The Polytechnic of North London
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The Synthesis, Structure and Fungicidal Activity of Guanidinophosphonic Acids and their Aminophosphonic Precursors

by

David George Cameron, B.Sc., G.R.S.C.

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A B S T R A C T

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D.G.Cameron 1983

Alkanephosphonic acids of the classes α-amino, α-guanidino, α-(hydroxy)amino, α-thioureido, ω-amino, and ω-guanidino have been prepared, and also the ω-amino and ω-guanidino types having aza substituents in positions 2 and 3 in the alkyl chain. The ^{1}H, ^{13}C, and ^{31}P nmr spectroscopy of these compounds was examined in detail and the ^{13}C nmr was found to be particularly useful for positive identification of these phosphonic acids. The phosphorus-carbon coupling constants vary along the alkyl chain with ^{1}Jpc = 130-160, $^{2}Jpcc$ = 0-6, $^{3}Jpccc$ = 10-20, and $^{3}Jpcnc$ = 5-10 Hz. The spectra were recorded in solution in D_2O and also in a mixture of D_2O/D_2SO_4 and from a comparison of these results it has been shown that these phosphonic acids exist as zwitterions in solution. The first crystal structures of guanidinoalkanephosphonic acids are reported for 1-guanidino- and 3-guanidino-propanephosphonic acid and have confirmed that these compounds are zwitterions in the solid state with each exhibiting a high degree of hydrogen-bonding.

The use of Fast Atom Bombardment mass spectrometry has proven to be useful for confirmation of molecular weight with the M+1 ion being the base peak in most cases. Also a number of important fragmentations (such as the losses of H_3PO_3, NH_3, H_2NCN) have been observed. The novel reaction of an alkylguanidine with a dialkyl phosphite in the Atherton-Todd reaction was found to be a useful method for phosphorylating dodecylguanidine.

In vivo and *in vitro* screening tests showed that in general all the phosphonic acids tested possessed fungicidal activity against *Pyricularia oryzae*, *Rhizoctonia solani*, *Septoria nodorum*, *Botrytis cinerea*, *Dreschlera teres*, *Dreschlera sativa* and *Fusarium avenaceum*. 1-Aminopropane-phosphonic acid and *N*-(10-guanidinodecyl)aminomethanephos-phonic acid were found to have comparable fungicidal activity with the commercial fungicides Panoctine and Dodine.

D E C L A R A T I O N

Whilst registered as a candidate for this degree

I have not been registered as a candidate

for any other award

D. G. Cameron

In partial fulfilment of the requirements of the degree I have completed the M.Sc. lectures on Structural Methods (i.r., u.v., mass spectrometry and X-ray crystallography). In addition I have attended a conference on Crop Protection at The Royal Society, and also The International Conference of Phosphorus Chemistry in Nice (1983).

A C K N O W L E D G E M E N T S

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CONTENTS

INTRODUCTION

Fungicides may be described as either prophylactic (protective) or therapeutic (curative) and until about twenty years ago practically all the established products fell into the former category. The advent of organic fungicides in the 1930's with the introduction of derivatives of dithiocarbamic acid[1] was an important milestone in the quest for antifungal compounds capable of exerting a selective effect without damaging the host plant.

$$C_{12}H_{25}NHC(:NH)NH_2.CH_3CO_2H$$

(1)

Dodecylguanidinium acetate (1) known as dodine, introduced in 1956 by the American Cyanamid Company[2] was the first commercial guanidine fungicide and has since assumed particular importance in the control of fungal pathogens of commercial crops.[3] Used at a rate of 30-80 g of active ingredient per 100 L it is effective against the major fungal diseases of fruits, nuts and vegetables and of certain ornamentals and shade trees. Foliar

application has especially been recommended against Venturia spp. (on apples and pears) and cherry leaf spot against which it has some eradicant properties. It has been found that dodine affects the cell membrane permeability of fungi which results in the leakage of the cell contents and consequently death of the pathogens. A secondary effect is the inhibition of respiration. Resistance of the pathogens to dodine has been encountered in the field.[4]

Byrde, Clifford and Woodcock[5] prepared thirteen alkylguanidine acetates and tested them against conidia of Venturia inaequalis. They found that good fungistatic activity (measure of inhibition of the development of the fungi) was associated with a chain length of 11 - 16 carbons (Table 1).

Table 1: The effect of n-alkylguanidine acetates (10^{-5} M) on spore germination of Venturia inaequalis

$RNHC(:NH)NH_2.CH_3COOH$

R	GERMINATION (%)
C_6H_{13}	70.1
C_7H_{15}	76.2
C_8H_{17}	34.8
C_9H_{19}	34.2
$C_{10}H_{21}$	30.8
$C_{11}H_{23}$	3.0
$C_{12}H_{25}$	12.7
$C_{13}H_{27}$	0.0
$C_{14}H_{29}$	0.8
$C_{15}H_{31}$	0.8
$C_{16}H_{33}$	1.1
$C_{17}H_{35}$	69.7
$C_{18}H_{37}$	76.2

Bousquet[6] investigated the variation of insecticidal activity of aliphatic thiocyanates (RSCN) with chain length. He found that activity rises to a maximum at C_8 - C_{14} depending on species, but was usually at C_{10} or C_{12}. Hence, it would appear that a long alkyl chain is preferable if good biological activity is sought.

$$H_2NC(:NH)NH(CH_2)_nNHC(:NH)NH_2$$

(2)

Salts of α,ω-diguanidinoalkanes (2, n = 2-20) were prepared by the treatment of the appropriate diamine with O-methylisothiouronium sulphate in water (Scheme 1).[7]

$$H_2N(CH_2)_nNH_2 + \{MeOC(:NH)NH_2\}_2.H_2SO_4$$

$$\downarrow \quad \sim 50\ ^{o}C,\ 2\text{-}8\ h,\ -MeOH$$

$$H_2NC(:NH)NH(CH_2)_nNHC(:NH)NH_2.H_2SO_4$$

(Scheme 1)

These compounds were found to be effective against grey mould, anthracnose blast and Helminthosporum leaf spot.[8] In particular Murphy Chemical Ltd. found the salts of 1,8-diguanidino-octane and 1,10-diguanidinodecane to be particularly effective against Pyricularia oryzae.[9]

$$NH_2(CH_2)_nNH(CH_2)_nNH_2$$

(3)

Murphy Chemical Ltd. also carried out tests against seeed-borne pathogenic fungi on a range of diguanidino compounds derived from triamines of type 3 and reported by Evans Medical Ltd.[10] From this range 1,17-bis-guanidino-9-azaheptadecane (4) now known as guazatine was selected for further development as its sulphate was shown to have a broad spectrum of activity against economically important plant pathogenic fungi and also to present no phytotoxic hazard.[11]

$$H_2NC(:NH)NH(CH_2)_8NH(CH_2)_8NHC(:NH)NH_2.3HX$$

(4)

HX = monobasic acid

Inhibition zone techniques using the sulphate showed the compound to be effective against important seed borne diseases of cereals that are usually controlled by organomercurial seed dressings.[11]

(Scheme 2)

The preparation of 1,17-diamino-9-azaheptadecane (5) from 1,8-diamino-octane (Scheme 2) proved a difficult process both on the laboratory and industrial scale with low yield of the required triamine from the reforming reaction involving treatment of the diamine with Raney nickel (Scheme 2). The commercial product patented by KemaNobel AB[12] refers to a mixture of acetate salts of the starting 1,8-diamino-octane, triamine (5) and higher oligomers such as (6) obtained on treatment of the triamine mixture with cyanamide in aqueous acetic acid.

This technical product known under the trade name of Panoctine was found to show good activity in laboratory tests in wheat infected with Fusarium nivale and Septoria nodorum and in rye infected with Fusarium nivale.

To date there are no commercial fungicides containing the phosphonic acid group although biological activity has been reported for compounds containing this group. (see chapter 5).

The objective of this study was to synthesise compounds as potential fungicides that included the guanidine group, a phosphonic acid group and an alkyl chain and to investigate their fungicidal activity with respect to their structure. As we have seen, good fungicidal activity appears to be associated with a long alkyl chain (Table 1). Therefore we considered the synthesis of compounds containing long chains to be preferable to that of those having a short chain.

A review of the literature on amino- and guanidino-phosphonic acids revealed that there were many anomalous and conflicting results and that the guanidino compounds had not been properly characterised.

It was decided therefore, that in order to study the fungicidal structure-activity relationships of guanidino-phosphonic acids, reliable methods of determining their structures were first needed.

It has been found that ^{1}H nmr and infrared spectroscopy are of little use for the positive characterisation of their structure and whilst elemental analysis is a useful confirmation of purity, in some cases its use becomes limited if the compound can exist in various hydrated forms.

There is little reference to the ^{13}C and ^{31}P nmr spectroscopy of phosphonic acids in the literature and since amino- and guanidino-phosphonic acids are generally high melting zwitterionic compounds their mass spectra cannot be obtained using conventional methods. Our studies of the ^{1}H, ^{13}C, and ^{31}P nmr spectroscopy of phosphonic acids revealed that for the ^{13}C nmr in particular there is a definite pattern of phosphorus-carbon coupling constants. In addition a new technique, Fast Atom Bombardment (FAB) mass spectrometry has been employed which in general revealed the M+H ion of the phosphonic acid as the base peak.

CHAPTER 1

SYNTHESIS OF 1-AMINO- AND 1-GUANIDINO-ALKANEPHOSPHONIC ACIDS

1.1 SYNTHESIS OF 1-AMINOALKANEPHOSPHONIC ACIDS

The first efforts directed towards the synthesis of 1-aminoalkanephosphonic acids (7) are attributable to Kosolapoff.[13-15] Subsequent to this they have been prepared by a variety of different and elaborate multistage syntheses.[16-32] Oleksyszyn and Tyka[33] reported a convenient one-pot synthesis which gave 1-aminoalkanephosphonic acids in a yield of <u>ca.</u> 37% (Scheme 3).

$$(PhO)_3P + RCHO + H_2NCO_2R^1$$

(i) acetic acid
(ii) H^+/H_2O
(iii) propylene oxide

$$(HO)_2P(O)CH(R)NH_2$$

(7)

R^1 = Et or Ph

(Scheme 3)

Repetition of this synthesis with short chain length aldehydes such as ethanal and propanal gave the required phosphonic acids in comparable yields to those described by Oleksyszyn <u>et al.</u>[33] However, the use of octanal resulted in a very poor yield (5.2%) of the new phosphonic acid (7, R = C_7H_{15}). When decanal or dodecanal were used

none of the required phosphonic acids (7, R = $C_{10}H_{23}$ or $C_{12}H_{25}$) were isolated from the reaction mixtures.

The mechanism of this reaction is uncertain although it is likely that the aldehyde and carbamate initially combine to form a Schiff's base which subsequently undergoes a nucleophilic attack by the triphenyl phosphite to form the phosphonate (8)(Scheme 4).

(Scheme 4)

In a separate publication Oleksyszyn, Subotkowska and Mastalerz[34] reported that they had isolated compounds of type 8 from the reaction mixture in 35-54% yield.

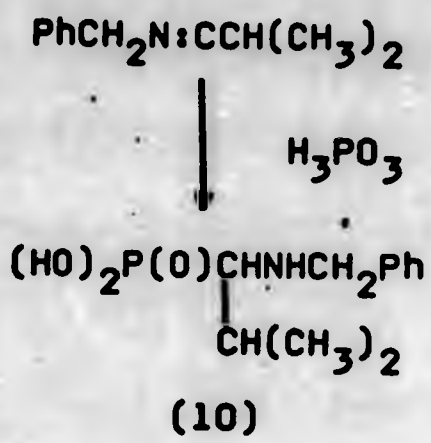
Similar reactions between imines and phosphorous acid have been reported by Redmore.[29] Thus the imine derived from benzaldehyde and benzylamine was reported to give an almost quantitative yield (98%) of N-benzyl-1-aminobenzyl-phosphonic acid (9) when allowed to react with phosphorous acid (Scheme 5).

$$PhCH_2N{:}CHPh + H_3PO_3 \longrightarrow (HO)_2P(O)CH(Ph)NHCH_2Ph$$

(9)

(Scheme 5)

However, if 2-methylpropanal was used instead of benzaldehyde (Scheme 6) the synthesis was much less satisfactory since the yield of product (10) was quite low (40%) in comparison to that of the benzyl analogue (9).

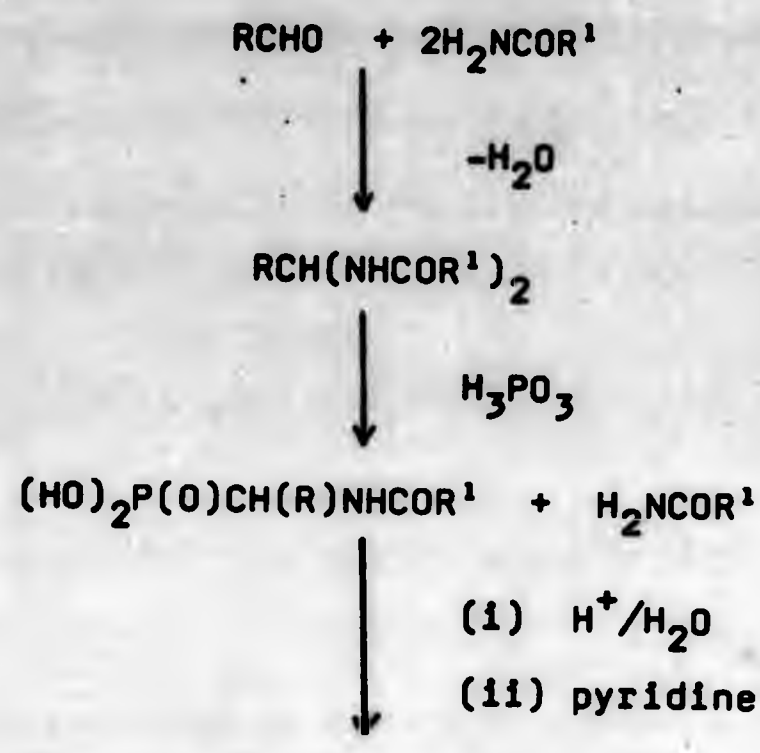


(10)

(Scheme 6)

In the above condensations Redmore[29] also noted that imines derived from aliphatic aldehydes gave only moderate yields of phosphonic acids together with amines from the concomitant reduction of the imines.

Oleksyszyn and Gruszecka[35] have reported that in the reaction of an amide, an aldehyde and phosphorous acid the reaction seems to involve the initial formation of an N,N′-alkylidene- or N,N′-arylidene-bisamide followed by its electrophilic attack on phosphorous acid (Scheme 7).

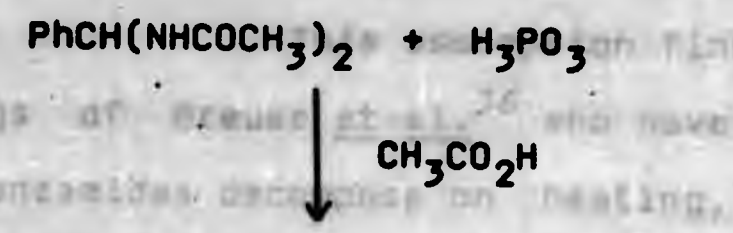


(7)

R = alkyl or aryl

(Scheme 7)

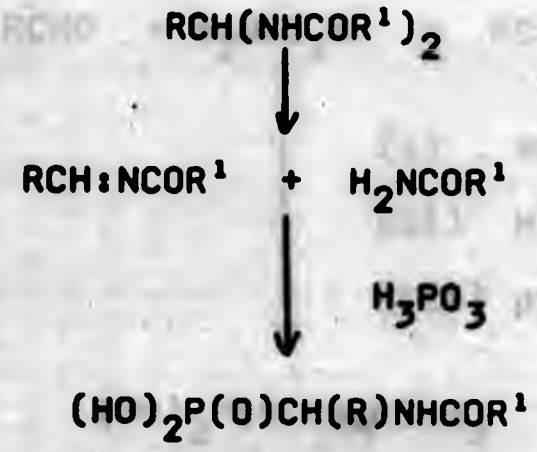
Again in this reaction the overall yields are low for aliphatic aldehydes, thus when acetaldehyde and benzamide were used the yield of the aminophosphonic acid (7, R = Me) was 27% whereas with benzaldehyde and acetamide the phosphonic acid (7, R = Ph) was obtained in 75% yield. They also found that when N,N-benzylidenebisacetamide and phosphorous acid were allowed to react in acetic acid N-acetyl-1-aminobenzylphosphonic acid (11) and acetamide were formed in nearly quantitative yields (Scheme 8).



(11)

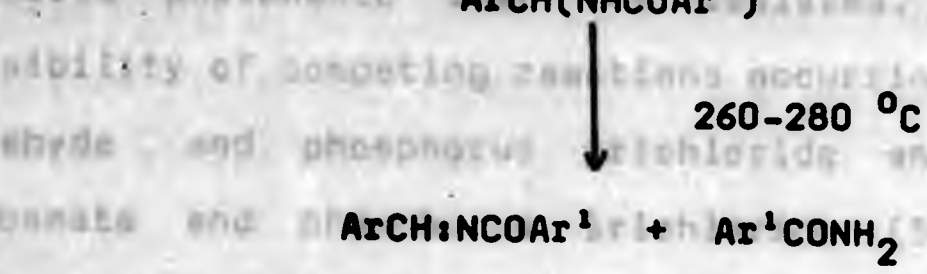
(Scheme 8)

However, the evidence for this pathway is inconclusive as there is no record of any N,N′-arylidenebisamides being isolated from the reaction mixture and it is also possible that if they were formed, they could then form an imine under the reaction conditions with subsequent nucleophilic attack by the phosphorous acid to yield the required 1-aminoalkanephosphonic acids (Scheme 9).



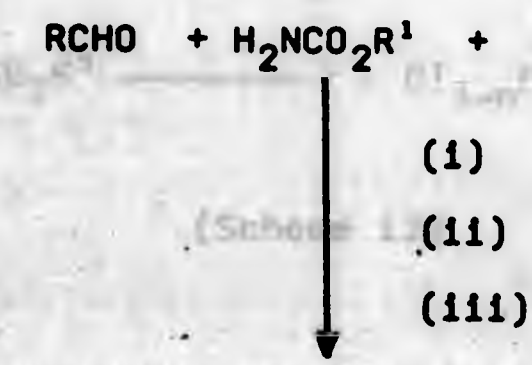
(Scheme 9)

This assumption finds support in the findings of Breuer *et al.*[36] who have shown that *N*,*N*′-arylidenebenzamides decompose on heating, to benzamide and *N*-benzoylbenzaldimines (Scheme 10).



(Scheme 10)

Oleksyszyn, Tyka and Mastalerz[37] have also shown that one can use phosphorus trichloride for the preparation of 1-aminoalkanephosphonic acids (Scheme 11).



(7)

(Scheme 11)

We repeated this reaction as desribed by Oleksyszyn et al.[37] but the results for longer chain aldehydes were again discouraging. When octanal was used the yield of 1-amino-octanephosphonic acid (7, R = C_7H_{15}) was low (3.8%) whereas for decanal and dodecanal none of the required phosphonic acid was isolated. As there is a possibility of competing reactions occurring between the aldehyde and phosphorus trichloride and between the carbamate and phosphorus trichloride (Scheme 12), an attempt was made to prepare the Schiff's base of ethyl carbamate and octanal first, by heating these reagents under reflux in benzene in the presence of acetic acid. A

$$PCl_3 + RCHO \xrightarrow[\text{(ii) } H_2O]{\text{(i) below 35 } ^oC} (HO)_2P(O)CH(R)OH$$

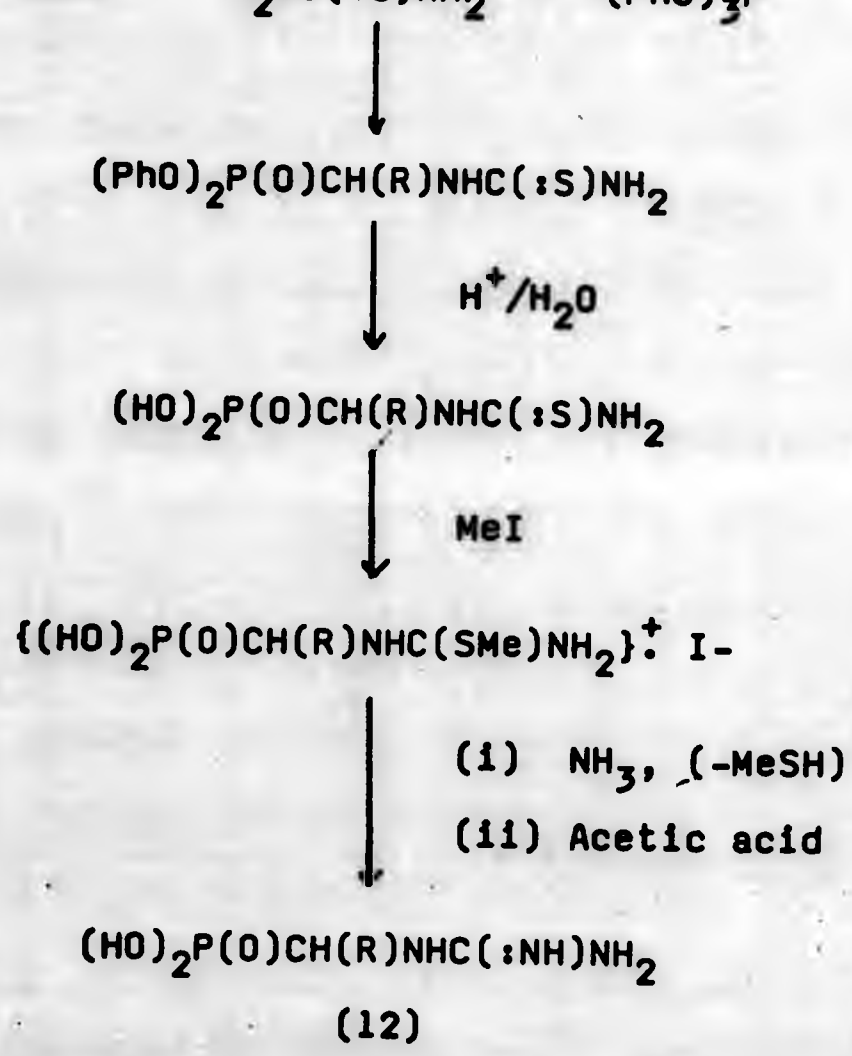
$$PCl_3 + n\ NH_2CO_2R^2 \longrightarrow Cl_{3-n}P(NHCO_2R^2)_n + nHCl$$

(Scheme 12)

Dean and Stark apparatus was used but no water was formed. On addition of the phosphorus trichloride, 86% of the theoretical amount of water accumulated in the Dean and Stark apparatus but no 1-amino-octanephosphonic acid (7, R = C_7H_{15}) was obtained after hydrolysis.

1.2 SYNTHESIS OF 1-GUANIDINOALKANEPHOSPHONIC ACIDS

The 1-guanidinoalkanephosphonic acids are a relatively unknown class of compounds, the only reference to them being by Oleksysyzyn, Tyka and Mastalerz[38] who reported the synthesis of four homologues (12, R = Me, Et, i-C_3H_7, n-C_3H_7) by a convenient one-pot synthesis from an aldehyde, triphenyl phosphite and thiourea, though the isolated yields were low (13-22%, Scheme 13).



(Scheme 13)

Oleksyszyn *et al.*[38] stated that the final crystallisation was performed by dissolving the reaction product in water (100 cm^3), followed by the addition of methanol (30 cm^3) and acidification with acetic acid. Repetition of this synthesis using ethanal yielded no product initially, since crystallisation failed to occur even after several weeks at 4 ^oC. However, it was found that concentration of this solution (to *ca.* 20-30 cm^3) and storage at 4 ^oC resulted after several days in a crystalline product. The homologue (12, R = Me) was obtained in a comparable yield and with a similar melting point to that described by Oleksyszyn *et al.*[38] (found m.p. 285-6 ^oC, lit. m.p. 287 ^oC) but the homologue (12, R = Et) was obtained on two occasions with a molecule of acetic acid of crystallisation (m.p. 289 ^oC) and characterised as such in contrast to the product of Oleksyszyn *et al.*[38] who stated that the compound was obtained as the free guanidine (m.p. 296-298 ^oC). This solvent of crystallisation was removed by recrystallisation from aqueous ethanol containing a few drops of acetone, when 1-guanidinopropanephosphonic acid was obtained as a fine white crystalline solid m.p. 303 ^oC.

Using this method difficulties were again experienced when longer chain aldehydes were used. In the case of 1-guanidino-octanephosphonic acid (12, R = C_7H_{15}) the isolated yield was less than 1% whereas if decanal or dodecanal were used instead of octanal no product was

isolated. The reason for the low yields experienced even with the short chain homologues is unclear.

Because the overall yield of 1-guanidino-octane-phosphonic acid was very low it was considered advisable to repeat the reaction several times, and to combine the separated aqueous layers in order to obtain a suitable quantity of the phosphonic acid for initial biological investigations. Therefore the reaction was performed six times on a 0.2 molar scale. The resultant aqueous layers were combined, the volatile components were distilled off on a rotary evaporator and the resultant residue was treated with methyl iodide and then ammonia as before. However, in this case none of the required 1-guanidino-octanephosphonic acid crystallised even after several months.

The organic layers from the above reactions were also combined and the volatile components distilled off. After allowing the residue to stand for several weeks the precipitate that formed was filtered off, and recrystallised from diethyl ether to give a novel phosphonic acid 1-thioureido-octanephosphonic acid (13) in low yield (3.2%).

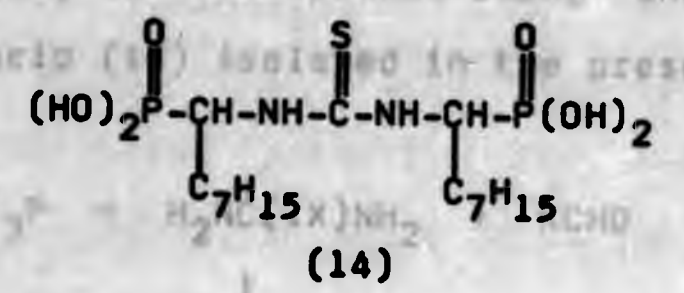
$(HO)_2P(O)CH(C_7H_{15})NHC(:S)NH_2$

(13)

It would appear that the longer alkyl chain rendered this phosphonic acid more soluble in the organic layer than in water. Compound 13 was in fact found to be only sparingly soluble in hot water and insoluble in cold water. However, repetition of this procedure with decanal or dodecanal yielded no solid from the organic layer, even after standing for over a year.

In order to prepare a further batch of the thiourea (13) the reaction and isolation were repeated as before except that the combined organic layers were dissolved in acetone after evaporation of the volatile components in the hope that this would aid precipitation. The solid formed on standing for several weeks was found to have m.p. 263 ^{o}C whereas the sample of 13 previously isolated melted at 166-168 ^{o}C. The ^{13}C nmr spectra of these two products were practically identical except that for the first product (13) the thiourea carbon was revealed as a doublet ($^{3}J_{PCNC}$ 8.8 Hz) whereas for the second product the thiourea carbon appeared as a triplet (J 7.0 Hz). There was very little difference between the chemical shifts of the other carbon atoms in these molecules or in the phosphorus-carbon coupling constants. It appeared that the carbon atom of the thiourea group which was revealed as a triplet was coupled to two identical phosphorus species, identified as phosphonic acid groups by $^{31}P-\{^{1}H\}^{bb}$ nmr which gave one signal at 20.5 ppm. The only formula that fitted these spectral data was that of

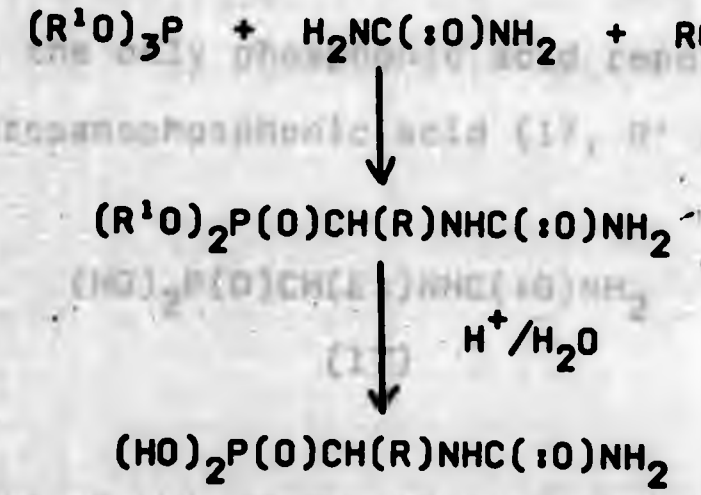
the diphosphonic acid (14).



(14)

The elemental analysis agreed with this ratio of elements while FAB ms confirmed the molecular weight as 460.

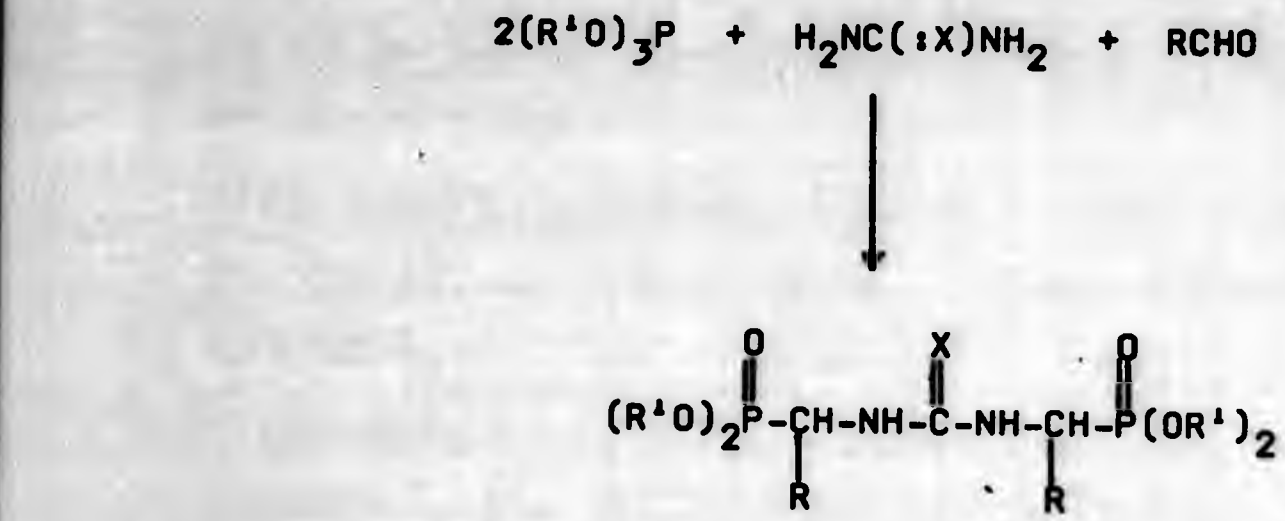
Though the synthesis of 1-guanidinoalkanephosphonic acids was reported by Oleksyszyn et al.[38] an analogous condensation leading to 1-ureidoalkanephosphonic acids (15) was described by Birum (Scheme 14).[39]



(15)

(Scheme 14)

Birum[39] found that by altering the ratio of reactants the corresponding diphosphonates (16) could be prepared (Scheme 15), these compounds being analogous to the diphosphonic acid (14) isolated in the present work.



(16)

X = O or S

(Scheme 15)

However, the only phosphonic acid reported by Birum was 1-ureidopropanephosphonic acid (17, R^1 = Et).[39] The

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

(17)

^1H nmr spectrum of this compound was recorded in DMSO-d_6 and appears to provide the only literature reference to the observation of $P(OH)_2$ and NH protons of an aminoalkanephosphonic acid. It was reported that the NH group

gave a broad signal at 6.2 ppm whilst the $P(OH)_2$ and the NH_2 protons were revealed as a broad signal at 8.5 ppm. The ^1H nmr spectra (DMSO-d_6) of the two thiourea derivatives prepared in the present work were found to give a slightly different pattern. For 1-thioureido-octanephosphonic acid (13), in addition to the protons of the alkyl chain three other signals were observed which were removed by exchange with D_2O. These signals were at 7.1 {C(:S)NH_2}, 7.6 {PCNH, d, 3JPCNH 9.3 Hz}, and 9.7 {P(O)$(OH)_2$}. The diphosphonic acid (14), however, revealed only two other signals as expected for this structure: 7.0 {P(O)$(OH)_2$}, and 8.0 {PCNH}.

Thus, using the methods described by Oleksyszyn et al.[33,37,38] three 1-aminoalkanephosphonic acids (7, R = Me, Et, and C_7H_{15}), three 1-guanidinoalkane-phosphonic acids (12, R = Me, Et, and C_7H_{15}), and two novel thioureido analogues (13 and 14) were prepared, in low yield but in sufficient quantity for initial biological screening.

1.3 STRUCTURAL CHARACTERISATION AND IDENTIFICATION OF 1-AMINO- AND 1-GUANIDINO-ALKANEPHOSPHONIC ACIDS

Infrared and ^{1}H nmr spectra of 1-aminoalkanephosphonic acids have been reported[23,27,30,37,40] and Oleksyszyn et al.[38] reported data for the 1-guanidinoalkanephosphonic acids.

The infrared and the ^{1}H nmr spectra of these compounds were also recorded in the present work but it was concluded that better methods of identification were required. An investigation of the ^{13}C nmr spectra of the compounds was therefore carried out.

$(HO)_2P(O)CH(R)NHC(:NH)NH_2$

(12)

The ^{13}C nmr of 1-guanidinoethanephosphonic acid (12, R = Me) was found to reveal the PCH carbon as a doublet ($^{1}J_{PC}$ 158.1 Hz) and the guanidine carbon also as a doublet ($^{3}J_{PCNC}$ 4.4 Hz). However, the methyl group did not show up as a doublet (as might be expected since it is only two bonds removed from phosphorus) but as a singlet.

The spectra of the propane analogue (12, R = Et) again revealed the PCH and guanidine carbons as doublets, as also was the methyl carbon. In this case, however the

methylene carbon (CH_2) was a singlet. A single frequency off-resonance decoupled spectrum of each of these two compounds was obtained which confirmed the assignments of the signals in each case thereby showing that for these two compounds the $^2J_{PCC}$ coupling constant is zero (or very close to zero).

Table 2: Phosphorus-carbon coupling constants (Hz) in the ^{13}C nmr spectra of N-sustituted aminoalkanephosphonic acids (18)

$(HO)_2P(O)CH(R)NH-X$

(18)

R	X	$^1J_{PC}$	$^2J_{PCC}$	$^3J_{PCCC}$	$^3J_{PCNC}$
C_2H_5	H	153.9	0	8.8	-
CH_3	$C(:NH)NH_2$	158.1	0	-	4.4
C_2H_5	$C(:NH)NH_2$	158.1	0	13.3	3.7
C_7H_{15}	H	153.2	0	15.1	-
C_7H_{15}	$C(:NH)NH_2$	160.5	0	13.4	4.4
C_7H_{15}	$C(:S)NH_2$	151.5	0	11.0	8.8

For these compounds we see that generally $^1J_{PC}$ has a large value (150-160 Hz) whilst the $^2J_{PCC}$ coupling constant is zero. Also the $^3J_{PCCC}$ coupling constant is usually larger than the corresponding $^3J_{PCNC}$.

