crystalline white solid, m.p. 261 °C (lit. m.p. 264-266 °C),[33] ^1H NMR (D_2O) δ1.11(t, CH_3, $^3J_{HCCH}$ 6.0 Hz), 1.39-2.20 (br m, 2H, CH_2), 2.85-3.40 (m,1H, CH).

8.2 Modified preparation of N-benzyl-α-aminopropane-phosphonic acid hydrochloride

Propanal (5.80 g, 0.1 mol), was added to a stirred solution of benzylamine (10.7 g, 0.1 mol), in water (30 cm^3) cooled at 0 °C. Dimethyl phosphite (12.4 g 0.1 mol), precooled to -5 °C was added dropwise (0.5 h) and the resultant cloudy mixture was initially stirred at 0 °C (8 h), then at room temperature (12 h). Concentrated hydrochloric acid (100 cm^3) was added and the solution was heated under reflux (8 h). The reaction mixture was cooled and extracted with toluene (4 x 20 cm^3). The aqueous phase was separated and concentrated *in vacuo* to give a pale yellow

residue, which was dissolved in a mixture of acetone and ether (45 : 20 cm^3) and stored at 4 °C for several days. The precipitated product was filtered, washed with acetone (2 x 10 cm^3) and dried in a vacuum oven at 60 °C to give N-benzyl-α-amino-propanephosphonic acid hydrochloride (15.9 g, 72.6%) as a fine white solid, m.p. 179-181 °C (lit. m.p. 182-184 °C),[44] (Found: C, 44.8; H, 6.4; N, 5.2 Calc for $C_{10}H_{17}ClNO_3P$ C, 45.1; H, 6.3; N, 5.3%) ^1H NMR (D_2O) δ 1.0 (t, 3H, CH_3, $^3J_{HCCH}$ 7 Hz), 1.79 -2.17 (m, 2H, CH_2), 3.11-3.50 (m, 1H, CH), 4.39 (s, 2H, CH_2Ph), 7.51 (s, 5H, aromatic): ^{13}C NMR (D_2O) δ 10.9 (d, CH_3, $^3J_{PCCC}$ 6 Hz), 21.3 (s, CH_2CH_3), 49.9 (s, CH_2Ph), 53.5 (d, CH, $^1J_{PC}$ 153.3 Hz), 131.6 (s, ortho C, aromatic), 132.3 (s, meta C, aromatic), 132.9 (s, para C, aromatic), 133.7 (s, CCH_2NH, aromatic): ^{31}P NMR (D_2O) δ 14.8 (s).

8.3 Preparation of α-aminopropanephosphonic acid from dimethyl N-diphenylmethyl-α-aminopropanephosphonate

Propanal (5.80 g, 0.1 mol), was added to a stirred solution of diphenylmethylamine (18.3 g, 0.1 mol), in water (30 cm^3) cooled at 0 °C. Dimethyl phosphite (12.4 g 0.1 mol), precooled to -5 °C was added dropwise (0.5 h) and the resultant white semi-solid mass was initially stirred at 0 °C (8 h), and then at room temperature (12 h). Concentrated hydrochloric acid (100 cm^3) was added and the solution was heated under reflux (8 h). A solid was formed upon cooling which was filtered, washed with water (2 x 10 cm^3), ether (5 x 10 cm^3) and dried in a vacuum oven at 60 °C. After drying, diphenylmethylammonium chloride (10.3 g, 46.9%) was obtained as a crystalline white solid, m.p. 295-297 °C (lit. m.p. 298 °C).[107] The I.R. spectrum of this solid was identical with that of

authentic diphenylmethylammonium chloride. The mother liquor was washed with ether (5 x 10 cm^3), the aqueous phase separated, and concentrated *in vacuo* to give a viscous residue. Methanol (12 cm^3) was added and the resultant pale yellow solution was heated under reflux. Propylene oxide (10 cm^3) was added to give an immediate precipitate which was filtered off, washed with cold ethanol (2 x 4 cm^3) and dried in a vacuum oven at 70 °C to give α-aminopropanephosphonic acid (4.0 g, 28.8%) as a crystalline white solid, m.p. 261-262 °C, (lit. m.p. 264-266 °C),[33] (Found: C, 25.3; H, 7.2; N, 10.3 . Calc. for $C_3H_{10}NO_3P$: C, 25.9; H, 7.1; N, 10.0%); ^1H NMR (D_2O) δ 1.11 (t, 3H, CH_3, $^3J_{HCCH}$ 6.0 Hz), 1.39-2.20 (br m, 2H, CH_2), 2.85-3.40 (m, 1H, CH); ^{13}C NMR (D_2O) δ 13.06 (d, CH_3, $^3J_{PCCC}$ 9.2 Hz), 24.71 (d, CH_2, $^2J_{PCC}$ 1.8 Hz) 53.66 (d, CH, $^1J_{PC}$ 142.8 Hz). ^{31}P NMR (D_2O) δ 14.1 (s).

8.4 Repeat preparation of α-aminopropanephosphonic acid from dimethyl N-diphenylmethyl-α-aminopropane-phosphonate

Propanal (5.80 g, 0.1 mol), was added to a stirred solution of diphenylmethylamine (18.3 g, 0.1 mol), in methanol (80 cm^3) cooled at 0 °C. Dimethyl phosphite (12.4 g 0.1 mol), precooled to -5 °C, was added dropwise (0.5 h) and the resultant cloudy solution was initially stirred at 0 °C (8 h), then at room temperature (12 h). A sample of this mixture was concentrated *in vacuo* and the resultant viscous oil was examined by ^1H nmr; ^1H NMR (MeOD) δ 1.05 (t, 3H, CH_3 $^3J_{HCCH}$ 7.5 Hz),1.30-2.30 (br m, 2H, CH_2), 1.90 (s overlapping with multiplet, NH), 2.50-3.10 (m, 1H, CH), 3.60,3.80 (br s with shoulders, $POCH_3$ $^3J_{POCH}$ 12.0 Hz), 5.20 (s, 1H, $CHPh_2$),

7.10-7.50 (br m, 10H, aromatic). This suggests that the sample consists entirely of the intermediate dimethyl N-diphenylmethyl-α-aminopropanephosphonate. Concentrated hydrochloric acid (100 cm^3) was added and the solution was heated under reflux (8 h). A white solid was formed upon cooling. This was filtered, washed with water (2 x 10 cm^3), ether (5 x 10 cm^3) and dried in a vacuum oven at 60 °C. After drying, diphenylmethylammonium chloride (8.0 g, 36.4%) was obtained as a crystalline white solid, m.p. 295-296 °C, (lit. m.p. 298 °C).[107] The I.R. spectrum of this solid was identical with that of authentic diphenylmethylammonium chloride. The mother liquor was extracted with ether (5 x 10 cm^3), the aqueous phase was then separated and concentrated *in vacuo* to give an oily residue. Methanol (15 cm^3) was added and the resultant pale yellow solution was warmed under reflux. Propylene oxide (13 cm^3) was added to give an immediate precipitate which was filtered off, washed with cold ethanol (2 x 4 cm^3) and dried in a vacuum oven at 60 °C to yield α-aminopropanephosphonic acid (6.5 g, 47.1%) as a crystalline white solid, m.p. 259-261 °C, (lit. m.p. 264-266 °C).[33] ^1H NMR (D_2O) δ 1.11 (t, 3H, CH_3, $^3J_{HCCH}$ 6.0 Hz), 1.39-2.20 (br m, 2H, CH_2), 2.85-3.40 (m, 1H, CH); ^{13}C NMR (D_2O) δ 13.06 (d, CH_3, $^3J_{PCCC}$ 9.2 Hz), 24.71 (d, CH_2, $^2J_{PCC}$ 1.8 Hz) 53.66 (d, CH, $^1J_{PC}$ 142.8 Hz).

8.5 Attempted hydrogenolysis of N-benzyl-α-amino-propanephosphonic acid hydrochloride for the synthesis of α-aminopropanephosphonic acid

N-benzyl-α-aminopropanephosphonic acid hydrochloride (5.0 g, 0.018 mol), in methanol (100 cm^3) and 5% palladium on charcoal (1.0 g) were charged into a steel autoclave. The reaction mixture

was treated with hydrogen for 3 h (100 °C, 400 psi) and cooled. The catalyst was filtered, and the resultant pale yellow liquid was concentrated *in vacuo* to give a residue (5.3 g). ^{1}H NMR (D_2O) δ 1.0 (t, 3H, C<u>H</u>$_3$, $^3J_{HCCH}$ 7 Hz), 1.79 -2.17 (m, 2H, C<u>H</u>$_2$), 3.11-3.49 (m, 1H, C<u>H</u>), 4.39 (s, 2H, C<u>H</u>$_2$Ph), 7.51 (s, 5H, <u>aromatic</u>). Crystallisation of the residue with water/acetone yielded unreacted N-benzyl-α-aminopropanephosphonic acid hydrochloride (4.3 g, 86.0% recovery) as a crystalline white solid. Repetition of the above experiment using twice the quantity of catalyst (2.0 g), also failed to give the desired α-aminopropanephosphonic acid. Again, the product obtained was the unreacted parent compond (4.1 g, 82.0%).

8.6 Preparation of crude dimethyl N-benzyl-α-amino-propanephosphonate and its attempted hydrogenolysis

Propanal (14.5 g, 0.25 mol), was added to a stirred solution of benzylamine (29.9 g, 0.28 mol), in water (30 cm^3) cooled at 0 °C. Dimethyl phosphite (32.0 g, 0.29 mol), precooled to -5 °C was added dropwise (0.5 h), and the resultant cloudy mixture was stirred initally at 0 °C (8 h) and then at room temperature overnight. A sample (1 cm^3) of this mixture was extracted with deuterated chloroform (5 cm^3) dried (Na_2SO_4), filtered, and examined by ^{1}H nmr spectrum. This showed that the only detectable compound present was dimethyl <u>N</u>-benzyl-α-aminopropane-phosphonate,^{1}H NMR ($CDCl_3$) δ 1.0 (t, 3H, C<u>H</u>$_3$ $^3J_{HCCH}$ 6.5 Hz), 1.41-2.80 (m, 2H, C<u>H</u>$_2$CH$_3$), 2.60-3.10 (m, 1H, C<u>H</u>), 3.40 (s, <u>NH</u> exchanged with D_2O after 10 min), 3.70, 3.88 (br d, 6H, POC<u>H</u>$_3$ $^3J_{POCH}$ 10 Hz), 3.95 (s, 2H, C<u>H</u>$_2$Ph), 7.30 (br s, 5H, <u>aromatic</u> signal appear sharper after D_2O shake). The above mixture in water was directly used for

hydrogenation without further purification.

The above procedure was repeated on several occasions whereby isolation of the crude product involved extraction with dichloromethane. The resultant organic extract was dried, filtered, and concentrated *in vacuo* to yield a mobile oil. This oil was subsequently dissolved in different solvents for hydrogenolysis.

On a various occassion, methanol was used as the solvent for the initial synthesis of crude dimethyl N-benzyl-α-aminopropanephosphonate instead of water.

8.7 Attempted hydrogenolysis of the crude dimethyl N-benzyl-α-aminopropanephosphonate in water

Crude dimethyl N-benzyl-α-aminopropanephosphonate (32.1 g, 0.124 mol) in water, prepared according to the above procedure, and 5% palladium on charcoal (6.5 g), were introduced into a steel autoclave. Additional water (15 cm^3) was added and the mixture was initially treated with hydrogen (50 °C, 340 psi) for 3 h. Heating was stopped and a sample of material was removed, filtered, and concentrated *in vacuo*. The resultant viscous oil was examined by ^1H nmr spectroscopy which indicated that no reaction had occurred. The solution was therefore, further treated with hydrogen (90 °C, 420 psi) for an additional 5 h. The reaction mixture was cooled and the catalyst was filtered off leaving a pale yellow solution. The latter was concentrated *in vacuo* to yield a viscous yellow oil (29.8 g), whose ^1H nmr spectrum suggested mainly loss of methyl protons from the ester group, ^1H NMR (D_2O) δ 1.0 (t, 3H, CH_3 $^3J_{HCCH}$ 6.5 Hz), 1.41-2.80 (m, 2H, CH_2CH_3), 2.60-3.10 (m, 1H, CH), 3.40 (s, NH exchanged with D_2O after 8 min), 3.70,

3.88 (br d, 6H, POC$\underline{H}_3$ $^3J_{POCH}$ 10 Hz decreased relatively in proportion to the other peaks), 3.95 (s, 2H, C$\underline{H}_2$Ph), 7.30 (br s, 5H, aromatic).

8.8 Attempted hydrogenolysis of crude dimethyl N-benzyl-α-aminopropanephosphonate in dichloromethane

Crude dimethyl N-benzyl-α-aminopropanephosphonate (32.1 g, 0.124 mol), in water, prepared by the above procedure was extracted with dichloromethane (3 x 50 cm^3). The organic phase was separated, dried (Na_2SO_4) and filtered. The resultant clear solution was treated with hydrogen (100 °C, 440 psi) in the presence of 5% palladium on charcoal (6.5 g) for 7 h. The reaction mixture was cooled, filtered and concentrated *in vacuo* to give a yellow oil (28.6 g), whose ^1H nmr spectrum suggested mainly loss of methyl protons from the ester group, ^1H NMR (D_2O) δ 1.0 (t, 3H, C$\underline{H}_3$ $^3J_{HCCH}$ 6.5 Hz), 1.41-2.80 (m, 2H, C$\underline{H}_2$CH_3), 2.60-3.10 (m, 1H, C$\underline{H}$), 3.40 (s, NH exchanged gradually with D_2O), 3.70, 3.88 (br d, 6H, POC$\underline{H}_3$ $^3J_{POCH}$ 10 Hz decreased approximately 80% in proportion to the other peaks), 3.95 (s, 2H, C$\underline{H}_2$Ph), 7.30 (br s, 5H, aromatic). No apparent loss in the peak area of the benzyl peaks were observed.

8.9 Attempted hydrogenolysis of crude dimethyl N-benzyl-α-aminopropanephosphonate in methanol

Crude dimethyl N-benzyl-α-aminopropanephosphonate (32.1 g, 0.123 mol), prepared and isolated according to the above procedure was mixed with methanol (125 cm^3) and 5% palladium on charcoal (6.5 g), and charged into an autoclave. The mixture was initially treated with hydrogen (104 °C, 600 psi) for 3 h. Heating was

stopped and a sample of material was removed, filtered, and concentrated *in vacuo*. The resultant viscous oil was examined by ^1H nmr spectroscopy which indicated that no reaction had occurred. The reaction mixture was removed from the autoclave and filtered to yield a clear solution. Additional 5% palladium on charcoal (6.5 g) was added and the mixture was further treated with hydrogen (100 °C, 650 psi) for 15 h, cooled and filtered. The resultant pale yellow solution with a characteristic smell of toluene, was concentrated *in vacuo* to give an oily pale yellow residue (25.3 g). The ^1H nmr spectrum of this oil suggested mainly loss of protons from the ester group. Additionally, a small decrease in the peak area for the aromatic region in relation to the other peaks was observed which suggested partial debenzylation was in progress. ^1H NMR (D_2O) δ 1.0 (t, 3H, CH_3 $^3J_{HCCH}$ 6.5 Hz), 1.41-2.80 (m, 2H, CH_2CH_3), 2.60-3.10 (m, 1H, CH), 3.40 (s, NH exchanged with D_2O gradually), 3.70, 3.88 (br d, 6H, $POCH_3$ $^3J_{POCH}$ 10 Hz decreased relatively in proportion to the other peaks), 3.95 (s, 2H, CH_2Ph), 7.30 (br s, 5H, aromatic, decreased partially in proportion to other peaks).

9.0 Attempted hydrogenation of crude dimethyl N-benzyl-α-amino-propanephosphonate in acetic acid

Crude dimethyl N-benzyl-α-aminopropanephosphonate (16.0 g, 0.06 mol), prepared according to the above procedure, was extracted with dichloromethane (3 x 50 cm^3), the organic phase was separated, dried (Na_2SO_4), and filtered. The clear solution was concentrated *in vacuo* and treated with acetic acid (100 cm^3). This solution and 5% palladium on charcoal (1.3 g) were charged

into an autoclave. The mixture was treated with hydrogen for 6 h (100 °C, 500 psi), cooled, and the catalyst was filtered off. The resultant solution was concentrated *in vacuo* to give an extremely viscous brown oil, whose ^1H nmr indicated total loss of methyl protons from the ester groups, ^1H NMR (D_2O) δ 1.0 (t, 3H, $C\underline{H}_3$ $^3J_{HCCH}$ 6.5 Hz), 1.41-2.80 (m, 2H, $C\underline{H}_2CH_3$), 2.60-3.10 (m, 1H, C<u>H</u>), 3.40 (s, N<u>H</u> exchanged with D_2O gradually), 3.95 (s, 2H, $C\underline{H}_2Ph$), 7.30 (br s, 5H, <u>aromatic</u>). No apparent loss in benzyl peaks was observed.

9.1 A modified preparation of crude dimethyl N-benzyl-α-aminopropanephosphonate hydrochloride

Propanal (14.5 g, 0.25 mol), was added to a stirred solution of benzylamine (26.7 g, 0.25 mol), in water (30 cm^3), cooled at 0 °C. Dimethyl phosphite (27.5 g, 0.25 mol), precooled to -5 °C was added dropwise (0.5 h) whilst the cloudy mixture was stirred initally at 0 °C (8 h), and then at room temperature overnight. The solution was treated with sodium chloride (10.6 g), and the pH of the solution was adjusted to 2-3 by the addition of concentrated hydrochloric acid (13.8 cm^3). Dichloromethane (50 cm^3) was added and the mixture was stirred for 15 min. The phases were separated and the aqueous layer was re-extracted with dichloromethane (4 x 25 cm^3). The combined organic phases were dried (Na_2SO_4), filtered, and concentrated *in vacuo* to yield a viscous oil (70.3 g, 95.6%). The oil was examined by ^1H nmr spectroscopy which showed that the only detectable compound present was the desired crude *dimethyl N-benzyl-α-aminopropanephosphonate hydrochloride*, ^1H NMR ($CDCl_3$) δ 1.0 (t, 3H, $C\underline{H}_3$ $^3J_{HCCH}$ 6.1 Hz),

1.50-1.95 (m, 2H, CH_2),2.89-3.40 (m, 1H, CH), 3.30 (s, NH exchanged with D_20), 3.60,3.90 (br d, 6H, $POCH_3$ $^3J_{POCH}$ 10 Hz), 4.25 (s, 2H, CH_2Ph), 7.35 (br s, 5H, aromatic, signal appears much sharper after D_2O exchange).

9.2 Attempted hydrogenolysis of the above crude dimethyl N-benzyl-α-aminopropanephosphonate hydrochloride in dichloromethane

Crude dimethyl N-benzyl-α-aminopropanephosphonate hydrochloride (18.3 g, 0.062 mol), prepared by the above procedure, was extracted with dichloromethane (150 cm^3), dried (Na_2SO_4), and filtered. The resultant clear solution was mixed with 5% palladium on charcoal (3.30 g) and charged into an autoclave. The mixture was initially treated with hydrogen (20 °C, 535 psi) for 3 h. Heating was stopped and a sample was removed from the autoclave. It was filtered, concentrated and examined by ^1H nmr spectroscopy, which indicated that no changes had occurred. The mixture was treated with hydrogen for a further 3 h (100 °C, 595 psi), cooled, filtered and concentrated *in vacuo* to give a pale green deliquesecent solid (9.3 g). ^1H nmr spectra of this solid suggested mainly loss of methyl protons from the ester group, ^1H NMR ($CDCl_3$) δ 1.0 (t, 3H, CH_3 $^3J_{HCCH}$ 6.1 Hz), 1.50-1.95 (m, 2H, CH_2),2.89-3.40 (m, 1H, CH), 3.30 (s, NH exchanged with D_20), 3.60, 3.90 (br d, 6H, $POCH_3$ $^3J_{POCH}$ 10 Hz, peaks decreased by approximately 90%), 4.25 (s, 2H, CH_2Ph), 7.35 (br s, 5H, aromatic).

9.3 Preparation of tetrakis(2,2,2-trichloroethyl)N,N-thiourylene-(-1,1-dipropyl)-1,1-diphosphonate

A mixture of thiourea (1.14 g, 0.015 mol), tris-2,2,2-

trichloroethyl phosphite (14.3 g, 0.03 mol) and propanal (1.85 g, 0.032 mol) in sodium dried toluene (10 cm^3) was stirred and warmed to 100 °C. Further heating at 108-110 °C for 1 h afforded a light yellow solution having ^{31}P nmr peaks at 24.9 (major) and 137.6 (minor) ppm. Concentration of the resultant solution under reduced pressure (90 °C, 13 mm Hg), yielded a viscous yellow oil (11.2 g) that completly solidified at room temperature after several weeks. Recrystallisation of this solid from acetone twice and from acetonitrile gave a crystalline white solid which was filtered off and dried in a vacuum oven at 60 °C. *Tetrakis(2,2,2-trichloroethyl) N,N-thiourylene(-1,1-dipropyl)-1,1-diphosphonate* (35) was obtained as a crystalline white solid (4.86 g, 48.9% based on thiourea), m.p. 210-212 °C, (Found: C, 20.7; H, 2.7; N, 3.2; $C_{15}H_{22}Cl_{12}N_2O_6P_2S$ requires: C, 21.2; H, 2.6; N, 3.3%); ^1H NMR ($CDCl_3$) δ 1.06 (t, 3H, $C\underline{H}_3$ $^3J_{HCCH}$ 7.1 Hz), 4.43 (br m, $C\underline{H}_2$) 4.50-4.95 (complex m consisting of 11 lines, 8H, $POC\underline{H}_2$), 5.03-5.53 (m, 1H, $C\underline{H}$), 7.73 (d, $N\underline{H}$ $^3J_{PCNH}$ 9.8 Hz exchanged with D_2O within 5 min); ^{13}C NMR ($CDCl_3$) δ 10.1 (d, $\underline{C}H_3$ $^3J_{PCCC}$ 11.8 Hz), 23.4 (s, $\underline{C}H_2$), 52.1 (d, $\underline{C}H$ $^1J_{PC}$ 147.6 Hz), 76.2 (d, $PO\underline{C}H_2$ $^2J_{POC}$ 6.7 Hz), 76.5 (d, $PO\underline{C}H_2$ $^2J_{POC}$ 6.1 Hz), 94.9 (d, $CH_2\underline{C}Cl_3$ $^3J_{POCC}$ 6.5 Hz), 185.3 (t, $\underline{C}$=S, $^3J_{PCNC}$ 8.9 Hz); ^{31}P NMR ($CDCl_3$) δ 24.6 (s); m/z (%) 841 (M+H, 0.80), 808 (2.40), 806 (1.6), 500 (10.0), 498 (5.9), 466 (6.3), 464 (4.4), 440 (1.1), 99.8 (100).

9.4 Preparation of tetrakis(2,2,2-trichloroethyl) N,N-urylene-(-1,1-dipropyl)-1,1-diphosphonate

A mixture of urea (0.90 g, 0.015 mol), tris-2,2,2-trichloroethyl phosphite (14.29 g, 0.03 mol) and propanal (1.85 g,

0.032 mol) in sodium dried toluene (10 cm^3) was stirred and warmed to 80 °C. Further heating at 108-110 °C for 1 h yielded a light yellow solution having ^{31}P nmr peaks at 23.9 (major) and 137.2 ppm (trace). Concentration of the resultant solution under reduced pressure (90 °C, 13 mm Hg), yielded a viscous yellow oil (13.8 g) which solidified at room temperature after several weeks. Recrystallisation of this solid from acetone (twice) and from acetonitrile (once) gave a crystalline white solid which was filtered off and dried in a vacuum oven at 60 °C. *Tetrakis(2,2,2-trichloroethyl) N,N-urylene(-1,1-dipropyl)-1,1-diphosphonate* (36) was obtained as a crystalline white solid (6.99 g, 56.2%), m.p. 204-205 °C, (Found: C, 21.7; H, 2.8; N, 3.1; $C_{15}H_{22}Cl_{12}N_2O_7P_2$ requires: C, 21.6; H, 2.7; N, 3.3%); ^1H NMR ($CDCl_3$) δ 1.03 (t, 3H, $C\underline{H}_3$ $^3J_{HCCH}$ 6.9 Hz), 4.40 (br m, $C\underline{H}_2$) 4.50-4.95 (complex m, consisting of 11 lines, 8H, $POC\underline{H}_2$), 5.0-5.55 (m, 1H, C<u>H</u>), 7.65 (d, <u>NH</u> $^3J_{PCNH}$ 10.0 Hz exchanged with D_2O within 5 min); ^{13}C NMR ($CDCl_3$) δ 10.3 (d, $\underline{C}H_3$ $^3J_{PCCC}$ 11.7 Hz), 23.8 (s, $\underline{C}H_2$), 51.9 (d, $\underline{C}H$ $^1J_{PC}$ 146.9 Hz), 76.3 (d, $PO\underline{C}H_2$ $^2J_{POC}$ 6.7 Hz), 76.5 (d, $PO\underline{C}H_2$ $^2J_{POC}$ 6.2 Hz), 93.9 (d, $CH_2\underline{C}Cl_3$ $^3J_{POCC}$ 6.0 Hz), 158.3 (t, C=O, $^3J_{PCNC}$ 9.3 Hz); ^{31}P NMR ($CDCl_3$) δ 23.9 (s); m/z (%) 825 (M+H, 0.3), 680 (5.8), 678 (4.1), 530 (2.6), 486 (29.6), 482 (21.2), 401 (16.8), 339 (23.5), 335 (74.8), 140.8 (100).