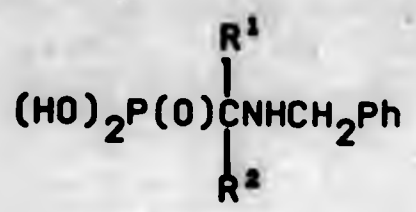
$(HO)_2P(O)CH_2NH_2$ (19)

$(HO)_2P(O)CH_2NHC(:NH)NH_2$ (20)

Aminomethanephosphonic acid (19) and guanidinomethephosphonic acid (20) are the first members of the homologous series of 1-amino- and 1-guanidino-alkanephosphonic acids respectively (for their preparation see Chapter 2). The ^{13}C nmr spectra of these two compounds were found to agree with the general observations made above since both were found to have a $^{1}J_{PC}$ value of 149.9 Hz whilst 20 revealed the guanidino group as a doublet as would be expected ($^{3}J_{PCNC}$ 4.1 Hz).

The only reference to the ^{13}C nmr spectroscopy of aminoalkanephosphonic acids and indeed of phosphonic acids in general appears to be that of Redmore[29] for a series of N-benzyl-1-aminoalkanephosphonic acids (21, Table 3).

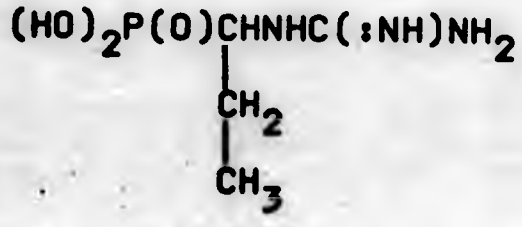
Table 3: ^{13}C nmr Phosphorus-carbon coupling constants (Hz) for N-benzyl-1-aminoalkanephosphonic acids (21)



(21)

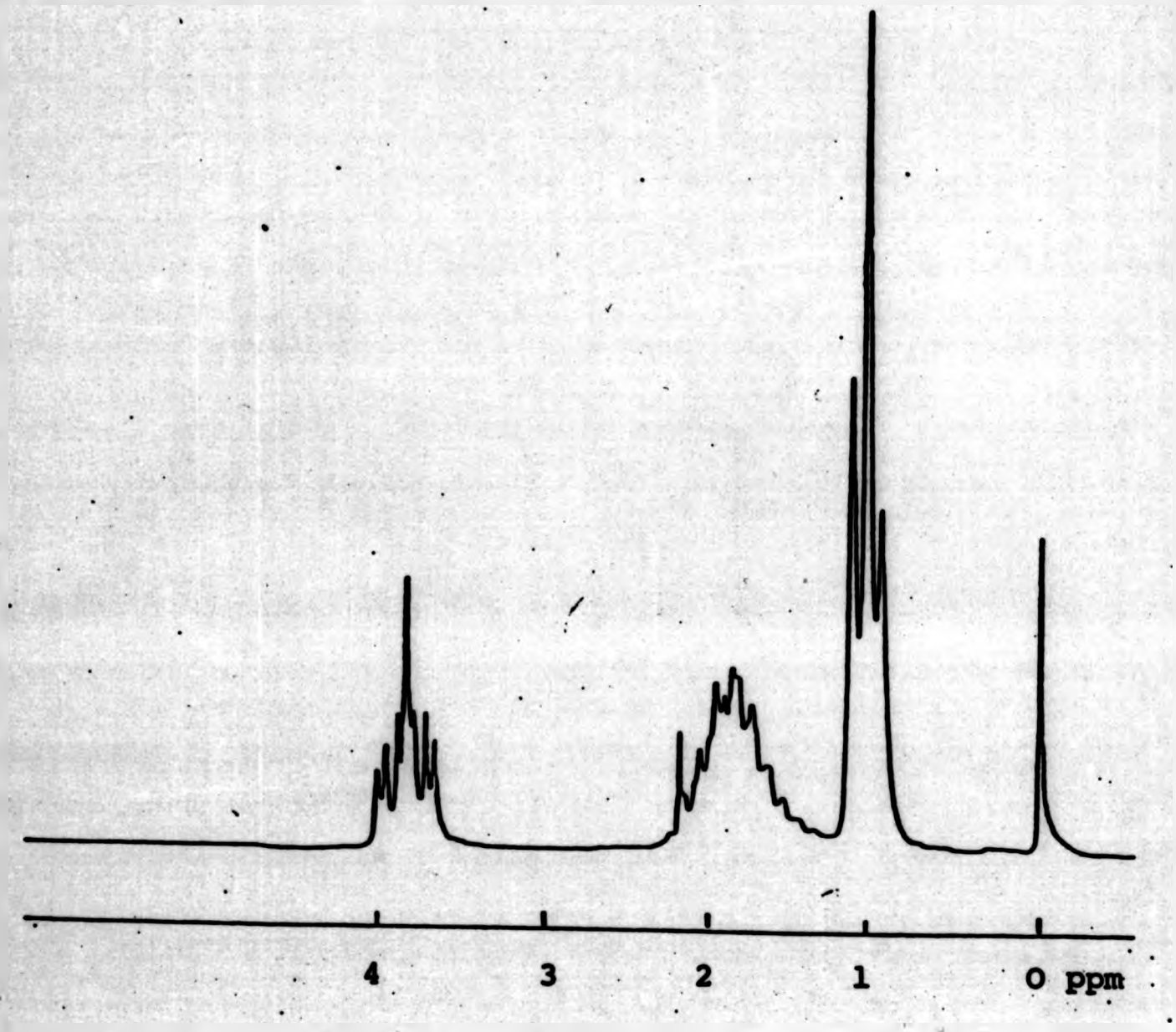
R^1	R^2	$^1J_{PC}$	$^2J_{PC}(R^1)$	$^2J_{PC}(R^2)$
H	H	138	-	-
Me	H	136	0	0
Et	H	135	0	0
Et	Me	143	6.0	0

It can be seen from Table 3 that $^2J_{PC}$ is only greater than zero in one case. Unfortunately no values for $^3J_{PCCC}$ or $^3J_{PCNC}$ were recorded in this communication.



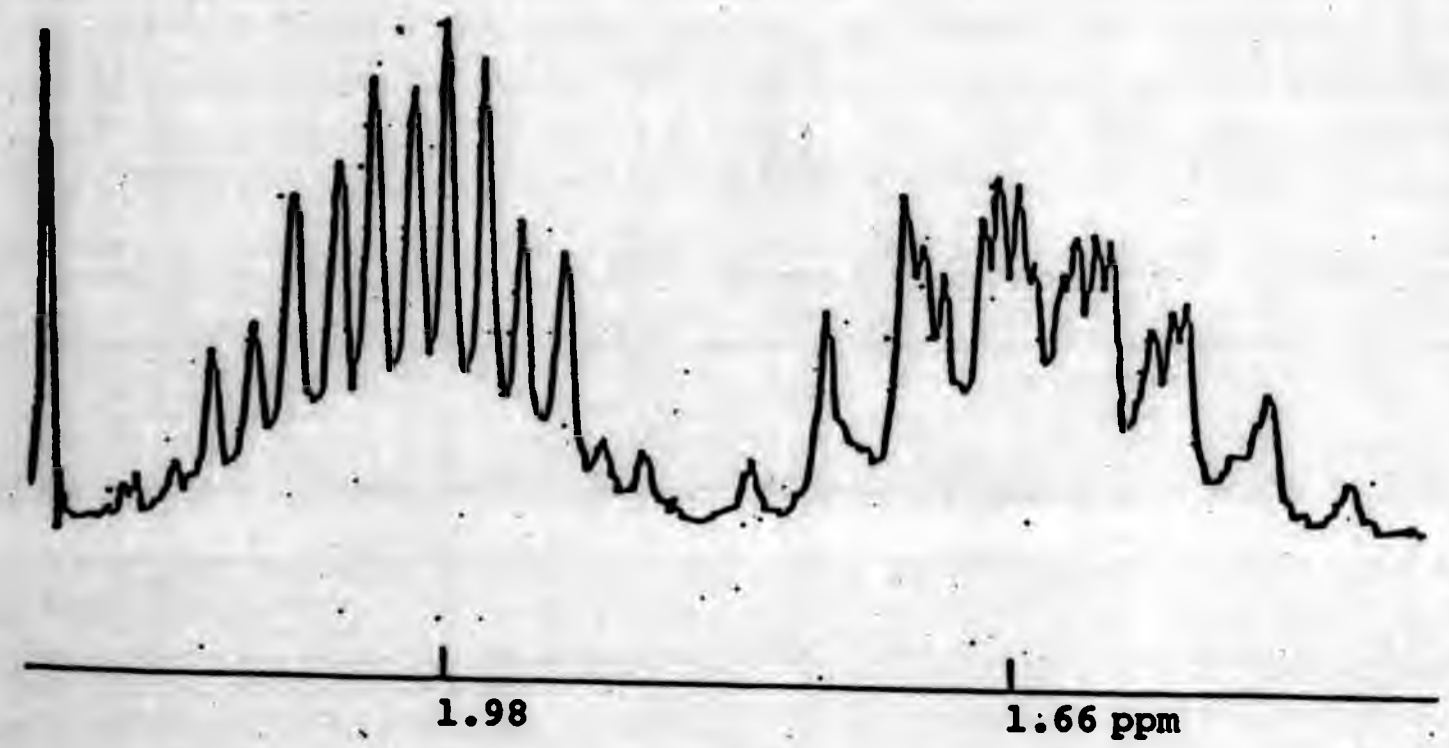
(22)

The following ^{1}H nmr data for 1-guanidinopropane-phosphonic acid (22) were reported by Oleksyszyn *et al.*[38] in D_2O/D_2SO_4 1.37 (t, 3H, J_{H-H} 7 Hz), 1.68- 2.50 (m, 2 H), 3.88-4.30 (m, 1H) and in the present work a similar spectrum was obtained at 80 MHz (Fig. 1).



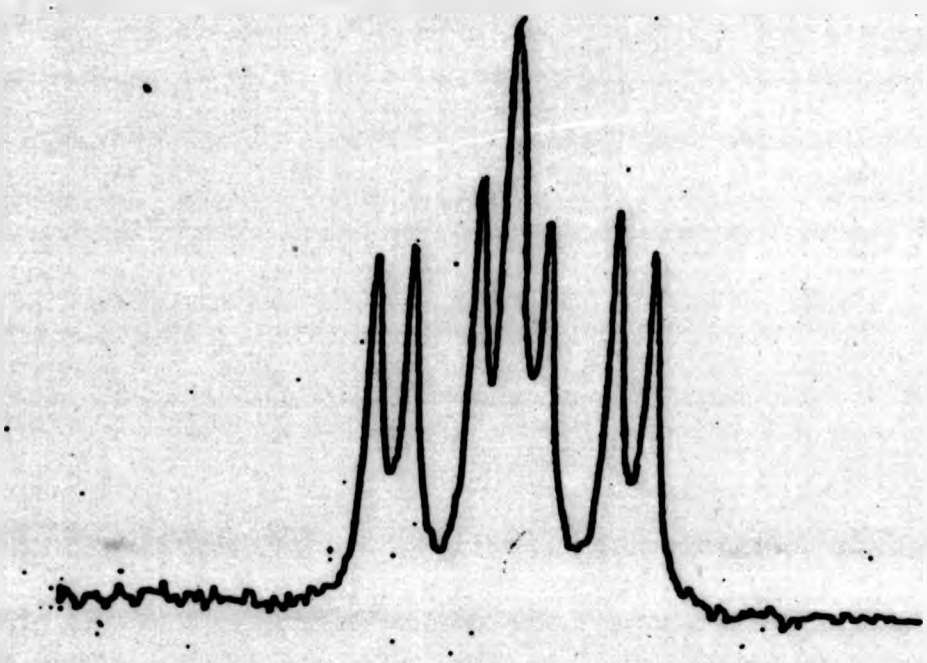
(Fig. 1)

However, the information obtained from this spectrum was of little use since the peaks could not be assigned with certainty. The spectrum was therefore recorded at 220 MHz, but was found to be more complicated than expected since the multiplet due to the CH_2 resolved into two distinct multiplets centred at 1.66 and 1.98 ppm (Fig. 2).



(Fig. 2)

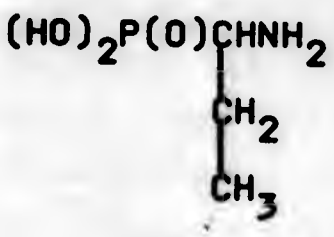
These two multiplets consist of ca. 30 separate peaks whereas a maximum of sixteen would be expected as a result of coupling to phosphorus, and to the CH and CH_3 protons (i.e. 2x2x4 = 16). Similarly the signal due to the CH hydrogen (Fig. 3) consists of seven peaks whereas only six peaks would be expected due to splitting by phosphorus and the CH_2 group.



(Fig. 3)

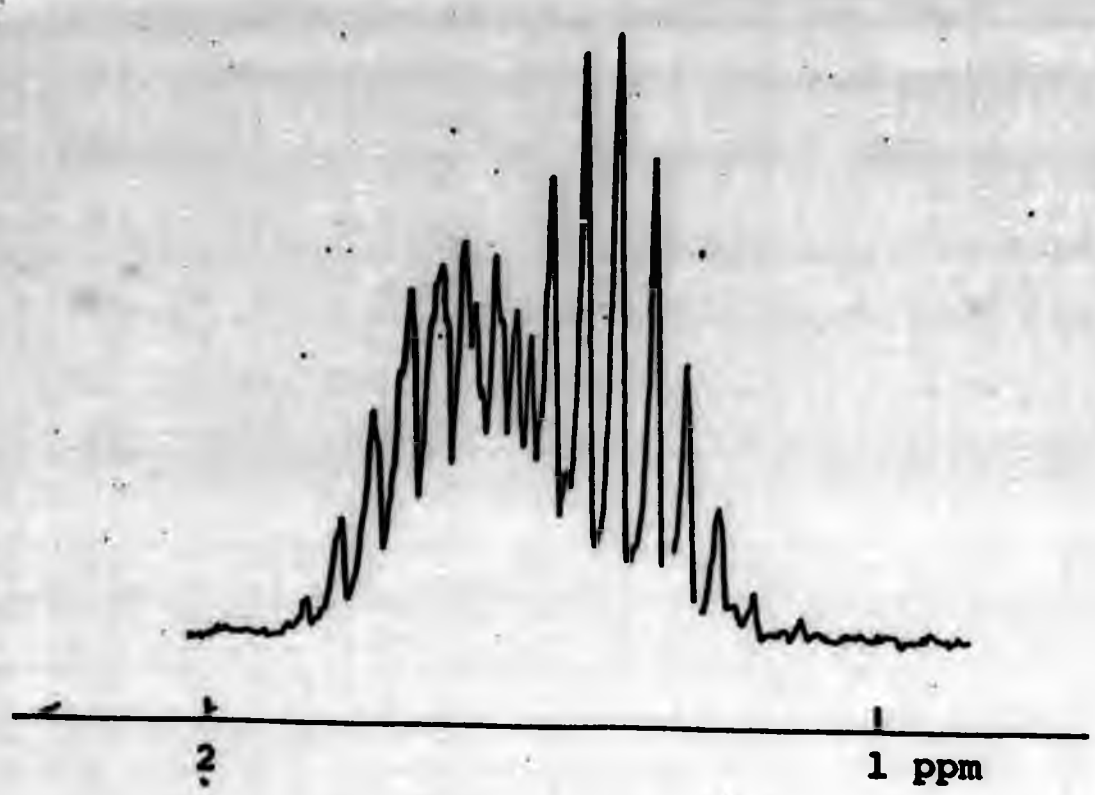
The ^1H nmr spectrum of 1-guanidinopropanephosphonic acid can be explained by the fact that the two hydrogen atoms of the CH_2 group are not equivalent and as such give an AB coupling pattern. This was confirmed by spin-decoupling of the spectrum at selective frequencies and observing the rest of the spectrum. Spin-decoupling at

1.66 or 1.98 ppm resulted in the signal at 3.80 ppm collapsing to a doublet of doublets as would be expected for an AB coupling of this type. However, repetition of this spin-decoupling at 80 MHz at the centre of the multiplet resulted in the signal at 3.80 ppm collapsing to a doublet since we were effectively spin-decoupling at both 1.66 and 1.98 ppm at this frequency.



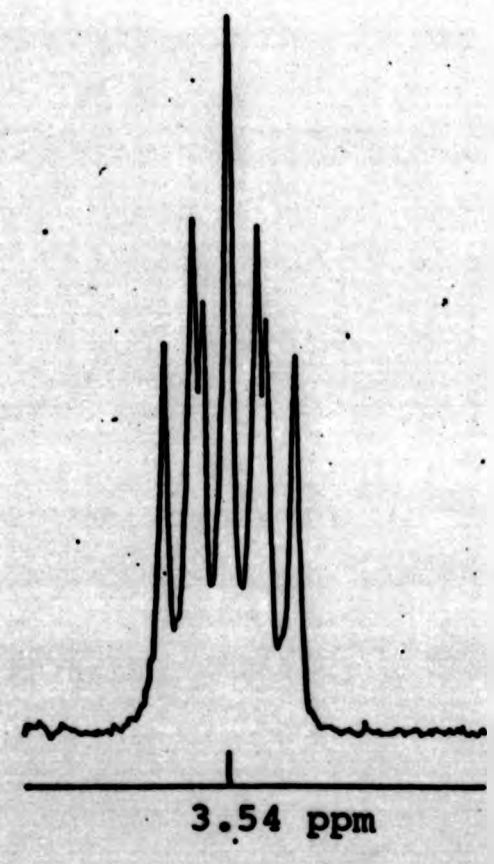
(23)

In the case of the corresponding amino analogue 1-aminopropanephosphonic acid (23), it was again found that the hydrogens of the methylene group displayed an AB pattern, though the distinction between the two multiplets was not so clearcut in this case (Fig. 4).



(Fig. 4)

Also as we have seen for 1-guanidinopropanephosphonic acid the number of signals for the CH proton was found to be seven (Fig. 5).



(Fig. 5)

The non-equivalence of methylene protons has been reported in organic compounds such as 1-phenylpropan-2-ol.[41] It appears that methylene protons adjacent to a chiral centre will be non-equivalent, despite the fact that there is free rotation about the carbon-carbon bond. Such protons are described as diasteriotopic, since replacement of one of the two hydrogens of the methylene group by a group X produces a pair of diasterioisomers.

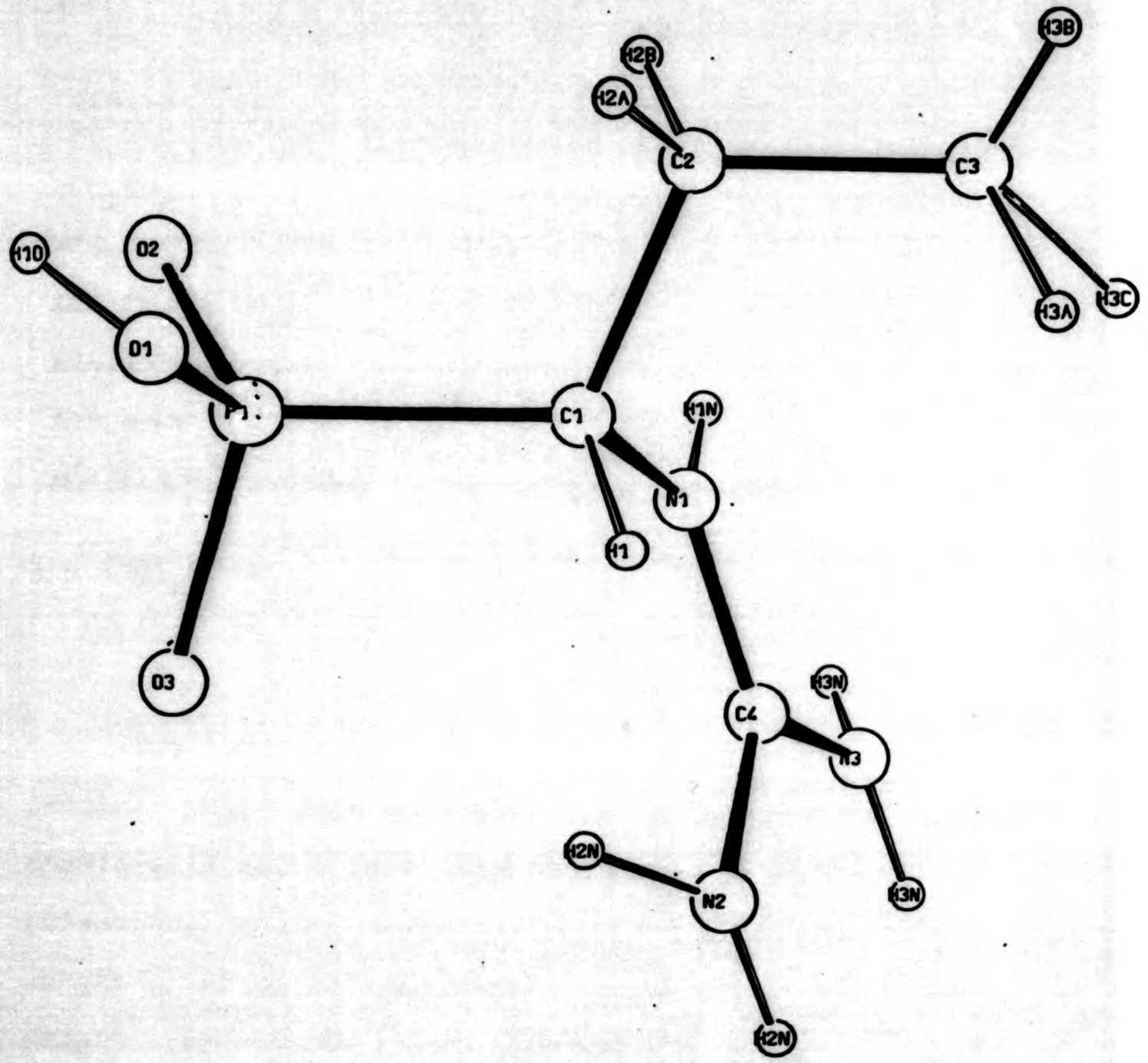
The $^{15}N-\{^{1}H\}^{bb}$ nmr spectrum of 1-guanidinoethanephosphonic acid (12, R = Me) in $H_2SO_4/H_2O/D_2O$ revealed only two signals as expected since guanidine compounds have been shown to have two equivalent outer nitrogen atoms.[42]

1.4 CRYSTAL STRUCTURE OF 1-GUANIDINOPROPANEPHOSPHONIC ACID

At this stage it was considered important to confirm the structure of a typical 1-guanidinoalkanephosphonic acid in the solid state by X-ray crystallography and to determine whether these compounds are zwitterionic or not. Although the X-ray crystal structures of a number of aminophosphonic acids have been determined,[43-48] none has been previously reported for a guanidino type. The compound chosen for this investigation was 1-guanidinopropanephosphonic acid (12, R = Et) in view of its rather complex ^{1}H nmr spectrum.

A saturated solution was prepared in boiling water and portions transferred to previously heated tubes of different diameters. The best crystals were found in the smallest diameter tube, an nmr tube of 0.3 cm diameter, but were found to be unstable. The reason for this is unclear since the compound itself was found to be remarkably chemically stable. Therefore another crystal was selected and wedged into a 0.5 mm diameter Lindemann tube containing a drop of water and mounted on to a quartz needle.

The structure was solved using the direct methods technique which revealed that the compound was in fact a zwitterion having no P=O, one P-OH, and two terminal C-NH_2 bonds (Fig. 6).


H3B
H2B
H2A
C2
C3
H3C
H3A
H1O
O2
O1
P1
C1
H1N
N1
H1
O3
H3N
C4
N3
H2N
N2
H3N
H2N

(Fig. 6)

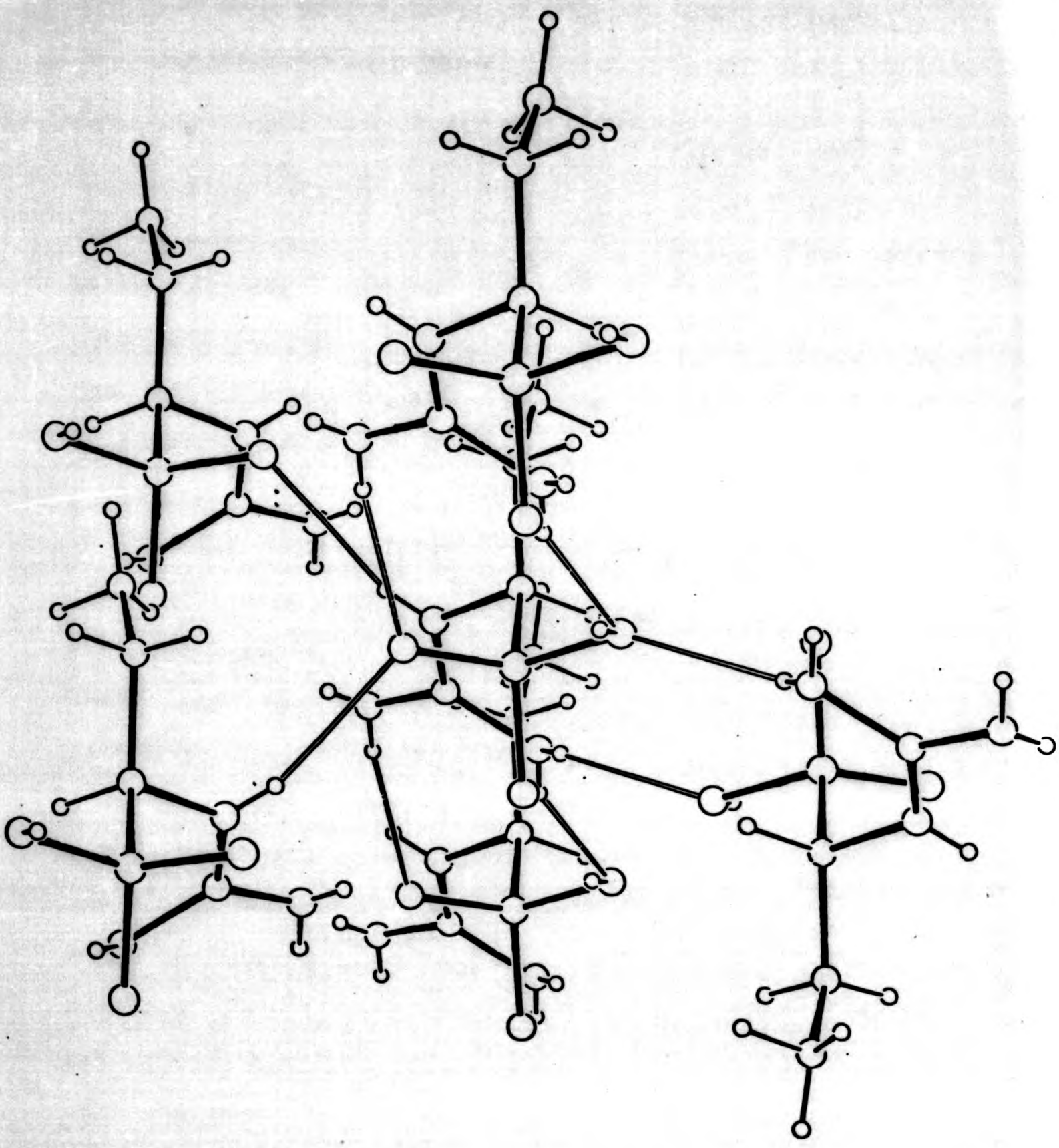
Table 4: Bond lengths (Å) about phosphorus in aminoalkane-phosphonic acids and in 1-guanidinopropane-phosphonic acid

Formula	P-C	P-OH	P-O	P-O	ref.
XCH_2NH_2	1.82	1.51	1.51	1.49	43
$XCH_2CH_2NH_2$	1.80	1.51	1.51	1.50	44
$XCH_2CH_2CH_2NH_2$	1.81	1.53	1.53	1.51	45
$XCH_2NHCH_2CO_2H$	1.82	1.50	1.50	1.50	46
$XCH_2NHCH_2CO_2H$	1.82	1.50	1.50	1.50	47
$XCH(Et)NHC(:NH)NH_2$	1.81	1.52	1.59	1.50	-

$X = (HO)_2P(O)$

From Table 4 we see that the P-C and P-OH bond lengths that were determined for 1-guanidinopropanephosphonic acid agree well with the values found for other phosphonic acids. One of the P-O bonds was of similar length (1.50 Å) to those found earlier but the P-O bond length of 1.59 Å is significantly longer than has previously been recorded. This is apparently the result of the crystal packing arrangement and the presence of strong hydrogen bonding involving this P-O oxygen atom (Fig. 7). The co-ordination around the phosphorus atom departs from regular tetrahedral, the angles varying from

104.9 ^{o} to 116.6 ^{o}. The guanidino group is planar with the three C-N bonds about the guanidino carbon being 1.31, 1.32 and 1.35 Å, the sum of the three angles being 360 ^{o}. The planarity of the guanidinium group does not itself prove the zwitterionic character of this compound but the identification of all the hydrogens does.



(Fig. 7)

1.5 FAB MASS SPECTROMETRY OF 1-AMINO- AND 1-GUANIDINO-ALKANEPHOSPHONIC ACIDS

Phosphonic acids, especially 1-amino- and 1-guanidino-alkanephosphonic acids are high melting solids and as such it is impossible to record their mass spectra using standard methods since they are too involatile to enter the gas phase e.g. 1-guanidinoethanephosphonic acid did not give a spectrum even at 360 ^{o}C at 10^{-6} torr using a standard electron impact source.

In 1980 Barber *et al.*[49,50] reported a new ion source, the Fast Atom Bombardment (FAB) source. Essentially the FAB source produces argon atoms with about 5 KeV energy. These are directed on to a sample introduced into the system by first depositing it, mixed with glycerol, on to a metal stage which is fixed to the shaft of a solid sample insertion probe. This is then introduced to the ion source through an axially mounted vacuum lock, in order to intercept the fast atom beam. Both negative and positive ions characteristic of the molecule are emitted, and after appropriate acceleration and focussing are mass-analysed by the mass spectrometer in the normal way. FAB has so far been used to obtain mass spectra from a wide variety of compounds such as potassium iodide[51] and polypeptides[52] which were previously difficult or impossible to study directly in an underivatised form using other types of ion source.

Hence, in view of these reports we investigated the FAB mass spectrometry of the phosphonic acids prepared in the present work. It has been found that in general the FAB mass spectra of phosphonic acids give a very strong M+1 ion (usually the base peak), adduct ions such as 2M+1 and M+glycerol+1 and also ions due to fragmentation.

Table 5: Relative intensities (%) of molecular ions in the FAB mass spectra of N-substituted 1-amino-alkanephosphonic acids (18)

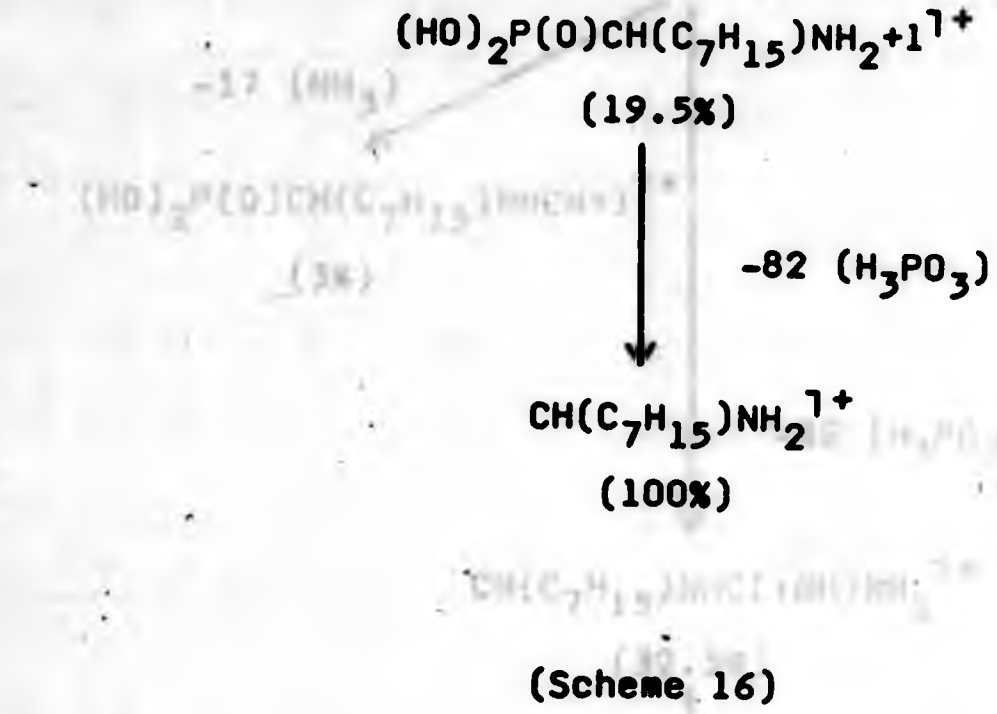
$(HO)_2P(O)CH(R)NH-X$

(18)

R	X	M+1	2M+1	M+G+1	M+2G+1
Me	H	100	7.3	89.0	13.5
Et	H	100	53.1	6.4	-
C_7H_{15}	H	19.5	11.9	-	-
Me	$C(:NH)NH_2$	100	-	13.1	-
Et	$C(:NH)NH_2$	100	-	1.0	-
C_7H_{15}	$C(:NH)NH_2$	100	7.5	2.6	-
C_7H_{15}	$C(:S)NH_2$	43.4	1.1	-	-

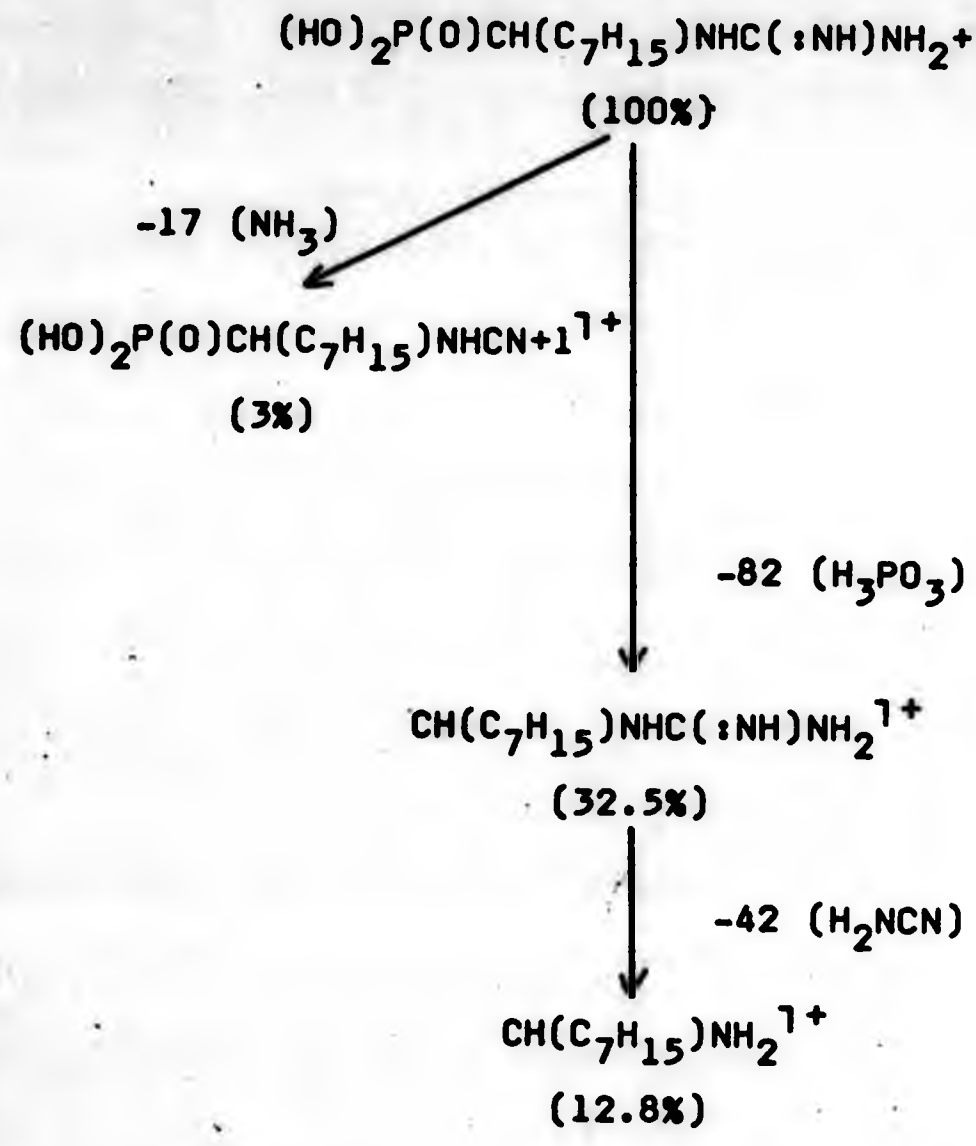
G = glycerol

It was established by link scanning that a major fragmentation in the compounds is the loss of the phosphonic acid group, a process exemplified by 1-amino-octanephosphonic acid as shown (Scheme 16).