9.5 Preparation of tetrakis(2,2,2-trifluoroethyl) N,N-thiourylene-(-1,1-dipropyl)-1,1-diphosphonate

A mixture of thiourea (2.81 g, 0.037 mol), tris-2,2,2-trifluoroethyl phosphite (25.0 g, 0.076 mol) and propanal (4.40 g,

0.076 mol) in sodium dried toluene (10 cm^3) was stirred and warmed to 80 °C. Further heating at 90-96 °C for 1 h yielded a fluorescent yellow solution. Concentration of this solution under reduced pressure (90 °C, 13 mm Hg), gave a viscous yellow oil (25.5 g) that completely solidified after several weeks at room temperature. Acetone (15 cm^3) was added, and the resultant white mass was filtered off, and dried to give ***tetrakis(2,2,2-trifluoroethyl) N,N-thiourylene(-1,1-dipropyl)-1,1-diphosphonate*** (38) as a fine white solid (8.95g, 37.4%), m.p. 146-149 °C. The mother liquor from the above filtration was treated with toluene (ca. 30 cm^3) and left at room temperature for several days . A white solid precipitated which was filtered off, and dried in a vacuum oven to yield a second crop (9.03 g, 37.7%). The combined crops were recrystallised twice from acetone to give pure ***tetrakis(2,2,2-trifluoroethyl) N,N-thiourylene(-1,1-dipropyl)-1,1-diphosphonate*** (38) as crystalline white needles (14.7 g, 61.3%), m.p. 154-155 °C, (Found: C, 28.5; H, 3.4; N, 4.2; $C_{15}H_{22}F_{12}N_2O_6P_2S$ requires: C, 27.8; H, 3.3; N, 4.4%); ^1H NMR ($CDCl_3$) δ 1.0 (t, 3H, $C\underline{H}_3$ $^3J_{HCCH}$ 7.1 Hz), 1.20-2.07 (br m, 2H, $C\underline{H}_2$) 4.40-5.0 (complex m consisting of 8 lines, 8H, $POC\underline{H}_2$), 5.31-5.57 (m, 1H, $C\underline{H}$), 7.45 (d, $\underline{NH}$ $^3J_{PCNH}$ 10.3 Hz exchanged with D_2O within 5 min); ^{13}C NMR ($CDCl_3$) δ 9.5 (d, $\underline{C}H_3$ $^3J_{PCCC}$ 13.4 Hz), 23.1 (d, $\underline{C}H_2$ $^2J_{PCC}$ 3.0 Hz), 51.8 (d, $\underline{C}H$ $^1J_{PC}$ 155.0 Hz), 62.1 (d, $\underline{C}H_2OP$ $^2J_{POC}$ 7.1 Hz), 62.6 (q, $O\underline{C}H_2CF_3$ $^2J_{CCF}$ 122 Hz), 62.9 (d, $\underline{C}H_2OP$ $^2J_{POC}$ 7.1 Hz), 124.1 (q, $\underline{C}F_3$, $^1J_{CF}$ 296 Hz)185.5 (s, $\underline{C}$=S); ^{31}P NMR ($CDCl_3$) δ 27.05, 27.25; m/z (%) 648 (M^+, 28.8), 403 (32.1), 387 (21.0), 369 (M-$\{F_3CCH_2O\}_2P\{O\}H_2S$, 5.9), 287 (9.3), 156 (12.7), 100 (24.5), 58.1 (100).

9.6 Preparation of tetrakis(2,2,2-trifluoroethyl) N,N-urylene-(-1,1-dipropyl)-1,1-diphosphonate

A mixture of urea (2.28 g, 0.038 mol), tris-2,2,2-trifluoroethyl phosphite (25.0 g, 0.076 mol) and propanal (4.40 g, 0.076 mol) in sodium dried toluene (10 cm^3) was stirred and warmed to 80 °C. Further heating at 90-96 °C for 1 h gave a clear colourless solution. Concentration of this solution under reduced pressure (90 °C, 13 mm Hg), yielded a yellow viscous oil (24.8 g) that completely solidified after several weeks at room temperature. Acetone (15 cm^3) was added, and the resultant white solid was filtered off. After drying in a vacuum oven at 80 °C, *tetrakis(2,2,2-trifluoroethyl) N,N-urylene(-1,1di-propyl)-1,1-diphosphonate* (37) was obtained as a fine white solid (10.3 g, 42.9%), m.p. 146-149 °C. The mother liquor from the above filtration was treated with toluene (ca. 15 cm^3) and left at room temperature for several days A white solid was precipitated which was filtered off and dried in a vacuum oven at 80 °C to yield a further crop of the product (9.03 g, 37.6%). The combined crops were recrystallised twice from acetone to give *tetrakis(2,2,2-trifluoroethyl) N,N-urylene(-1,1-dipropyl)-1,1-diphosphonate* (37) as crystalline white needles (13.9 g, 57.9%), m.p. 156-158 °C, (Found: C, 28.6; H, 3.4; N, 4.5; $C_{15}H_{22}F_{12}N_2O_7P_2$ requires: C, 28.4; H, 3.4; N, 4.5%); ^{1}H NMR ($CDCl_3$) δ 1.05 (t, 3H, CH_3 $^3J_{HCCH}$ 7.1 Hz), 1.50-2.20 (br m, 2H, CH_2) 4.40-5.05 (complex m, consisting of 8 lines, 8H, $POCH_2$)$_2$ 5.35-5.59 (m, 1H, CH), 7.49 (d, NH $^3J_{PCNH}$ 10.2 Hz, exchanged with D_2O within 5 min); ^{13}C NMR ($CDCl_3$) δ 9.8 (d, CH_3 $^3J_{PCCC}$ 13.3 Hz), 22.9 (d, CH_2 $^2J_{PCC}$ 3.1 Hz), 51.9 (d, CH $^1J_{PC}$ 155.3), 62.2 (d, CH_2OP $^2J_{POC}$ 7.0 Hz), 62.6(q, OCH_2CF_3 $^2J_{CCF}$

122 Hz), 62.9 (d, $\underline{C}H_2OP$ $^2J_{POC}$ 7.2 Hz), 124.1 (q, $\underline{C}F_3$, $^1J_{CF}$ 295.5 Hz); 158.6 (s, $\underline{C}$=O); ^{31}P NMR ($CDCl_3$) δ 27.0 (s); m/z (%) 632 (M^+, 2.1), 387 (26.4), 330 (3.2), 287 (10.4), 274 (2.7), 245 (3.1), 141 (6.7), 98.9 (3.1), 84.1 (11.1), 58.0 (100).

9.7 Preparation of tetrakis(2,2,2-trifluoroethyl) N,N-urylene di(-3-methylsulphenyl-1,1-dipropyl)-1,1-diphosphonate

Redistilled tris(2,2,2-trifluoroethyl) phosphite (12.5 g, 0.038 mol), urea (1.14 g, 0.019 mol), and 3-(methylthio)propanal (3.90 g, 0.038 mol) in sodium-dried toluene (10 cm^3), were stirred, whilst boron trifluoride-etherate (1.50 cm^3), in toluene (10 cm^3) was added dropwise at room temperature (15 min). The mixture was heated at 95-105 °C under reflux (1.5 h), after which the volatile materials were removed under reduced pressure (70 °C, 13 mm Hg). Ethanol (15 cm^3) was added to the resultant brown oil (12.6 g), and the solution was left at 4 °C for several months. White needles were formed which were filtered off, washed with ether (1 cm^3) and dried in a vacuum oven at 50 °C. After drying, *tetrakis(2,2,2-trifluoroethyl) N,N-urylene di(-3-methylsulphenyl-1,1-dipropyl)-1,1-diphosphonate* (48) was obtained as a fine white solid (0.3 g), m.p. 119-120 °C. The combined washings and the mother liquor were concentrated *in vacuo* (40 °C, 13 mm Hg) to yield a brown oil, which was treated with ethanol (13 cm^3) and the solution was stored at 4 °C. A second crop of the product which crystallised after several weeks was filtered off, washed with ether (1 cm^3) and dried in the oven at 60 °C. The above procedure was repeated six times to give further crops of product. The combined crops

(2.01 g, 14.6%) were recrystallised from ethanol and water to yield *tetrakis(2,2,2-trifluoroethyl) N,N-urylene di(-3-methylsulphenyl-1,1-dipropyl)-1,1-diphosphonate* (48) was obtained as crystalline white needles, (1.75 g, 12.7%), m.p. 122-123 °C (Found: C, 28.1; H, 3.4; N, 4.1; $C_{17}H_{26}F_{12}N_2O_7P_2S_2$ requires: C, 28.2; H, 3.5; N, 4.0%); ^{1}H NMR (MeOD) δ 1.50-2.30 (m, 2H, C$\underline{H}_2$CH), 2.08 (s, 3H, C$\underline{H}_3$), 2.65 (t, 2H, C$\underline{H}_2$-S $^3J_{HCCH}$ 7.1 Hz), 4.31-4.80 (complex m, $F_3CC\underline{H}_2O$), 5.0-5.55 (m, 1H, C$\underline{H}$), 6.49 (br d, PC$\underline{NH}$ $^3J_{PCNH}$ 9.5 Hz, exchanged with D_2O within 5 min); ^{13}C NMR (MeOD) δ15.0 (s, S-$\underline{C}H_3$), 29.9 (d, $\underline{C}H_2CH$ $^2J_{PCC}$ 3.1 Hz), 30.9 (d, $\underline{C}H_2$-S, $^3J_{PCCC}$ 16.3 Hz), 46.8 (d, $\underline{C}H$ $^1J_{PC}$ 160.8 Hz), 63.3 (d, $\underline{C}H_2OP$ $^2J_{POC}$ 7.0 Hz), 63.6 (q, O$\underline{C}H_2CF_3$ $^2J_{CCF}$ 123 Hz), 63.8 (d, $\underline{C}H_2OP$ $^2J_{POC}$ 7.2 Hz), 122.5 (q, $\underline{C}F_3$, $^1J_{CF}$ 298 Hz)158.6 (s, $\underline{C}$=O); ^{31}P NMR (MeOD) δ 27.1 (s); m/z (%) 724 (M^+,10.2), 663 (8.8), 624 (M- F_3CCH_2OH, 12.3), 479 (M-{$F_3CCH_2O)_2P(O)CH(CH_2)_2SCH_3$}, 3.7), 288 (10.0), 246 (12.2), 69.9 (100).

9.8 Oxidation of tetrakis(2,2,2-trifluoroethyl)N,N-urylene (-3-methylsulphenyl-1,1-dipropyl)-1,1-diphosphonate

Hydrogen peroxide (30%, 0.63 cm^3), was added dropwise at 0 °C to a stirred suspension of tetrakis(2,2,2-trifluoroethyl) N,N-urylene(-3-methylsulphenyl-1,1-dipropyl)-1,1-diphosphonate (0.90 g, 0.012 mol), in glacial acetic acid (9.10 cm^3). After stirring for 2 h, the solution was concentrated under reduced pressure, and diluted with water (0.50 cm^3) and methanol (4.50 cm^3). The resultant clear solution was warmed, and treated with acetone (7.20 cm^3). A cloudy solution was formed upon cooling, which was concentrated *in vacuo* to give a clear oil. The oil was treated with methanol and water, and the resultant solution was stored at 4 °C

for several days. A white solid gradually precipitated which was filtered off, and dried in a vacuum oven at 50 °C. *Tetrakis(2,2,2-trifluoroethyl)N,N-urylene(-3-methylsulphinyl-1,1-dipropyl)-1,1-diphosphonate* (49) was obtained as crystalline white needles (0.59 g, 63.0%), m.p. 150-151 °C (Found: C, 26.1; H, 3.3; N, 3.7; $C_{17}H_{26}F_{12}N_2O_7P_2S_2$ requires: C, 26.9; H, 3.4; N, 3.7%); ^{1}H NMR (MeOD) δ 1.55-2.35 (m, 2H, C$\underline{H}_2$CH), 2.15 (s, 3H, C$\underline{H}_3$), 2.85 (t, 2H, C$\underline{H}_2$-S $^3J_{HCCH}$ 7.1 Hz), 4.31-4.80 (complex m, $\underline{F}_3$CC$\underline{H}_2$O), 5.0-5.55 (m, 1H, C$\underline{H}$), 6.49 (br d, PCN$\underline{H}$ $^3J_{PCNH}$ 9.5 Hz, exchanged with D_2O within 5 min); ^{13}C NMR (MeOD) δ 16.5 (s, S-$\underline{C}H_3$), 29.8 (d, $\underline{C}H_2CH$ $^2J_{PCC}$ 3.1 Hz), 35.7 (d, $\underline{C}H_2$-S, $^3J_{PCCC}$ 16.1 Hz), 46.6 (d, $\underline{C}H$ $^1J_{PC}$ 160.2 Hz), 63.4 (d, $\underline{C}H_2OP$ $^2J_{POC}$ 7.0 Hz), 63.6 (q, O$\underline{C}H_2CF_3$ $^2J_{CCF}$ 122 Hz), 63.9 (d, $\underline{C}H_2OP$ $^2J_{POC}$ 7.1 Hz), 122.7 (q, $\underline{C}F_3$, $^1J_{CF}$ 296 Hz)158.6 (s, $\underline{C}$=O); 158.6 (s, $\underline{C}$=O,); ^{31}P NMR (MeOD) δ 27.8 (s); m/z (%) 756 (M^+, 2.2), 548 (4.3), 392 (M -{F_3CCH_2}$_2${O}PCHNH{CH_2}$_2$S{O}CH_3},12.3), 360 ({F_3CCH_2}$_2${O}PCHNHC{O}{CH_2}$_2$S{O}CH_3 - CH_3OH, 11.6), 328 (21.1), 292 (22.2), 278 (12.8), 247 (F_3CCH_2}$_2${O}PCHNHC{O}{CH_2}$_2$S - CHNHC{O}{CH_2}$_2$S, 15.0), 246 (74.5), 229 (16.3), 81.9 (100).

9.9 Preparation of bis(2,2,2-trifluroethyl)-α-phenyl-ureidopropane phosphonate

Redistilled tris-2,2,2-trifluoroethyl phosphite (12.5 g, 0.038 mol), phenylurea (5.60 g, 0.038 mol), and propanal (2.32 g, 0.040mol) were stirred in sodium-dried toluene (10 cm^3), whilst boron trifluoride-etherate (1.5 cm^3), in toluene (10 cm^3) was added dropwise at room temperature (15 min). The reaction mixture was heated at 95-105 °C under reflux (2.5 h), cooled, and the volatile components were distilled off on a rotary evaporator to yield a

dark brown residue (16.3 g). This residue was dissolved in ethanol (15 cm^3), treated with light petroleum ether (40 cm^3), and stored at 4 °C. A white solid, precipitated gradually over several weeks. It was filtered off, washed with ethyl acetate (2 x 8 cm^3), and dried to yield *bis(2,2,2-trifluroethyl)-α-phenylureidopropane-phosphonate* (39) (1.61 g) as a pale pink solid. The mother liquor was concentrated *in vacuo* to give a brown residue, which was dissolved in ethyl acetate (12 cm^3). This solution was then treated with light petroleum ether (35 cm^3) and stored at 4 °C for several weeks. A second crop of the product (5.90 g) which crystallised after several weeks was filtered off, washed with ethyl acetate (10 cm^3) and dried in a vacuum oven at 50 °C. The above procedure was repeated to yield a further crop (1.82 g). The combined product (9.33 g) was recrystallised from water and ethanol to yield *bis(2,2,2-trifluroethyl)-α-phenylureidopropanephosphonate* (39) as a crystalline white solid (8.20 g, 48.6%), m.p.154-155 °C (Found: C, 39.1; H, 4.0; N, 6.4; $C_{14}H_{17}F_6N_2O_4P$ requires: C, 39.8; H, 4.0; N, 6.6%); ^1H NMR (MeOD) δ 0.98 (t, 3H, $C\underline{H}_3$ $^3J_{HCCH}$ 6.1 Hz),1.40-2.0 (br m, 2H, $C\underline{H}_2$), 3.55-4.0 (m, 1H, $C\underline{H}$), 3.85-4.30 (complex multiplet, 4H, $POC\underline{H}_2$), 6.95-7.05 (br d, $\underline{NH}$ $^3J_{PCNH}$ 9.3 Hz, exchanged with D_2O) 7.50 (br s, 5H, aromatic); ^{13}C NMR (MeOD) 9.5 (d, $\underline{C}H_3$ $^3J_{PCCC}$ 13.4 Hz), 23.1 (d, $\underline{C}H_2$ $^2J_{PCC}$ 3.0 Hz), 51.8 (d, $\underline{C}H$ $^1J_{PC}$ 155.0 Hz), 62.2 (d, $\underline{C}H_2OP$ $^2J_{POC}$ 7.0 Hz), 62.6(q, $O\underline{C}H_2CF_3$ $^2J_{CCF}$ 122 Hz), 62.9 (d, $\underline{C}H_2OP$ $^2J_{POC}$ 7.2 Hz), 124.1 (q, $\underline{C}F_3$, $^1J_{CF}$ 295.5 Hz); 128.8 (s, ortho $\underline{C}$ aromatic), 129 (s, meta $\underline{C}$ aromatic), 129.5 (s, para $\underline{C}$ aromatic) 158.6 (t, $\underline{C}$=O, $^3J_{PCNC}$ 8 Hz); ^{31}P NMR (MeOD) δ 25.4 (s); m/z (%) 422 (M^+ 3.1), 314 (9.0), 268 (24.6), 240 (15.7), 177 (4.5), 135 (1.1), 93.0 (100).

10 Preparation of α-ureido-3-(S-methylsulphenyl)-propanephosphonic acid

Freshly distilled 3-(methylsulphenyl)propanal (2.20 g, 0.02 mol), was added dropwise (1 h) to a stirred mixture of powdered urea (1.20 g, 0.02 mol) and tris-2,2,2-trichloroethyl phosphite (10.0 g, 0.02 mol) at 95-100 °C. The mixture was heated for an additional 0.5 h and evaporated down (60 °C, 13 mm Hg) to yield an orange gelatinous residue. This was dissolved in a mixture of acetonitrile (3 cm^3) and water (0.7 cm^3), gently reflux for 1 h and concentrated *in vacuo*. Ethyl acetate (60 cm^3) was added and the resultant yellow residue was stored at 4 °C.

A white solid precipitated gradually over several weeks was decanted from the remaining residue, washed with ether (2 x 4 cm^3) and dried. *α-Ureido-3-{methylsulphenyl}propanephosphonic acid* (54) was obtained as a fine white powder (0.76 g, 15.6%) m.p. 160 °C, (Found: C, 25.9; H, 5.7; N, 12.6; $C_5H_{13}N_2O_4PS$ requires: C, 26.3; H, 5.7; N, 12.3%); ^1H NMR (D_2O) δ 1.55-2.31 (m, 2H, C$\underline{H}_2$CH), 2.0 (s, 3H, C$\underline{H}_3$), 2.60 (t, 2H, C$\underline{H}_2$-S $^3J_{HCCH}$ 7.1 Hz), 3.90-4.35 (m, 1H, C$\underline{H}$); ^1H NMR ($CDCl_3$) δ 1.0-1.72 (m, 2H, C$\underline{H}_2$CH), 1.85 (s, 3H, C$\underline{H}_3$), 2.55 (t, 2H, C$\underline{H}_2$-S $^3J_{HCCH}$ 7.1 Hz), 3.70-4.10 (m, 1H, C$\underline{H}$), 6.12 (br s, 1H, NH), 8.60 (br, 4H, OH and NH_2); ^{13}C NMR (D_2O) δ 14.6 (s, S-$\underline{C}H_3$), 29.1 (d, $\underline{C}H_2$CH $^2J_{PCC}$ 1.6 Hz), 30.7 (d, $\underline{C}H_2$-S, $^3J_{PCCC}$ 15.8 Hz), 46.5 (d, $\underline{C}$H $^1J_{PC}$ 161.3 Hz), 158.6 (t, $\underline{C}$=O, $^3J_{PCNC}$ 10.3 Hz); ^{31}P NMR (D_2O) δ 18.1 (s); m/z (FAB, %) 457 (2M+H, 14.7), 267 (10.4), 251 (15.4), 229 (M+H, 83.2), 212 (M+H- NH_3, 9.0), 187 (M+H-HCNO, 47.4), 114 (10.2), 104 (100).

The combined mother liquor, washings, and the original residue were concentrated *in vacuo*, and then treated with ethyl

acetate (50 cm^3). No further crop of the product was obtained on storage at 4 °C for several months.

10.1 Preparation of tetraphenyl N,N -thiourylene-(1,1-dipropyl)-1,1-diphosphonate

A mixture of thiourea (5.70 g, 0.075 mol), triphenyl phosphite (46.5 g, 0.15 mol) and propanal (8.70 g, 0.15 mol) in sodium dried toluene (50 cm^3) was stirred and heated to 100 °C. The temperature rose spontaneously to 105 °C within a few minutes without external warming. The reaction mixture was warmed at 105-110 °C (1 h) to give a light yellow solution. Concentration of this solution under reduced pressure (90 °C, 13 mm Hg), yielded a viscous oil (44.3 g), that solidified completely on standing after several weeks at room tempearture. Recrystallisation twice from acetone and from dichloromethane afforded *tetraphenyl N,N -thiourylene-(1,1-dipropyl)- 1,1-diphosphonate* (34) as a shiny white solid, (24.7 g, 52.8%), m.p. 199-201 °C, (Found: C, 58.3; H, 5.3; N, 4.3; $C_{31}H_{34}N_2O_6P_2S$ requires: C, 59.6; H, 5.4; N, 4.5%), ^1H NMR ($CDCl_3$) δ 0.88 (t, 3H, $C\underline{H}_3$ $^3J_{HCCH}$ 8.1 Hz), 1.31-1.50 (m, 1H, $C\underline{H}_2${A}), 1.90-2.10 (m, 1H, $C\underline{H}_2${B}), 5.62-5.80 (m, 1H, C<u>H</u>),7.10-7.32 (m, 20, aryl), 7.66-7.68 (d, N<u>H</u>, $^3J_{PCNH}$ 10.1 Hz); ^{13}C NMR ($CDCl_3$) δ 10.9 (d, $\underline{C}H_3$ $^3J_{PCCC}$ 12.8), 24.7 (s, $\underline{C}H_2$), 50.0 (d, $\underline{C}H$ $^1J_{PC}$ 152.6), 145.6 (complex m, <u>aromatic</u> 4 x C_6H_5), 184.3 (t, <u>C</u>=S, $^3J_{PCNC}$ 8.6 Hz); ^{31}P NMR ($CDCl_3$) δ 17.8 (s); m/z (%) 624 (M+, 4.1), 531 (M-OPh,10.4), 437 (531-PhOH,13.9), 391 (14.3), 357 (18.7), 333 (M-$\{PhO)_2P\{O\}CHNHCH_2CH_3$, 23.0), 297 (9.8), 217 (17.8),156 (23.9), 141 (15.2), 100 (65.8), 94 (100).

10.1 Preparation of tetraphenyl N,N thiourylene-(3,3-dimethylsulphenyl-1,1-dipropyl)-1,1-diphosphonate

A mixture of thiourea (2.80 g, 0.038 mol), triphenyl phosphite (23.6 g, 0.076 mol) and 3-(methylsulphenyl)propanal (7.90 g, 0.076 mol) in sodium dried toluene (25 cm^3) was stirred and heated under reflux (1 h). The resultant light yellow solution was concentrated under reduced pressure (90 °C, 13 mm Hg), yielding a viscous oil (26.9 g). A solid mass was formed when the oil was left at room temperature for several months. This was filtered, recrystallised twice from ethanol and water. *Tetraphenyl N,N thiourylene-(3,3-dimethylsulphenyl-1,1-dipropyl)-1,1-diphosphonate* (47) was obtained as a light white solid, (12.8 g, 48.7%), m.p. 118-120 °C, (Found: C, 53.9; H, 5.33; N, 3.92; $C_{33}H_{37}N_2O_6P_2S_3$ requires: C, 55.3; H, 5.30; N, 3.91%); ^1H NMR ($CDCl_3$) δ 1.5-2.2 (m, 2H, $C\underline{H}_2CH$), 2.0 (s, 3H, $C\underline{H}_3$), 2.6 (t, 2H, $C\underline{H}_2$-S $^3J_{HCCH}$ 7.0 Hz), 5.0-5.5 (m, 1H, C<u>H</u>), 7.1-7.3 (m, 20, aryl), 7.6-7.6 (d, NH, $^3J_{PCNH}$ 10.1 Hz); ^{13}C ($CDCl_3$), 15.0 (s, CH_3). 27.9 (d, $\underline{C}H_2CH$ $^2J_{PCC}$ 3.1), 28.9 (d, $\underline{C}H_2$-S-CH_3 $^3J_{PCCC}$ 16.8), 51.1 (d, $\underline{C}H$ $^1J_{PC}$ 151.4), 145.6 (complex m, <u>aromatic</u> 4 x C_6H_5), 182.7 (t, <u>C</u>=S, $^3J_{PCNC}$ 7.9 Hz); ^{31}P NMR ($CDCl_3$) δ 18.9 (s); m/z (%) 716 (M+, 1.34), 622 (M-PhOH,0.61), 529 (5.70), 380 (M- $\{(PhO)_2P\{O\}CHNH(CH_2)_2SCH_3\}$, 11.3), 379 (4.35), 332 (11.0), 318 (17.2), 148 (37.2), 94.0 (100).