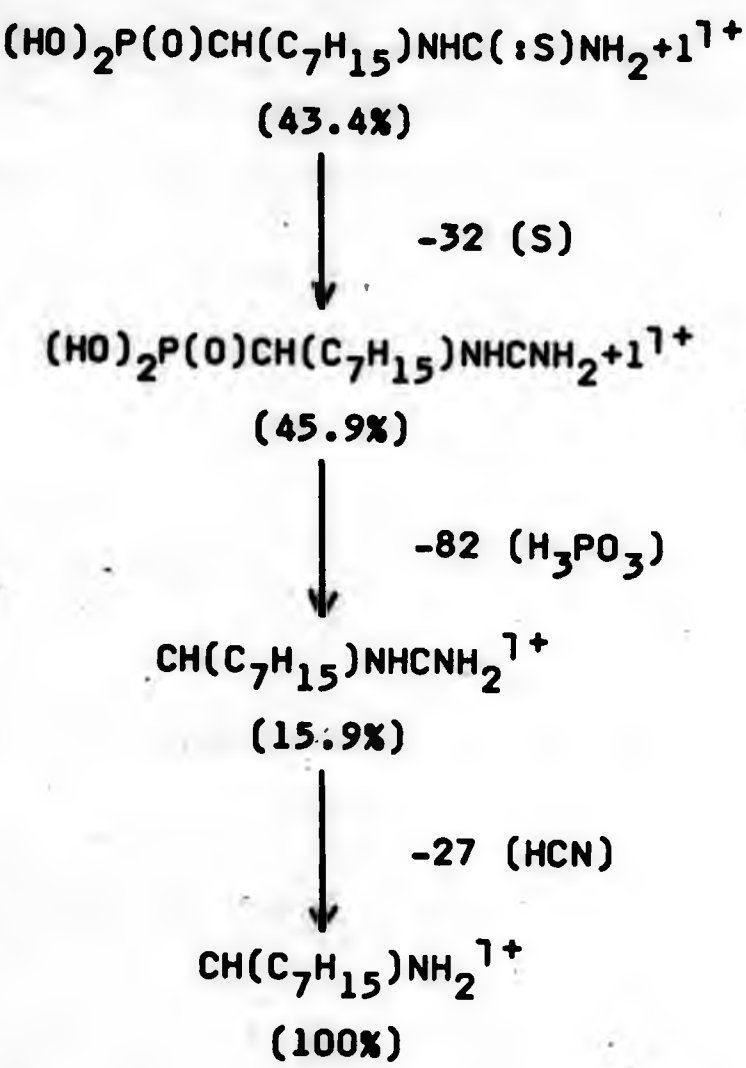
(Scheme 16)

The analogue 1-guanidino-octanephosphonic acid, was also found to fragment to a minor extent by initial loss of ammonia (Scheme 17).



(Scheme 17)

1-Thioureido-octanephosphonic acid appears to fragment by the initial loss of sulphur, followed by the phosphonic group and HCN (Scheme 18), although in this case the pathways have not been confirmed by link scan techniques.



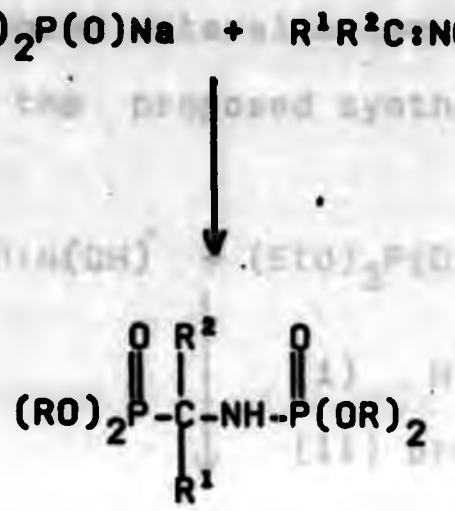
(Scheme 18)

In these three examples the various fragmentation pathways lead to the same characteristic ion, $CH(C_7H_{15})NH_2]^+$, in each case.

1.6 REACTION OF DIETHYL PHOSPHITE WITH OCTANALDOXIME

In view of the failure of the one-pot synthesis of the longer-chain homologues of 1-amino- and 1-guanidino-alkanephosphonic acids it was decided to seek alternative methods of preparation of these compounds in which the carbon-nitrogen fragment of the molecule would be formed first before subsequent reaction with the phosphorus reagent. It appeared that an oxime might be suitable for this purpose since oximes of aliphatic aldehydes are stable, known compounds, and are easily prepared.

A review of the literature revealed only two references which were pertinent to the reaction of phosphites with oximes. Zimin *et al.*[53] reported the condensation of sodium dialkyl phosphites with oximes giving the diphosphonates (24) in a yield of 14-30% (Scheme 19).

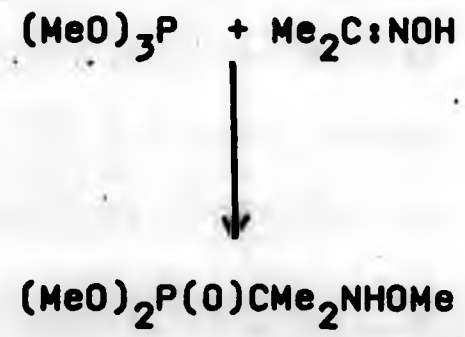


(24)

R = Et, Pr, Me_2CH; R^1 = Me, Et, Ph; R^2 = H, Me; R^1R^2 = $(CH_2)_5$.

(Scheme 19)

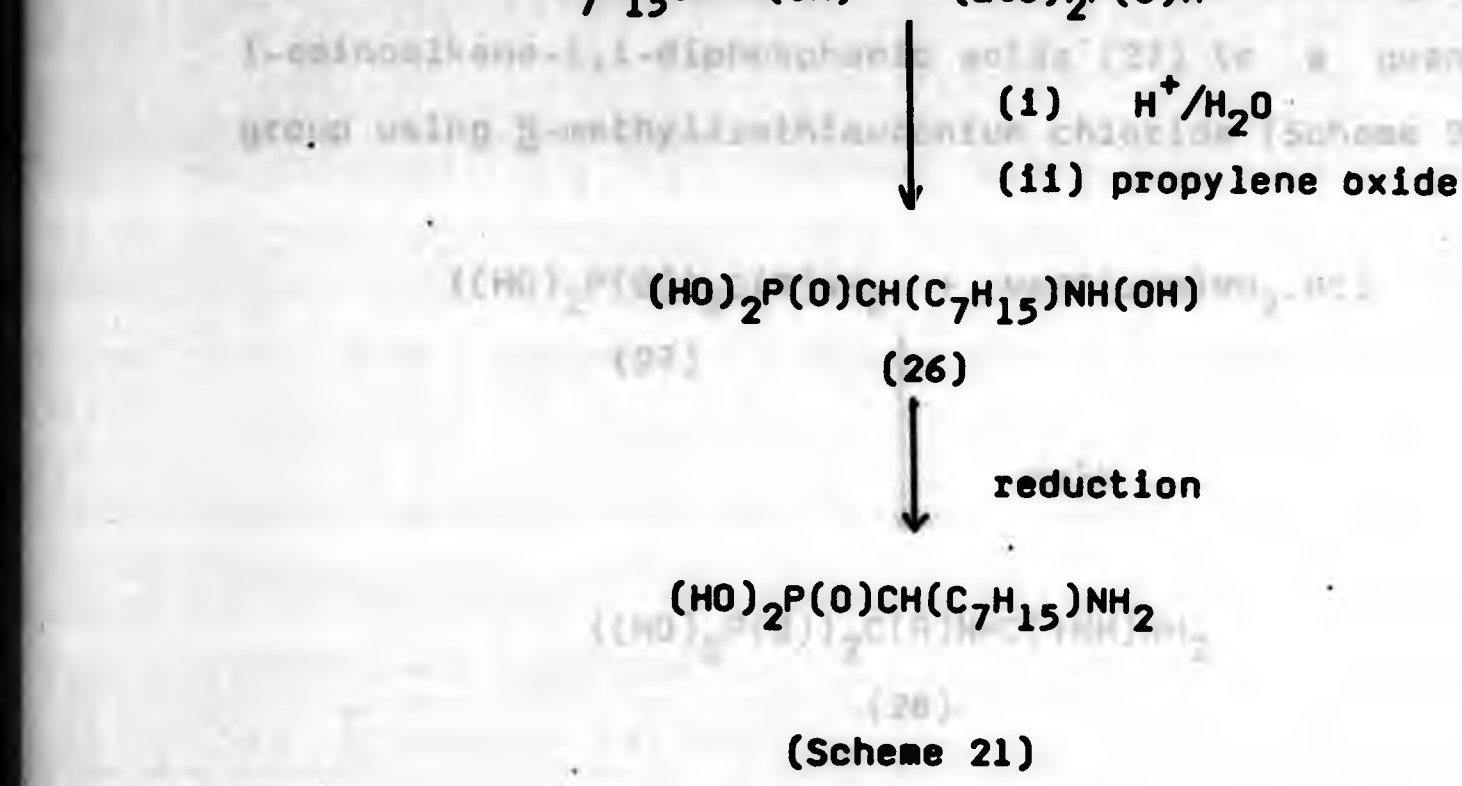
Osipova et al.[54] reported that the reaction of trimethyl phosphite with acetone oxime at 70-80 °C for 4 - 6 h gave the phosphonate (25) in a yield of 58% (Scheme 20).



(25)

(Scheme 20)

As a model compound octanaldoxime was prepared and used to investigate the proposed synthetic route (Scheme 21) which gave the required N-(hydroxy)-1-amino-octane-phosphonic acid (26), a novel type of phosphonic acid, as a fine white crystalline solid but in low yield (5%). Sufficient material was nevertheless obtained to characterise the compound by nmr spectroscopy and elemental analysis.



(Scheme 21)

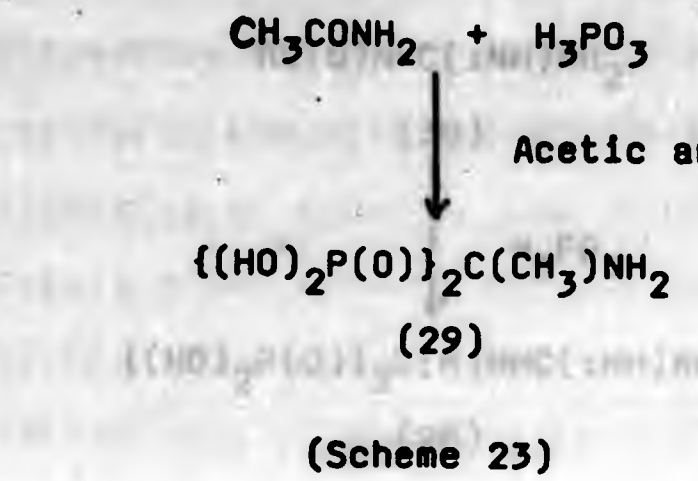
1.7 1-GUANIDINOALKANE-1,1-DIPHOSPHONIC ACIDS

A possible synthetic route to compounds of this type (28) is that of conversion of the amino group of 1-aminoalkane-1,1-diphosphonic acids (27) to a guanidine group using S-methylisothiouronium chloride (Scheme 22).

$$\underset{(27)}{\{(HO)_2P(O)\}_2C(R)NH_2} + MeSC(:NH)NH_2.HCl \xrightarrow{-MeSH} \underset{(28)}{\{(HO)_2P(O)\}_2C(R)NHC(:NH)NH_2}$$

(Scheme 22)

The 1-aminoalkane-1,1-diphosphonic acids (27) are a well-known class of compounds. Ploeger et al.[55] reported the preparation of thirty-one various members of this series. We prepared the first member, 1-aminoethane-1,1-diphosphonic acid (29, R = Me), according to the method of Krueger and Michel[56] by condensation of phosphorous acid and acetamide in the presance of acetic anhydride (Scheme 23).



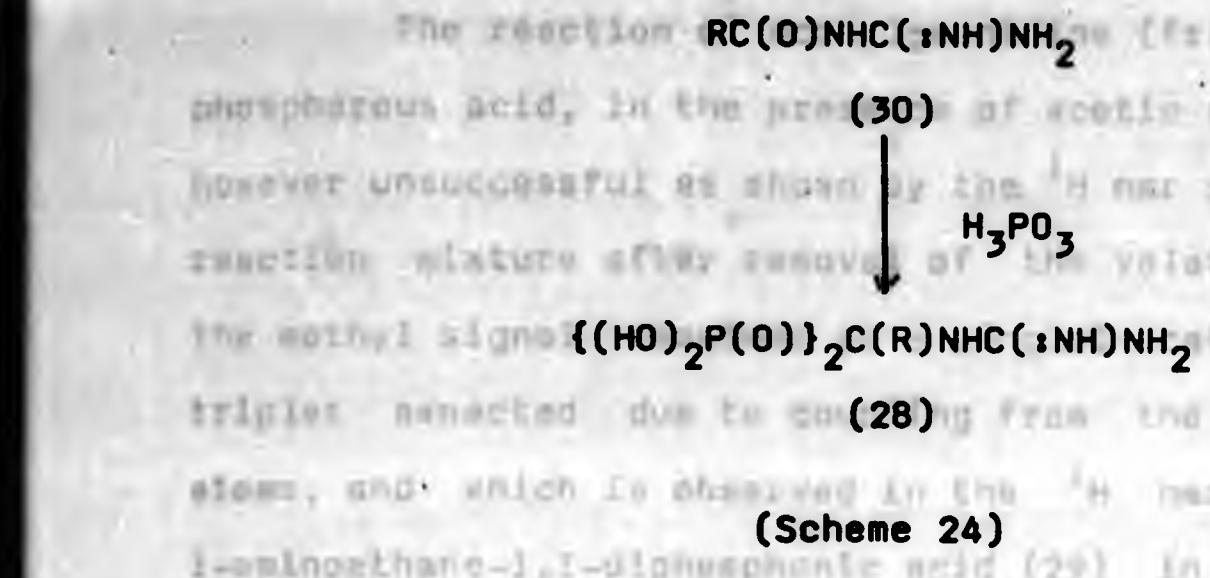
(29)

(Scheme 23)

1-Aminoethane-1,1-diphosphonic acid (29) was thus obtained as a fine white crystalline solid which was found to be insoluble in common organic solvents and only very slightly soluble in water. However, it was soluble in aqueous acid and aqueous base. Therefore the guanidation was attempted in both acidic and basic media, but the unreacted phosphonic acid was recovered in each case.

It must be assumed that the guanidation failed because of steric hindrance of the amino group by the phosphonic groups since we have shown that aminoalkanephosphonic acids in general can be guanidated in basic conditions in good yield.

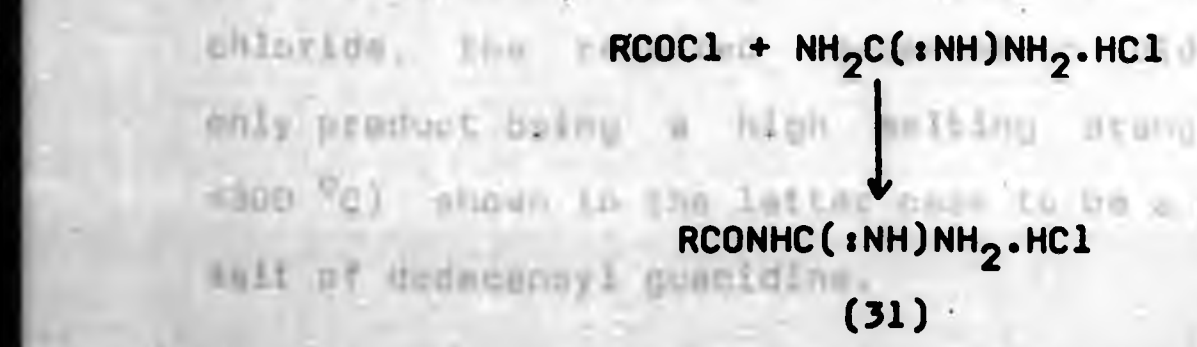
In view of these results it was decided to investigate an alternative synthetic route in which the phosphonic acid groups were to be introduced into the compound already containing the guanidino group (Scheme 24). This would involve the reaction of an acylguanidine (30) with phosphorous acid.



(Scheme 24)

The preparation of the acyl guanidine (30, R = $C_{11}H_{23}$) was not possible from lauramide and S-methylisothiouronium chloride, presumably because of the low nucleophilicity of amides.

A review of the literature of acyl guanidines revealed only one reference to these compounds by Korndorfer in 1903,[57] and by his method it was possible to prepare two homologues (31, R = CH_3 and $C_{11}H_{23}$) as their hydrochlorides by heating the respective acyl chlorides with an excess of guanidine hydrochloride in a sealed tube (Scheme 25).



(Scheme 25)

The reaction of acetylguanidine (free base) with phosphorous acid, in the presence of acetic anhydride, was however unsuccessful as shown by the ^{1}H nmr spectrum of the reaction mixture after removal of the volatile components. The methyl signal remained as a singlet rather than the triplet expected due to coupling from the two phosphorus atoms, and which is observed in the ^{1}H nmr spectrum of 1-aminoethane-1,1-diphosphonic acid (29) in $NaOH/D_2O$.

$$RC(O)NHC(:O)NH_2 \xrightarrow{PCl_3/H_3PO_3} \{(HO)_2P(O)\}_2C(R)NHC(:O)NH_2$$

(Scheme 26)

An analogous reaction has been reported between acyl ureas, phosphorus trichloride, and phosphorous acid in chlorinated solvents such as chlorobenzene or 1,1,2,2-tetrachloroethane (Scheme 26).[58] Using this procedure with acetylguanidinium chloride or with dodecanoylguanidinium chloride, the required condensation did not occur, the only product being a high melting orange solid (m.p. <300 ^{o}C) shown in the latter case to be a phosphorous acid salt of dodecanoyl guanidine.

CHAPTER 2

ω-GUANIDINO- and ω-AMINO-ALKANEPHOSPHONIC ACIDS

2.1 SYNTHESIS OF ω-GUANIDINOALKANEPHOSPHONIC ACIDS

It was desirable to synthesise a series of ω-guanidinoalkanephosphonic acids (32) in order to investigate their fungicidal activity and to compare it with that possessed by the 1-guanidinoalkanephosphonic acids with which they are structurally isomeric.

$$(HO)_2P(O)(CH_2)_nNHC(:NH)NH_2$$

(32)

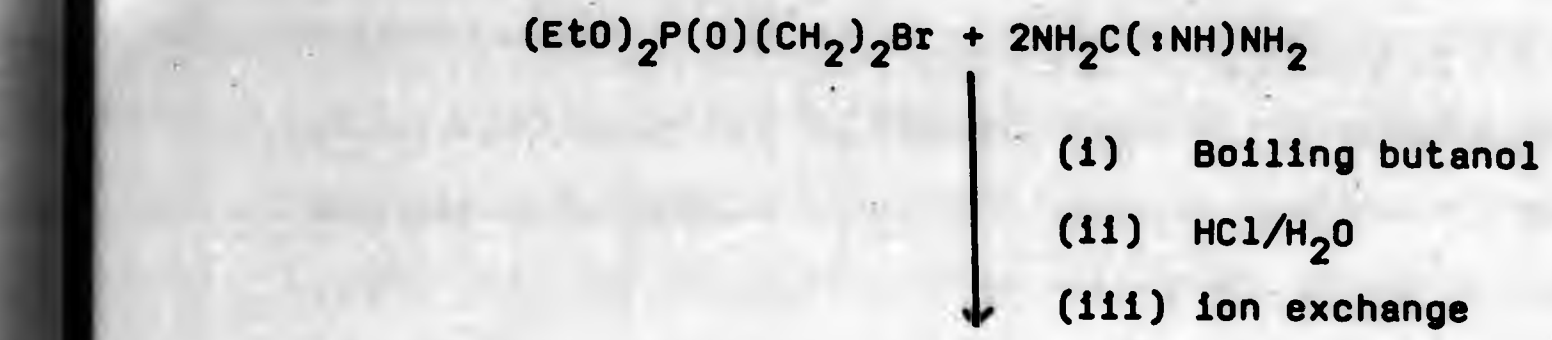
The ω-guanidinoalkanephosphonic acids are a relatively unknown class of compound. The first reference to them was by Moreaud, Lacosre and Neuzil[59] who reported the synthesis of three homlogues (32, n = 1,2,3) for use in investigating various biological reactions in animals. The only chemical data reported related to guanidinomethanephosphonic acid (32, n = 1) which was obtained as the monosodium salt dihydrate, m.p. 240 °C, (Found: C, 11.03; H, 5.35; N, 18.91; P, 14.05. Calc. for $C_2H_{11}N_3NaO_5P$: C, 11.36; H, 5.25; N, 19.95; P, 14.67%).

Oleksyszyn, Tyka and Mastalerz[38] then reported 32 (n = 1) as the sesquihydrate (m.p. 321-322 °C). In a separate publication Oleksyszyn et al.[60] reported the synthesis of the homologue 32 (n = 2) and stated that '2-guanidinoethanephosphonic acid has been mentioned by

French workers but apparently was never obtained in pure form. The synthesis described was stimulated by a request from the Laboratoire de Biochemie Medicale, Universite de Bordeaux, for a sample of pure 2-guanidinoethanephosphonic acid, needed for biochemical studies'.

In order to obtain more information on the synthesis and identification of the homologues (32, n = 2 and 3) a copy of the thesis of Moreaud[61] was consulted and in fact no experimental details were reported for the preparation of 3-guanidinopropanephosphonic acid (32, n = 3). Moreaud[61] stated that a sample of 2-guanidinoethanephosphonic acid (32, n = 2) was donated to them by Oleksyszyn et al. and also that aminomethanephosphonic acid (32, n = 1) was synthesised as the hemihydrate (m.p. 321 ^{o}C) using the method described by Oleksyszyn et al.[38]

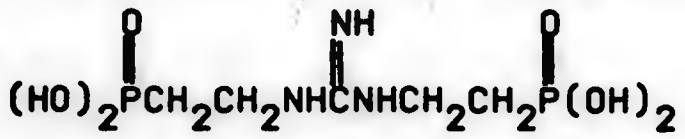
In view of these disparities in the literature it was decided to investigate the synthesis and characterisation of a series of ω-guanidinoalkanephosphonic acids, a suitable starting point being the synthesis of 2-guanidinoethanephosphonic acid (Scheme 27) as described by Oleksyszyn et al.[60]



(33)

(Scheme 27)

The product so obtained had a virtually identical melting point, 230-232 ^{o}C (lit. m.p. 228 ^{o}C),[60] although the elemental analysis (Table 6) indicated that it was not the required compound but the bis-phosphonic acid (34).



(34)

Table 6: Elemental analysis (%) for 33 and 34

Element	Calc. For 33	Calc. For 34	Found	
C	21.6	21.8	21.57,	21.55
H	6.0	5.5	5.60,	5.61
N	25.2	15.3	14.74,	14.72
P	18.6	22.6	22.63,	-

This unexpected result was explained by the fact that the molar ratio of O,O-diethyl 2-bromoethanephosphonate to guanidine used was 1 : 2 whereas a higher ratio may be necessary in order to prevent the formation of compounds such as 34. With this in mind an attempt was made to prepare a series of O,O-diethyl ω-bromoalkanephosphonates (35)(Scheme 28) for subsequent reaction with an large excess of guanidine.

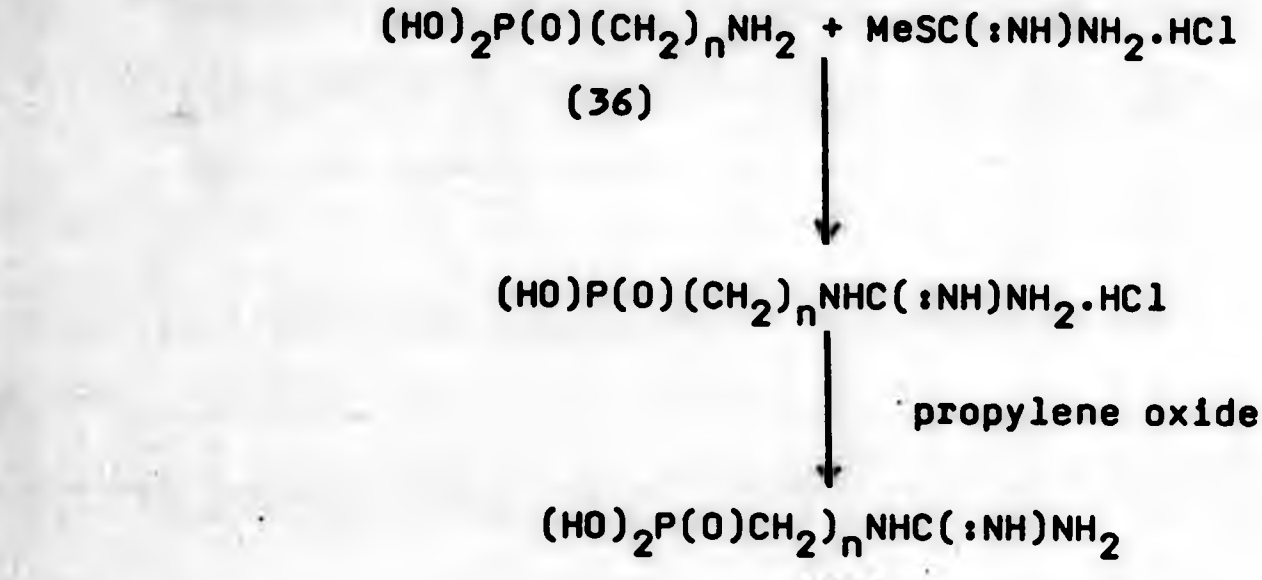
$$(EtO)_3P + Br(CH_2)_nBr \longrightarrow (EtO)_2P(O)(CH_2)_nBr + EtBr$$

(35)

(Scheme 28)

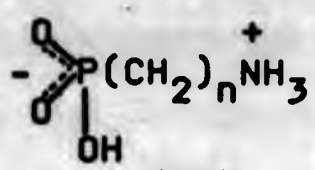
When 1,8-dibromo-octane was used to prepare the phosphonate (35, n = 8), ethyl bromide (70.2%) was evolved as expected and the excess of 1,8-dibromo-octane was distilled off under reduced pressure. Attempts to distil the residue were unsuccessful, however, due to gas evolution and decomposition which resulted in a thermoplastic, high melting, rubbery solid. This result is similar to that of Kosolapoff[62] who found that under the same conditions the product obtained using trimethylene dibromide decomposed on distillation.

It was therefore decided to attempt the preparation of the required ω-guanidinoalkanephosphonic acids from the corresponding ω-aminoalkanephosphonic acids (36) by reaction with S-methylisothiouronium chloride (Scheme 29). The reaction of S-methylisothiouronium salts with primary amines is well known.[10,63]



(Scheme 29)

However, no reaction occurred, this being thought to be attributable to the zwitterionic character of the ω-aminoalkanephosphonic acids. X-Ray crystallographic data[43-45] show that in the solid state the amino group is protonated (37) in comparable manner to that of the aminocarboxylic acids (38), and the same structure can be assumed to occur in aqueous solution.



(37)

(38)

It was therefore necessary to liberate the free primary amino group by addition of a base such as potassium hydroxide to allow conversion to a guanidine group using S-methylisothiouronium chloride. The proposed reaction scheme was:-

$$(HO)_2P(O)(CH_2)_nNH_2 + 2MeSC(:NH)NH_2.HCl + 4KOH$$

$$\downarrow$$

$$(KO)_2P(O)(CH_2)_nNH_2 + 2MeSC(:NH)NH_2 + 2KCl + 4H_2O$$

$$\downarrow \quad -MeSH$$

$$(KO)_2P(O)(CH_2)_nNHC(:NH)NH_2$$

$$\downarrow \quad \text{acidification (HCl)}$$

$$(HO)_2P(O)(CH_2)_nNHC(:NH)NH_2.HCl + 2KCl$$

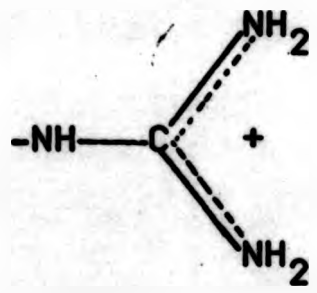
$$\downarrow \quad \text{propylene oxide}$$

$$(HO)_2P(O)(CH_2)_nNHC(:NH)NH_2$$

(32)

This synthetic route was employed successfully for a range of ω-aminoalkanephosphonic acids (36, n = 1, 2, 3, 4, 6 and 8). The reaction was carried out by dissolving the ω-aminoalkanephosphonic acid (1 mol. eq.), S-methyl-isothiouronium chloride (2 mol. eq.), and potassium hydroxide (4 mol. eq.) in water and heating the resultant solution at between 60 and 80 ^{o}C for 4 hours whilst the evolving methanethiol was collected in potassium permanganate traps. The reaction mixture was then acidified with concentrated hydrochloric acid until the pH was ca. 1 and the volatile components were distilled off on a rotary evaporator. The oily residue so formed was dissolved in methanol and the insoluble potassium chloride (ca. 75%) was filtered off. Addition of propylene oxide until the pH was 6 gave the required ω-guanidinoalkane-phosphonic acid as either a white solid or as a thick oily liquid. In either case the product was washed with methanol, crystallised from water-methanol and dried in a vacuum oven at ca. 60 ^{o}C to yield the required ω-guanidinoalkanephoshonic acid. It was desirable to dry the compounds in this way since air-drying, or drying in a desiccator, was not sufficient to remove the associated solvents completely.

These ω-guanidinoalkanephosphonic acids were found to be high melting (>200 ^{o}C) solids, insoluble in organic solvents and only soluble in aqueous media (acidic, basic or neutral). The compounds were characterised by elemental analysis, ^{1}H, ^{13}C and ^{31}P nmr spectroscopy, and also by FAB ms which revealed the M+1 ion as the base peak in each case. In addition a single crystal X-ray structure determination was performed on 32 (n = 3) which revealed the zwitterionic nature of the molecule as expected. Also a ^{15}N nmr spectrum of 4-guanidinobutane-phosphonic acid (32, n = 4) in D_2O/H_2O revealed the characteristic pattern of a guanidino group[42] with only two signals being present at -299.4 (NH) and -313.8 (NH_2) ppm (Fig. 8).



(Fig. 8)

Table 7: Elemental analysis (%), melting points and molecular weight data (FAB ms) for ω-guanidinoalkanephosphonic acids (32)

$$(HO)_2P(O)(CH_2)_nNHC(:NH)NH_2$$

(32)

Found

n	m.p. ^oC	C	H	N	P	$M+1]^+$
1	331-332	15.6	5.2	28.0	20.2	154
2	228-229	21.6	6.0	23.9	18.2	168
3	278	26.5	6.7	23.0	17.1	182
4	265-266	30.1	7.0	21.3	15.9	196
6	280-282	36.5	8.2	18.8	13.9	224
8	261	43.1	8.6	15.6	11.9	252

Requires

n	formula	C	H	N	P	Mol. wt.
1	$C_2H_8N_3O_3P$	15.7	5.2	27.5	20.3	153
2	$C_3H_{10}N_3O_3P$	21.6	6.0	25.1	18.6	167
3	$C_4H_{12}N_3O_3P$	26.5	6.6	23.2	17.1	181
4	$C_5H_{14}N_3O_3P$	30.8	7.2	21.5	15.9	195
6	$C_7H_{18}N_3O_3P$	37.7	8.1	18.8	13.9	223
8	$C_9H_{22}N_3O_3P$	43.0	8.8	16.7	12.3	251

2.2 SPECTRAL PROPERTIES OF ω-GUANIDINOALKANEPHOSPHONIC ACIDS

From a literature review of these compounds it was evident that their positive identification could not be carried out entirely by the previously accepted methods of infrared, ^{1}H nmr sectroscopy and elemental analysis. It was therefore decided to examine other spectral properties, in particular their ^{13}C and ^{31}P nmr spectra.

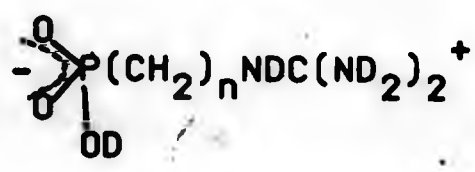
2.2.1 ^{13}C AND ^{31}P nmr SPECTROSCOPY OF ω-GUANIDINOALKANEPHOSPHONIC ACIDS

The ^{31}P chemical shifts in aqueous solution lie in the expected range for phosphonic acid derivatives (between 14 and 27 ppm downfield from 85% H_3PO_4), the extent of shielding of phosphorus decreasing with increasing chain length, i. e. as the guanidinium group becomes removed further from phosphorus (the opposite of what would be expected on the basis of electronegativity effects).

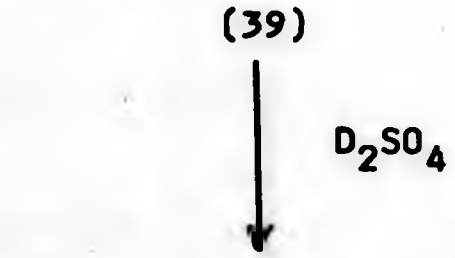
From Table 8 we can see that the chemical shift of the phosphorus moves downfield on addition of sulphuric acid-d_2 indicating that the phosphorus species has changed from that of a zwitterionic form (39) to that of 40 (Scheme 30).

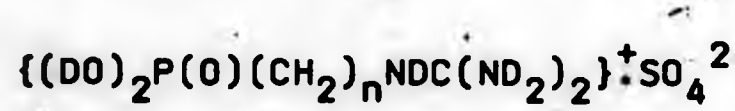
Table 8: Effect of addition of D_2SO_4 on the ^{31}P chemical shifts (ppm) of the ω-guanidinoalkanephosphonic acids

n	D_2O	$D_2O+D_2SO_4$
1	14.2	19.0
2	20.6	28.8
3	24.7	38.6
4	25.7	35.2
6	27.1	33.2
8	-	39.3



(39)





(40)

(Scheme 30)

On the addition of acid the zwitterion (39) would be converted to form 40 and hence the phosphorus becomes less shielded and the chemical shift moves downfield. We would also expect the phosphorus to influence the neighbouring atoms in a different way in these two forms and this effect is illustrated below (Tables 9 and 10).

Table 9: ^{13}C nmr phosphorus-carbon coupling constants (Hz) for ω-guanidinoalkanephosphonic acids in D_2O and D_2O/D_2SO_4 solution

	D_2O			D_2O/D_2SO_4		
n	$^1J_{PC}$	$^2J_{PCC}$	$^3J_{PCCC}$	$^1J_{PC}$	$^2J_{PCC}$	$^3J_{PCCC}$
1	145.2	-	-	149.9	-	-
2	131.6	0.0	-	136.3	2.7	-
3	134.3	4.1	17.0	137.0	4.1	19.7
4	133.3	4.4	16.2	135.0	4.7	16.3
6	133.1	4.3	16.5	-	-	-
8	-	-	-	132.9	5.4	17.0

From Table 9 it can be seen that addition of D_2SO_4 to the solution results in a significant increase in the phosphorus-carbon coupling values thereby confirming that the phosphorus is now in a different chemical environment. However, this does not necessarily imply that the reason for these changes is due to the zwitterionic nature of these compounds. If these compounds were zwitterions in solution then the guanidine group would be in a protonated

state and as such its chemical shift would not be expected to alter on addition of acid, while the chemical shift of the PCH_2 carbon would be expected to be different by a significant amount.

Table 10: Comparison of the ^{13}C chemical shifts (ppm) of ω-guanidinoalkanephosphonic acids in D_2O and D_2O/D_2SO_4 solution

	D_2O		$D_2O+D_2SO_4$	
n	PCH_2	Guanidine	PCH_2	Guanidine
2	30.4	159.6	29.1	160.2
3	27.7	159.8	25.6	159.6
4	30.1	159.9	27.9	159.8

The results in Table 10 show that on addition of D_2SO_4 the chemical shift of the PCH_2 carbon moves upfield by up to 2.2 ppm while that of the guanidine carbon is relatively unaffected thereby confirming that these ω-guanidinoalkanephosphonic acids are present as zwitterionic species when in aqueous solution.

An interesting feature of the ^{13}C nmr spectra of these compounds is the way the coupling constant varies along the alkyl chain (Table 9). Except for the first member of this series, guanidinomethanephosphonic acid, in which both the phosphonic and guanidine groups are bonded to the same carbon atom (this compound is also the first member

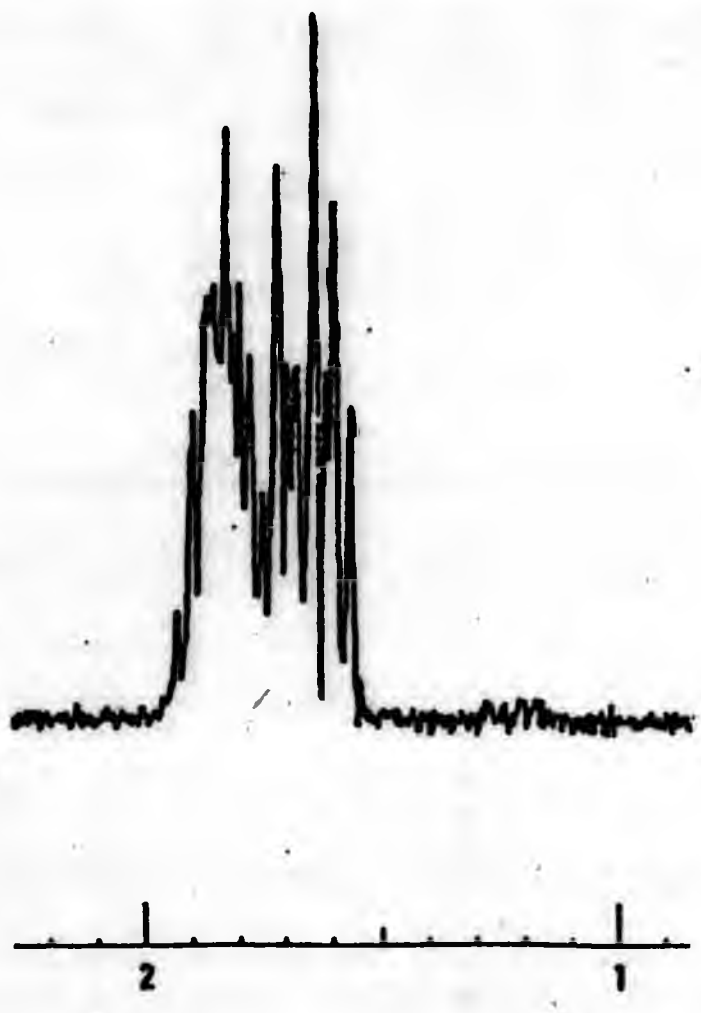
of the homologous series of 1-guanidinoalkanephosphonic acids discussed earlier) the $^{1}J_{PC}$ value appears to be about 133 Hz (Table 9). However, the $^{2}J_{PCC}$ values are ca. 4 Hz except for 2-guanidinoethanephosphonic acid for which it was found to be zero. The $^{3}J_{PCCC}$ coupling constants for these compounds are larger than the corresponding $^{2}J_{PCC}$ values (c.f. 1-guanidinoalkanephosphonic acids, Chapter 1).

2.2.2 ^{1}H nmr SPECTRA OF ω-GUANIDINOALKANEPHOSPHONIC ACIDS

Since these ω-guanidinoalkanephosphonic acids were found to be insoluble in organic solvents the ^{1}H nmr spectra were recorded as solutions, in D_2O. The effect was, however, that the $P(OH)_2$ and $NHC(:NH)NH_2$ protons were not observed since they rapidly exchanged with the deuterium atoms of the D_2O. Therefore the only signals observed in the ^{1}H nmr experiment were those due to the hydrogens of the methylene chain. Even so, the ^{1}H nmr spectra of these compounds vary suprisingly in complexity.

For guanidinomethanephosphonic acid the ^{1}H nmr spectrum reveals the CH_2 group as a doublet ($^{2}J_{PCH}$ 12.2 Hz). The spectrum of 2-guanidinoethanephosphonic acid was, however, much more complicated with the PCH_2 group being revealed as an overlapping doublet of triplets ($^{3}J_{HCCH}$ 7.8 Hz, $^{2}J_{PCH}$ 17.1 Hz) and the CH_2N protons as a complex multiplet whereas a further doublet of triplets

was expected. The 80 MHz ^1H nmr of 3-guanidinopropane-phosphonic acid revealed very little structural information since the PCH_2CH_2 protons were observed as a broad multiplet. At 220 MHz the multiplet was replaced by two overlapping complex multiplets which were second order (Fig. 9).



(Fig. 9)

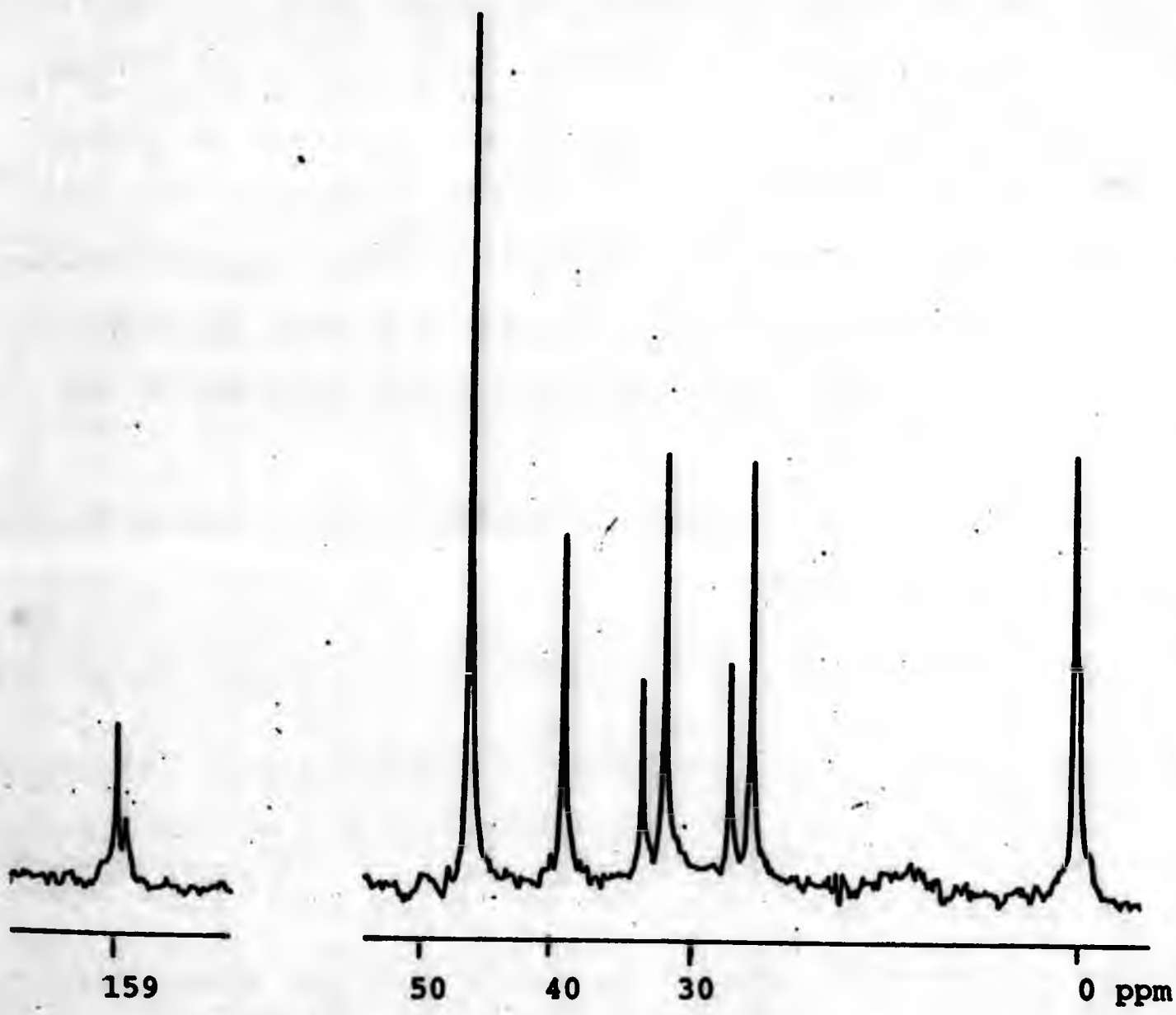
The longer-chain compounds of this series gave spectra which consist of a broad multiplet centered at ca. 1.5 ppm and a triplet at ca. 3.2 ppm. Therefore it can be concluded that for this series of compounds ^1H nmr has limited use for identification of the structure.

2.2.3 INFRARED SPECTROSCOPY OF ω-GUANIDINOALKANEPHOSPHONIC ACIDS

Although infrared spectroscopy is a powerful tool for the organic chemist, the infrared spectra of the guanidinophosphonic acids are of limited value for the identification of these compounds. They are characterised by a broad diffuse band from about 2500-3700 cm^{-1}, strong bands at 1600-1700 cm^{-1} (NH and NH_2) and by P-OH and P-O bands at 900, 1070 and 1260 cm^{-1} which are difficult to assign with certainty.

Infrared was nevertheless useful in these particular syntheses as an indication of whether the amino group had been successfully converted to a guanidino group. A comparison of the spectrum of the product of the reaction with that of the corresponding ω-aminoalkane-phosphonic acid shows a marked difference in the region 1600-1700 cm^{-1} if a guanidine group is present.

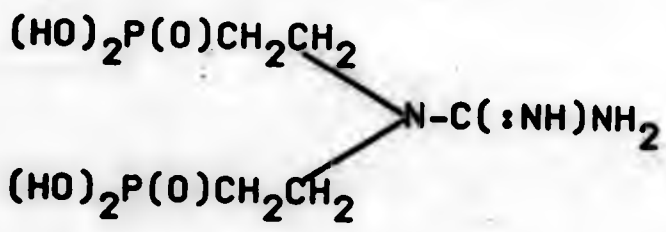
Having prepared this series of compounds and examined their spectral characteristics and having found some characteristic trends, the anomalous product obtained on repeating the method described by Oleksyszyn *et al.*[60] for the preparation of 2-guanidinoethanephosphonic acid, was re-examined. The ^{13}C nmr spectrum indicated that there were in fact two compounds present (Fig. 10).



(Fig. 10)

The minor species appeared to be 2-guanidino-ethanephosphonic acid (33) by comparison with the ^{13}C spectrum of the authentic compound, whilst FAB ms revealed that the major component of the mixture had a molecular weight of 275, confirming a diphosphonic acid of formula $C_5H_{15}N_3O_6P_2$.

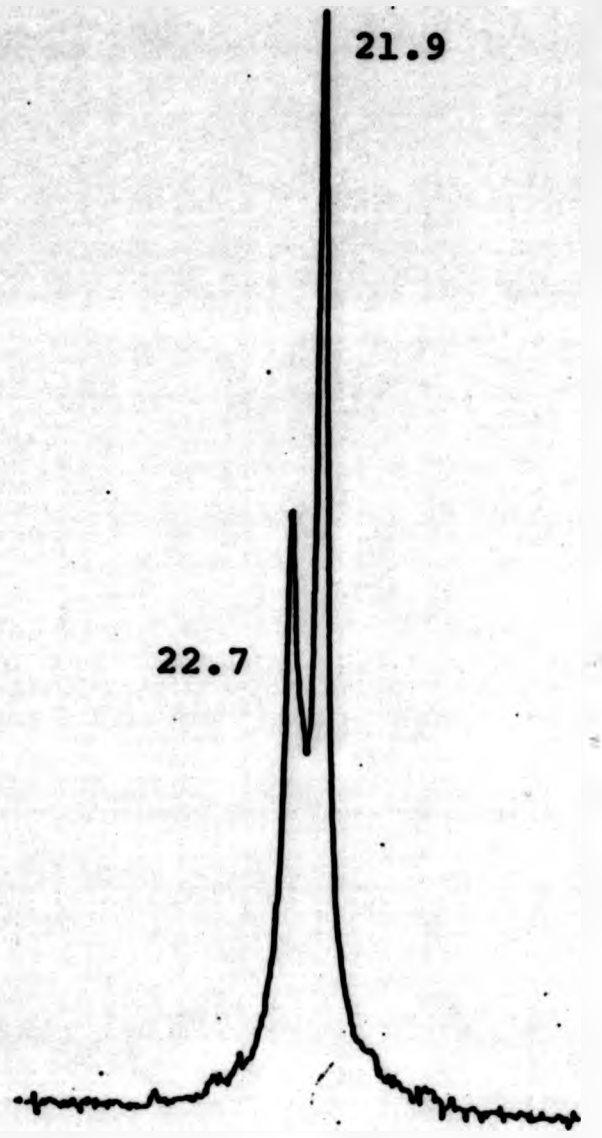
A re-examination of the ^{13}C nmr spectrum showed that while there was little difference between the chemical shifts of the PCH_2 or guanidine carbons of either compound in the mixture there was a large difference (7.1 ppm) in the chemical shifts of the CH_2-guanidine carbons which suggested that the structure of the bis-phosphonic acid was in fact not 34 but could possibly be 41.



(41)

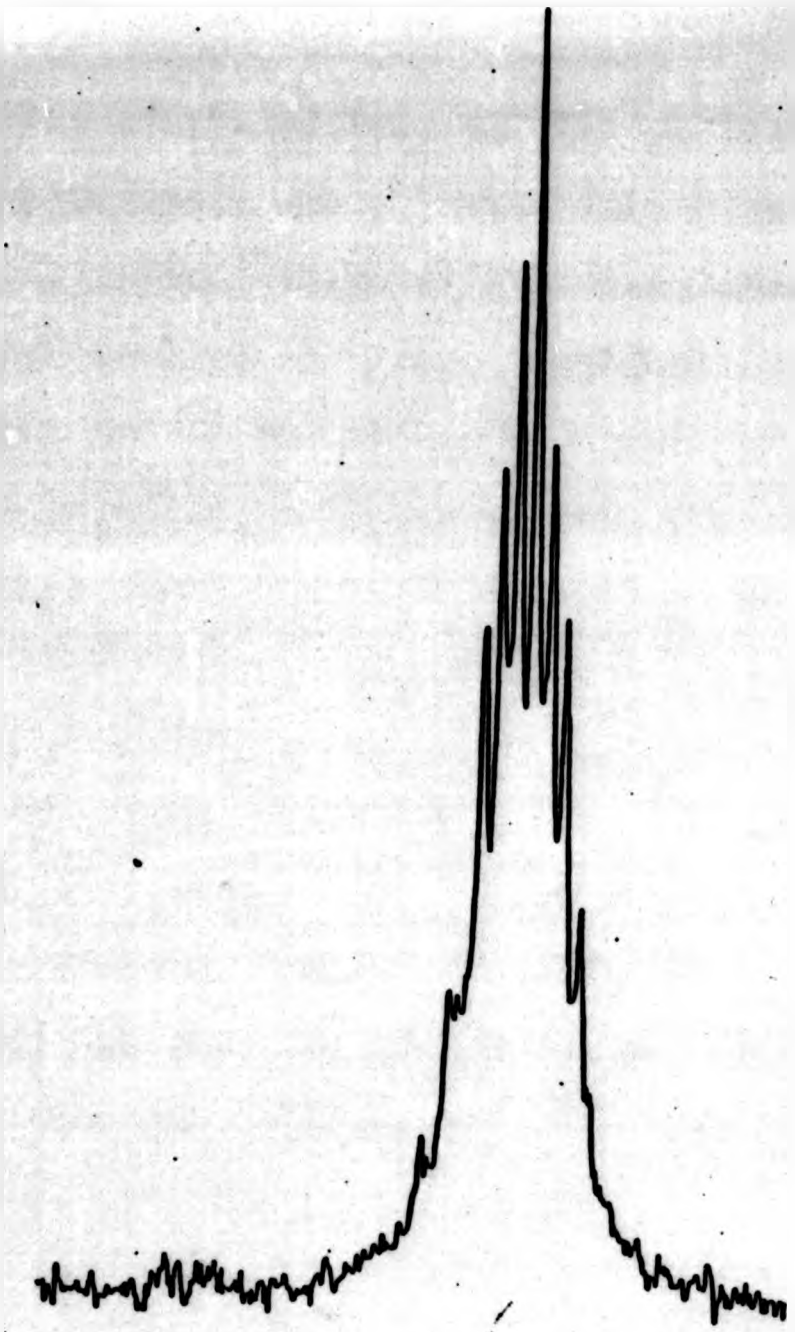
The $^{31}P-\{^{1}H\}^{bb}$ nmr spectrum of this mixture in D_2O also showed the presence of two components, with one major peak at 21.9 ppm and one minor peak at 22.7 ppm (Fig. 11). Oleksyszyn *et al.*[60] reported a ^{31}P chemical shift of 21.2 ppm for the product he obtained whereas the authentic sample of 33 prepared in the present work work had a

chemical shift of 20.6 ppm (both samples recorded in D_2O).



(Fig. 11)

An attempt to determine the composition of the mixture from the relative areas for each species by integration of the ^{31}P spectrum (proton coupled), was unsuccessful as there was complete overlap of the signals (Fig. 12).



(Fig. 12)

Normally integration of $^{31}P-\{^{1}H\}^{bb}$ spectra is not meaningful since phosphorus species which are in different chemical environments are subject to different Nuclear Overhauser Enhancements (NOE's) and also different relaxation times (T1's). In this case however, since both phosphorus species are in similar enviroments (PCH_2CH_2) the NOE can be assumed to be the same in each case. We cannot assume, however, the T1's to be equal for the two

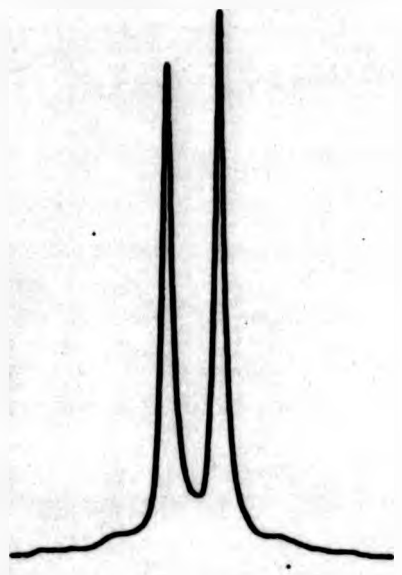
components of the mixture as the zwitterionic nature of the diphosphonic acid (41) would be expected to be different from that of the mono-analogue (33). The possibilities of internal protonation are different in each case due to the different ratio of available sites for protonation (nitrogens) to the donating species, $P(O)(OH)_2$. The $^{31}P-\{^1H\}^{bb}$ spectra of 33 and of the mixture were therefore rerun in a mixture of D_2O/D_2SO_4 so that all the phosphonic acid species present would be fixed as $(DO)_2P(O)(CH_2)_2$-. As expected, there was a substantial change in the chemical shift of each of the species present (Table 11). Therefore, as both species would now be in similar chemical environments it was assumed for the purposes of this investigation that their respective T1's would be the same.

Table 11: Comparison of $^{31}P-\{^1H\}^{bb}$ chemical shifts (ppm)

SOLVENT	(33)	MIXTURE
D_2O	20.6	21.9, 22.7
D_2O/D_2SO_4	28.8	27.4, 28.3

The relative areas of each peak were found to be in a ratio of 1:3.2 which gave the composition of the mixture as 72.4% : 27.6% for 41 and 33 respectively.

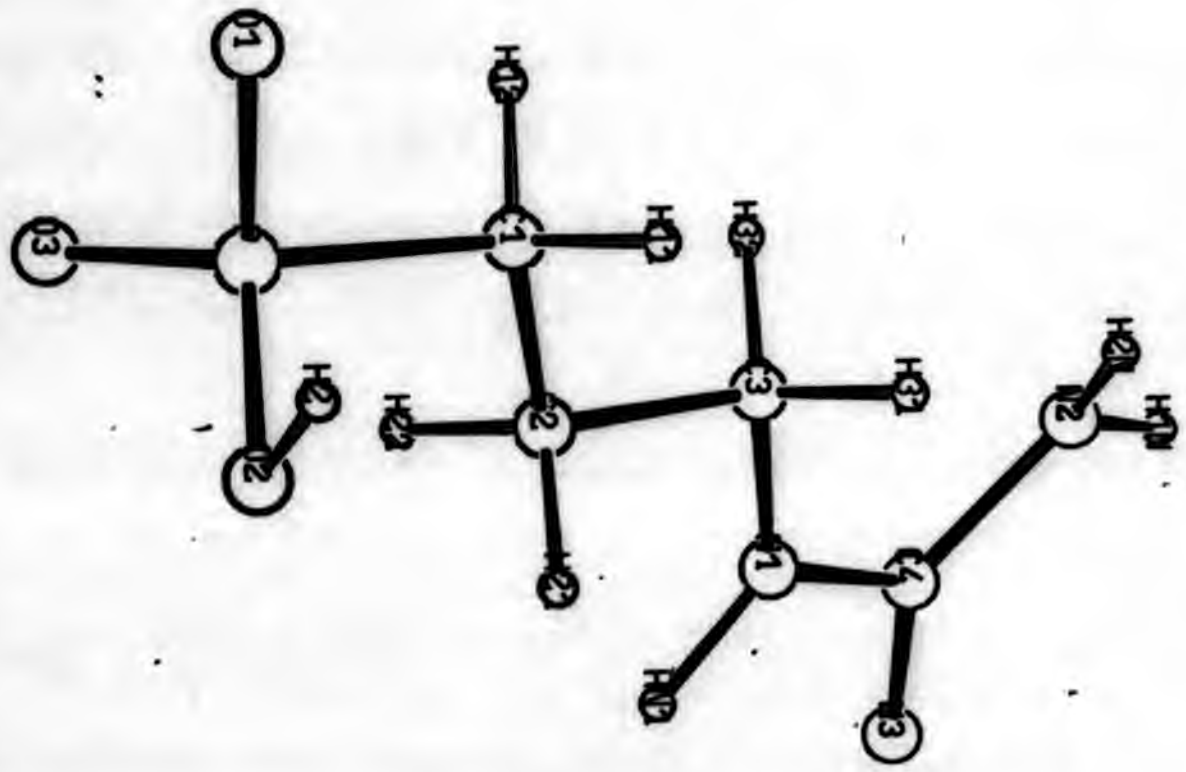
It was confirmed that the minor component of the mixture was 2-guanidinoethanephosphonic acid (33) by adding a sample of authentic 33 to the nmr solution, when the signal for the minor component increased, (Fig. 13).



(Fig. 13)

2.2.4 CRYSTAL STRUCTURE OF 3-GUANIDINOPROPANEPHOSPHONIC ACID

The structure of 3-guanidinopropanephosphonic acid was determined by X-ray crystallography (Fig. 14).



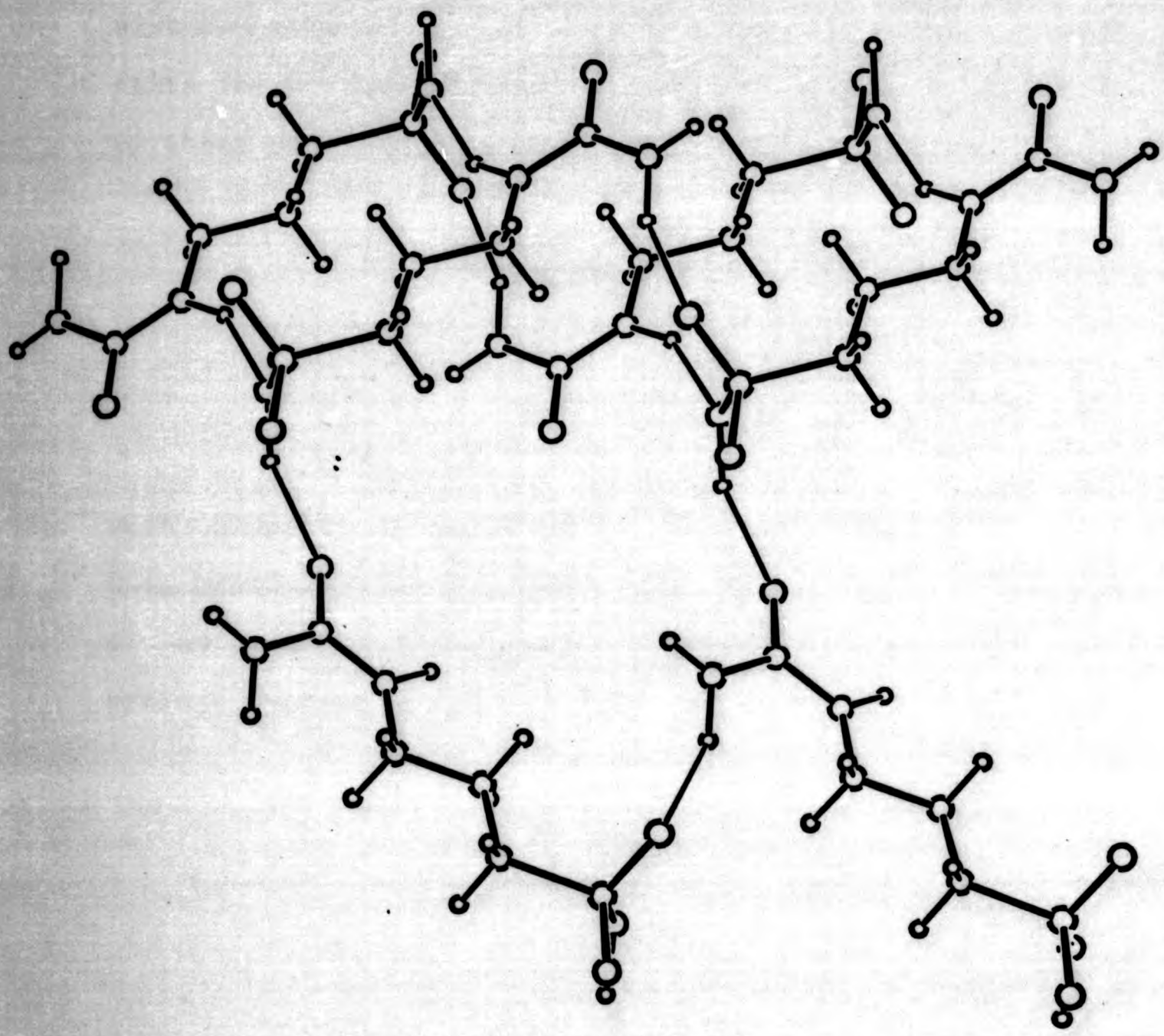
(Fig. 14)

Table 12: Bond lengths (Å) about phosphorus in aminoalkane-phosphonic acids and in 1- and 3-guanidinopropane-phosphonic acid

Formula	P-C	P-OH	P-O	P-O	ref.
XCH_2NH_2	1.82	1.51	1.51	1.49	43
$XCH_2CH_2NH_2$	1.80	1.51	1.51	1.50	44
$XCH_2CH_2CH_2NH_2$	1.81	1.53	1.53	1.51	45
$XCH_2NHCH_2CO_2H$	1.82	1.50	1.50	1.50	46
$XCH_2NHCH_2CO_2H$	1.82	1.50	1.50	1.50	47
$XCH(Et)NHC(:NH)NH_2$	1.81	1.52	1.59	1.50	-
$X(CH_2)_3NHC(:NH)NH_2$	1.81	1.52	1.54	1.51	-

$X = (HO)_2P(O)$

The bond lengths we determined for 3-guanidinopropanephosphonic acid (Table 12) agree well with the literature values. The co-ordination around phosphorus departs from the regular tetrahedron, the angles varying between 105.2 ^{o} to 114.4 ^{o}; the average of the six angles is 109.4 ^{o} (for Tables of bond lengths and angles see appendix). The guanidino group is planar, with the three C-N bond lengths about the guanidino carbon being 1.38, 1.32 and 1.40 Å with the sum of the three angles being 359 ^{o}. There is extensive intermolecular hydrogen bonding in this compound (Fig. 15).



(Fig. 15)

2.3 SYNTHESIS OF ω-AMINOALKANEPHOSPHONIC ACIDS

In order to prepare the aforementioned ω-guanidinoalkanephosphonic acids it was first necessary to synthesise the corresponding ω-aminoalkanephosphonic acids (36) as their precursors.

$(HO)_2P(O)(CH_2)_nNH_2$

(36)

Compounds 36 (n = 1 to 5) are known and have been prepared by the Michaelis-Arbuzov condensation of an N-(ω-bromoalkyl)phthalimide (42) with a trialkyl phosphite or sodium dialkyl phosphite, followed by hydrolysis of the product (Scheme 31).[64-66]

$Br(CH_2)_nNPht$

(42)

↓ $(RO)_3P$ or $(RO)_2P(O)Na$

$(RO)_2P(O)(CH_2)_nNPht$

↓ H^+/H_2O

$(HO)_2P(O)(CH_2)_nNH_2$

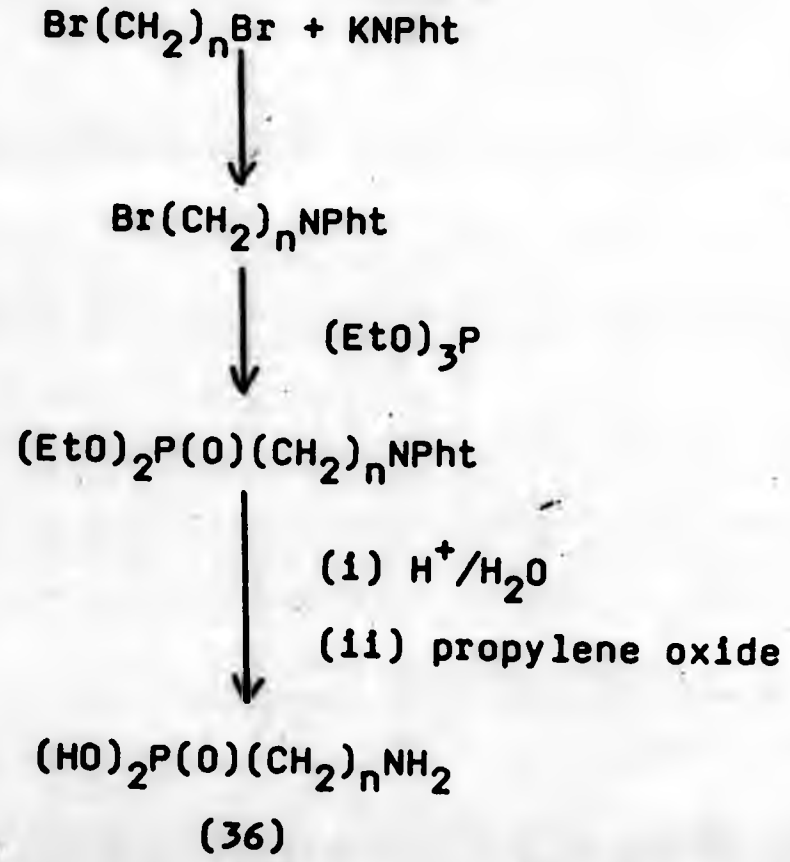
(36)

(Scheme 31)

NPht = phthalimido

N-(ω-Bromoalkyl)phthalimides (42) are known compounds and homologues in which the alkyl chain contains 1 to 4 carbon atoms are readily available.[67] However, since we were interested in preparing a range of ω-amino-alkanephosphonic acids with long as well as short chain lengths a general synthetic scheme starting from readily available reagents was required.

A feasible synthetic route to these compounds (36) appeared to be that using the readily accessible α,ω-dibromoalkanes (Scheme 32), but when an excess of 1,8-dibromo-octane and potassium phthalimide were allowed to



(36)

(Scheme 32)

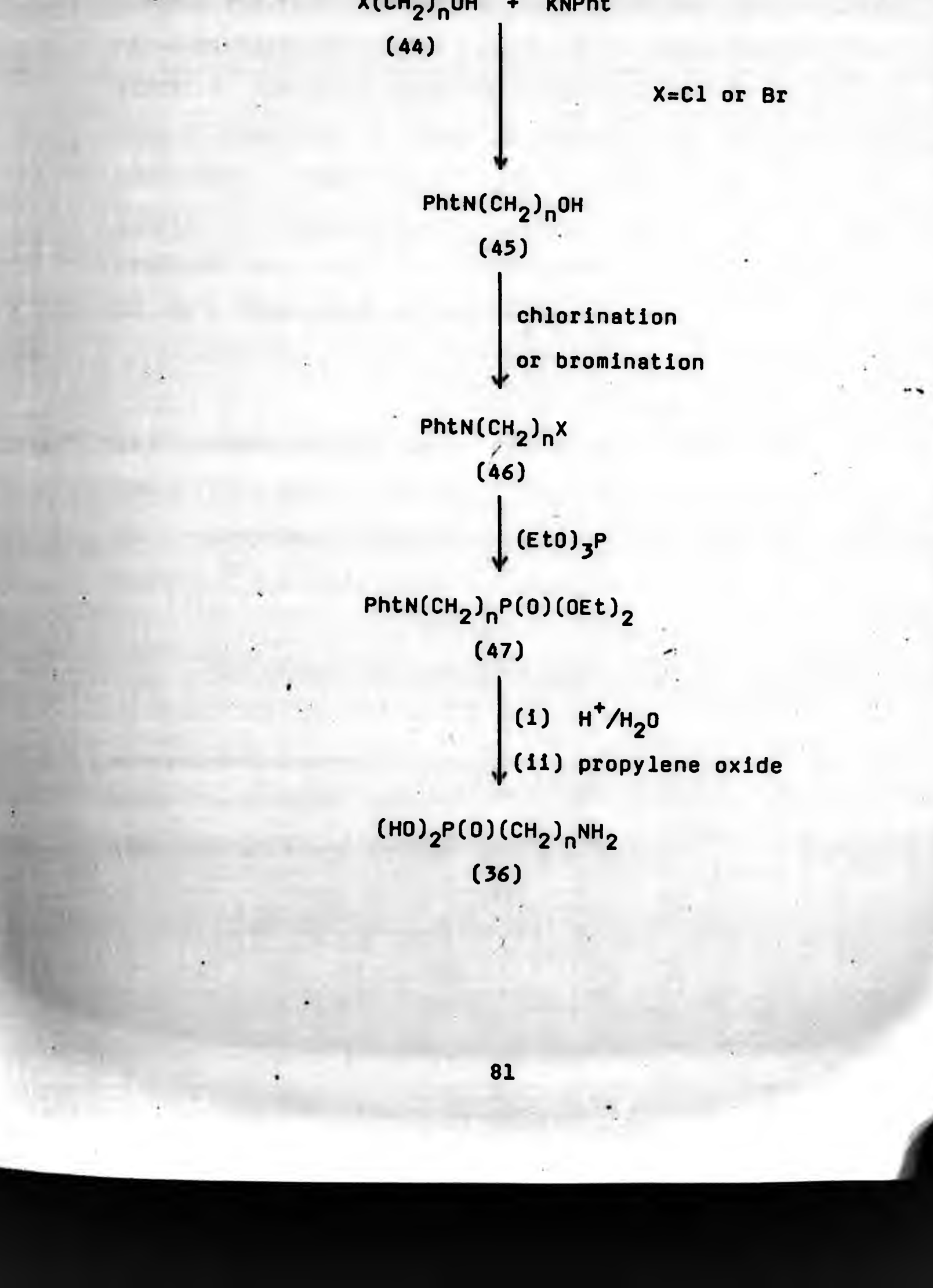
react under reflux in dimethylformamide, the only isolated product was the diphthalimido derivative (43, n = 8).

$$PhtN(CH_2)_nNPht$$

(43)

Ing and Mannske[68] have reported the analogous reaction of trimethylene dibromide with potassium phthalimide and found that the bromide (42, n = 3) was isolated in a yield of 38% whilst the diphthalimide (43, n = 3) was obtained in 14.6% yield starting from 1000g of trimethylene dibromide.