10.2 General method for the synthesis of N-(diphenylmethyl)-α-amino alkanephosphonous acids

The aldehyde (1 mol) in water (250 cm^3) was added dropwise to a refluxing solution of diphenylmethylamine hydrochloride (0.1 mol) in water (500 cm^3) and aqueous hypophosphorous acid (1 mol).

Precipitation commenced when two thirds of the aldehyde had been added. The reaction mixture was refluxed for an additional 2 h and then cooled. The resultant white solid was filtered off, washed with acetone and dried in a vacuum oven at 60 °C to give the N-(diphenyl)-α-methylaminoalkanephosphonous acid (59) as a fine white solid.

10.3 Synthesis of N-(diphenylmethyl)-α-aminoethanephosphonous acid

Acetaldehyde (4.40 g, 0.1 mol), in water (25 cm^3), was added dropwise to a refluxing solution of diphenylmethylamine hydrochloride (21.9 g, 0.1 mol) and 50% aqueous hypophosphorous acid (13.2 g, 0.1 mol) in water (50 cm^3). The resultant mixture was refluxed for 2 h and then cooled. Work-up according to the general procedure gave N-(diphenylmethyl)-α-aminoethanephosphonous acid (22.8 g, 86%) as a fine white solid, m.p. 219-220 °C (lit. m.p. 220-221 °C),[108] ^1H NMR (NaOD) δ 1.25 (3H, d of d, CH_3 $^3J_{HCCH}$ 7.8 Hz, $^3J_{PCCH}$ 16.2 Hz), 2.95-3.54 (1H, m, CH), 5.30 (1H, s, CH), 7.50 (10H, br s, aromatic); ^{31}P NMR (NaOD) δ 31.5 (br s, $^1J_{PH}$ 507 Hz).

10.4 Synthesis of N-(diphenylmethyl)-α-aminopropanephosphonous acid

Propanal (5.80 g, 0.1 mol), in water (25 cm^3), was added dropwise to a refluxing solution of diphenylmethylamine hydrochloride (21.9 g, 0.1 mol) and 50% aqueous hypophosphorous acid (13.2 g, 0.1 mol) in water (50 cm^3). The resultant mixture was refluxed for 2 h and then cooled. Work-up according to the general procedure gave N-(diphenylmethyl)-α-aminopropanephosphonous

acid (21.5 g, 76.1%) as a fine white solid, m.p. 199-200 °C (lit. m.p. 202 °C),[108] ^{1}H NMR (NaOD) δ 1.15 (3H, t, C$\underline{H}_3$, $^3J_{HCCH}$ 6 Hz), 1.45-2.25 (2H, br m, C$\underline{H}_2$), 2.75 -3.30 (1H, m, C$\underline{H}$), 5.30 (1H, s, C$\underline{H}$Ph$_2$), 7.45 (10H, br s, aromatic): ^{31}P NMR (NaOD) δ 30.5 (br s, $^1J_{PH}$ 510 Hz).

10.5 Synthesis of N-(diphenylmethyl)-α-aminobutanephosphonous acid

Butanal (7.2 g, 0.1 mol), in water (25 cm^3), was added dropwise to a refluxing solution of diphenylmethylamine hydrochloride (21.9 g, 0.1 mol), and 50% aqueous hypophosphorous acid (13.2 g, 0.1 mol) in water (50 cm^3). The resultant mixture was refluxed for a further 2 h and then cooled. Work-up according to the general procedure afforded N-(diphenylmethyl)-α-aminobutanephosphonous acid (18.5 g, 60.0%) as a fine white crystalline solid, m.p. 213-214 °C (lit. m.p. 215-216 °C),[108] ^{1}H NMR (NaOD) δ 1.05 (3H, t, C$\underline{H}_3$ $^3J_{HCCH}$ 5.5 Hz), 1.35-1.95 (2H, m, C$\underline{H}_2$), 2.45-2.90 (2H, m, C$\underline{H}_2$), 3.30-3.90 (1H, m, C$\underline{H}$) 5.30 (1H, s, C$\underline{H}$Ph$_2$) 7.45 (10H, br s, aromatic): ^{31}P NMR (NaOD) δ 30.7 (br s, $^1J_{PH}$ 513 Hz).

10.6 Synthesis of N-(diphenylmethyl)-α-aminopentanephosphonous acid

Pentanal (8.6 g, 0.1 mol), in water (25 cm^3), was added dropwise to a refluxing solution of diphenylmethylamine hydrochloride (21.9 g, 0.1 mol), and 50% aqueous hypophosphorous acid in water (50 cm^3). The resultant mixture was refluxed for an additional 2 h and then cooled. Work-up according to the general procedure gave N-(diphenylmethyl)-α-aminopentanephosphonous

acid (15.1 g, 49.0%) as a white crystalline solid, m.p. 203 °C (lit.m.p. 209-210 °C),[108] ^{1}H NMR (NaOD) δ 1.11 (3H, t, C<u>H</u>$_3$ $^3J_{HCCH}$ 5.6 Hz), 1.39 (4H, br s, C<u>H</u>$_2$), 1.45-2.1 (2H, m, CHC<u>H</u>$_2$), 3.32-3.71 (1H, m, C<u>H</u>) 5.30 (1H, s, C<u>H</u>Ph$_2$) 7.45 (10H, br s, <u>aromatic</u>): ^{31}P (NaOD) δ 30.6 (br s, $^1J_{PH}$ 514 Hz) :

10.7 Synthesis of N-(diphenylmethyl)-α-aminohexane-phosphonous acid

Hexanal (10.0 g, 0.1 mol), in water (25 cm^3), was added dropwise to a refluxing solution of diphenyl methylamine hydrochloride (21.9 g, 0.1 mol), and 50% aqueous hypophosphorous acid (13.2 g, 0.1 mol), in water (50 cm^3). The reaction mixture was refluxed for a further 2 h and then cooled. Work-up according to the general procedure gave *N-(diphenylmethyl)-α-aminohexane-phosphonous acid* (14.1 g, 44.1%), as white crystalline solid, m.p. 192 °C, (Found: C, 67.6; H, 7.6; N, 4.1; $C_{19}H_{26}NO_2P$ requires: C, 68.7; H, 7.8; N, 4.2%), ^{1}H NMR (NaOD) δ 1.10 (3H, t, C<u>H</u>$_3$ $^3J_{HCCH}$ 5.7 Hz), 1.39 (6H, br s, C<u>H</u>$_2$), 1.45-2.0 (2H, m, CHC<u>H</u>$_2$), 3.30-3.70 (1H, m, C<u>H</u>) 5.30 (1H, s, C<u>H</u>Ph$_2$) 7.45 (10H, br s, <u>aromatic</u>): ^{31}P NMR (NaOD) δ 30.6 (br s, $^1J_{PH}$ 513 Hz).

10.8 General method for the synthesis of α-aminoalkane-phosphonous acids

The <u>N</u>-(diphenylmethyl)-α-aminoalkanephosphonous acid (10 g) was heated with an excess of 48% hydrobromic acid (5 times by weight) at 100 °C for 3-4 h until two distinct phases had separated. The mixture was evaporated to dryness under reduced pressure (15 mm Hg, 80 °C) and the residue taken up in water (<u>ca.</u>

40 cm^3). The aqueous solution was washed several times with ether to remove diphenylmethyl bromide and then evaporated to dryness to give an oily residue of α-aminoalkanephosphonous acid hydrobromide. Ethanol (ca. 7 cm^3/g) was added to dissolve the residue and the resultant solution was treated with propylene oxide dropwise until maximum precipitation had occurred (ca. 30-40 cm^3). The α-aminoalkanephosphonous acid (57) was filtered off, washed with ethanol (10 cm^3), ether (10 cm^3), and finally dried in a vacuum oven at 60 °C.

10.9 Synthesis of α-aminoethanephosphonous acid

A mixture of N-(diphenylmethyl)-α–aminoethanephosphonous acid (10 g, 0.037 mol), and 48% aqueous hydrobromic acid (50 g), was heated at 100 °C until two distinct phases appeared (3 h). Work-up according to the general procedure gave α-aminoethanephosphonous acid (3.2 g, 78.2%) as a white solid, m.p. 222 °C (lit. m.p. 223-224 °C dec),[109] Found: C, 20.6; H, 7.9; N, 12.1. Calc. for $C_2H_9NO_2P$: C, 21.4; H, 8.0; N, 12.5%; ^1H NMR (D_2O) δ 1.25 (3H, d of d, CH_3 $^3J_{HCCH}$ 7.4 Hz), 2.80-3.54 (1H, m, CH); ^{13}C NMR (D_2O) δ 14.1 (s, CH_3), 49.1 (d, CH, $^1J_{PC}$ 93.5 Hz); ^{31}P NMR (D_2O) 21.4 (br s, $^1J_{PH}$ 531 Hz); FAB ms: m/z (%) 293 (11), 219 (2M+H, 23), 167 (78), 153 (2M+H-H_3PO_2, 33), 110 (M+H, 63), 93 (G+H, 37), 60 (98), 44 (M+H- H_3PO_2, 100).

11.0 Synthesis of α-aminopropanephosphonous acid

A mixture of N-(diphenylmethyl)-α–aminopropanephosphonous acid (10 g, 0.036 mol) and hydrobromic acid (50 g) was heated at 100 °C until two phases became distinct (3 h). Work-up according to the general procedure gave α-aminopropanephosphonous acid

(2.79 g, 63.0%) as a crystalline white solid, m.p. 225 °C (lit. m.p. 226-227 °C dec)[109] (Found: C, 28.9; H, 7.1; N, 11.0. Calc. for $C_3H_{10}N0_2P$: C, 29.2; H, 7.3; N, 11.3%); ^1H NMR (D_2O) δ 1.15 (3H, t, C<u>H</u>$_3$, $^3J_{HCCH}$ 6 Hz), 1.45-2.25 (2H, br m, C<u>H</u>$_2$), 2.75-3.30 (1H, m, C<u>H</u>); ^{13}C NMR (D_2O) δ 12.6 (d, <u>C</u>H$_3$, $^3J_{PCCC}$ 8.6 Hz), 22.7 (s, <u>C</u>H$_2$), 54.3 (d, <u>C</u>H, $^1J_{PC}$ 92.8 Hz); ^{31}P NMR (D_20) δ 20.5 (br s, $^1J_{PH}$ 528 Hz); FAB ms: m/z (%) 247 (2M+H, 32.4), 182 (2M+H-H_2PO_2, 7.9), 181 (2M+H-H_3PO_2, 16.1), 168 (18.4), 167 (2M+H-HPO_3, 98.5), 133 (27.5), 124 (M+H, 76.4), 106 (16.8), 101(10.1), 100 (13.7), 89 (100), 87 (53.3).

11.1 Synthesis of α-aminobutanephosphonous acid

A mixture of <u>N</u>-(diphenylmethyl)-α–aminobutanephosphonous acid (10 g, 0.035 mol) and hydrobromic acid (50 g) was heated at 100 °C until two phases became distinct (3 h). Work-up according to the general procedure gave α-aminobutanephosphonous acid (2.81 g, 60.1%) as a white crystalline solid, m.p. 235-236 °C (lit. m.p. 236-237 °C),[109] (Found: C, 33.9; H, 8.1; N, 9.8; Calc. for $C_4H_{12}NO_2P$: C, 34.8; H, 8.6; N, 10.1%); ^1H NMR (D_2O) δ 1.05 (3H, t, C<u>H</u>$_3$, $^3J_{HCCH}$ 5.5 Hz), 1.35-1.95 (2H, m, C<u>H</u>$_2$), 2.45-2.90 (2H, m, C<u>H</u>$_2$), 3.30-3.90 (1H, m, C<u>H</u>); ^{13}C NMR (D_2O) δ 15.7 (s, <u>C</u>H$_3$), 21.4 (d, <u>C</u>H$_2$, $^3J_{PCCC}$ 9.5 Hz), 31.0 (s, <u>C</u>H$_2$), 53.3 (d, <u>C</u>H, $^1J_{PC}$ 93.0 Hz); ^{31}P NMR (D_2O) δ 20.6 (br s, $^1J_{PH}$ 529 Hz); FAB ms: m/z (%) 275 (2M+H, 26.3), 209 (2M+H-H_3PO_2, 24.5), 192 (13.6), 138 (M+H, 100), 136 (29.2), 98 (15.8), 86 (41.6), 84 (24.8).

11.2 Synthesis of α-aminopentanephosphonous acid

A mixture of N-(diphenylmethyl)-α-aminopentane-phosphonous acid (10.0 g, 0.032 mol) and hydrobromic acid (50 g) was heated at 100 °C until two phases became distinct (4 h). Work-up according to the general procedure gave α-aminopentane-phosphonous acid (2.89 g, 59.2%) as a white solid, m.p. 230-231 °C (lit. m.p. 230-232 °C),[109] (Found: C, 38.9; H, 9.2; N, 9.0; Calc. for $C_5H_{14}NO_2P$: C, 39.4; H, 9.2; N,9.2%); ^{1}H NMR (D_2O) δ 0.98 (3H, t, CH_3 $^3J_{HCCH}$ 5.9 Hz), 1.39-1.99 (4H, br s, CH_2), 1.95-2.51(2H, m, CH_2CH), 3.15-3.65 (1H, m, CH); ^{13}C NMR (D_20) δ 15.7 (s, CH_3), 24.4 (s, CH_2CH_3), 30.0 (d, CH_2CH_2CH $^3J_{PCCC}$ 9.0 Hz), 36.2 (s, CH_2CH), 54.0 (d, CH, $^1J_{PC}$ 93.0); ^{31}P NMR (D_20) δ 20.9 (br s, $^1J_{PH}$ 532); FAB ms: m/z (%) 303 (2M+H, 1.44), 238 (2M+H-H_2PO_2, 22.5), 156 (65.1), 152 (M+H, 14.3), 87 (M+H-H_2PO_2, 13.5), 86 (M+H-H_3PO_2, 100), 84 (8.3).

11.3 Synthesis of α-aminohexanephophonous acid

A mixture of N-(dipnenylmethyl)-α-aminohexane-phosphonous acid (10 g, 0.031 mol) and hydrobromic acid (50 g) were heated at 100 °C until two phases became distinct (4 h). Work-up according to the general procedure gave *α-aminohexanephosphonous acid* (2.83 g, 55.1%) as a feathery white solid, m.p. 205- 206 °C (Found: C, 42.9; H, 9.1; N, 7.9. $C_6H_{16}NO_2P$ requires: C, 43.3; H, 9.6; N, 8.4;%); ^{1}H NMR (D_2O) δ 0.90 (3H, t, CH_3 $^3J_{HCCH}$ 5.0 Hz), 1.34-1.95 (6H, br s, CH_2), 2.10-2.59 (2H, m, CH_2CH), 3.25-3.80 (1H, m, CH); ^{13}C NMR (D_2O) δ 16.1 (s, CH_3), 24.4 (s, CH_2CH_3), 27.5 (d, CH_2CH_2, $^4J_{PCCCC}$ 8.5 Hz), 29.1 (s, CH_2CH_2CH), 33.4 (s, CH_2CH), 53.6 (d, $CHCH_2$, $^1J_{PC}$ 92.1 Hz); ^{31}P NMR (D_2O) δ 20.7 (br s, $^1J_{PH}$ 532 Hz); FAB ms: m/z (%) 331 (2M+H,

15.2), 266 (2M+H-H_2PO_2, 62.2), 185 (11.9), 184 (91.5), 167 (11.1), 166 (M+H, 25.0), 101 (26.1), 100 (M+H-H_3PO_2, 100).

11.4 Synthesis of methyl(α-aminopropane)phosphinic acid

Freshly distilled propanal (2.17 g, 0.038 mol), was added dropwise at room temperature during 0.5 h to a stirred mixture of benzyl carbamate (3.80 g, 0.025 mol), methyldichlorophosphine (2.90 g, 0.025 mol) and glacial acetic acid (5 cm^3). The mixture was heated under reflux for 1 h, treated with 4 M hydrochloric acid (20 cm^3) and further refluxed for 0.5 h. The cooled brown solution was extracted with toluene (2 x 10 cm^3), ether (2 x 10 cm^3) and then the aqueous solution was boiled with charcoal (1.0 g), filtered and evaporated to dryness under reduced pressure (15 mm Hg, 80 °C). The resultant brown residue was dissolved in methanol (10 cm^3) and treated with propylene oxide (150 cm^3) to give a pale yellow oil. The supernatant layer was decanted and the oil was washed with dichloromethane (10 cm^3), ethyl acetate (10 cm^3) and finally allowed to crystallise from ethanol/water. Crystallisation was induced after several months at 4 °C. The product was filtered off, washed with acetone (3 x 3 cm^3) and dried in a vacuum oven to give *methyl(α-aminopropane)phosphinic acid* (62) (1.1 g, 31.0%) as a fine white crystalline solid, m.p. 265-266 °C, (Found: C, 33.9; H, 7.8; N, 9.6; $C_4H_{12}NO_2P$ requires: C, 34.8; H, 8.69; N, 10.1%); ^1H NMR (MeOD) δ 0.95-1.5 (d, 3H, $^3J_{PC\underline{H}_3}$ 12 Hz), 1.25 (t, 3H, $C\underline{H}_3CH_2$, $^3J_{HCCH}$ 6 Hz), 1.6-2.0 (m, 2H, $C\underline{H}_2$), 2.7-3.4 (m, 1H, C<u>H</u>); ^{13}C NMR (MeOD) δ 13.1 (d, $\underline{C}H_3$, $^3J_{PCCC}$ 13 Hz); 15.5 (d, $P\underline{C}H_3$ $^1J_{PC}$ 95 Hz); 24.1 (s, $\underline{C}H_2$), 55.5 (d, $\underline{C}H$, $^1J_{PC}$ 94.3 Hz); ^{31}P NMR (MeOD) δ 35.0 (s); FAB ms: m/z (%) 313 (26), 274 (2M+H, 23), 176 (35), 138 (M+H), 131 (39), 128 (39), 58 (M+H-

$PO_2H_2CH_3$, 100).

11.5 Synthesis of phenyl(α-aminopropane)phosphonous acid

Freshly distilled propanal (2.17 g, 0.038 mol), was added dropwise at room temperature during 0.5 h to a stirred mixture of benzyl carbamate (3.8 g, 0.025 mol), diphenyl phenylphosphonite (7.35 g, 0.025 mol) and glacial acetic acid (5 cm^3). The mixture was heated under reflux for 1 h, treated with 4 M hydrochloric acid (20 cm^3) and further refluxed for 0.5 h. The cooled brown solution was extracted with toluene (2 x 10 cm^3), and the aqueous solution boiled with charcoal (1.0 g), filtered and evaporated to dryness under reduced pressure (15 mm Hg, 80 °C). The resultant yellow residue was dissolved in methanol (10 cm^3) and treated with propylene oxide (50 cm^3) to give a white solid. The precipitated product was filtered off, washed with acetone and dried in a vacuum oven at 60 °C to give phenyl(α-aminopropane)phosphinic acid (67) (2.2 g, 43.5%) as a fine white crystalline solid, m.p. 255 °C (lit. m.p. 255-256 °C),[40] (Found C, 53.1; H, 6.2; N, 6.2. Calc. for $C_9H_{14}NO_2P$; C, 54.0; H, 7.0; N, 7.0%); ^1H NMR (MeoD) δ 1.35 (t, 3H, $C\underline{H}_3$ $^3J_{HCCH}$ 6 Hz), 1.80-2.50 (m, 2H, $C\underline{H}_2$), 3.88-4.31 (m, 1H, C<u>H</u>), 7.75-8.38 (br m, 5H, <u>aromatic</u>): ^{13}C NMR (MeoD) δ 13.2 (d, $\underline{C}H_3$, $^3J_{PCCC}$ 9 Hz), 24.0 (s, $\underline{C}H_2$), 56.1 (d, $^1J_{PC}$ 96 Hz), 135.0 (s, ortho C <u>aromatic</u>). 136.0 (s, meta C <u>aromatic</u>),137.0 (s, para C <u>aromatic</u>); ^{31}P NMR (MeoD) δ 24.1 (s); FAB ms: FAB ms: m/z (%) 399 (2M+H, 18), 200 (M+H, 49.1), 183 (M+H-NH_3, 28.2), 140 (23), 143 (18), 58 (M+H-PO_2H_2Ph, 100).

11.6 Synthesis of N-benzyloxycarbonyl-α-aminopropane-phosphonous acid

Sodium hydroxide (4 M) was added to α-aminopropane-phosphonous acid (3.1 g, 0.025 mol), in water (15 cm^3) until the pH was adjusted to 9.5. The solution was cooled to 0 °C, whilst benzyl chloroformate (4.1 g, 0.027 mol), in ether (7 cm^3), was added dropwise over 1h. Stirring was continued for 12 h and the pH of 9.5 was maintained by intermittent addition of (4 M) sodium hydroxide. The mixture was extracted with ether (2 x 15 cm^3) and the aqueous solution was slowly added to a mixture of water, concentrated hydrochloric acid and ice (18 cm^3, 18 cm^3, and 50 g respectively). The solid product was filtered off, dried and allowed to recrystallise from ethyl acetate/light petroleum to give N-benzyloxycarbonyl-α-aminopropanephosphonous acid (64) (5.1 g, 78.5%) as a fine white solid, m.p.110 °C,(lit. m.p. 111 °C)[108] ^1H NMR (MeoD) δ 1.15 (t, 3H, CH_3 $^3J_{HCCH}$ 6 Hz), 1.45-2.25 (m, 2H, CH_2CH_3), 2.75-3.30 (m, 1H, CH) 5.15 (s, CH_2), 7.55 (s, aromatic); ^{13}C NMR (MeoD) δ 13.1 (d, CH_3, $^3J_{PCCC}$ 8.8 Hz), 23.9 (s, CH_2CH), 49.1 (d, CH, $^1J_{PC}$ 130 Hz), 67.7 (s, CH_2Ph), 128.8 (s, ortho C aromatic), 129.0 (s, meta C aromatic), 129.5 (s, para C aromatic), 138.3 (s, C=O); ^{31}P NMR (MeoD) δ 20.9 (s); FAB ms: m/z (%) 516 (2M+1, 1.0), 258, 280 (30.6), (M+1, 14.4), 148 (M+H - $EtCH_2P(O)O$, 7.2), 115 (5.8), 91 (100).

11.7 Synthesis of monomethyl (N-benzyloxycarbonyl)-α-aminopropane phosphinate

A mixture of N-benzyloxycarbonyl-α-aminopropane-phosphonous acid (1.50 g, 0.006 mol), anhydrous methanol (0.36 g,

0.01 mol), trichloroacetonitrile (0.80 g, 0.006 mol) and anhydrous pyridine (10 cm^3) was refluxed for 4 h, whilst protected from moisture. The reaction mixture was evaporated under reduced pressure (13 mm Hg, 40 °C) and the yellow oily residue was treated with cold saturated sodium bicarbonate solution (20 cm^3). The resultant trichloroacetamide was separated by extraction with ethyl acetate (3 x 8 cm^3) and the aqueous layer was acidified to pH 1 with 6 M hydrochloric acid. The product separated as a pale yellow oil, which was extracted with ethyl acetate and allowed to crystallise from petroleum ether/ethyl acetate to give methyl N-benzyloxycarbonyl-(α-aminopropane)phosphinate (65) as a white crystalline solid m.p. 102 °C (lit. m.p. 104 °C)[108] ^1H NMR (MeoD) δ 0.95 (t, $C\underline{H}_3$, $^3J_{HCCH}$ 6 Hz), 1.45-2.20 (m, $C\underline{H}_2CH_3$), 3.30-3.95 (m, 1H, C<u>H</u>), 3.74 (d, $POC\underline{H}_3$, $^3J_{POCH}$ 11 Hz), 5.20 (s, $C\underline{H}_2Ph$) 7.35 (br s, 5H, <u>aromatic);</u> ^{13}C NMR (MeoD) δ 11.1 (d, $\underline{C}H_3$, $^3J_{PCCC}$ 7 Hz), 23.9 (s, $\underline{C}H_2CH_3$), 48.5 (d, <u>C</u>H, $^1J_{PC}$ 130.5 Hz), 54.2 (d, $PO\underline{C}H_3$, $^2J_{POC}$ 5 Hz), 67.7 (s, CH_2Ph), 128.8 (s, ortho <u>C</u> aromatic), 129 (s, meta <u>C</u> aromatic), 129.5 (s, para <u>C</u> aromatic), 138.3 (s, <u>C</u>=O); ^{31}P NMR (MeoD) δ 24.7 (s).