In view of these problems it became obvious that a monofunctional halogen compound such as 44 would be more suitable for the initial reaction with phthalimide and the following reaction scheme was proposed.



This scheme was first used with 6-chlorohexan-1-ol (44, n = 6), prepared from 1,6-hexanediol as described by Coleman and Bywater.[69] Condensation with potassium phthalimide gave N-(6-hydroxyhexyl)phthalimide (45, n = 6) as a white waxy solid which was subsequently treated with thionyl chloride to form the chloro analogue, N-(6-chlorohexyl)phthalimide (46, n = 6, X = Cl). Condensation with triethyl phosphite under the conditions of the Michaelis-Arbuzov reaction, followed by removal of the volatile components, hydrolysis with hydrochloric acid, and subsequent treatment with propylene oxide then gave the required compound, 6-aminohexanephosphonic acid (32, n = 6), as a fine white crystalline solid.

Similarly, 8-chloro-octan-1-ol and 11-bromoundecan-1-ol were converted to the phthalimido derivatives (45, n = 8 or n = 11), and brominated using the Vilsmeier reagent, bromomethylenedimethylammonium bromide,[70] to yield 46 (n = 8 or 11, X = Br).

The readily available bromoalkylphthalimides (46, n = 1,2,3 and 4) were obtained[67] and were converted to the corresponding ω-aminoalkanephosphonic acids along with the bromo homologues described above, to yield a series of compounds of varying chain length (Table 13).

Table 13: Elemental analysis (%), melting points and molecular weight data (FAB ms) for ω-amino-alkanephosphonic acids (36)

Found

n	m.p. °C	C	H	N	P	M+1[1+]
1	328	10.1	5.1	12.6	27.8	112
2	272-273	19.3	6.4	11.2	24.5	126
3	278	25.9	7.0	10.5	21.8	140
4	275	30.1	7.8	9.0	20.3	154
6	274	39.4	8.6	7.9	17.2	182
8	254-255	45.5	9.3	7.8	-	210
11	256	-	-	-	-	252

Requires

n	formula	C	H	N	P	Mol. wt.
1	CH_6NO_3P	10.8	5.4	12.6	27.9	111
2	$C_2H_8NO_3P$	19.2	6.4	11.2	24.8	125
3	$C_3H_{10}NO_3P$	25.9	7.2	10.1	22.3	139
4	$C_4H_{12}NO_3P$	31.4	7.8	9.1	20.3	153
6	$C_6H_{16}NO_3P$	39.8	8.8	7.7	17.1	181
8	$C_8H_{20}NO_3P$	45.9	9.3	6.7	14.8	209
11	$C_{11}H_{26}NO_3P$	52.6	10.4	6.7	12.4	251

These compounds were identified by elemental analysis, ^{1}H, ^{13}C, and ^{31}P nmr spectroscopy and FAB ms which revealed the M+1 ion as the base peak in each case. The ω-aminoalkanephosphonic acids were found to be high melting zwitterionic compounds, insoluble in organic solvents and only soluble in aqueous media (acidic, basic or neutral).

There are several references to the preparation of aminomethanephosphonic acid (36, n = 1) each quoting a different melting point, i.e. 268.5 °,[18] 296-399 °,[73] 308-310 °,[74] 310 °,[75] 318-320 ° (decomp.)[76] and 325-330 °C[77] whereas the product obtained in the present work melted at 328 °C.

A review of the literature revealed that while 2-aminoethanephosphonic acid (36, n = 2) is a well-known compound as a consequence of its being isolated from many forms of life, including man,[71,72] the other members of the series are not so well known.

Kosolapoff[13] prepared 3-aminopropanephosphonic acid (36, n = 3) from 3-bromopropanephosphonic acid and ammonium hydroxide and recorded a melting point of 274 °C which is close to our own figure of 278 °C.

Chavane[65] prepared a series of ω-aminoalkanephosphonic acids (36, n = 2,4,5 and 10). However, it would appear from the melting points recorded by him that the compounds were never obtained in a pure form and in some cases were probably not the expected compound.

For 2-aminoethanephosphonic acid (36, n = 2) Chavane recorded m.p. 250 °C[65] whereas we found m.p. 272-273 °C. However, the literature revealed the following melting points for this compound:- 262-5 °,[78] 270 °,[79] 274-6 °,[80] 280-1 °,[81] 281-2 °,[82] 282-3 °,[83] 285 °,[13] 295-7 °,[84] and 296-9 °C.[85]

For 4-aminobutanephosphonic acid (36, n = 4) he found m.p. 133-134 °C which we thought to be rather low for a zwitterionic compound of this type. 4-Aminobutanephosphonic acid prepared by us was found to have m.p. 275 °C. Chavane[65] did not isolate 5-aminopentanephosphonic acid (36, n = 5) in the pure state, only as the barium salt for which no data were reported.

Chavane[65] found 10-aminodecanephosphonic acid (36, n = 10) to melt at 35-36 °C which appears to be impossibly low for a compound of this class, especially in view of the fact that our homologue 11-aminoundecanephosphonic acid (36, n = 11) was found to have m.p. 256 °C.

In the course of the preparation of 4-aminobutanephosphonic acid (36, n = 4) a sample of the intermediate O,O-diethyl 4-phthalimidobutanephosphonate (47, n = 4) was isolated as a white waxy solid m.p. 67-71 ^{o}C and characterised by the usual methods.

$$PhtN(CH_2)_nP(O)(OEt)_2$$

(47)

2.4 SPECTRAL PROPERTIES OF ω-AMINOALKANEPHOSPHONIC ACIDS

From tables 14 and 15 it can be seen that on addition of D_2SO_4 the chemical shift of the phosphorus moves downfield and the phosphorus-carbon coupling constants increase (as noted earlier for the ω-guanidino derivatives) thereby confirming that the chemical environment of the phosphorus has changed.

Table 14: Comparison of the ^{31}P chemical shifts (ppm) of ω-aminoalkanephosphonic acids in D_2O and D_2O/D_2SO_4 solution

n	D_2O	D_2O/D_2SO_4
1	11.0	15.4
2	18.8	26.5
3	23.7	31.1
4	25.9	34.5
6	26.7	33.3
8	-	39.0
11	-	41.2

Table 15: ^{13}C nmr Phosphorus-carbon coupling constants (Hz) for ω-aminoalkanephosphonic acids in D_2O and D_2O/D_2SO_4 solution

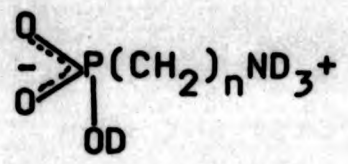
	D_2O			D_2O/D_2SO_4		
n	$^1J_{PC}$	$^2J_{PCC}$	$^3J_{PCCC}$	$^1J_{PC}$	$^2J_{PCC}$	$^3J_{PCCC}$
1	141.9	-	-	149.9	-	-
2	131.6	0.0	-	139.0	0.0	-
3	135.5	4.3	17.7	137.7	4.7	20.3
4	133.8	4.4	16.9	135.0	4.7	17.0
6	133.1	4.4	16.2	132.2	5.3	17.0
8	-	-	-	132.2	5.4	17.0

We see from Table 16 that while addition of D_2SO_4 results in a change in the chemical shift of the PCH_2 carbon by ca. 2ppm there is very little change in the chemical shift of the CH_2NH_2.

Table 16: Comparison of ^{13}C nmr chemical shifts (ppm) for ω-aminoalkanephosphonic acids in D_2O and D_2O/D_2SO_4 solution

	D_2O		D_2O/D_2SO_4	
n	PCH_2	CH_2NH	PCH_2	CH_2NH_2
1	41.3	-	37.6	-
2	28.9	38.5	27.3	37.9
3	27.9	43.3	25.8	42.9
4	30.0	42.0	27.5	42.2

Therefore we can conclude that in solution in D_2O ω-aminoalkanephosphonic acids are zwitterionic species having the structure (48).



(48)

2.5 FAB MASS SPECTROMETRY OF ω-AMINO- AND ω-GUANIDINO-ALKANEPHOSPHONIC ACIDS

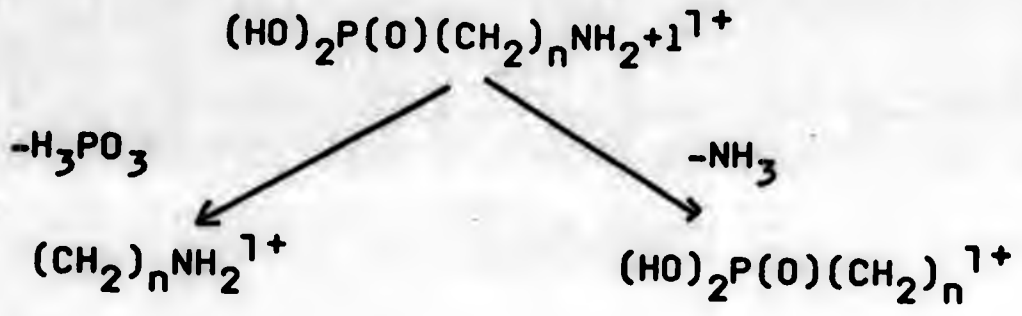
As we have seen for the 1-amino- and 1-guanidino-alkanephosphonic acids the M+1 ions are very strong, and for the ω-amino- and ω-guanidino-alkanephosphonic acids they are the base peaks in every case (Table 17).

Table 17: Relative intensities (%) of molecular ion signals for ω-amino- and ω-guanidino-alkanephosphonic acids

$(HO)_2P(O)(CH_2)_nNH\text{-}X$

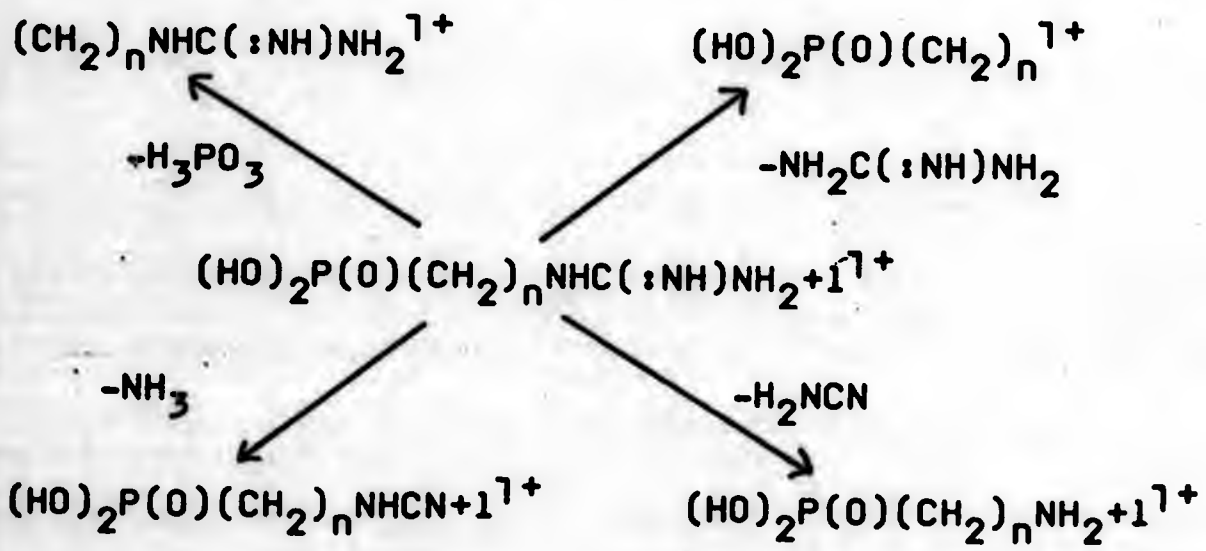
n	X	$M+1^{1+}$	$2M+1^{1+}$	$M+G+1^{1+}$	$M+2G+1^{1+}$
1	H	100	2.1	48.3	7.7
1	$C(:NH)NH_2$	100	5.5	12.8	3.0
2	H	100	4.8	34.5	8.1
2	$C(:NH)NH_2$	100	18.8	7.9	1.6
3	H	100	3.7	23.2	7.2
3	$C(:NH)NH_2$	100	2.6	4.2	4.2
4	H	100	13.8	12.9	2.3
4	$C(:NH)NH_2$	100	3.2	6.5	0.0
6	H	100	7.8	8.5	2.4
6	$C(:NH)NH_2$	100	2.5	2.8	0.7
8	H	100	2.4	-	-
11	H	100	-	-	-

The fragmentation of the ω-aminoalkanephosphonic acids is quite simple (Scheme 33), involving initial loss of either the phosphonic, or the amino group.



(Scheme 33)

However, the fragmentation of the ω-guanidinoalkanephosphonic acids is more complex as the guanidino group may be lost as such or it may fragment by the loss of ammonia or cyanamide (Scheme 34).



(Scheme 34)

CHAPTER 3

PREPARATION AND REACTIONS OF 1-CHLOROALKANEPHOSPHONIC ACIDS WITH NUCLEOPHILES

3.1 SYNTHESIS OF 1-CHLOROALKANEPHOSPHONIC ACIDS

In view off the difficulties experienced in the synthesis of long-chain 1-amino- and 1-guanidino-alkanephosphonic acids it was decided to seek an alternative method of preparation via the reactions of 1-chloroalkanephosphonic acids (49) with amines or guanidines (Scheme 35).

$(HO)_2P(O)CH(R)Cl$

(49)

$\downarrow$ R^1NH_2

$(HO)_2P(O)CH(R)NHR^1$

(50)

R^1 = alkyl, $NH_2C(:NH)$-, R-NHC(:NH)-

(Scheme 35)

1-Chloroalkanephosphonic acids (49) have been known for nearly a century,[86] and have been prepared by chlorination of the analogous 1-hydroxyalkanephosphonic acids (51).

$(HO)_2P(O)CH(R)OH$

(51)

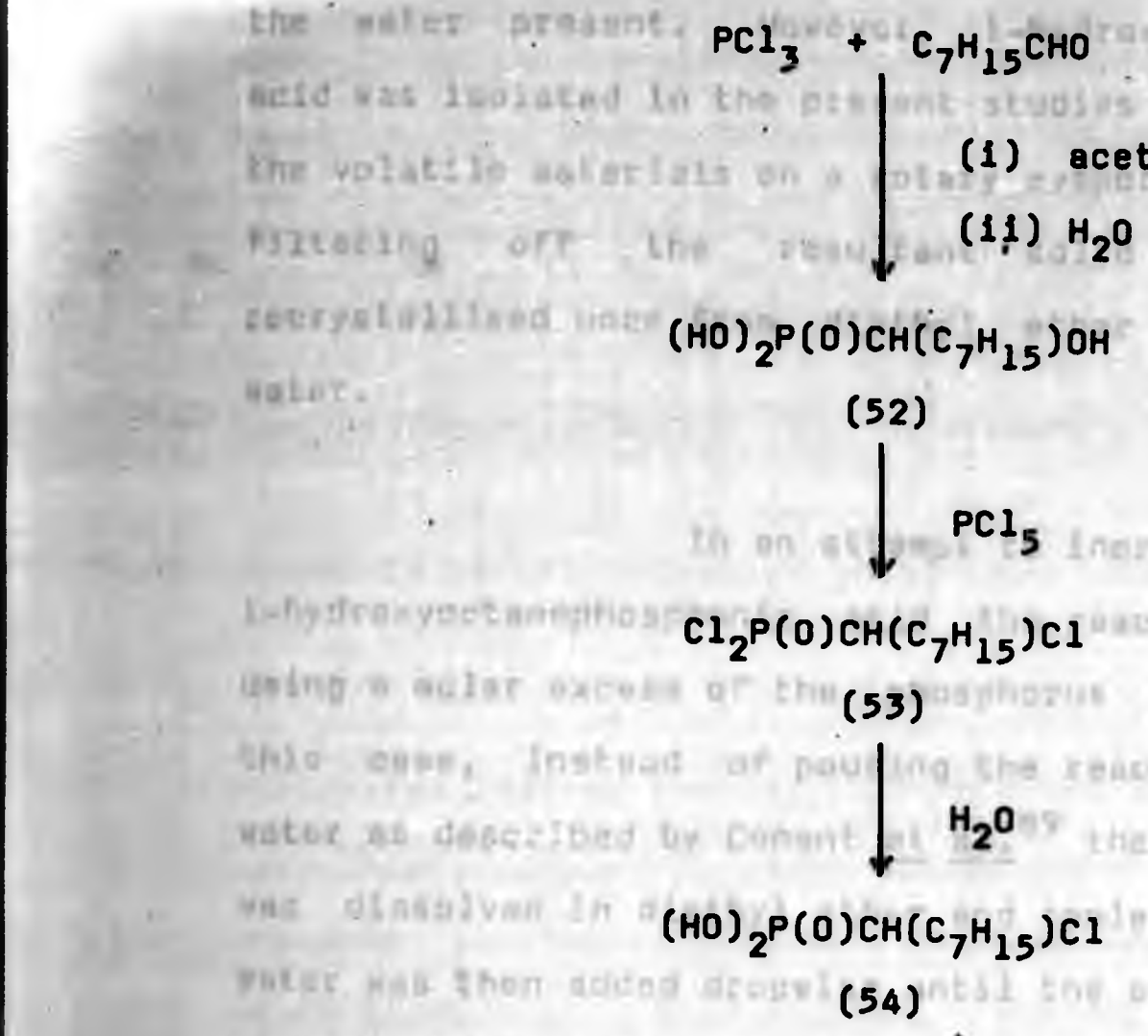
1-Hydroxyalkanephosphonic acids were first prepared by Fosseck[87,88] and later by Conant, MacDonald and Kinney[89] from the corresponding aldehydes (Scheme 36). As the present work was concerned mainly with the longer chain derivatives the first step was to prepare 1-hydroxy-

$$PCl_3 + RCHO \xrightarrow[\text{(ii) } H_2O]{\text{(i) Acetic acid}} (HO)_2P(O)CH(R)OH$$

(51)

(Scheme 36)

octanephosphonic acid (51, R = C_7H_{15}) by the method described by Conant et al.[89] and then to chlorinate this compound by the method of Fosseck,[86] to give the previously unknown homologue, 1-chloro-octanephosphonic acid (54, Scheme 37).



(Scheme 37)

The preparation of 1-hydroxyoctanephosphonic acid (52) was accomplished smoothly, though the yield was low (ca. 20%), probably because of the difficulty in isolating the product. Conant et al.[89] reported difficulty in the isolation of 1-hydroxyheptanephosphonic acid (51, R = C_6H_{13}) which was therefore separated as the lead salt in order to determine the yield. These 1-hydroxyalkanephosphonic acids they stated, were allowed to crystallise over several weeks from the gum that was formed on steam distillation of the reaction mixture and evaporation of

the water present. However, 1-hydroxyoctanephosphonic acid was isolated in the present studies by distilling off the volatile materials on a rotary evaporator at 80 °C and filtering off the resultant solid which was then recrystallised once from diethyl ether and twice from water.

In an attempt to increase the yield of 1-hydroxyoctanephosphonic acid the reaction was repeated using a molar excess of the phosphorus trichloride. In this case, instead of pouring the reaction mixture into water as described by Conant et al.[89] the reaction mixture was dissolved in diethyl ether and cooled in an ice-bath. Water was then added dropwise until the evolution of gas ceased and an aqueous phase was seen to separate. The organic layer was then separated, washed with water and dried, and the volatile components distilled off on a rotary evaporator. The residue so formed was triturated with petroleum spirit to yield the unexpected product, 1-chloro-octanephosphonic acid, (19.9% yield).

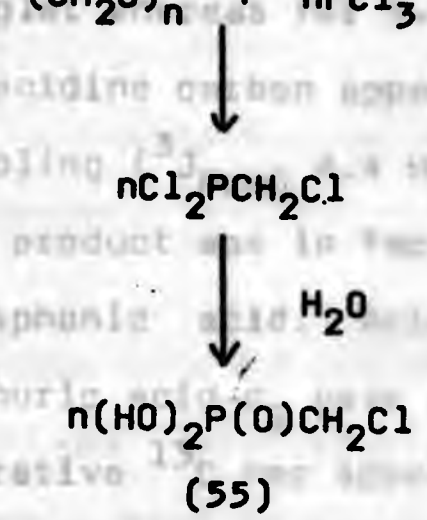
The isolation of 1-chloro-octanephosphonic acid instead of the expected 1-hydroxyoctanephosphonic acid may have been due to the presence of the molar excess of phosphorus trichloride in the reaction mixture. Conant et al.[90] reported the chlorination of a 1-hydroxyaryl-phosphonic acid by dissolving it in hydrochloric acid and passing hydrogen chloride gas through the solution for 1

hour. In our modified work-up procedure the addition of water to the ether solution of the reaction mixture resulted in the copious evolution of hydrogen chloride and consequently in a strongly acidic solution. The chlorination therefore may have occurred at this stage by the hydrogen chloride in a similar manner to that described by Conant et al.[90] or at an earlier stage in the procedure by the excess of phosphorus trichloride.

Attempts to form 1-chloro-octanephosphonyl dichloride (53) by treating 1-hydroxyoctanephosphonic acid with thionyl chloride, were unsuccessful as distillation resulted in decomposition, although hydrolysis of the crude product gave the required 1-chloro-octanephosphonic acid (54) in a yield of 40.1%. Using phosphorus pentachloride as decribed by Fosseck[86] the required 1-chloro-octanephosphonyl dichloride (53) was obtained as a clear, free running oil, in good yield (67.8% after distillation). This compound was then hydrolysed by the addition of water to yield the 1-chloro-octanephosphonic acid.

The products of these three preparations of 1-chloro-octanephosphonic acid were found by nmr to be identical.

Chloromethanephosphonic acid (55) is a well known compound whose reactions with a number of nucleophiles have been studied. It is used for example in the manufacture of glyphosate by reaction with glycine in aqueous solution. It is easily prepared by heating phosphorus trichloride and paraformaldehyde in a sealed tube at 240 °C for 12 h[91,92] and hydrolysis of the product (Scheme 38).



(Scheme 38)

3.2 REACTION OF 1-CHLOROALKANEPHOSPHONIC ACIDS WITH GUANIDINES

Oleksyszyn *et al.*[60] reported that guanidine replaces bromine of O,O-diethyl 2-bromoethanephosphonate on heating under reflux in butan-1-ol. In view of this result it seemed feasible to treat 1-chloro-octanephosphonic acid with guanidine under the same conditions, but the melting point of the product so formed was found to be 235 ^{o}C whereas 1-guanidino-octanephosphonic acid prepared previously (see chapter 1) was found to melt at 331-332 ^{o}C. Furthermore the ^{13}C nmr spectrum revealed the guanidine signal as a singlet whereas for 1-guanidino-octanephosphonic acid the guanidine carbon appears as a doublet due to phosphorus coupling ($^{3}J_{PCNC}$ 4.4 Hz). It was therefore suspected that the product was in fact a guanidine salt of 1-chloro-octanephosphonic acid. Acidification of the nmr solution with sulphuric acid-d_2 gave a precipitate which was shown by comparative ^{13}C nmr spectroscopy (DMSO-d_6) to be 1-chloro-octanephosphonic acid while the ^{13}C nmr spectrum of the filtrate in D_2O/D_2SO_4 revealed only one signal at 160.7 ppm due to the guanidinium carbon. Elemental analysis indicated that the solid obtained was in fact a mixture of the mono- and bis-guanidinium salts of 1-chloro-octanephosphonic acid.

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It appeared that there were several possible reasons for the failure of guanidine to displace the chlorine of 1-chloro-octanephosphonic acid e.g.

1. The guanidinium salts formed are insoluble in the solvent (butan-1-ol) thereby precluding any subsequent reaction.
2. The chlorine atom in 1-chloro-octanephosphonic acid is too sterically hindered for nucleophilic displacement under these conditions.
3. Guanidine is too poor a nucleophile to displace chlorine easily.

Similar results were obtained in pyridine in which the addition salt was also insoluble, and also with chloromethanephosphonic acid in butan-1-ol which gave only bis-guanidinium chloromethanephosphonate (56), m.p. 200-203 ^{o}C.

$(HO)_2P(O)CH_2Cl$

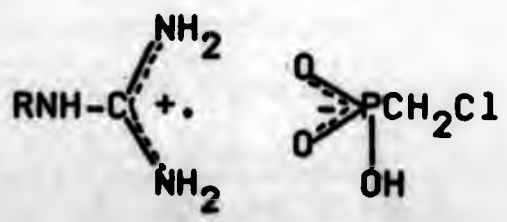
$\downarrow$ $NH_2C(:NH)NH_2$

$\{NH_2\text{-}C(NH_2)\text{-}NH_2\}_2 \cdot O_2P(O)CH_2Cl$

(56)

This structure was confirmed by elemental analysis, FAB ms which gave the M+1 ion at m/z 249 and ^{13}C nmr spectroscopy in D_2O which revealed the signal due to the guanidine carbon as a singlet, whereas the guanidine signal of authentic guanidinomethanephosphonic acid, m.p. 314 ^{o}C appears as a doublet, $^{3}J_{PCNC}$ 4.1 Hz.

The reaction with chloromethanephosphonic acid was then repeated with dodecylguanidine instead of guanidine in the hope that its alkyl chain would enhance the solubility of the acid addition salt thereby allowing substitution to take place. No precipitate was observed at the end of the experiment and the addition of acetone to the reaction mixture gave a precipitate which was filtered off and recrystallised. However, ^{13}C nmr again revealed the guanidine group as a singlet instead of the expected doublet; also the chemical shift and coupling constant of the PCH_2 were consistent with the salt structure. Elemental analysis indicated that in this case the product was the 1:1 addition salt (57).



(57)

The results overall suggest that guanidine is a rather weak nucleophile which is unable to displace chlorine easily. This problem may; however, be increased by the presence of a bulky phosphonic acid grouping on the α-carbon atom and also, in certain cases by the formation of insoluble guanidinium phosphonates.

3.3 REACTION OF 1-CHLOROALKANEPHOSPHONIC ACIDS WITH α,ω-DIAMINOALKANES

A review of the literature revealed that Schwarzenbach *et al.*[93] reported the condensation of chloromethanephosphonic acid with primary amines in the presence of sodium hydroxide (Scheme 39) leading to a diphosphonic acid (58).

$$(HO)_2P(O)CH_2Cl + 2NaOH + RNH_2 \longrightarrow \{(HO)_2P(O)CH_2\}_2NR + 2NaCl$$

(58)

(Scheme 39)

A similar reaction involving a diamine was reported by Bersworth[94] (Scheme 40) who showed that with the tetra-phosphonic acid (59) the mono- (60) and tri-substistuted

$$4(HO)_2P(O)CH_2Cl + NH_2CH_2CH_2NH_2 \xrightarrow{Na2CO_3} \{(HO)_2P(O)CH_2\}_2NCH_2CH_2N\{CH_2P(O)(OH)_2\}_2$$

(59)

(Scheme 40)

compound (61) are formed if slightly more than two moles of reagent are used per mole of ethylene diamine, the major product being the tetra-substituted compound (59).

$(HO)_2P(O)CH_2NHCH_2CH_2NH_2$

(60)

$\{(HO)_2P(O)CH_2\}_2NCH_2CH_2NHCH_2P(O)(OH)_2$

(61)

Victor Chemical Works[95] obtained a patent for the preparation of alkanolaminoalkanephosphonic acids (62) by the condensation of alkanolamines and chloromethanephosphonic acid (Scheme 41).

$$(HO)_2P(O)CH_2Cl + (HO)_nRN(R^1)H \xrightarrow{NaOH} (HO)_2P(O)CH_2N(R^1)R(OH)_n$$

(62)

(Scheme 41)

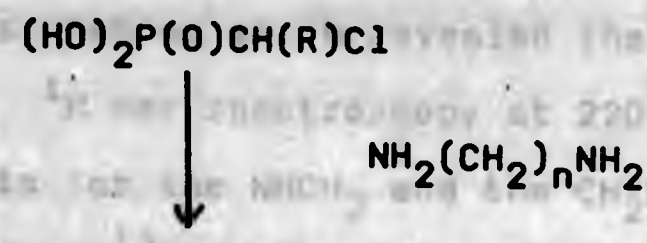
Moedritzer and Irani[96] investigated the reaction of chloromethanephosphonic acid with amines in sodium hydroxide solution and found that .there was significant hydrolysis of the carbon-chlorine bond of chloromethanephosphonic acid yielding hydroxymethanephosphonic acid (63). This compound was a contaminant of the desired phosphonic acid and was difficult to remove.

$(HO)_2P(O)CH_2OH$

(63)

Uhlg and Achilles[97] prepared N-(2-aminoethyl)aminomethanephosphonic acid (60) monohydrate by condensing ethylene diamine (6.4 mol. eq.) with chloromethanephosphonic acid (1.6 mol. eq.) in the presence of sodium hydroxide (5.3 mol. eq.). By varying the ratio of the reactants they also prepared and purified the di- (59) and tri-substituted (61) analogues mentioned by Bersworth et al.[94]

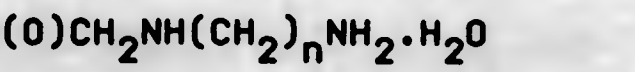
The above mentioned workers prepared these compounds in order to investigate their properties as chelating agents. In the present work the reactions of chloromethanephosphonic acid with a range of α,ω-diamines have been studied (Scheme 42).



(Scheme 42)

A minimum ratio of diamine:phosphonic acid of 3:1 is required since one mol. eq. of diamine would initially form a 1:1 addition salt, the second mol. eq. of diamine would displace the chlorine and the third mol. eq. would be required as a hydrogen chloride acceptor. In order to obviate any unwanted condensations (such as that at either end of the diamine) the ratio we used was in fact 5:1.

A complication can arise from the precipitation of an insoluble addition salt, this being observed in the reactions of 1,8-diamino-octane with either chloromethanephosphonic acid or 1-chloro-octanephosphonic acid in pyridine. However, the substitution reaction with chloromethanephosphonic acid proceeds well in water, in which the 1:1 salt is very soluble. The product, N-(8-aminooctyl)aminomethanephosphonic acid which was isolated as the monohydrate (64, n = 8) was completely characterised



(64)

by elemental analysis, FAB ms which revealed the M+1 ion as the base peak, ^{1}H nmr spectroscopy at 220 MHz which gave separate triplets for the $NHCH_2$ and the CH_2NH_2 of the methylene chain, and by ^{13}C nmr spectroscopy in which the $NHCH_2$ signal was found to be a doublet ($^{3}J_{PCNC}$ 6.1 Hz). The results obtained with a variety of diamines are summarised in Table 18.

Table 18: Elemental analysis (%), melting points and molecular weight (FAB ms) data for N-(ω-amino-alkyl)aminomethanephosphonic acid monohydrates (65)

$$(HO)_2P(O)CH_2NH(CH_2)_nNH_2.H_2O$$

(65)

Found

n	m.p. °C	C	H	N	M+1^{1+}
2	248-250	20.3	7.2	15.7	155
4	258	29.8	8.3	13.0	183
6	235	36.1	9.3	12.2	211
8	242	42.0	9.3	11.1	239
10	238	46.4	9.6	9.3	267
12	234	49.9	10.0	9.0	295

Requires

n	formula	C	H	N	Mol.Wt.
2	$C_3H_{13}N_2PO_4$	20.9	7.6	16.3	172
4	$C_5H_{17}N_2PO_4$	30.0	8.5	14.0	200
6	$C_7H_{21}N_2PO_4$	36.8	9.2	12.3	228
8	$C_9H_{25}N_2PO_4$	42.2	9.8	11.0	256
10	$C_{11}H_{29}N_2PO_4$	46.5	10.2	9.9	284
12	$C_{13}H_{33}N_2PO_4$	50.0	10.6	9.0	312

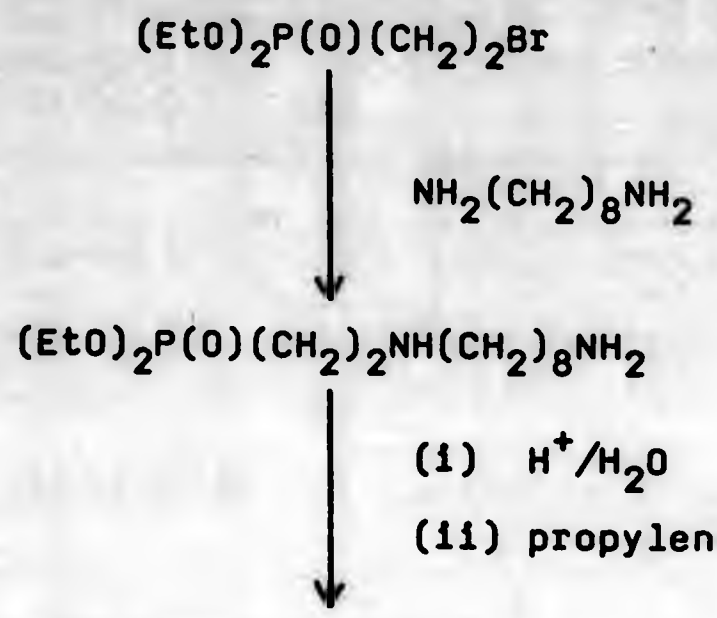
The compounds of this homologous series were identified by elemental analysis, FAB ms, ^{1}H nmr (220 MHz), ^{13}C and ^{31}P nmr spectroscopy. In addition a $^{15}N-\{^{1}H\}^{bb}$ nmr spectrum of N-(2-aminoethyl)aminomethanephosphonic acid monohydrate (65, n = 2) revealed two signals at -348.0 (NH_2) and -354.4 ppm (NH). Thermogravimetric analysis of N-(6-aminohexyl)aminomethanephosphonic acid monohydrate gave a weight loss between 140 ^{o} and 180 ^{o}C which corresponded to the expected weight loss for one molecule of water of crystallisation.

The triamine analogue (66) was synthesised from 1,13-diamino-7-azatridecane and the series was extended to

$(HO)_2P(O)CH_2NH(CH_2)_6NH(CH_2)_6NH_2$

(66)

include N-(8-amino-octyl)-2-aminoethanephosphonic acid monohydrate (67) in which there is an extra methylene group between the phosphorus and nitrogen atoms (Scheme 43).