11.8 Synthesis of N-(2,2,2-trichloroethoxycarbonyl)-α-aminopropanephosphonous acid

A solution of α-aminopropanephosphonous acid (3.10 g, 0.025 mol), dissolved in aqueous sodium hydroxide (1 g, in 12.5 cm^3 of water) was cooled to 0 °C and stirred. 2,2,2-Trichloroethyl chloroformate (5.29 g, 0.025 mol) in ether (5.0 cm^3) was then added dropwise, with simultaneous addition of aqueous sodium hydroxide (1 g, in 6.1 cm^3 of water). The mixture was stirred for 4 h during which a white precipitate formed .The solid product was

filtered off, washed with water (3 x 5 cm^3), ether (2 x 10 cm^3) and recrystallised from ethanol/water. After drying in a vacuum oven at 60 °C *N-(2,2,2-trichloroethoxycarbonyl)-α-aminopropane-phosphonous acid* (4.99 g, 66.7%) was obtained as white needles, m.p. 121-121.5 °C (Found: C, 23.9; H, 3.5; N, 4.6; $C_6Cl_3H_{11}NO_4P$ requires: C, 24.0; H, 3.7; N, 4.6%); ^1H NMR (MeOD) δ 1.10 (3H, CH_3 $^3J_{HCCH}$ 6.3 Hz), 1.40-2.25 (br m, CH_2), 2.70-3.30 (1H, m, CH), 5.20 (s, CH_2CCl_3); ^{13}C (MeOD) δ 11.1 (d, CH_3, $^3J_{PCCC}$ 8.0 Hz); 21.1 (d, CH_2, $^2J_{PCC}$ 2 Hz); 48.3 (d, CH, $^1J_{PC}$ 129.6 Hz); 75.7 (s, CH_2CCl_3); 97.1 (s, CCl_3); 156.9 (d, C=O, $^3J_{PCNC}$ 3 Hz); ^{31}P NMR (MeOD) δ 23.4 (s).

11.9 General method for the oxidation of α-aminoalkane-phosphonous acids to α-aminoalkanephosphonic acids

A solution of α-aminoalkanephosphonous acid (0.015 mol) and saturated bromine water (15 cm^3) was heated to 100 °C for 3 h. The mixture was evaporated to dryness under reduced pressure (15 mm Hg, 70 °C), and the oily residue was treated with water several times and re-evaporated until a white solid was obtained. The solid was then dissolved in ethanol (8 cm^3) and propylene oxide was added until precipitation was complete. The product was filtered off, washed with ethanol and dried in a vacuum oven at 60 °C to yield the α-aminoalkanephosphonic acid as crystalline white solid.

12.0 Synthesis of α-aminoethanephosphonic acid

A solution of α-aminoethanephosphonous acid (1.65 g, 0.015 mol) and saturated bromine water (15 cm^3) was heated to 100 °C for 3 h. Work-up of the resultant orange solution according to the

general procedure gave α-aminoethanephosphonic acid (1.68 g, 89%) as a fine white crystalline solid, m.p. 271-272 °C (lit. m.p. 272-274 °C);[33] ^{1}H NMR (D_2O) δ1.27 (3H, d of d, C$\underline{H}_3$ $^3J_{HCCH}$ 7.8 Hz, $^3J_{PCCH}$ 16.2 Hz), 2.90-3.65 (1H, m, CH).

12.1 Synthesis of α-aminopropanephosphonic acid

A solution of α-aminopropanephosphonous acid (1.86 g, 0 .015 mol) and saturated bromine water (15 cm^3) was heated to 100 °C for 3 h. Work-up of the resultant orange solution according to the general procedure yielded α-aminopropanephosphonic acid (1.80 g, 86.7%) as a white crystalline solid, m.p. 259-260 °C (lit. 264-266 °C);[33] ^{1}H NMR (D_2O) δ 1.20 (3H, t, C$\underline{H}_3$ $^3J_{HCCH}$ 7.5 Hz), 1.33-2.25 (2H, br m, C$\underline{H}_2$), 2.7-3.3 (1H, m, C$\underline{H}$); ^{13}C (D_2O) 12.8 (d, $\underline{C}H_3$, $^3J_{PCCC}$ 9.1 Hz), 23.1 (s, $\underline{C}H_2$), 53.1 (d, $\underline{C}H$, $^1J_{PC}$ 153.4 Hz); ^{31}P NMR (D_20) δ 14.6 (br s) .

12.2 Synthesis of α-aminobutanephosphonic acid

A solution of α-aminobutanephosphonous acid (2.07 g, 0.015 mol) and saturated bromine water (15 cm^3) was heated to 100 °C for 3 h. Work-up of the resultant orange solution according to the general procedure afforded α-aminobutanephosphonic acid (1.88 g, 82.3%) as a white crystalline solid, m.p. 261-262 °C (lit. m.p. 262-264 °C),[33] ^{1}H NMR (D_2O) δ 0.90 (t, C$\underline{H}_3$, $^3J_{HCCH}$ 5.2 Hz), 1.12-2.20 (m, 4H, C$\underline{H}_2$), 3.45-3.90 (m, 1H, C$\underline{H}$); ^{13}C (D_20) 12.9 (s, $\underline{C}H_3$), 23.3 (s, $\underline{C}H_2$), 25.9 (d, $\underline{C}H_2$, $^3J_{PCCC}$ 14.1 Hz), 50.7 (d, $\underline{C}H$, $^1J_{PC}$ 151.8 Hz); ^{31}P NMR (D_2O) δ 19.9 (br s).

12.3 Synthesis of α-aminopentanephosphonic acid

A solution of α-aminopentanephosphonous acid (2.28 g, 0.015 mol) and saturated bromine water (15 cm^3) was heated to 100 °C for 3 h. Work-up according to the general procedure gave α-aminopentanephosphonic acid (2.06 g, 82.3%) as a white crystalline solid, m.p. 261-262 °C (lit. m.p. 260-263 °C);[34] ^{13}C (D_2O/D_2SO_4) δ 12.8 (s, $\underline{C}H_3$), 22.8 (s, $CH_3\underline{C}H_2$), 26.1 (d, $CHCH_2\underline{C}H_2$, $^3J_{PCCC}$ 14.9 Hz), 26.7 (s, $\underline{C}H_2$), 49.9 (d, $\underline{C}H$, $^1J_{PC}$ 152.1 Hz); ^{31}P NMR (D_2O) δ15.9 (br s).

12.4 Synthesis of α-aminohexanephosphonic acid

A solution of α–aminohexanephosphonous acid (3.32 g, 0.02 mol) and saturated bromine water (30 cm^3) was heated to 100 °C for 4 h. Work-up according to the general procedure yielded α-aminohexanephosphonic acid (2.67 g, 74.0%) as a fine white solid, m.p. 260-261 °C (lit. m.p. 261-262 °C)[54] (Found: C, 38.9; H, 8.5; N, 7.4. Calc. for $C_6H_{16}NO_3P$: C, 39.7; H, 8.8; N, 7.7%); ^{13}C (D_20/D_2SO_4) δ 16.3 (s, $\underline{C}H_3$), 24.8 (s), 25.7 (d, $CHCH_2\underline{C}H_2$, $^3J_{PCCC}$ 14.9 Hz), 30.5, 31.0, (singlets), 50.1 (d, $\underline{C}H$ $^1J_{PC}$ 152.3 Hz); ^{31}P NMR (D_20/D_2SO_4) δ18.1 (br s).

12.5 Oxidation of α-aminopropanephosphonous acid to α-aminopropanephosphonic acid with hydrogen peroxide

A solution of α-aminopropanephosphonous acid (1.01 g, 0.008 mol) and 30% hydrogen peroxide (1.02 g, 0.009 mol) was heated under reflux for 6 h, and cooled. The clear solution was evaporated to dryness under reduced pressure (15 mm Hg, 70 °C) to yield a clear mobile oil. Crystallisation from water/ethanol gave a white solid which was filtered off, washed with ethanol and dried

in a vacuum oven at 50 °C to give α-aminopropanephosphonic acid (0.72 g, 64.3%) as a white crystalline solid, m.p. 260-261 °C (lit. m.p. 264-266 °C)[33] ^{1}H NMR (D_2O/D_2SO_4) δ 1.11 (3H, t, C$\underline{H}_3$ $^3J_{HCCH}$ 7.4 Hz), 1.25-1.65 (2H, br m, C$\underline{H}_2$), 3.54 (1H, m, C$\underline{H}$).

12.6 Attempted synthesis of α-guanidinopropanephosphonous acid

α-Aminopropanephosphonous acid (3.35 g, 0.027mol), S-methylisothiouronium chloride (6.84 g, 0.054 mol), and potassium hydroxide (4.55 g, 0.081 mol) were dissolved in water (14 cm^3) and heated at 60 °C (4 h) whilst the evolving methanethiol was collected in potassium permanganate traps. The reaction mixture was then acidified to pH 2 with concentrated hydrochloric acid and the volatile components distilled off on a rotary evaporator. Methanol (100 cm^3) was added to the residue and the resultant potassium chloride (6.1 g, 75.6% after drying) was filtered off. Propylene oxide (ca. 50 cm^3) was added to the filtrate until maximum precipitation had occurred. The solid product was filtered off, washed with ethanol (15 cm^3), and dried in a vacuum oven to yield the unreacted α-aminopropanephosphonous acid (2.8 g, 83.5%) as a white crystalline solid, m.p. 225 °C; (Found: C, 29.7; H, 7.7; N, 11.4 Calc. for $C_3H_{10}NO_2P$: C, 29.2; H, 7.3; N, 11.3%); ^{13}C NMR (D_2O) δ 12.6 (d, $\underline{C}H_3$, $^3J_{PCCC}$ 8.6 Hz), 22.7 (s, $\underline{C}H_2$), 54.3 (d, $\underline{C}H$, $^1J_{PC}$ 92.8 Hz).

12.7 Preparation of methylphosphonous dichloride

Aluminium trichloride (66.6 g, 0.50 mol) and phosphorus trichloride (45.4 g, 0.33 mol) were heated and stirred in a three-

necked round-bottom flask, mounted with an empty Cardice condenser (fitted with a calcium chloride drying tube). When the temperature of the mixture reached 70 °C the condenser was charged with Cardice/acetone. Chloromethane (dried over calcium chloride) was then passed in to the mixture at the point of stirring. The chloromethane flow rate was controlled in order to maintain the mixture temperature at 70 °C. When all the solid had dissolved (ca. 1 h) the rate of chloromethane absorption increased; therefore the rate of flow was stepped up. When crystals began to separate on the walls of the flask (ca. 2 h) the rate of chloromethane addition was reduced to a very slow stream. Heating was continued for a further hour during which a semi-solid mush was formed; chloromethane addition was then stopped. The mixture was further heated and stirred for an additional hour, afterwhich the condenser was removed and heating stopped.

The solid formed was cooled to 0 °C and di-n-butyl phthalate, (250 cm^3) precooled to 4 °C, was added with vigorous stirring. This mixture was allowed to reach room temperature with continuous stirring. When most of the solid had dissolved, the mixture was heated and degassed at 75 °C/2 mm Hg. It was then rapidly cooled (30 °C) and powdered antimony (27.0 g) added. The dense mixture was stirred vigorously at 55 °C (1 h). Methylphosphonous dichloride (30.1 g, 78.0%) was flashed from the mixture as a colourless liquid at 75 °C/2 mm Hg, and was collected in an acetone/Cardice trap.

Distillation under nitrogen (dried over calcium chloride) yielded methylphosphonous dichloride (20.2 g, 56.4%) as a colourless pungent liquid, b.p. 82-83 °C/60 mm Hg, (lit. b.p. 84-85 °C/60 mm Hg),[110] ^1H NMR ($CDCl_3$) δ 2.18 (d, 3H, PCH_3 $^2J_{PCH}$

18.0 Hz).

It was noted, during the course of several experiments, that controlled and continuous stirring was essential in order to facilitate successful and repeatable synthesis.