(67)

(Scheme 43)

All these phosphonic acids were found to be high melting crystalline solids, insoluble in organic solvents but soluble in aqueous media (acidic, basic or neutral), their solubility decreasing as the chain length is increased.

3.3.1 ^{1}H, ^{13}C AND ^{31}P NMR DATA FOR N-(ω-AMINOALKYL)AMINOMETHANEPHOSPHONIC ACIDS

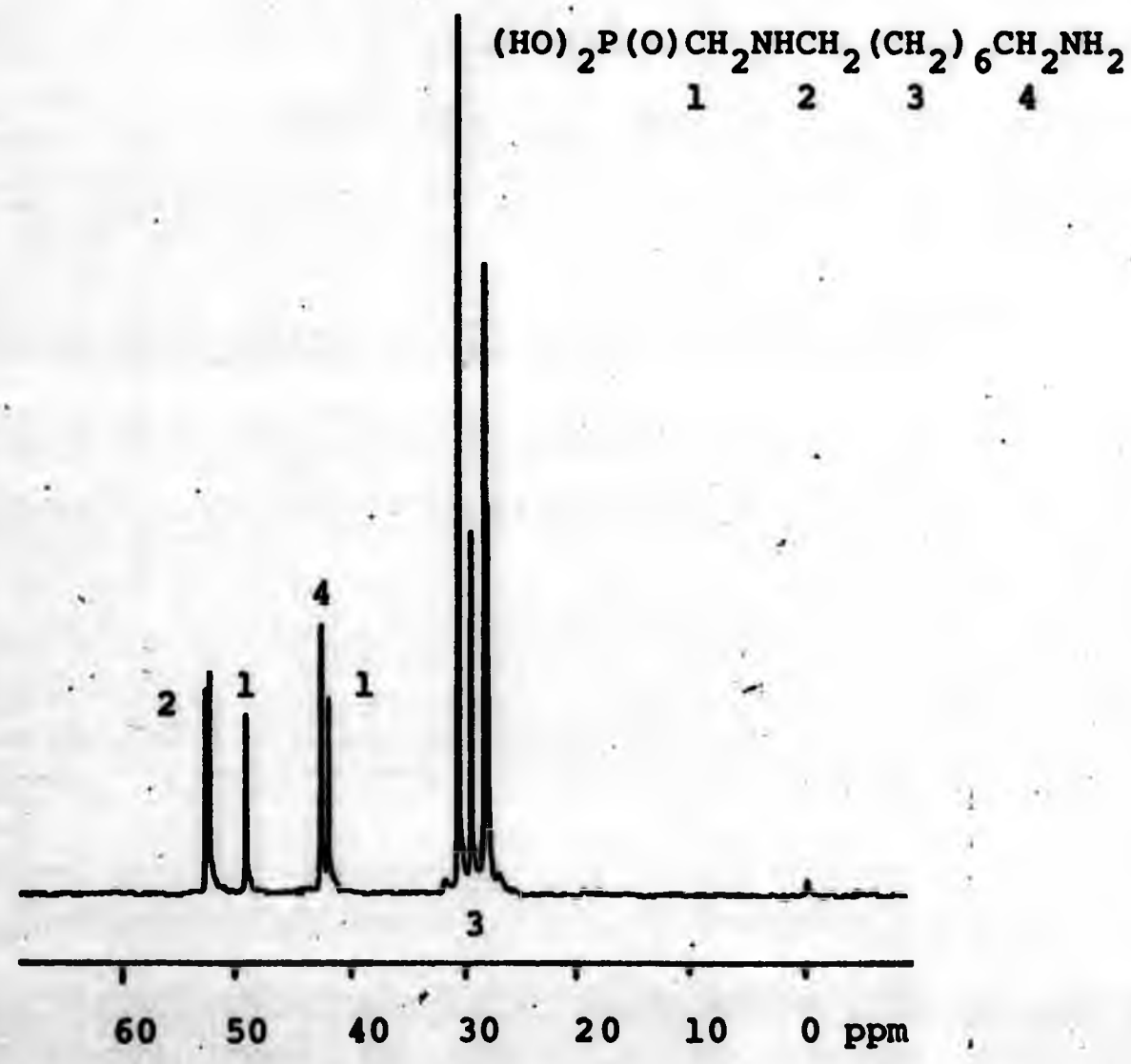
An examination of the spectral characteristics of these compounds showed a number of general trends. Excluding the first member of this series, it can be seen from the ^{13}C spectra that on average the $^{1}J_{PC}$ and $^{3}J_{PCNC}$ values are unaffected by variation in chain length (Table 19).

Table 19: Phosphorus carbon coupling constants (Hz) for N-(ω-aminoalkyl)aminomethanephosphonic acids

solvent: D_2O/D_2SO_4

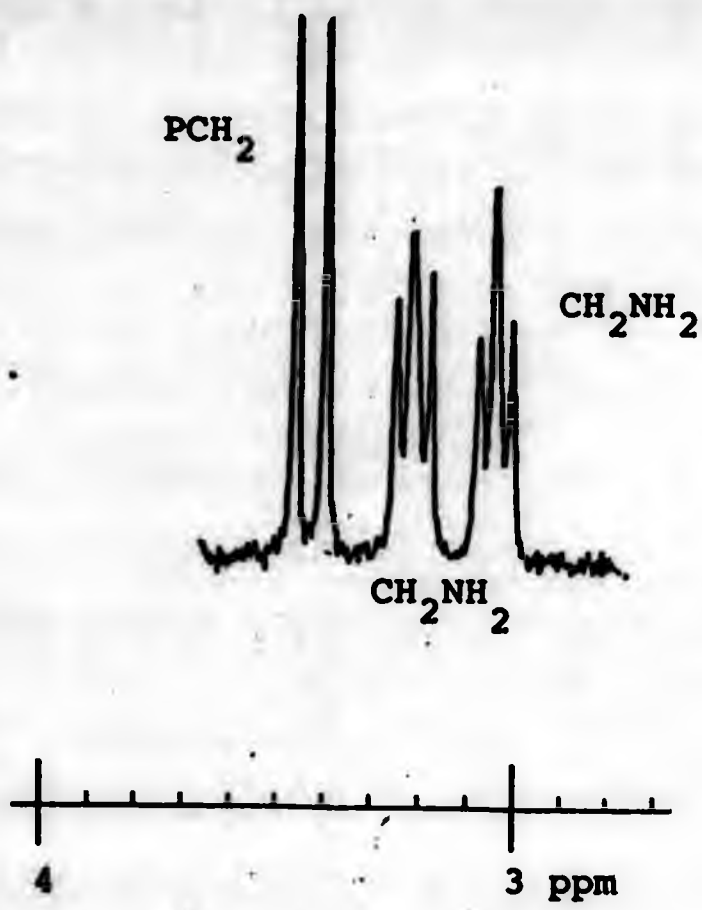
n	$^{1}J_{PC}$	$^{3}J_{PCNC}$
2	135.3	4.4
4	147.8	8.2
6	148.5	7.7
8	146.5	7.5
10	148.5	6.8
12	150.1	7.3

In general the ^{13}C nmr spectra of these compounds in D_2O/D_2SO_4 have a fingerprint region between 41 and 53 ppm which consists of a doublet for the PCH_2, a singlet for the terminal CH_2 of the alkyl chain, and a doublet for the $NHCH_2$ carbon atom. This is exemplified in the ^{13}C nmr spectrum of N-(8-amino-octyl)aminomethanephosphonic acid (Fig. 16).



(Fig. 16)

Similarly a fingerprint region is also observed in the ^1H nmr spectra at 220 MHz in D_2O/D_2SO_4 (Fig. 17).



(Fig. 17)

However, if the spectrum is recorded at 60 or 80 MHz this fine pattern is not revealed. Instead only a broad triplet and doublet are observed which offer very little structural information since we have found that at these fields the spectra hardly diifer from those of the addition salts of chloromethanephosphonic acid with diamines.

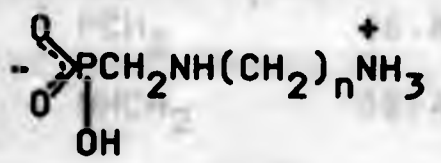
^{31}P nmr data for the N-(ω-aminoalkyl)aminomethanephosphonic acids are given in Table 20 from which it can be seen that the addition of D_2SO_4 not only results in a new distinct chemical shift but also in a change of the value of the coupling constant. On this basis we can assign a zwitterionic structure to these compounds.

Table 20: ^{31}P chemical shifts (ppm) and $^2J_{HCP}$ coupling constants (Hz) for N-(ω-aminoalkyl)aminomethanephosphonic acids in D_2O and D_2O/D_2SO_4 solution

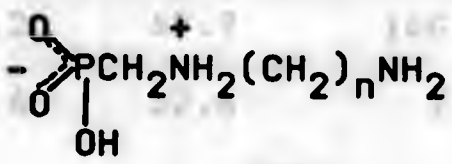
reference: 85% H_3PO_4

	D_2O		$D2O/D_2SO_4$	
n	δ	$^2J_{HCP}$	δ	$^2J_{HCP}$
2	7.9	11.8	12.7	14.0
4	7.2	11.8	13.6	14.0
6	7.6	11.4	14.1	14.3
8	8.7	11.4	13.5	13.8
10	7.4	11.8	14.2	14.0
12	7.4	11.2	14.8	14.0

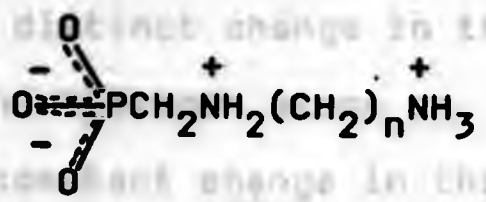
However, unlike the α-amino- and ω-amino-alkanephosphonic acids, these compounds have two available sites for internal protonation, and the zwitterionic forms 68, 69, and 70 are therefore possible.



(68)



(69)



(70)

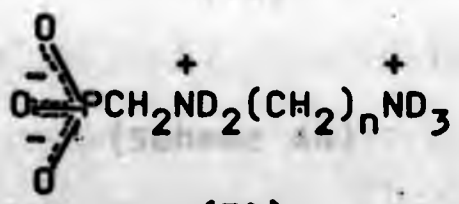
Table 21: Effect of addition of D_2SO_4 on the ^1H nmr spectrum of N-(6-aminohexyl)aminomethanephosphonic acid

	D_2O		D_2O/D_2SO_4	
ASSIGNMENT	δ	J	δ	J
CH_2NH_2	3.02	7.9	3.06	7.9
PCH_2	2.97	12.3	3.50	14.1
$NHCH_2$	3.18	7.7	3.25	7.7

Table 22: Effect of addition of D_2SO_4 on the ^{13}C spectrum of N-(8-amino-octyl)aminomethanephosphonic acid

	D_2O		D_2O/D_2SO_4	
ASSIGNMENT	δ	J	δ	J
CH_2NH_2	42.3	-	42.6	-
PCH_2	46.8	128.2	45.7	146.5
$NHCH_2$	52.4	11.4	52.6	7.5

The results summarised in Tables 21 and 22 show that while there is a distinct change in the chemical shift of the PCH_2 carbon and hydrogen atoms on addition of D_2SO_4 there is no concomitant change in the carbon or hydrogen chemical shifts of the other two CH_2 groups attached to nitrogen. This confirms that their level of protonation is the same in D_2O solution or D_2O/D_2SO_4 solution and since we have shown that ω-aminoalkanephosphonic acids have their amino group protonated in D_2O solution by the phosphonic acid group and also that 1-aminoalkane-phosphonic acids exhibit the same protonation we may conclude that in aqueous solution N-(ω-aminoalkyl)amino-methanephosphonic acids exist in the di-zwitterion form (71).



(71)

3.4 PREPARATION OF GUANIDINO DERIVATIVES FROM N-(ω-AMINOALKYL)-AMINOALKANEPHOSPHONIC ACIDS

The conversion of the primary amino group of the N-(ω-aminoalkyl)aminoalkanephosphonic acids (65, n = 4, 6, 8, 10 and 12) to a guanidino group was accomplished according to Scheme 44, and an identical procedure was applied to N-(8-amino-octyl)-2-aminoethanephosphonic acid (67).

$$(HO)_2P(O)CH_2NH(CH_2)_nNH_2 + 4KOH + 2MeSC(:NH)NH_2.HCl$$

$\downarrow$ H_2O

$$(KO)_2P(O)CH_2NH(CH_2)_nNH_2 + 2MeSC(:NH)NH_2 + 2KCl$$

$\downarrow$ -MeSH

$$(KO)_2P(O)CH_2NH(CH_2)_nNHC(:NH)NH_2$$

$\downarrow$ HCl

$$(HO)_2P(O)CH_2NH(CH_2)_nNHC(:NH)NH_2.HCl + 2KCl$$

$\downarrow$ propylene oxide

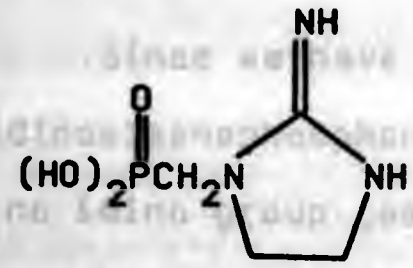
$$(HO)_2P(O)CH_2NH(CH_2)_nNHC(:NH)NH_2$$

(72)

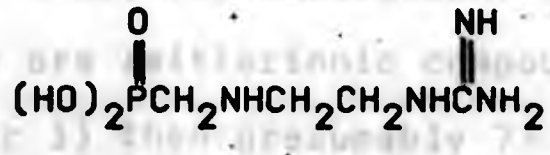
(Scheme 44)

However, the product obtained from N-(2-aminoethyl)-aminomethanephosphonic acid monohydrate (65, n = 2) showed some rather unusual physical properties. It had a melting point of 345-349 °C which is ca. 200 °C higher than that of the other members of the series, whilst the ^{13}C nmr spectrum showed that the expected $^{3}J_{PCNC}$ coupling was absent, and that the guanidine carbon was revealed as a doublet suggesting a rather unusual $^{6}J_{PCNCCNC}$ coupling of 2.2 Hz. The FAB mass spectrum revealed the M+1 ion at 180 instead of the expected 197, indicating a molecular weight of 179.

The only possible structure that fits these results appears to be 73 and not the expected product 74.

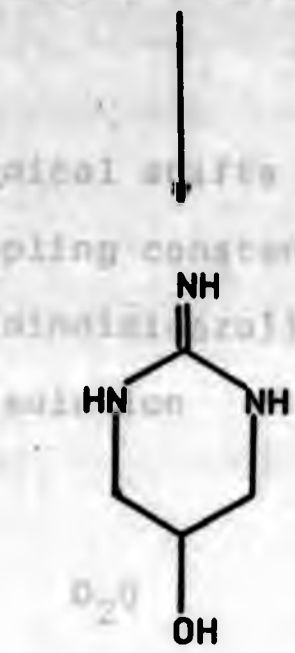


(73)



(74)

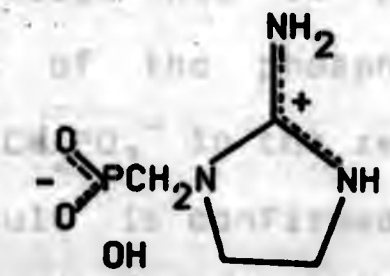
Compound 73 has molecular weight 179 and since it is cyclic the guanidine carbon is now only 3 bonds away from the phosphorus atom making the apparent $^{6}J_{PCNCCNC}$ coupling a more realistic $^{3}J_{PCNC}$. 2-Imino-5-hydroxytetra-hydro-pyrimidinium sulphate (75) was reported to be formed by a similar reaction (Scheme 45).[98]



(75)

(Scheme 45)

Since we have shown by X-ray crystallography that guanidinoalkanephosphonic acids are zwitterionic compounds with no imino group (see Chapter 1) then presumably 73 is also a zwitterionic compound having the structure 76.



(76)

This conclusion is confirmed by the nmr spectra of this compound when recorded at different pH values (tables 23 and 24).

Table 23: ^{13}C nmr chemical shifts (ppm) and phosphorus-carbon coupling constants (Hz) for 1-phosphonomethyl-2-iminoimidazolidine (73) in D_2O and D_2O/D_2SO_4 solution

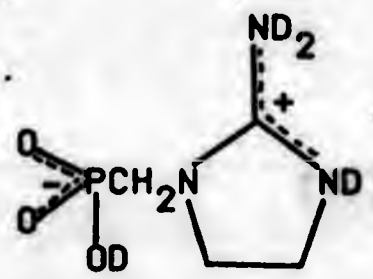
	D_2O		D_2O/D_2SO_4	
Assignment	δ	J	δ	J
CH_2NH	43.7	-	43.9	-
PCH_2	46.0	147.4	44.4	157.3
NCH_2	52.5	-	52.5	-
$NC(:NH)NH_2$	162.0	2.2	160.8	2.0

We can see from Table 23 that while addition of D_2SO_4 does not affect the chemical shifts of the NCH_2CH_2NH carbon atoms the chemical shift of the PCH_2 is altered and more importantly the coupling constant is different by some 10 Hz. This would not be possible unless the chemical environment of the phosphorus atom had been changed from that of $CH_2PO_3^-$ in the zwitterion to that of $P(O)(OH)_2$. The result is confirmed by the ^{31}P nmr data (Table 24) which show that a significant downfield shift occurs in acid.

Table 24: ^{31}P chemical shifts (ppm) of 1-phosphonomethyl-2-iminoimidazolidine (73) in D_2O and D_2O/D_2SO_4 solution

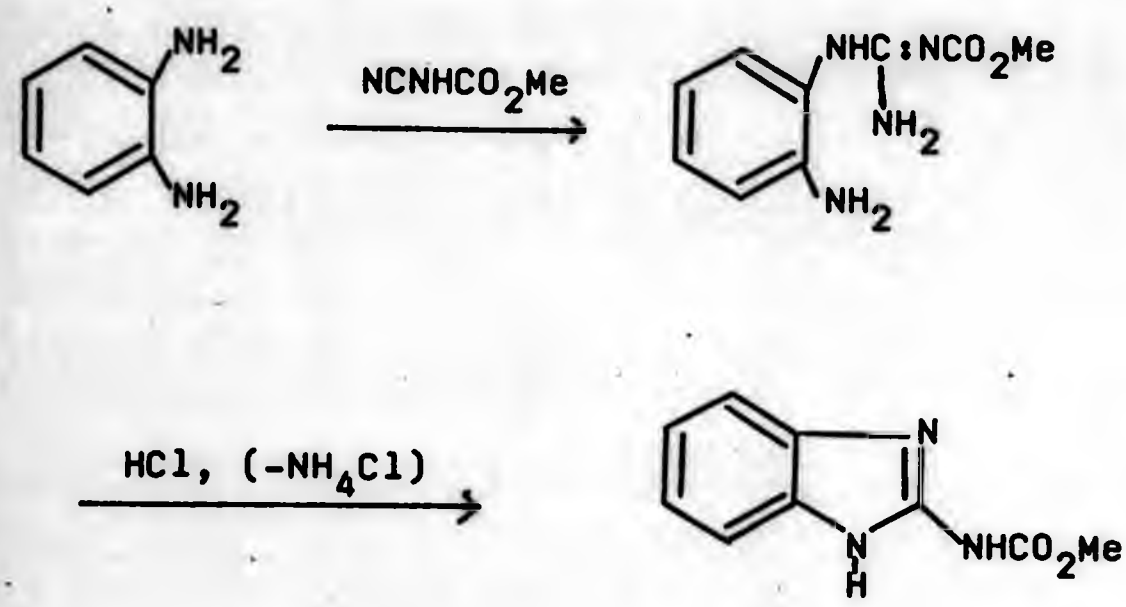
Solvent	δ
D_2O	13.4
D_2O/D_2SO_4	19.8

The ^{15}N nmr spectrum of this compound in D_2O/H_2O reveals only two signals as expected; the tertiary nitrogen in the molecule is not seen, as there are no protons attached directly to it and therefore it experiences no Nuclear Overhauser Enhancement. These two signals are in fact in a ratio of ca. 2:1 indicating that one nitrogen has two protons attached to it while the other only has one, a result consistent with the zwitterion structure 77 in D_2O solution.

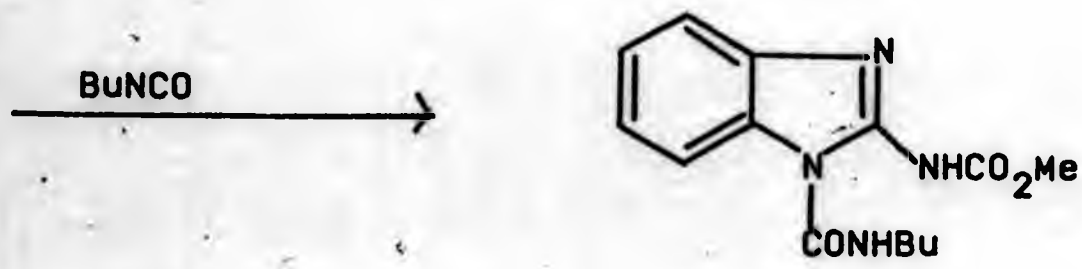


(77)

The elimination of ammonia from a substituted guanidine has been observed in the cyclisation of o-phenylenediamine with methyl cyanocarbamate to give carbendazim (78) (the precursor of benomyl, 79) (Scheme 46).[99]



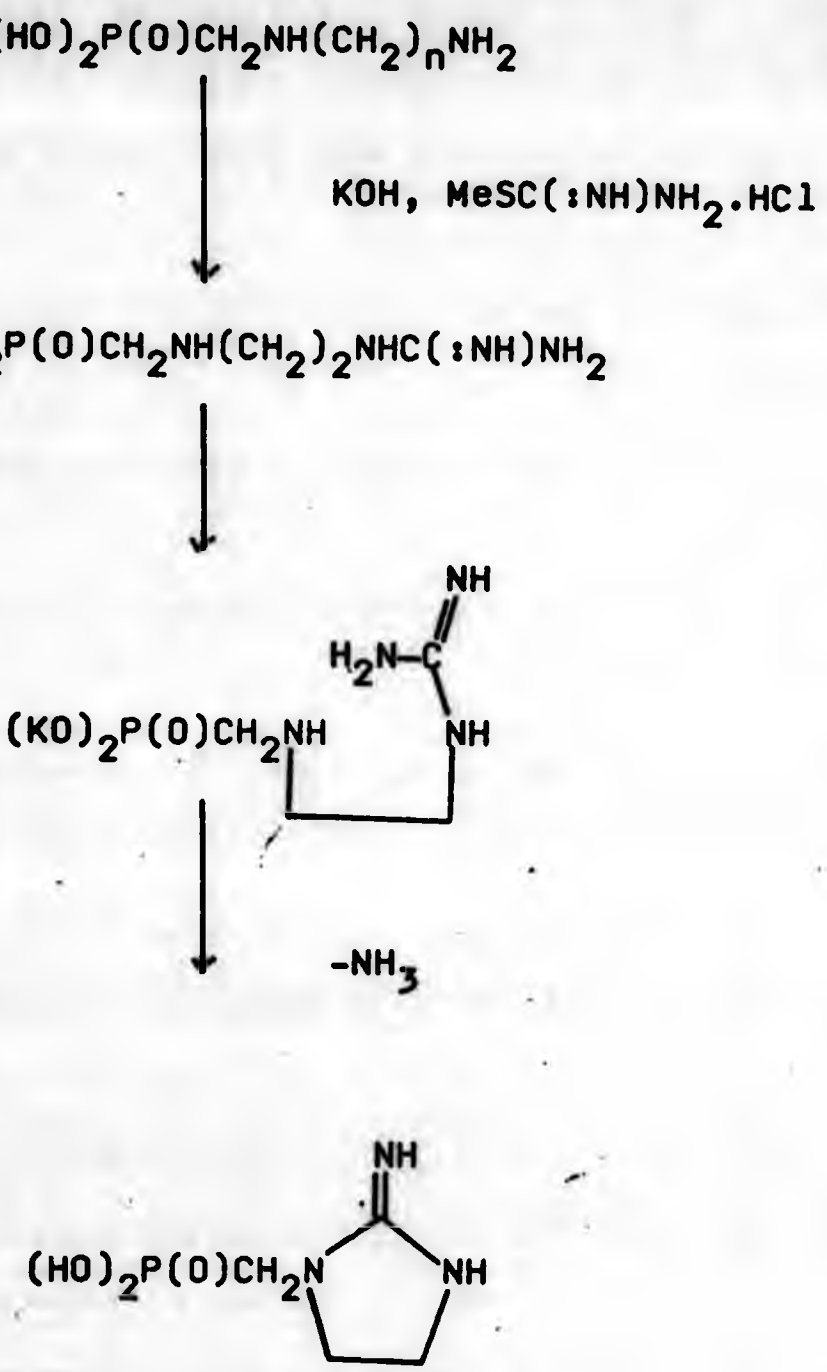
(78)



(79)

(Scheme 46)

It would appear therefore, that the cyclic product (73) obtained in the present work may have been formed in a similar manner (Scheme 47).

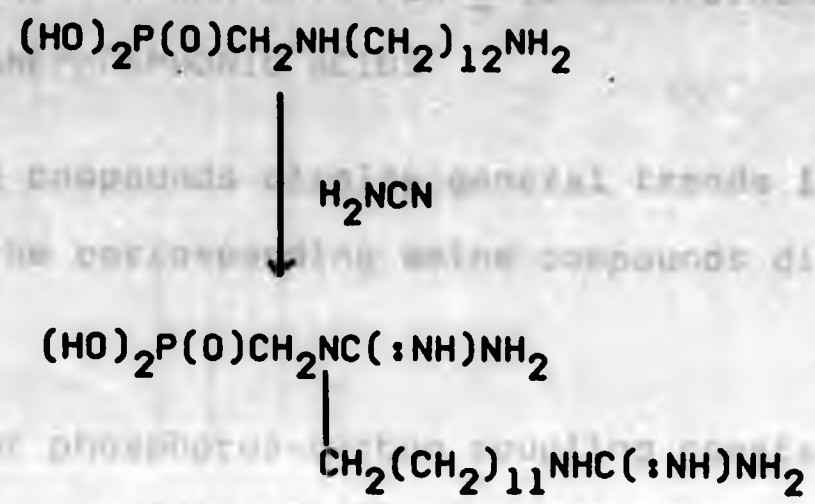


(73)

(Scheme 47)

The N-(ω-guanidinoalkyl)aminoalkanephosphonic acids (72) are white crystalline solids, insoluble in organic solvents but soluble in aqueous media (acidic, basic or neutral). They were characterised by ^{1}H nmr (220 MHz), ^{13}C nmr, ^{31}P nmr and FAB ms which revealed the M+1 ion as the base peak in most cases. However, elemental analysis has indicated that these compounds are hydrates, with some analysis corresponding to the presence of one molecule of water of crystallisation and others to two. Thermogravimetric analysis of 72 (n = 6 and 8) has shown a loss which corresponds to one molecule of water although after this loss the compounds have decomposed and it is possible that water may also be lost at this stage.

In the synthesis of these compounds (Scheme 44) the reagent employed for guanidation was S-methylisothiouronium chloride and consequently only the primary amino group was converted to a guanidine moiety. However, it was of interest to attempt to guanidate the secondary amino group in addition (Scheme 48), in order to examine the physical and fungicidal properties of the products, and for this purpose cyanamide was used as it is an unspecific reagent that randomly converts both primary and secondary amino groups to guanidine.[100]



(80)

(Scheme 48)

When this reaction was attempted with N-(12-amino-dodecyl)aminomethanephosphonic acid the product obtained was not the expected compound (80) but N-(12-ureido-dodecyl)aminomethanephosphonic acid monohydrate (81).

$$(HO)_2P(O)CH_2NH(CH_2)_{12}NHC(:O)NH_2.H_2O$$

(81)

The reason for this unexpected result is not clear but may be due to the very high pH of the reaction mixture which caused the terminal guanidino group that had formed to undergo hydrolysis.

3.4.1 ^{1}H, ^{13}C AND ^{31}P NMR DATA FOR N-(ω-GUANIDINOALKYL)-AMINOALKANEPHOSPHONIC ACIDS

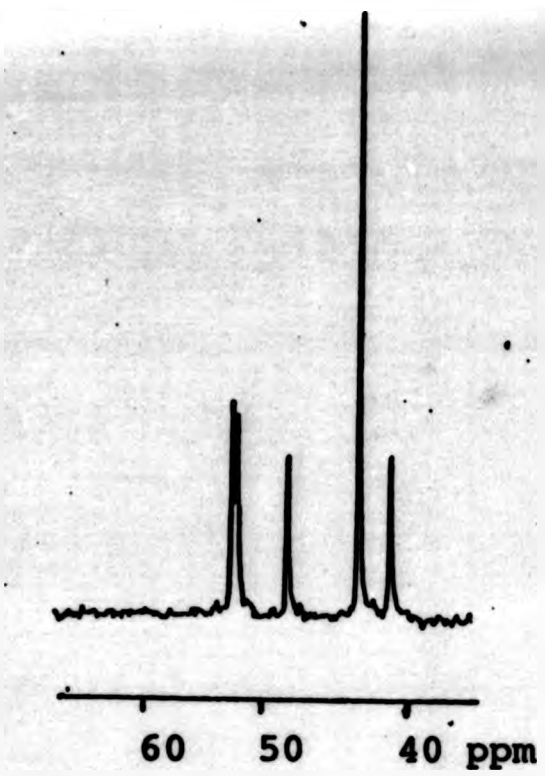
These compounds display general trends in their spectra as did the corresponding amino compounds discussed before.

Table 25: ^{13}C nmr phosphorus-carbon coupling constants (Hz) of N-(ω-guanidinoalkyl)aminomethanephosphonic acids

solvent: D_2O/D_2SO_4

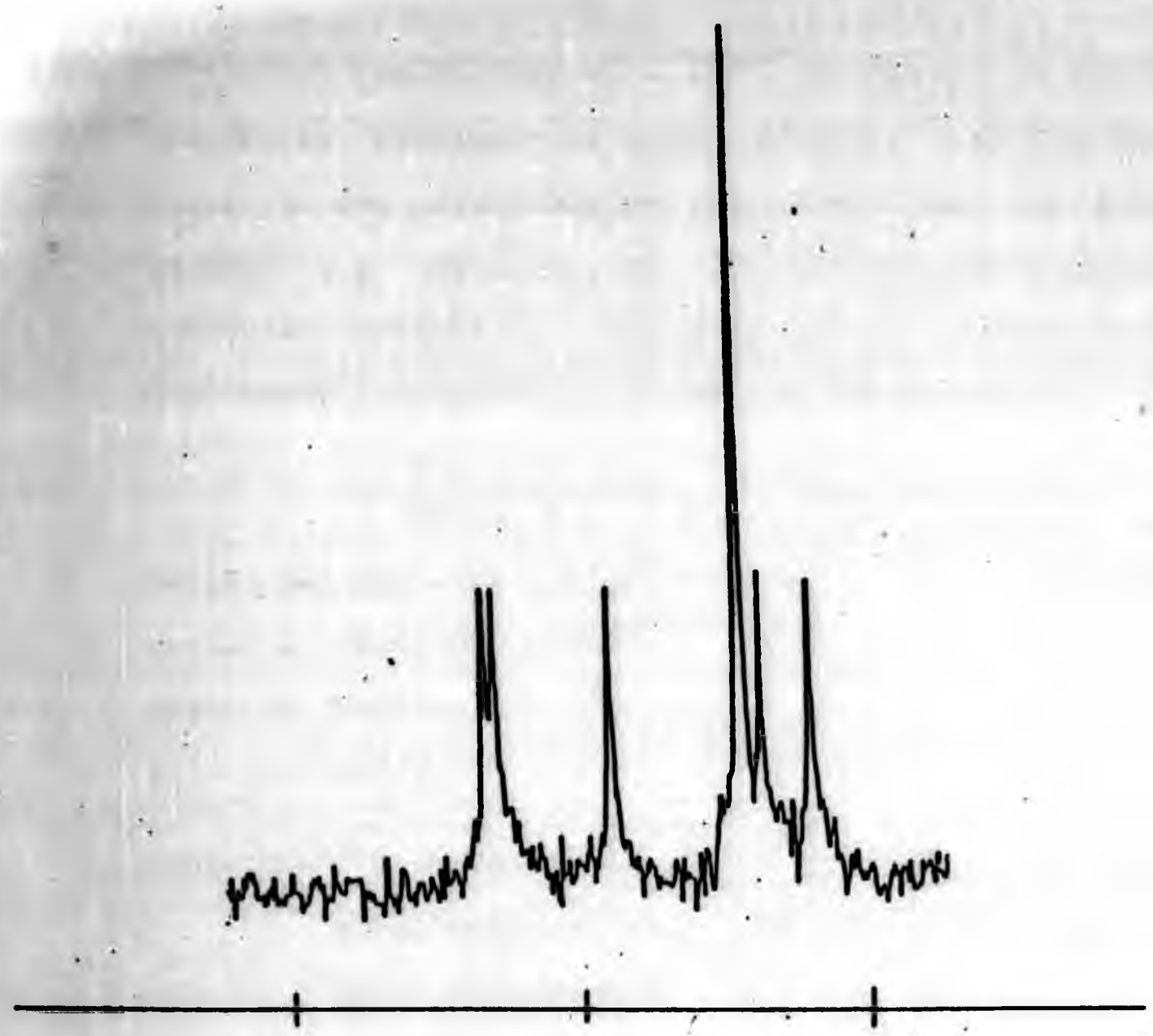
n	$^{1}J_{PC}$	$^{3}J_{PCNC}$
4	147.2	7.5
6	149.9	7.5
8	149.9	8.1
10	146.5	7.5
12	148.5	7.5

Again we see that the value of the $^{1}J_{PC}$ and $^{3}J_{PCNC}$ coupling values remain constant with respect to variation in chain length. A similar fingerprint region is apparent in the ^{13}C nmr spectra of these compounds which is exemplified by N-(8-guanidino-octyl)aminomethane-phosphonic acid (Fig. 18).



(Fig. 18)

This region is usually the same for both the amino and guanidino compounds except that the chemical shift of the terminal carbon of the polymethylene chain appears between 1 and 2 ppm upfield in the guanidino compounds. This shift proved useful in our initial preparations of these compounds since any unreacted amino material could easily be identified if present. Thus when we attempted to guanidate N-(12-aminododecyl)aminomethanephosphonic acid monohydrate we found that because of its low solubility in water a precipitate was formed in the reaction flask while the reaction was occurring. This precipitate gave an extra signal in the fingerprint region which was due to unreacted starting aminophosphonic acid (Fig. 19).



(Fig. 19)

Since it was not found possible to separate the two components of this mixture by fractional crystallisation the reaction was repeated at higher temperature and the crude product of the reaction was analysed by ^{13}C nmr before attempting any further purification.

Whereas the 220 MHz ^{1}H nmr spectra of the amino precursors revealed separate triplets for the two CH_2 groups of the polymethylene chain attached to nitrogen atoms, the spectra of the corresponding guanidino compounds revealed an overlapping pair of triplets and in some cases only a broad triplet for these groups.

^{31}P nmr data for these compounds are given in Table 26. As with the amino compounds, addition of D_2SO_4 causes a distinct change to lower field in the ^{31}P chemical shifts of the guanidino derivatives in accord with protonation of the phosphonate oxygen atoms.

Table 26: ^{31}P nmr chemical shifts (ppm) of N-(ω-guanidinoalkyl)aminomethanephosphonic acids in D_2O and D_2O/D_2SO_4 solution

n	D_2O	D_2O/D_2SO_4
4	7.8	13.3
6	-	14.6
8	8.0	13.0
10	8.8	12.9
12	8.6	15.1

The effects of added acid on the ^{1}H and ^{13}C nmr spectra are given in Tables 27 and 28 and show that there is a large change in the phosphorus-carbon coupling

Table 27: ^{1}H nmr chemical shifts (ppm) and phosphorus-hydrogen coupling constants (Hz) for the PCH_2 hydrogens of N-(ω-guanidinoalkyl)aminomethanephosphonic acids in D_2O and D_2O/D_2SO_4 solution

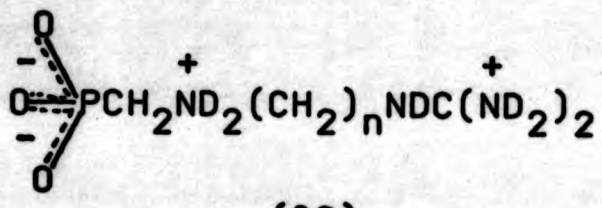
	D_2O		D_2O/D_2SO_4	
n	δ	$^{2}J_{PCH}$	δ	$^{2}J_{PCH}$
4	3.02	12.0	3.43	13.8
6	3.01	12.0	3.46	14.0
8	3.03	12.0	3.37	13.5

Table 28: Effect of addition of D_2SO_4 on the ^{13}C nmr spectrum of N-(8-guanidino-octyl)aminomethane-phosphonic acid

ASSIGNMENT	δ	J	δ	J
$\underline{C}H_2NHC(:NH)$	44.1	-	43.8	-
PCH_2	48.0	132.2	45.2	149.9
$NHCH_2$	52.5	6.8	53.1	8.1

constants and chemical shifts for the hydrogen and for the carbon of the PCH_2 group whilst the chemical shifts of the other carbons attached to nitrogen do not alter

appreciably. The results are entirely consistent with the zwitterionic structure (82) for these compounds in solution.



(82)

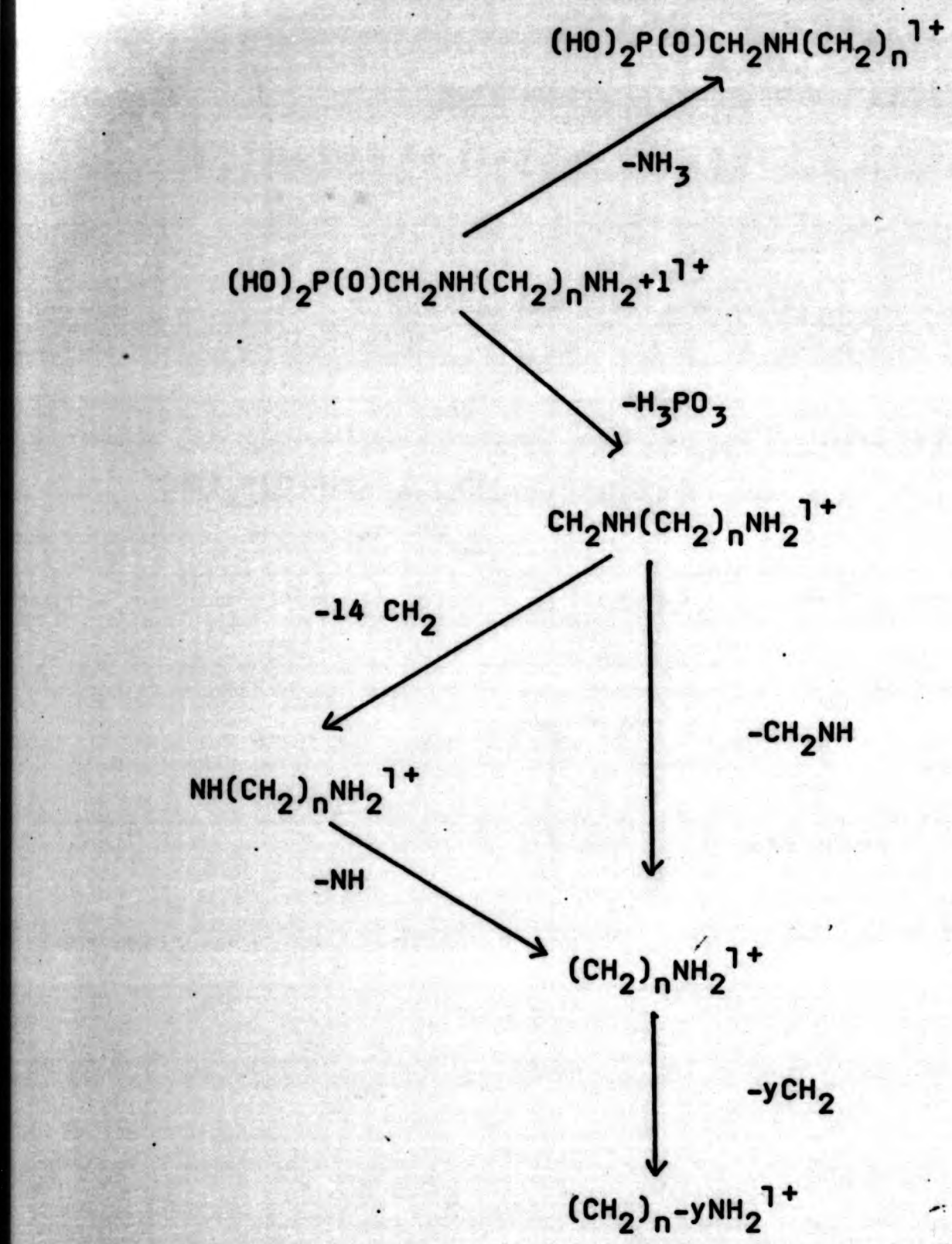
3.5 FAB MASS SPECTROMETRY OF N-(ω-AMINOALKYL)AMINO-ALKANEPHOSPHONIC ACIDS

Table 29: Relative intensities (%) of molecular ions in the FAB mass spectra of N-(ω-aminoalkyl)aminomethane-phosphonic acids

$(HO)_2P(O)CH_2NH(CH_2)_nNH_2$

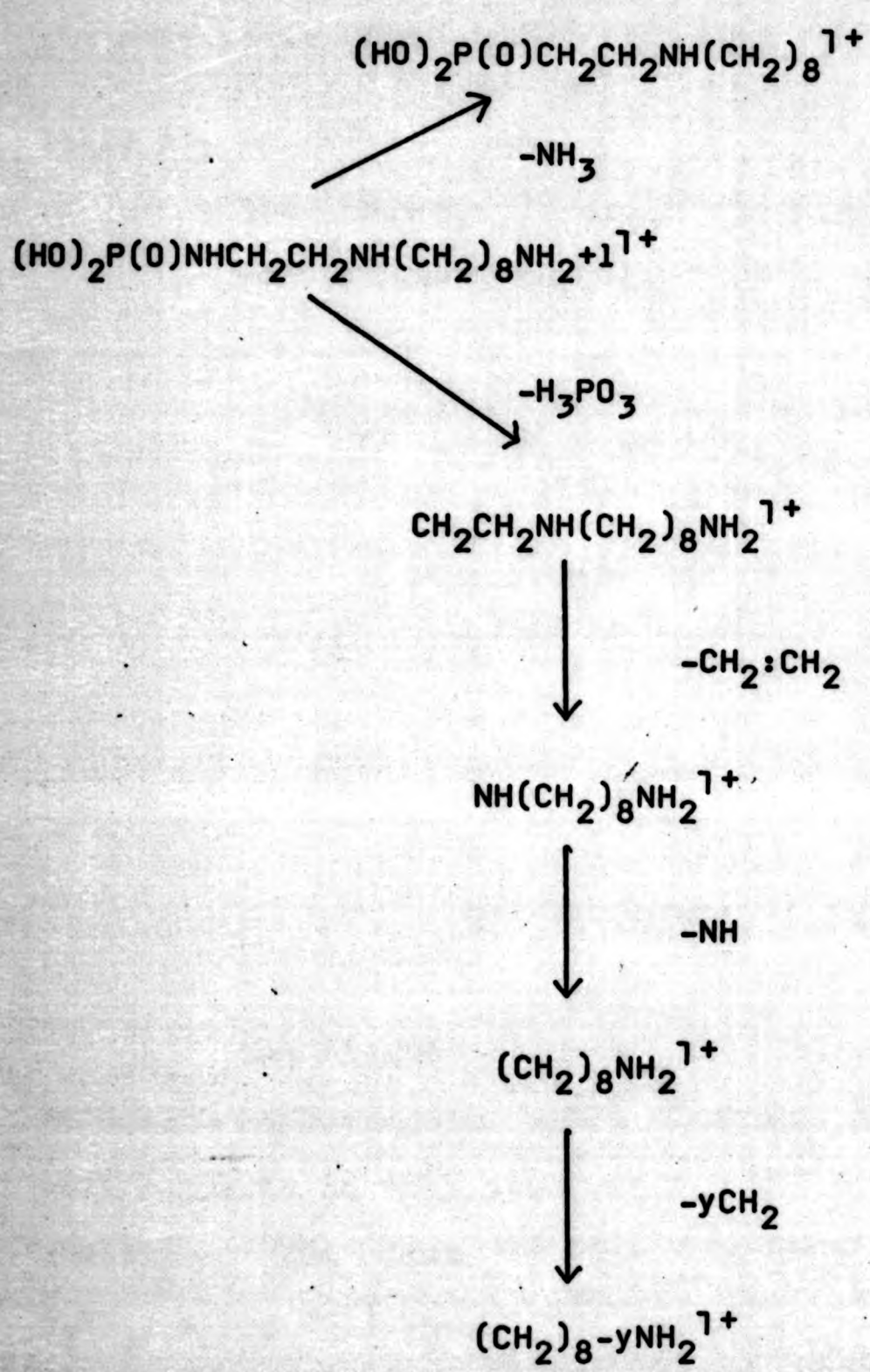
n	$M+1]^+$	$2M+1]^+$	$M+G+1]^+$
2	100	26.7	7.1
4	100	11.7	-
6	100	2.8	-
8	100	-	2.5
10	36.7	-	-
12	66.8	-	0.5

Molecular ions recorded in the FAB mass spectra of the N-(ω-aminoalkyl)aminomethanephosphonic acids are given above in Table 29. Here again the intensities of the M+1 ions are quite strong although for these compounds the fragmentation appears to be more complex (Scheme 49) than that of the previous phosphonic acids we have studied.


(HO)2P(O)CH2NH(CH2)n]1+
-NH3
(HO)2P(O)CH2NH(CH2)nNH2+1]1+
-H3PO3
CH2NH(CH2)nNH2]1+
-14 CH2
-CH2NH
NH(CH2)nNH2]1+
-NH
(CH2)nNH2]1+
-yCH2
(CH2)n-yNH2]1+

(Scheme 49)

N-(8-Amino-octyl)aminoethanephosphonic acid (67) appears to fragment in a similar manner (Scheme 50).



(Scheme 50)

3.6 FAB MASS SPECTROMETRY OF N-(ω-GUANIDINOALKYL)-AMINOALKANEPHOSPHONIC ACIDS

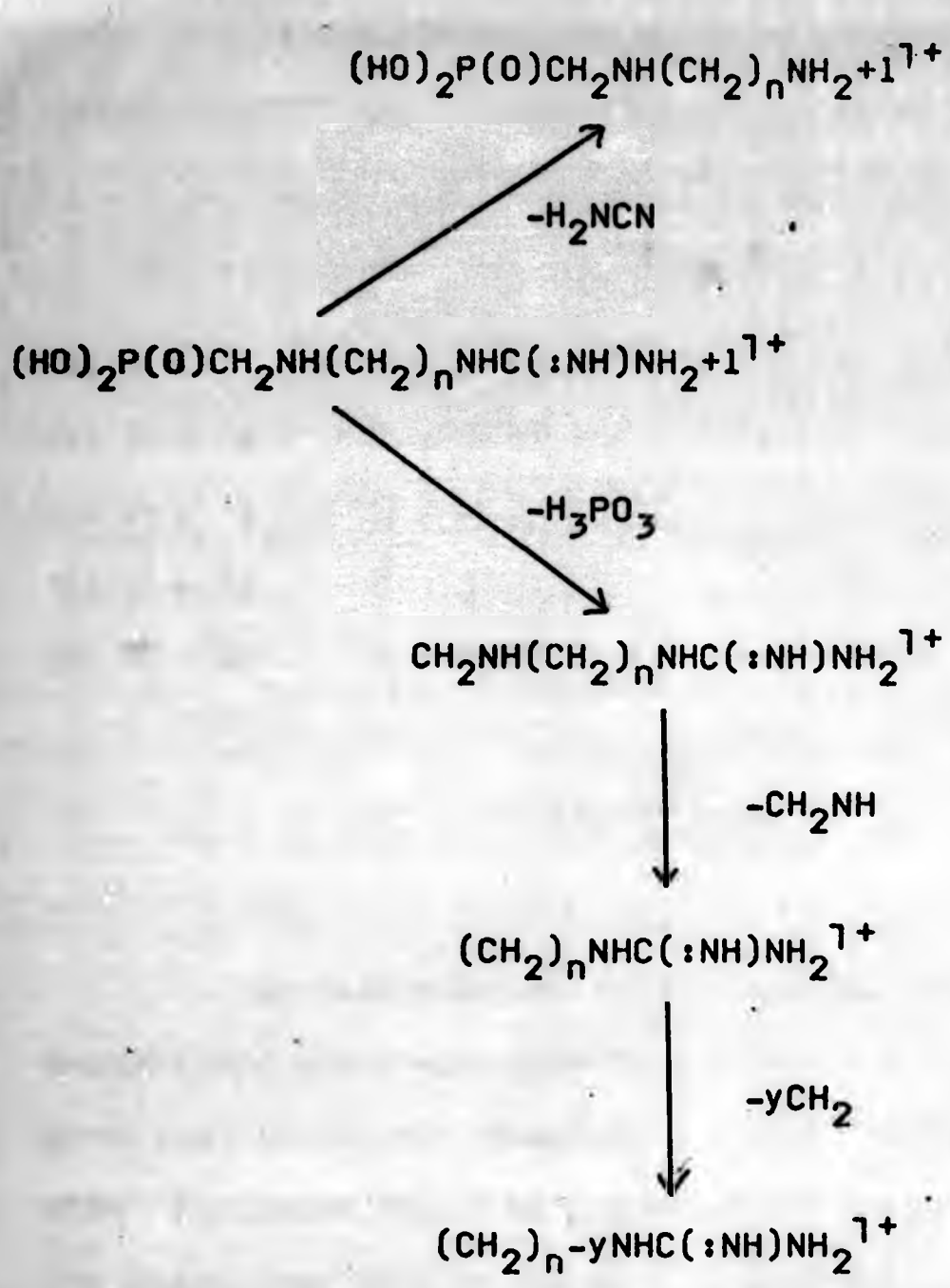
These guanidino compounds again reveal the M+1 ions as the base peaks (Table 30).

Table 30: Relative intensities (%) of the molecular ion in the FAB mass spectra of N-(ω-guanidinoalkyl)-aminoalkanephosphonic acids

$(HO)_2P(O)(CH_2)_mNH(CH_2)_nNHC(:NH)NH_2$

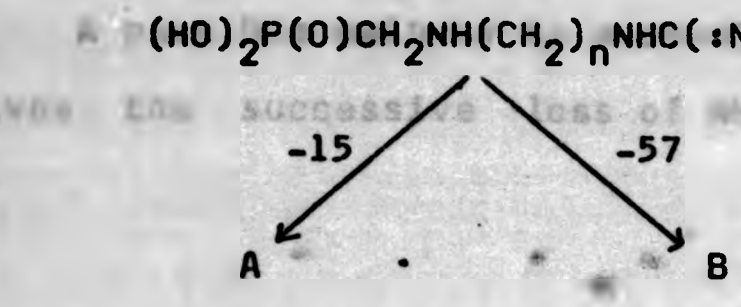
m	n	$M+1]^+$
1	4	100
1	6	100
1	8	100
2	8	100
1	10	100
1	12	100

The fragmentation of the N-(ω-guanidinoalkyl)-aminomethanephosphonic acids (Scheme 51) is similar in most respects to that observed for the corresponding amino analogues, the loss of the phosphonic acid group (as H_3PO_3) being followed by the stepwise loss of CH_2NH and of CH_2 units. In addition, the initial loss of NH_3 from the amino compounds is paralleled by the loss of cyanamide from the guanidine.



(Scheme 51)

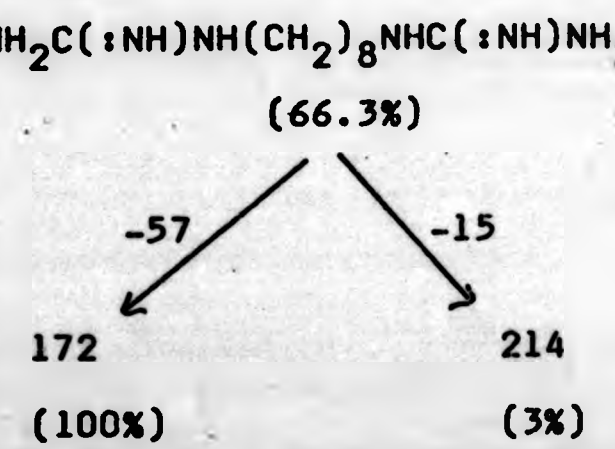
However, fragmentations involving the losses of 15 and 57 (Scheme 52) were also observed for these compounds.



for n = 4	A = 1.5%	B = 4.7%
for n = 6	A = 9.3%	B = 56.9%
for n = 8	A = 4.9%	B = 12.6%
for n = 10	A = 2.9%	B = 7.6%
for n = 12	A = 2.2%	B = 1.3%

(Scheme 52)

In our studies of the FAB ms of 1-guanidino- and ω-guanidino-alkanephosphonic acids no losses of 15 or 57 have been observed; however, similar fragmentations were also recorded for the sulphate of 1,8-diguanidino-octane for which the loss of 57 was predominant, giving the base peak at m/z 172 (Scheme 53).



(Scheme 53)

A possible pathway to account for these results involves the successive loss of NH and cyanamide (Scheme 54).

$$RCH_2NHC(:NH)NH_2{+}1]^+$$

$$\downarrow \quad -NH$$

$$RCH_2NHCNH_2{+}1]^+$$

$$\downarrow \quad -H_2NCN$$

$$RCH_3]^+$$

(Scheme 54)

R = $(HO)_2P(O)CH_2NH(CH_2)_{n-1}$

or $NH_2C(:NH)NH(CH_2)_{n-1}$

CHAPTER 4

PHOSPHORYLATED DERIVATIVES OF DODECYLGUANIDINE AND OF AMINES

In this synthetic programme we have been concerned so far with the synthesis of compounds containing the phosphonic acid and the guanidine groups not joined directly together, but by carbon chains of varying length. It was therefore of interest also to prepare derivatives in which the guanidine and phosphorus moieties were connected directly.

4.1 REACTION OF DIALKYL PHOSPHITES WITH DODECYLGUANIDINE

The Atherton-Todd reaction has been applied to an extremely wide variety of amines[101] but apparently not to guanidine compounds. It was our intention, therefore to condense the fungicide dodecylguanidine (83) with a dialkyl phosphite under these conditions (Scheme 55).

$$(RO)_2P(O)H + 2\ C_{12}H_{25}NHC(:NH)NH_2 \quad (83)$$

$$\downarrow\ CCl_4$$

$$(RO)_2P(O)NHC(:NH)NHC_{12}H_{25} \quad (84)$$

(Scheme 55)

The reaction was carried out by the addition of the phosphite to dodecylguanidine in carbon tetrachloride. A mild exothermic reaction ensued and the reaction mixture was allowed to cool. Separation of the desired product (84) was achieved after initial difficulties by evaporating the solvent, dissolving the residue in diethyl ether, and allowing the solution to stand overnight after which the required phosphoramidate was filtered off and recrystallised from diethyl ether. Two examples of this novel class of compound were synthesised (84, R = Me and Et) and were characterised by the usual methods.

A literature search revealed that Cramer and Vollmar[102] reported the preparation (Scheme 56) of a series of related guanidines (85) and in a separate publication[103]

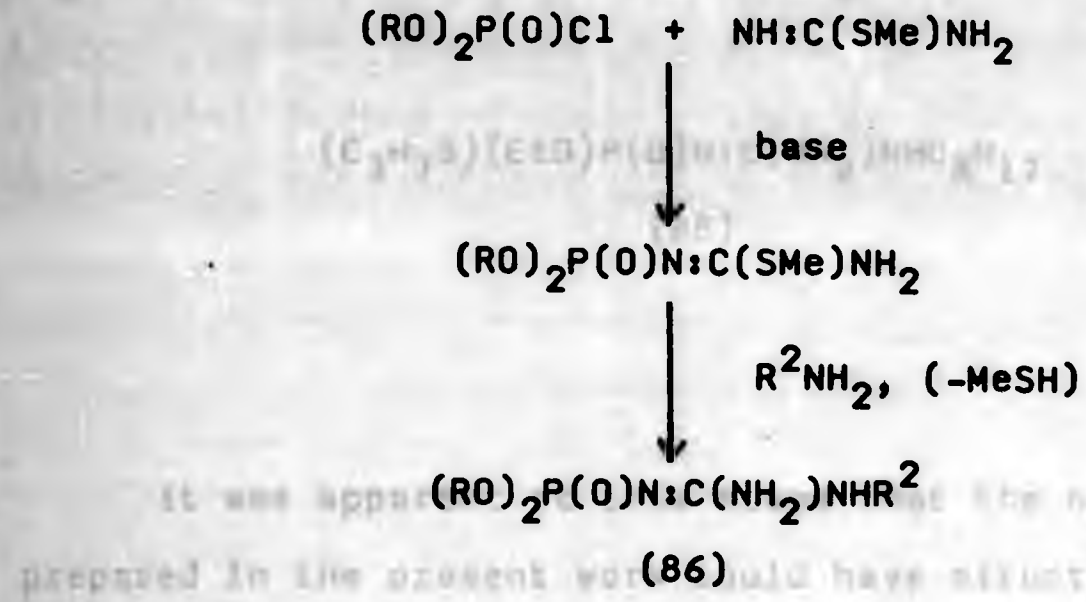
$$(RO)_2P(O)X + R^1NR^2C(:NH)NH_2 \longrightarrow (RO)_2P(O)N{:}C(NH_2)NR^1R^2$$

(85)

R = C_6H_5, R^1 = H or Me, R^2 = aryl, substituted aryl, H, Me, Et, or cyclohexyl, X = Cl or Br

(Scheme 56)

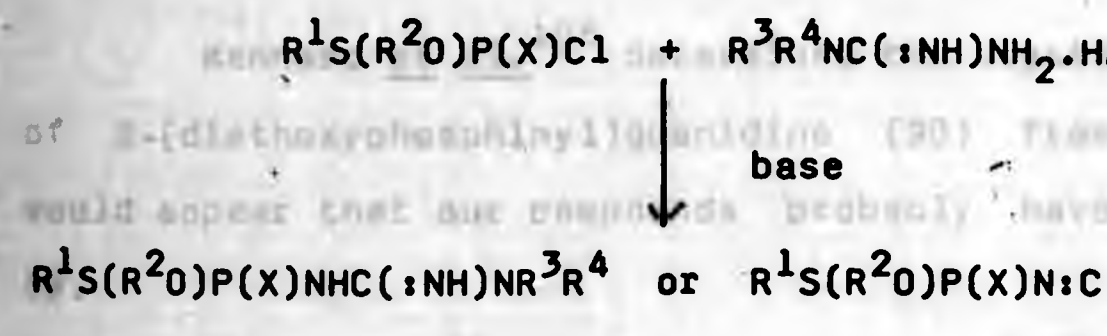
they reported a second method for the preparation of these and of some related compounds (86)(Scheme 57).



(86)

(Scheme 57)

A series of analogous thiophosphorylguanidine derivatives (87) were claimed as insectides in a German patent[104] (Scheme 58).



$R^1S(R^2O)P(X)NHC(:NH)NR^3R^4$ (87a) or $R^1S(R^2O)P(X)N:C(NH_2)NR^3R^4$ (87b)

X = O or S

HA = monobasic acid

(Scheme 58)

The closest compound reported in this patent[104] to the compounds prepared by us was the octyl analogue (88), although the method of preparation was different.

$$(C_3H_7S)(EtO)P(O)N{:}C(NH_2)NHC_8H_{17}$$

(88)

It was apparent at this stage that the new compounds prepared in the present work could have structure 84 or 89 or be a tautomeric mixture of both.

$$(RO)_2P(O)N{:}C(NH_2)NHC_{12}H_{25}$$

(89)

Kennard et al.[105] determined the crystal structure of 2-(diethoxyphosphinyl)guanidine (90) from which it would appear that our compounds probably have structure 89.

$$(EtO)_2P(O)N{:}C(NH_2)NH_2$$

(90)

An unusual feature of the ^{13}C nmr spectra of these compounds was that the guanidine carbon was revealed as a singlet and not as a doublet as expected. Mavrommatis *et al.*[106] have prepared a series of alkoxy- (91) and dimethylamino-phosphoramidates (92) in which they found that a $^{2}J_{PNC}$ coupling was always observed as was a $^{3}J_{PNCC}$.

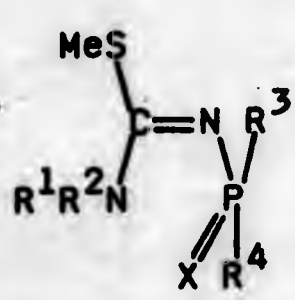
$(EtO)_2P(O)NHCH(CCl_3)NHCOR^1$

(91)

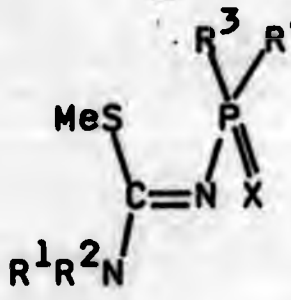
$(Me_2N)_2P(O)NHCH(CCl_3)NHCOR^1$

(92)

Negrebetskii *et al.*[107] have reported that S-alkyl-N-phosphinylisothioureas can exist in either a *syn* (93) or *anti* (94) form.



(93)



(94)

They found that $^{2}J_{PNC}$ coupling values vary from 0 - 10.3 Hz for the anti-arrangement of the phosphoryl and amino groups, but are zero or close to zero for the syn-arrangement, which is the predominant form especially at higher temperatures. Since the ^{13}C nmr spectra of our samples were recorded at the high temperature of 80 ^{o}C (because of the low solubility in DMSO-d_6 at room temperature) it may be reasonable to assume that the absence of $^{2}J_{PNC}$ coupling may be due to their existence predominantly in the syn-form at this temperature. However, in view of Mavrommatis's results[106] we decided to prepare the corresponding dimethylamino analogue (95) from N,N,N',N'-tetramethylphosphorodiamidic chloride and dodecylguanidine (Scheme 59).

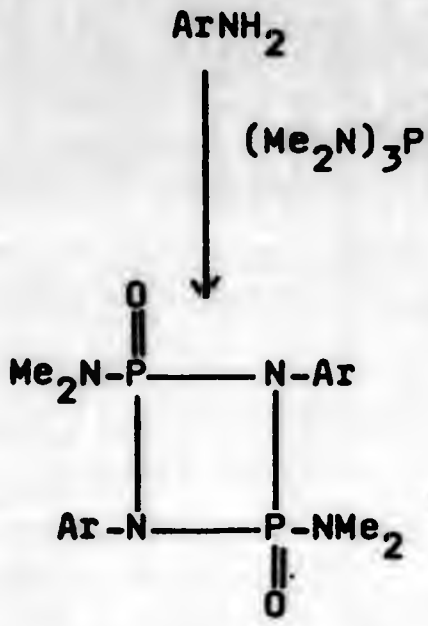
$$(Me_2N)_2P(O)Cl + 2C_{12}H_{23}NHC(:NH)NH_2 \longrightarrow (Me_2N)_2P(O)N{:}C(NH_2)NHC_{12}H_{25} + C_{12}H_{25}NHC(:NH)NH_2.HCl$$

(95)

(Scheme 59)

However, separation of the required product (95) from dodecylguanidinium chloride proved difficult, and the ^{13}C nmr spectrum of this mixture was recorded at 100 °C. In this case a $^{2}J_{PNC}$ coupling of 3.4 Hz was present which indicates that analogue 95 may exist in the anti-form, although further studies in this area are required.

4.2 PREPARATION OF N,N,N',N'-TETRAMETHYL-1,3-DIARYL-1,3,2,4-DIAZA-DIPHOSPHETIDINE-2,4-DIAMINE-2,4-DIOXIDES



(96)

Ar = aryl or substituted aryl

Three compounds (96) (Ar = phenyl, 2,4-dichlorophenyl and 3,5-dichlorophenyl) were prepared by heating the appropriate aromatic amine with hexamethylphosphoric triamide as described by Vesterager[108] for aniline. The dichlorophenyl analogues are new compounds and were found to be surprisingly insoluble in all solvents except hot pyridine or hot dimethyl sulphoxide. Their structures were confirmed by full elemental analysis and high resolution mass spectrometry.

With a view to incorporating the guanidino group into this type of molecule the reaction of dodecylguanidine with hexamethylphosphoric triamide was investigated but no reaction occurred and the dodecylguanidine was recovered unchanged.

CHAPTER 5

FUNGICIDAL ACTIVITY OF PHOSPHONIC ACIDS

CHAPTER 5

FUNGICIDAL ACTIVITY OF PHOSPHONIC ACIDS

5.1 NATURALLY OCCURRING AND SYNTHETIC BIOLOGICALLY ACTIVE PHOSPHONIC ACIDS

$(HO)_2P(O)CH_2CH_2NH_2$

(97)

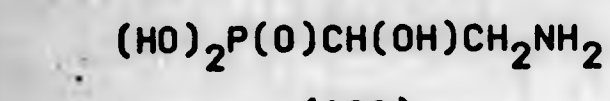
Until the isolation of 2-aminoethanephosphonic acid (97) from ciliated protozoa by Horiguchi and Kandatsu[84] all the organic phosphorus-containing compounds had been shown to have the carbon-containing portion of the molecule attached to oxygen, or less commmonly to nitrogen on the phosphorus atom.

2-Aminoethanephosphonic acid (97) was first isolated from a lipid hydrolysate[84] and was shown to be present in a lipid bound form.[80,81,109-114] It has subsequently been shown to be also included in protonaceous material.[115-9] Quin proposed that it could be bound into a polypeptide as a phosphate monoester, an amide or both.[120]

The isolation of 2-aminoethanephosphonic acid prompted the search for other naturally occurring compounds containing a P - C bond. The isolated compounds (98,[121] 99,[122] 100,[123] 101,[124] 102,[125-6] and 103,[127-9]) have been found to be predominantly phosphonic acids, some also containing nitrogen.

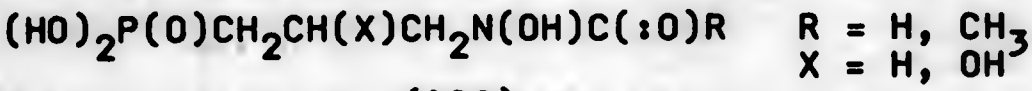
(98)

(99)

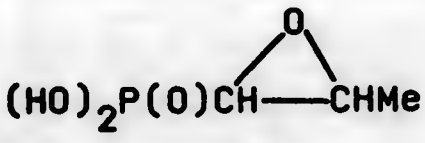


(100)

(101)

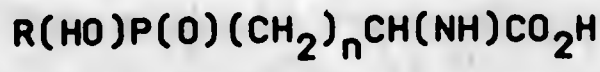


(102)



(103)

Kitteridge and Hughes,[130] in a search for likely precursors of 2-aminoethanephosphonic acid in living organisms, discovered the presence of 1-amino-2-phosphonopropionic acid (104, n = 1, R = OH) in the zoanthid Zoanthus sociatus and also in Tetrahymena.



(104)

Two synthetic analogues of this compound (104, n = 2, R = OH or Et) were previously reported by Mastalerz[131] who found them to be valuable inhibitors of cell-free glutamine-synthesising enzyme. Further studies of this inhibition have confirmed these results.[132-3]

However, Bayer et al.[134] isolated the analogous compound phosphinothricine (104, n = 2, R = Me) as its tripeptide phosphinothricyl-L-alanyl-L-alanine from cultures of Streptomyces viridochromogenes while Kondo et al.[135] also isolated this compound from Streptomyces hydroscopicus. It was found to be active against gram-negative and gram-positive bacteria and against the fungi Botrytis cinerea and the fungi that cause sheath blight and rice blast. In a patent[136] it has been claimed that 2-amino-3-{hydroxy(methyl)phosphinyl}-propionic acid (104, R=Me, n=1) shows fungicidal activity. Phosphinothricine (104, R = Me, n = 2) as its ammonium salt is being developed as a new herbicide for fruit and vine cultures.[137-8] It works more slowly than paraquat, but hinders the reappearence of perennial weeds for a longer period. Good results have been achieved at 1 Kg a.i./ha for annuals but perennials need higher doses.[139] The chemistry and biologial action of phosphinic acids has recently been reviewed by Maier.[140]

$(HO)_2P(O)CH_2NH_2$

(105)

Aminomethanephosphonic acid (105)[141-144] and glyphosate[145-146] (106) exhibit herbicidal and plant growth requlating properties. Glyphosate is an important commercial herbicide, usually formulated as its isopropylamine salt and sold under the trade name of Roundup. It is prepared by condensing chloromethanephosphonic acid and glycine in sodium hydroxide solution (Scheme 60).

$$(HO)_2P(O)CH_2Cl + H_2NCH_2CO_2H \xrightarrow{NaOH} (HO)_2P(O)CH_2NHCH_2CO_2H$$

(106)

(Scheme 60)

Kabachnik et al.[147] found that 1-aminophosphonic acids (107) possessed biological activity.

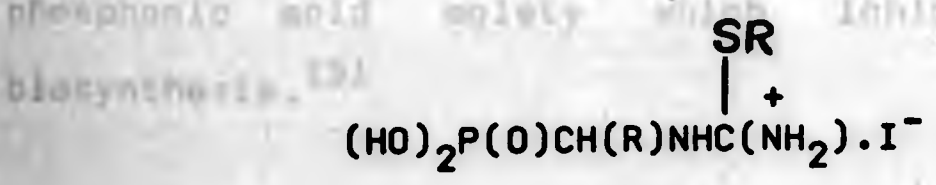
$(HO)_2P(O)CH(R)NH_2$

(107)

R = H, isoPr, isoBu, isoAm, Ph

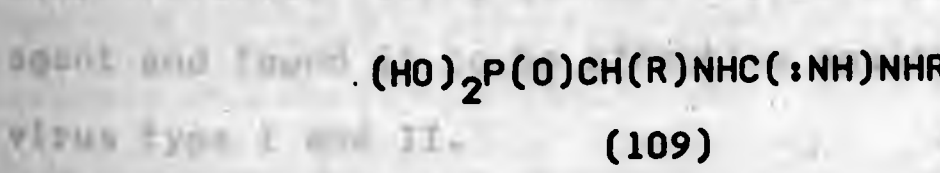
At high concentrations 1-aminobenzylphosphonic acid (107, R = Ph) was found to retard the growth of silkworm and bring about the death of chick embryos. It also retarded the propagation of tobacco mosaic virus and the growth of tobacco rootlets. Further studies suggested that these compounds were not true mimetics of aminocarboxylic acids since they did not compete with the latter in metabolism, and liver, kidney and plant tissue failed to show the ability to transform the carbon-bound phosphorus into inorganic phosphate.