12.8 Preparation of tris(2,2,2-trichloroethyl) phosphite

Phosphorus trichloride (12.5 g, 0.019 mol) in sodium dried ether (25 cm^3), was added dropwise to a stirred solution of 2,2,2-trichloroethanol (41.0 g, 0.019 mol), pyridine (21.6 g, 0.019 mol) and sodium dried ether (200 cm^3); the reaction being carried out at 0 °C. Precipitation commenced on addition of the phosphorus trichloride. The mixture was heated under reflux for 24 h, cooled and the resultant white solid filtered under nitrogen to yield pyridinium hydrochloride (7.81 g, 73.1% after drying). After removal of solvent by evaporation under reduced pressure, the crude phosphite was fractionally distilled with a 20 cm glass-ring column under reduced pressure. Tris(2,2,2-trichloroethyl) phosphite distilled as a clear colourless liquid (20.4 g, 47.3%) b.p. 156-158 °C at 1.5 mm Hg, $^{n}D_{22}$ 1.5176, (lit. b.p. 122 °C at 0.05 mm Hg);[111] (lit $^{n}D_{22}$ 1.5178),[111] ^{1}H NMR ($CDCl_3$) δ 4.57 (d, 2H, $C\underline{H}_2$ $^{3}J_{POCH}$ 7 HZ); ^{13}C NMR ($CDCl_3$) δ 74.5 (d, $\underline{C}H_2$, $^{2}J_{POC}$ 9.0 HZ), 96.1 (d, $\underline{C}Cl_3$ $^{3}J_{POCC}$ 5.5 HZ); ^{31}P NMR ($CDCl_3$) δ137.4 (s).

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TABLE 1 Fractional atomic coordinates and thermal parameters ($A^{\circ 2}$) for ^{14}C labelled 1-aminopropanephosphonic acid

Atom	x	y	z	U_{iso} or U_{eq}
P	0.1466(4)	0.3290(6)	0.4122(5)	0.027(2)
O(1)	0.0124(8)	0.3610(14)	0.3232(10)	0.028(6)
O(2)	0.1688(9)	0.2021(15)	0.5501(10)	0.037(6)
O(3)	0.2270(8)	0.2248(15)	0.3218(10)	0.037(6)
C(1)	0.2203(14)	0.5953(22)	0.4556(16)	0.035(4)
C(2)	0.3389(17)	0.5978(27)	0.5796(22)	0.064(6)
C(3)	0.4170(17)	0.8086(31)	0.5996(21)	0.071(6)
N	0.1207(9)	0.7582(17)	0.4680(12)	0.026(3)

TABLE 2 Fractional atomic coordinates for the hydrogen atoms for ^{14}C labelled 1-aminopropanephosphonic acid

Atom	x	y	z
Ho(3)	0.2387	0.2796	0.2251
H(1)	0.2404	0.6669	0.3510
H(2a)	0.3912	0.4677	0.5664
H(2b)	0.3186	0.5975	0.6669
H(3a)	0.3426	0.9032	0.5534
H(3b)	0.4838	0.8120	0.5403
H(3c)	0.4594	0.8561	0.7130
Hn(1)	0.1773	0.8996	0.5143
Hn(2)	0.0751	0.7850	0.3789
Hn(3)	0.1019	0.7463	0.5441

TABLE 3 Anisotropic thermal parameters ($A^{\circ 2}$) for ^{14}C labelled 1-aminopropanephosphonic acid

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
P	0.038(2)	0.008(2)	0.036(2)	-0.003(2)	0.016(2)	-0.005(2)
O(1)	0.026(6)	0.020(5)	0.040(6)	-0.008(5)	0.003(5)	-0.003(5)
O(2)	0.064(7)	0.021(6)	0.025(6)	0.005(5)	0.017(5)	-0.006(6)
O(3)	0.048(6)	0.034(6)	0.028(6)	0.004(5)	0.017(5)	0.015(6)

TABLE 4 Bond lengths (A°) for ^{14}C labelled 1-aminopropanephosphonic acid

P	-O(1)	1.487(9)	P	-O(2)	1.486(10)
P	-O(3)	1.550(12)	P	-C(1)	1.833(14)
C(1)	-C(2)	1.461(21)	C(1)	-N	1.526(19)
C(2)	-C(3)	1.55(3)			

TABLE 5 Bond angles (°) for ^{14}C labelled 1-aminopropanephosphonic acid

O(2)	-P	-O(1)	116.6(6)	O(3)	-P	-O(1)	112.4(5)
O(3)	-P	-O(2)	107.3(6)	C(1)	-P	-O(1)	108.1(6)
C(1)	-P	-O(2)	109.4(6)	C(1)	-P	-O(3)	102.1(7)
C(2)	-C(1)	-P	115(1)	N	-C(1)	-P	109(1)
N	-C(1)	-C(2)	115(1)	C(3)	-C(2)	-C(1)	116(1)

TABLE 6 Intermolecular distances (A°) for ^{W}C labelled 1-aminopropanephosphonic acid

atom1	atom2	dist	S	a	b	c
Hn(1)	...P	2.82	1	0.0	1.0	0.0
N	...P	3.51	-1	0.0	1.0	1.0
Hn(3)	...P	2.94	-1	0.0	1.0	1.0
Hn(2)	...P	3.12	2	0.0	0.0	0.0
O(2)	...P	3.53	-2	0.0	1.0	1.0
Ho(3)	...P	2.92	-2	0.0	1.0	0.0
N	...O(1)	2.90	-1	0.0	1.0	1.0
Hn(3)	...O(1)	2.14	-1	0.0	1.0	1.0
N	...O(1)	2.60	2	0.0	0.0	0.0
Hn(2)	...O(1)	1.93	2	0.0	0.0	0.0
N	...O(2)	2.87	1	0.0	1.0	0.0
H(3a)	...O(2)	2.66	1	0.0	1.0	0.0
Hn(1)	...O(2)	1.91	1	0.0	1.0	0.0
Hn(3)	...O(2)	2.92	1	0.0	1.0	0.0
N	...O(2)	3.16	-1	0.0	1.0	1.0
Hn(2)	...O(2)	2.97	-1	0.0	1.0	1.0
Hn(3)	...O(2)	2.88	-1	0.0	1.0	1.0
O(3)	...O(2)	2.51	-2	0.0	1.0	0.0
Ho(3)	...O(2)	1.62	-2	0.0	1.0	0.0
H(3a)	...O(3)	2.96	1	0.0	1.0	0.0
Hn(1)	...O(3)	2.88	1	0.0	1.0	0.0
H(2b)	...O(3)	2.84	-2	0.0	1.0	1.0
H(3c)	...C(2)	2.91	2	1.0	0.0	1.0
H(3b)	...C(3)	3.06	-1	1.0	2.0	1.0

Symmetry Transformations:

The second atom is related to the first atom, at (x,y,z), by the symmetry operation S with (a,b,c) added to the (x',y',z') of S.

Where S =

1 x, y, z

TABLE 7 Intramolecular distances (A°) for ^{14}C labelled 1-aminopropanephosphonic acid

C(2)	...P	2.80	N	...P	2.74
Ho(3)	...P	2.32	H(1)	...P	2.48
H(2a)	...P	2.60	H(2b)	...P	3.09
Hn(2)	...P	2.93	Hn(3)	...P	2.98
O(2)	...O(1)	2.53	O(3)	...O(1)	2.52
C(1)	...O(1)	2.69	N	...O(1)	2.90
Ho(3)	...O(1)	2.96	Hn(2)	...O(1)	2.73
O(3)	...O(2)	2.45	C(1)	...O(2)	2.72
C(2)	...O(2)	3.05	H(2a)	...O(2)	2.93
H(2b)	...O(2)	2.98	C(1)	...O(3)	2.64
C(2)	...O(3)	3.33	H(1)	...O(3)	2.76
H(2a)	...O(3)	2.91	C(3)	...C(1)	2.57
Ho(3)	...C(1)	2.99	H(2a)	...C(1)	2.03
H(2b)	...C(1)	1.98	H(3a)	...C(1)	2.37
Hn(1)	...C(1)	2.06	Hn(2)	...C(1)	1.95
Hn(3)	...C(1)	1.99	N	...C(2)	2.53
H(1)	...C(2)	2.17	H(3a)	...C(2)	1.91
H(3b)	...C(2)	2.20	H(3c)	...C(2)	2.22
Hn(1)	...C(2)	2.53	Hn(3)	...C(2)	2.70
N	...C(3)	3.16	H(1)	...C(3)	2.73
H(2a)	...C(3)	2.14	H(2b)	...C(3)	1.93
Hn(1)	...C(3)	2.59	H(1)	...N	2.05
H(2b)	...N	2.63	H(3a)	...N	2.51

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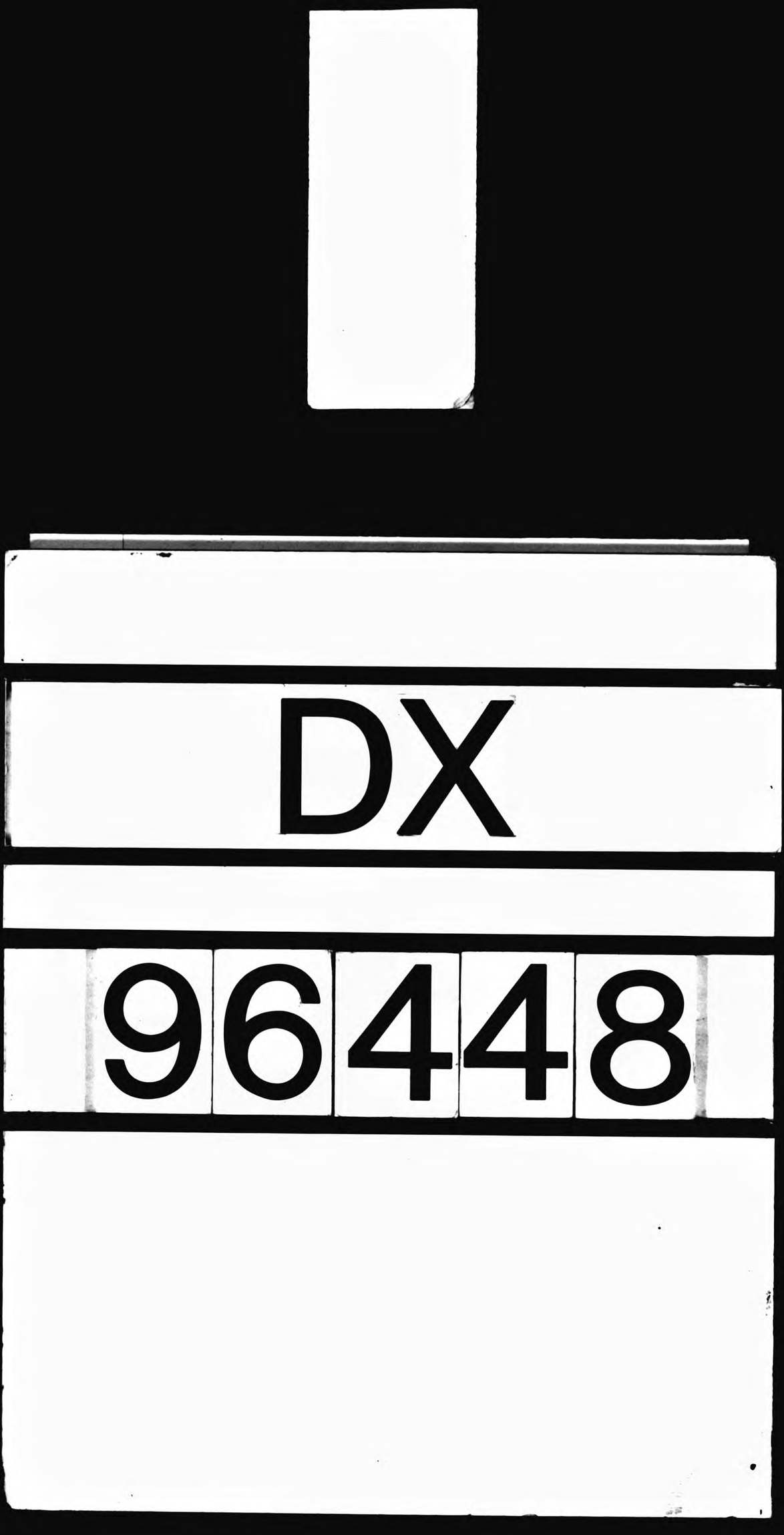
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