Oleksyszyn and Tyka[148] reported the preparation of 1-(S-alkylisothiouronium)benzylphosphonic acid iodides (108) and the analogous N- substituted 1-guanidinobenzyl-phosphonic acids (109).



$(HO)_2P(O)CH(R)NHC(NH_2).I^-$

(108)



(109)

They found that preliminary studies on herbicidal and fungicidal activity failed to produce encouraging results.

Allen *et al.* have reported[149-50] that phosphonopeptides such as L-alanyl-L-1-aminoethanephosphonic acid (110) inhibit the growth of various . important pathogenic bacteria such as *Klebsiella aerogenes*, *Enterobacter* sp., *Seratia marcesens*, *Salmonella typhimurium* and *Staphylococcus aureus in vitro* and in infected animals.

$(HO)_2P(O)CH(CH_3)NHC(:O)CH(CH_3)NH_2$

(110)

They found that these compounds are transported into bacteria by means of peptide permeases located in the bacterium cytoplasmic membrane. Within the cell they are cleaved enzymatically to liberate an aminoalkanephosphonic acid moiety which inhibits cell wall biosynthesis.[151]

Yaouanc *et al.*152 synthesised 5-(phosphonomethyl)-1(H)-tetrazole (111) (Scheme 61) as a potential antiviral agent and found it to be effective against Herpes simplex virus type I and II.

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$(HO)_2P(O)CH(CH_3)NHC(:O)CH(CH_3)NH_2$

(110)

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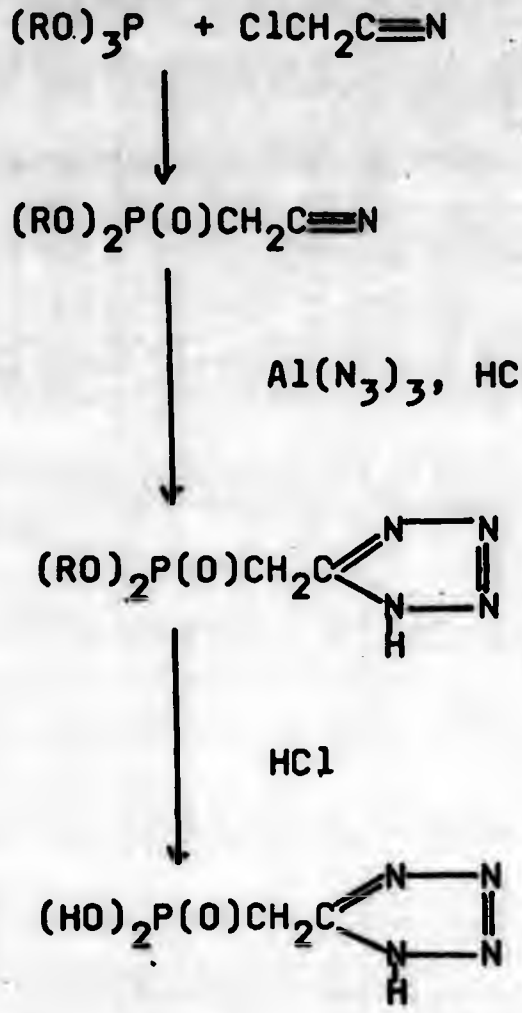


(111)

(Scheme 61)

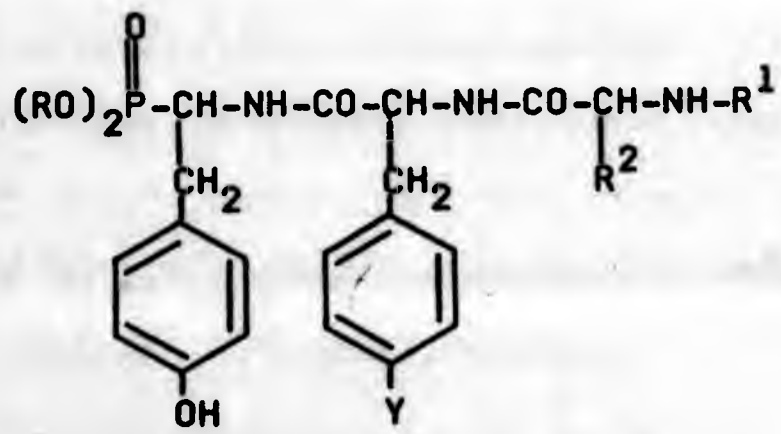
Another antiviral agent, phosphonoacetic acid (112) was found to inhibit replication of Herpes simplex virus types I and II.[153]

$(HO)_2P(O)CH_2CO_2H$

(112)

Preliminary results indicated that phosphonacetic acid is an inhibitor of viral-induced DNA polymerase, but not normal cell DNA polymerase, and that the inhibition is not a result of any interaction with template DNA.[154]

Quin[155] has reviewed the natural occurrence of compounds containing a phosphorus-carbon bond, whilst Hilderbrand et al.[156] have reviewed the distribution, metabolism and structure of naturally occurring alkylphosphonic acids.



(113)

R, R^1, R^3 = H, lower alkyl, substituted or non-substituted phenyl-alkyl or R^3CO-

R^2 = lower alkyl, Y = H or OH

The oligopeptides (113) have recently been claimed[157] to exhibit hypotensive activity. They were prepared by either synthetic methods or from Actinomadura or Actinomycetes. This is the first example of a 1-aminoalkanephosphonic acid that has been isolated from a living organism.

5.2 FUNGICIDAL SCREENING

5.2.1 *In vitro* Mycelial Growth On Agar

The fungi *Pyricularia oryzae* (subdivision *Deuteromycotina*), *Thanatephorus cucumeris* conidial stage *Rhizoctonia solani*, *Botrytis cinerea*, *Septoria nodorum*, *Fusarium avenaceum* and *Dreschlera sativa* were used in *in vitro* tests on agar plates.

The test compounds were suspended in the agar to give 300, 500 or 1000 ppm, and the suspension was sterilized and shaken thoroughly to distribute the compounds evenly before pouring into standard (9 cm diameter) Petri plates. A 5 mm plug with growing mycelia was placed upside down in the centre of each plate and the plates were then incubated at 28 ^{o}C. The growth diameter was measured and compared with untreated (control) plates.

5.2.2 *In vivo* Seed Treatment

Spring-barley (Tellus 374) infected with *Pyrenophora teres* (subdivision *Ascomycotina*) conidial stage of *Dreschlera teres* and winter-wheat (Holme 3055) infected with *Leptosphaeria nodorum* (subdivision *Ascomycotina*) conidial stage of *Septoria nodorum* were used in the experiments. The seeds were treated (10 min. in a laboratory seed-treatment machine) with formulations containing 20% (w/w or w/v) of test compound. When the

compound was sufficiently soluble in water, aqueous solutions were used. Compounds insoluble in water were applied as powders. The dosage rate was 2 cm^3 (2 g) per kilo of seed. 200 Seeds of each teatment were placed on a moistened filter paper and incubated at 10 ^oC (3 days) and then at 20 ^oC (4 days). The coleoptile and roots of the seeds were then examined for disease symptom and compared with untreated (control) seeds.

For the in vivo and in vitro tests the results are reported on a scale of 1 to 5 where:

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

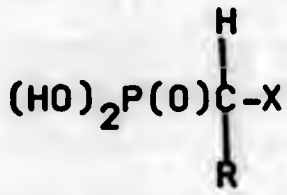
The following abbreviations are used in the Tables:-

P.o	Pyricularia oryzae
R.s	Rhizoctonia solani
B.c	Botrytis cinerea
S.n	Septoria nodorum
F.s	Fusarium avenaceum
D.s	Dreschlera sativa
D.t	Dreschlera teres

5.3 RESULTS OF FUNGICIDAL SCREENING

The results from the screening experiments are presented below for compounds of similar structure.

Table 31: Fungicidal activity of 1-substituted alkanephosphonic acids (114)



(114)

			in vitro				in vivo	
R	X	Conc.	P.o	R.s	B.c	S.n	D.t	S.n
H	NH_2	500	1	2	1	1	-	-
H	$NHC(:NH)NH_2$	300	1	1	1	-	-	-
Et	NH_2	500	1	3	1	2	3	3
Me	$NHC(:NH)NH_2$	300	1	1	1	-	2	2
Et	$NHC(:NH)NH_2$	300	1	1	1	-	1	2
C_7H_{15}	OH	500	4	1	1	1	-	-
C_7H_{15}	$NHC(:S)NH_2$	500	3	2	3	4	1	1
C_7H_{15}	*	500	3	4	3	4	1	1
C_7H_{15}	$NHC(:NH)NH_2$	300	1	2	1	3	1	1
Panoctine		500	5	5	5	5	1	2

* = $NHC(:S)NHCH(C_7H_{15})P(O)(OH)_2$

The results for the substituted octanephosphonic acids ($R=C_7H_{15}$) showed some rather interesting structure-activity relationships. 1-Thioureido-octanephosphonic acid showed moderate activity against *P. oryzae*, *B. cinerea* and *S. nodorum* *in vitro*, whilst the di-octanephosphonic acid analogue showed about the same activity for these fungi, but a higher leval of control against *R. solani*. 1-Hydroxyoctanephosphonic acid (X = OH), a synthetic intermediate was included in these tests as a marker for the octanephosphonic acid group. It was found to possess the best activity against *P. oryzae* but its activity against the other fungi was low.

A comparison of the 1-guanidinoalkanephosphonic acids (R = H, Me, Et and C_7H_{15}) shows that *in vitro* (300 ppm) the activity is very low, the better control being shown by the octane analogue. The *in vivo* results for these compounds conflict with those obtained for the *in vitro* tests since the shorter chain analogues (R = Me, Et) appear to be better than the octane analogue, however in all cases the activity was low.

1-Aminopropanephosphonic acid was found to possess moderate activity *in vitro* at 500 ppm against *R. solani* and *S. nodorum* though its control of *P. oryzae* and *B. cinerea* was low. However, at 1000 ppm it gave quite good control of *P. oryzae* but its activity against *B. cinerea* was still poor. It was more active *in vivo* against *D. teres* and *S. nodorum* than the commercial fungicide Panoctine.

Table 32: Fungicidal activity of ω-aminoalkanephosphonic acids *in vitro*

$(HO)_2P(O)(CH_2)_nNH_2$

(36)

Formula	Conc.	P.o	R.s	B.c	S.n	D.s
$(HO)_2P(O)CH_2NH_2$	500	1	2	1	1	-
$(HO)_2P(O)(CH_2)_2NH_2$	500	1	2	1	1	-
$(HO)_2P(O)(CH_2)_3NH_2$	500	2	3	2	2	-
$(HO)_2P(O)(CH_2)_4NH_2$	500	1	1	1	1	-
$(HO)_2P(O)(CH_2)_8NH_2$	1000	1	1	1	1	1
$(HO)_2P(O)(CH_2)_{11}NH_2$	1000	1	1	1	1	1
$(EtO)_2P(O)(CH_2)_4NPht$	500	3	1	3	1	-

NPht = phthalimido

The results in Table 32 indicate that the activity *in vitro* of these compounds increases up to 3-aminopropanephosphonic acid (36, n = 3) for *P. oryzae*, *R. solani*, *B. cinerea* and *S. nodorum* but increasing the chain length further results in loss of activity, even at 1000 ppm. Therefore in this series of compounds the optimum alkyl chain length appears to be three.

3-Aminopropanephosphonic acid is the structural isomer of 1-aminopropanephosphonic acid and a comparison of the fungicidal activty of these two compounds (Tables 31 and 32) shows that while both have similar activity against R. solani and S. nodorum the 3-amino analogue is superior against P. oryzae and B. cinerea. We have found 1-aminopropanephosphonic acid to be superior to Panoctine in vivo, therefore we might also expect 3-aminopropane-phosphonic acid to show interesting activity in vivo.

O,O-Diethyl 4-(N-phthalyl)butanephosphonate was found to be moderately active against the organisms tested.

Table 33: Antifungal activity of ω-guanidinoalkanephosphonic acids *in vitro*

$(HO)_2P(O)(CH_2)_nNHC(:NH)NH_2$

(32)

n	Conc.	P.o	R.o	B.s	S.n	F.a	D.s
1	300	1	1	1	-	-	-
2	300	1	1	1	1	-	-
3	300	1	1	1	-	-	-
4	300	1	1	1	-	-	-
6	300	2	1	1	-	-	-
8	1000	1	1	1	1	3	1

This homologous series of compounds failed to show any significant activity, though in this case most of the tests were at 300 ppm. However, 8-guanidino-octane-phosphonic acid (32, n = 8) tested at 1000 ppm also had little activity. These compounds are structural isomers of the 1-guanidinoalkanephosphonic acids whose fungicidal activity is described above (Table 31). It is apparent from a comparison of the results contained in Tales 31 and 33 that guanidinoalkanephosphonic acids have better activity if the guanidino group is α instead of ω.

Table 34: Antifungal activity of N-(ω-aminoalkyl)aminomethane-phosphonic acids *in vitro*

$(HO)_2P(O)CH_2NH(CH_2)_nNH_2$

(59)

n	Conc.	P.o	R.s	B.c	S.n	F.a	D.s
2	500	2	1	1	2	-	-
	1000	2	-	-	2	-	4
4	500	1	1	1	2	-	-
	1000	-	-	-	1	1	3
6	500	1	1	1	3	-	-
	1000	-	-	-	2	-	-
8	500	1	1	1	1	-	-
	1000	-	-	-	-	1	3
10	500	1	1	1	2	1	4
	1000	-	-	-	2	-	4
12	500	1	3	2	1	-	-
	1000	-	1	-	1	2	5
Panoctine	500	5	5	5	5	1	5

From the results in Table 34 it would appear that while these compounds have similar activity against *D. sativa* and *S. nodorum* their activity against *P. oryzae*, *R. solani*, *B. cinerea* and *F. avenaceum* was poor.

We can compare the fungicidal activity of N-(ω-aminoalkane)aminomethanephosphonic acids with ω-aminoalkanephosphonic acids· which have the same number of atoms between the phosphonic and primary amino groups. For 4-aminobutanephosphonic acid (Table 32) and N-(2-aminoethane)aminomethanephosphonic acid (Table 32) both compounds have low fungicidal activity, the better activity being shown by the latter compound. Similary 8-amino-octanephosphonic acid (Table 32) and N-(6-amino-hexyl)aminomethanephosphonic acid (Table 34) have comparable activity against *P. oryzae*, *R. solani* and *B. cinerea* whilst the latter compound is more active against *S. nodorum*.

Table 35: Antifungal activity of N-(ω-guanidinoalkyl)-aminomethanephosphonic acids *in vitro*

$(HO)_2P(O)CH_2NH(CH_2)_nNHC(:NH)NH_2$

(72)

n	Conc.	P.o	R.s	B.c	S.n	F.a	D.s
6	300	1	1	1	1	-	-
	1000	2	1	1	-	1	3
8	500	2	1	1	1	-	-
	1000	3	-	-	3	3	4
10	500	5	2	5	5	2	5
	1000	-	3	-	-	3	-
12	500	1	1	1	2	1	4
	1000	1	-	-	2	-	-
Panoctine	500	5	5	5	5	1	5

Antifungal activity appears to increase with chain length (Table 35). Optimum activity is achieved with a chain length of 10 carbon atoms. This homologue, N-(10-guanidinodecyl)aminomethanephosphonic acid monohydrate had good activity against the test fungi. It also appeared to possess some activity against F. avenaceum whereas the commercial compound Panoctine has none. We can compare the activity (at 1000 ppm) of N-(6-guanidinohexyl)aminomethanephosphonic acid (Table 35) with that of 8-guanidino-octanephosphonic acid (Table 33) since both

compounds have the same number of atoms between the phosphonic and guanidino groups. For R. solani and B. cinerea their activity is similar whereas the N-(6-guanidinohexyl)- compound is superior against P. oryzae and D. sativa while 8-guanidino-octanephosphonic acid is better against F. avenaceum.

Table 36: Antifungal activity of N-(ω-amino-octyl)- and N-(ω-guanidino-octyl)-aminoalkanephosphonic acids (115) in vitro at 500 ppm

$(HO)_2P(O)(CH_2)_mNH(CH_2)_8NH\text{-}X$

(115)

m	X	P.o	R.s	B.c	S.n	F.a	D.s
		in vitro (500 ppm)				in vivo	
1	H	1	1	1	1	-	-
2	H	1	1	1	1	1	4
1	$C(:NH)NH_2$	2	1	1	1	-	-
2	$C(:NH)NH_2$	1	1	1	1	1	3
Panoctine		5	5	5	5	1	5

We can see (Table 36) that inclusion of an extra methylene group between the phosphonic and secondary amino group groups does not appear to have affected the fungicidal activity.

N-(8-Amino-octyl)aminoethanephosphonic acid (115, m = 2, X = H) and 11-aminoundecanephosphonic acid (Table 32)

both have the same number of atoms between the phosphonic and primary amino groups. A comparison of the fungicidal activity of these two compounds reveals that while activity is low in both cases the former compound possessed better activity against D. sativa.

Table 37: Antifungal activity of analogues of dodecylguanidine

(116) $CH_3(CH_2)_{10}CH_2NHC(:NH)NH_2.CH_3CO_2H$

(117) $CH_3(CH_2)_{10}C(:O)NHC(:NH)NH_2.HCl$

(118) $CH_3(CH_2)_{10}NHC(NH_2):NP(O)(OMe)_2$

(119) $CH_3(CH_2)_{10}NHC(NH_2):NP(O)(OEt)_2$

(120) $(HO)_2P(O)CH_2NHCH_2(CH_2)_{10}CH_2NHC(:NH)NH_2$

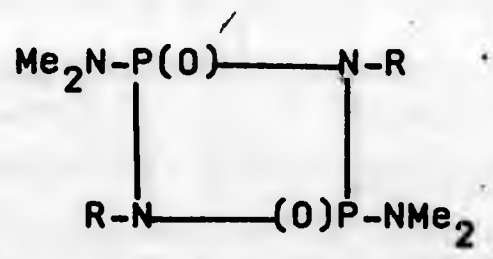
(121) $(HO)_2P(O)CH_2NHCH_2(CH_2)_8CH_2NHC(:NH)NH_2$

	in vitro (500 ppm)				*in vivo*	
Compound	P.o	R.s	B.c	S.n	D.t	S.n
(116)	4	4	5	4	1	2
(117)	2	3	3	4	1	1
(118)	4	4	5	5	2	1
(119)	4	4	5	4	2	1
(120)	11	1	1	2	-	-
(121)	5	2	5	5	-	-

A comparison of the activity of the commercial standard dodine (116) with the other compounds in Table 37 revealed some rather surprising variations. The acyl derivative (117) appears to have much less activity both

in vitro and *in vivo*. Replacement of the imino hydrogen in dodine by a dialkoxy phosphinyl group resulted in compounds (118 and 119) which have comparable activity *in vitro*. The *in vivo* results for (118) and (119) show better activity against *D. teres* than dodine but less activity against *S. nodorum*. Compound 120 (in which a hydrogen of the methyl group in dodine has been replaced by an aminomethanephosphonic acid group) has poor activity whilst compound 121 which has the same chain length as dodine has better activity than it against *P. oryzae*, *B. cinerea* and *S. nodorum* but less activity against *R. solani*.

Table 38: Antifungal activity of dichlorophenyl phosphetidines *in vitro* at 500 ppm



R	P.o	R.s
2,4-Dichlorophenyl	1	2
3,5-Dichlorophenyl	1	3

Both compounds showed some toxicity to *R. solani*, the better activity being displayed by the 3,5-substituted isomer.

CHAPTER 6

EXPERIMENTAL

6.1 STARTING MATERIALS AND SUPPLIER

Ethanal	Hopkins and Williams
Propanal	Hopkins and Williams
Octanal	Aldrich Chemical Company
Decanal	Aldrich Chemical Company
Dodecanal	Aldrich Chemical Company
Paraformaldehyde	British Drug House
Thiourea	Hopkins and Williams
Ethyl carbamate	Aldrich Chemical Company
Propylene oxide	Aldrich Chemical Company
1,2-Dibromoethane	Aldrich Chemical Company
1,8-Dibromo-octane	Aldrich Chemical Company
1,10-Dibromodecane	Aldrich Chemical Company
1,12-Dibromododecane	Aldrich Chemical Company
1,2-Diaminoethane	Aldrich Chemical Company
1,4-Diaminobutane	Aldrich Chemical Company
1,6-Diaminohexane	Aldrich Chemical Company
1,8-Diamino-octane	Aldrich Chemical Company
1,10-Diaminodecane	Aldrich Chemical Company
1,12-Diaminododecane	Aldrich Chemical Company
Aniline	Hopkins and Williams
2,4-Dichloroaniline	Koch Light Laboratories
3,5-Dichloroaniline	Aldrich Chemical Company
Lauroyl chloride	Aldrich Chemical Company
Acetyl chloride	Aldrich Chemical Company
Acetamide	Hopkins and Williams

6.1 STARTING MATERIALS AND SUPPLIER

Ethanal	.Hopkins and Williams
Propanal	Hopkins and Williams
Octanal	Aldrich Chemical Company
Decanal	Aldrich Chemical Company
Dodecanal	Aldrich Chemical Company
Paraformaldehyde	British Drug House
Thiourea	Hopkins and Williams
Ethyl carbamate	Aldrich Chemical Company
Propylene oxide	Aldrich Chemical Company
1,2-Dibromoethane	Aldrich Chemical Company
1,8-Dibromo-octane	Aldrich Chemical Company
1,10-Dibromodecane	Aldrich Chemical Company
1,12-Dibromododecane	Aldrich Chemical Company
1,2-Diaminoethane	Aldrich Chemical Company
1,4-Diaminobutane	Aldrich Chemical Company
1,6-Diaminohexane	Aldrich Chemical Company
1,8-Diamino-qctane	Aldrich Chemical Company
1,10-Diaminodecane	Aldrich Chemical Company
1,12-Diaminododecane	Aldrich Chemical Company
Aniline	Hopkins and Williams
2,4-Dichloroaniline	Koch Light Laboratories
3,5-Dichloroaniline	Aldrich Chemical Company
Lauroyl chloride	Aldrich Chemical Company
Acetyl chloride	Aldrich Chemical Company
Acetamide	Hopkins and Williams

Hydroxylamine hydrochloride	Hopkins and Williams
Triethylamine	Hopkins and Williams
1-Chloro-8-hydroxyoctane	Lancaster synthesis
1-Bromo-11-hydroxyundecane	Aldrich Chemical Company
Hexane-1,6-diol	Aldrich Chemical Company
N-Bromomethylphthalimide	Lancaster synthesis
N-(2-Bromoethyl)phthalimide	Aldrich Chemical Company
N-(3-Bromopropyl)phthalimide	Aldrich Chemical Company
N-(4-Bromobutyl)phthalimide	Aldrich Chemical Company
S-Methylisothiouronium sulphate	Aldrich Chemical Company
Guanidine hydrochloride	Aldrich Chemical Company
Thionyl chloride	British Drug House
Phosphorus trichloride	Aldrich Chemical Company
Phosphorus pentachloride	Rose Chemical Company
Phosphorous acid	Aldrich Chemical Company
Dimethyl phosphite	British Drug House
Diethyl phosphite	Aldrich Chemical Company
Triethyl phosphite	Aldrich Chemical Company
Triphenyl phosphite	Aldrich Chemical Company
Triphenylphosphine	Aldrich Chemical Company
Hexamethylphosphoric triamide	Aldrich Chemical Company
Bromine	Aldrich Chemical Company
Potassium phthalimide	Aldrich Chemical Company
Barium chloride dihydrate	Aldrich Chemical Company
Sodium metal	British Drug House
Potassium hydroxide	Hopkins and Williams
Sodium hydroxide	British Drug House

Magnesium sulphate	British Drug House
Kieselguhr	Hopkins and Williams
Selenium kjeldahl tablets	British Drug House
Phosphorus pentoxide	Hopkins and Williams
Hydrochloric acid	British Drug House
Hydrobromic acid	British Drug House
Sulphuric acid	British Drug House
Nitric acid	British Drug House
Ammonia solution	British Drug House
Hydrogen chloride	British Oxygen Company
Ammonia	British Oxygen Company

1,13-Diamino-7-azatridecane was obtained by purification by distillation of a sample of Batch Kettle Residue from the industrial preparation of 1,6-diaminohexane from adiponitrile (Monsanto Chemical Company). The compound was isolated in a pure state after fractionating three times through a 10 cm Vigreux column as a colourless oil which solidified on cooling, b.p. 152-154 ^{o}C at 0.04 mm, ^{13}C (D_2O/D_2SO_4) 25.8, 25.9 and 26.0 ($NH_2CH_2\underline{(CH_2)_3}$), 27.2 ($\underline{CH_2}CH_2NH$), 40.7 ($\underline{CH_2}NH_2$), 48.5 ($\underline{CH_2}NH$).

6.2 INSTRUMENTAL ANALYSIS

6.2.1 NUCLEAR MAGNETIC RESONANCE

Routine proton magnetic resonance (1H nmr) spectra were obtained using a Perkin Elmer R12B continuous wave spectrometer at a field of 60 MHz.

Higher field ^{1}H nmr spectra were recorded at 80.018 MHz on a Brucker WP-80 Fourier Transform spectrometer equipped with a BNC 28 computer, B-VT-1000 variable temperature unit and a 10 mm multinuclear probe head which also allowed us to record carbon (^{13}C) nmr spectra at 20.12 MHz and phosphorus (^{31}P) nmr spectra at 32.395 MHz.

High field ^{1}H nmr (220 MHz) spectra were obtained at 35 ^{o}C in 5 mm diameter sample tubes on a Perkin Elmer R34 continuous wave spectrometer equipped with a super-conducting magnet at the Physio Chemical Measurements Unit, Harwell (PCMU).

High Field ^{13}C and ^{15}N nmr spectra were recorded in 25 mm sample tubes on a Brucker WH 180WB Fourier Transform spectrometer equipped with a Nicolet 1180 computer, at PCMU.

Sodium 3-trimethylsilylpropionate (tsp) was used as internal standard for the ^{1}H and ^{13}C nmr when the spectra were recorded in aqueous solution. For non-aqueous solutions, tetramethylsilane (tms) was used as internal standard.

The ^{31}P chemical shifts were recorded relative to an 85% solution of phosphoric acid contained in an external concentric tube.

^{1}H, ^{13}C, and ^{31}P nmr chemical shifts are reported positive downfield from the standard in ppm.

Similarily ^{15}N chemical shifts were recorded relative to neat nitromethane contained in an external concentric tube. The chemical shifts are reported negative upfield of the standard.

Where D_2O/D_2SO_4 has been reported as the solvent the concentration of each is ca. 50%.

6.2.2 INFRARED SPECTROSCOPY

Infrared spectra over the region 700 - 4000 cm^{-1} were recorded as potassium bromide discs or as a film or smear between two sodium chloride plates on Pye Unicam SP2000 and SP3-200 spectrophotometers.

6.2.3 MASS SPECTROMETRY

Routine mass spectra of volatile organic compounds were recorded on an A.E.I. MS9 double focussing spectrometer.

High resolution electron impact (e.i.) mass spectra were recorded at PCMU on a V.G. Micromass ZAB-IF double focussing organic mass spectrometer with a mass range up to 1700 u at 8 Kv with a mass measurement accuracy of 2 in 10^6 at an electron energy of 70 eV. Accurate mass measurements were carried out at 10,000 resolution (10 % valley).

The mass spectra of involatile compounds were also recorded on this machine using a VG Fast Atom Bombardment (FAB) source and probe. Samples were prepared in glycerol solution and deposited on the stainless steel probe tip. The primary beam of Xenon atoms was produced from an ion gun (Ion Tech Ltd.) operating at 1.0 mA, 8 KV.

In reporting the spectra the abbreviation G is used to denote glycerol.

All accurate masses for compounds containing chlorine are reported for the ^{35}Cl isotope.

6.2.4 THERMOGRAVIMETRIC ANALYSIS

Thermogravimetric analysis (T.G.A.) was obtained using a Stanton thermobalance. A constant downward flow of nitrogen was maintained in the oven with a linear rise of temperature of 50 ^{o} or 100 ^{o}C/hour.

6.2.5 CARBON, HYDROGEN AND NITROGEN ANALYSIS

Microanalysis of carbon, hydrogen and nitrogen was carried out on Perkin Elmer 240B elemental analysers at the Polytechnic of North London and at Butterworths Laboratories Ltd.

6.2.6 CHLORINE ANALYSIS

A sample of the compound was accurately weighed by difference in a gelatin capsule. This was then inserted into a platinum basket together with a fuse of ashless filter-paper. The fuse was lit and the basket quickly placed into a 3 L flask previously charged with a solution of sodium hydroxide (ca. 30 cm^3) and oxygen.

After combustion was complete the contents of the flask were transferred to a 250 cm^3 conical flask with thorough washings to ensure complete transfer. The resultant solution was acidified with nitric acid, an appropriate quantity of silver nitrate added (usually

50 cm^3 of a 0.1 M solution) and this solution titrated with sodium thiocyanate solution (using Ferric alum indicator). The silver nitrate and thiocyanate solutions were standardised against AnalaR sodium chloride.

6.2.7 PHOSPHORUS ANALYSIS

An accurately weighed sample of the compound was transferred into a Kjeldahl flask together with concentrated sulphuric acid (ca. 15 cm^3) and one selenium Kjeldahl catalyst tablet. This solution was then heated under reflux (air condensor) for 2 hours and allowed to cool. Concentrated nitric acid was then added and the resultant solution again heated under reflux (ca. 12 h) and allowed to cool. The contents were then transferred to a 1 L beaker and the solution made alkaline with concentrated ammonia solution. It was then acidified to methyl red with concentrated hydrochloric acid and magnesia mixture (30 cm^3) added. Ammonia was again added until the solution was just basic and then it was left to stand overnight.

The precipitate that formed was filtered off through a no. 4 sinter crubible and washed with dilute ammonia solution (2x20 cm^3). The precipitate was dissolved in hot, dilute hydrochloric acid, magnesia mixture (5 cm^3) added and ammonia solution added until the solution was just basic and again left to stand overnight.

The precipitate that formed was filtered off, washed successively with ammonia solution (20 cm^3), ethanol (20 cm^3) and diethyl ether (2x20 cm^3) and placed in a desiccator. The precipitate of magnesium ammonium phosphate hexahydrate was weighed and hence the phosphorus content was determined.

The magnesia mixture was prepared by dissolving magnesium chloride hexahydrate (50 g) and ammonium chloride (100 g) in water (500 cm^3).

Phosphorus was also determined by Butterworth Laboratories Ltd. by fusion followed by spectophotometric techniques.

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LIST OF EXPERIMENTS

6.27 Preparation of guanidinomethanephosphonic acid

6.28 Preparation of 2-guanidinoethanephosphonic acid

6.29 Preparation of 3-guanidinoprqpanephosphonic acid

6.30 Preparation of 4-guanidinobutanephosphonic acid

6.31 Preparation of 6-guanidinohexanephosphonic acid

6.32 Preparation of 8-guanidino-octanephosphonic acid

6.33 Preparation of 1-hydroxyoctanephosphonic acid

6.34 Preparation of 1-chloro-octanephosphonic acid

6.35 Preparation of 1-chloro-octanephosphonyl dichloride

6.36 Preparation of chloromethanephosphonyl dichloride

6.37 Preparation of chloromethanephosphonic acid

6.38 Attempted condensation of 1-chloro-octanephosphonic acid and guanidine

6.39 Attempted condensation of chloromethanephosphonic acid and guanidine

6.40 Attempted condensation of chloromethanephosphonic acid and dodecylguanidine

6.41 Attempted condensation of 1-chloro-octanephosphonic acid and 1,8-diamino-octane

6.42 Attempted condensation of chloromethanephosphonic acid with 1,8-diamino-octane in pyridine

6.43 Preparation of N-(2-aminoethyl)aminomethane-phosphonic acid monohydrate

6.44 Preparation of N-(4-aminobutyl)aminomethane-phosphonic acid monohydrate

6.45 Preparation of N-(6-aminohexyl)aminomethane-phosphonic acid monohydrate

6.46 Preparation of N-(8-amino-octyl)aminomethane-phosphonic acid monohydrate

6.47 Preparation of N-(8-amino-octyl)-2-aminoethane-phosphonic acid monohydrate

6.48 Preparation of N-(10-aminodecyl)aminomethane-phosphonic acid monohydrate

6.49 Preparation of N-(12-aminododecyl)aminomethanephosphonic acid monohydrate

6.50 Preparation of N-(13-amino-7-azatridecyl)-aminomethanephosphonic acid monohydrate

6.51 Reaction of N-(2-aminoethyl)aminomethanephosphonic acid and S-methylisothiouronium chloride to yield 1-phosphonomethyl-2-iminoimidazolidine

6.52 Preparation of N-(4-guanidinobutyl)aminomethanephosphonic acid monohydrate

6.53 Preparation of N-(6-guanidinohexyl)aminomethanephosphonic acid monohydrate

6.54 Preparation of N-(8-guanidino-octyl)aminomethanephosphonic acid monohydrate

6.55 Preparation of N-(8-guanidino-octyl)-2-aminoethanephosphonic acid monohydrate

6.56 Preparation of N-(10-guanidinodecyl)aminomethanephosphonic acid monohydrate

6.57 Preparation of N-(12-guanidinododecyl)aminomethanephosphonic acid monohydrate

6.58 Preparation of N-(12-ureidododecyl)aminomethanephosphonic acid monohydrate

6.59 Preparation of octane-1,8-diguanidinium sulphate

6.60 Preparation of 1-dodecyl-2-(diethoxyphosphinyl)guanidine

6.61 Preparation of 1-dodecyl-2-(dimethoxyphosphinyl)guanidine

6.62 Reaction of N,N,N',N'-tetramethylphosphorodiamic-chloride with dodecylguanidine

6.63 Preparation of N,N,N',N'-tetramethyl-1,3-diphenyl-1,3,2,4-diazadiphosphetidine-2,4-diamine-2,4-dioxide

6.64 Preparation of N,N,N',N'-tetramethyl-1,3-bis-(2,4-dichloro-phenyl)-1,3,2,4-diazadiphosphetidine-2,4-diamine-2,4-dioxide

6.65 Preparation of N,N,N',N'-tetramethyl-1,3-bis-(3,5-dichloro-phenyl)-1,3,2,4-diazadiphosphetidine-2,4-diamine-2,4-dioxide

PREPARATION OF INTERMEDIATES AND REAGENTS

6.66 Preparation of octanaldoxime

6.67 Preparation of dodecanamide

6.68 Preparation of acetylguanidinium chloride

6.69 Preparation of dodecanoylguanidinium chloride

6.70 Preparation of O,O-diethyl 2-bromoethanephosphonate

6.71 Preparation of 6-chlorohexaN-1-ol

6.72 Preparation of N-(6-hydroxyhexyl)phthalimide

6.73 Preparation of N-(6-chlorohexyl)phthalimide

6.74 Attempted preparation of O,O-diethyl 8-bromo-octanephosphonate

6.75 Attempted preparation of N-(8-bromo-octyl)phthalimide

6.76 Preparation of N-(8-hydroxyoctyl)phthalimide

6.77 Preparation of N-(8-bromo-octyl)phthalimide

6.78 Preparation of N-(11-hydroxyundecyl)phthalimide

6.79 Preparation of N-(11-bromoundecyl)phthalimide

6.80 Preparation of dodecylguanidine

6.81 Preparation of bromomethylenedimethylammonium bromide

6.82 Preparation of S-methylisothiouronium chloride

6.3 PREPARATION OF 1-AMINOETHANEPHOSPHONIC ACID

Ethyl carbamate (4.45 g, 50 mmol), triphenyl phosphite (15.5 g, 50 mmol), and ethanal (3.08 g, 70 mmol) were heated under reflux (1 h) with glacial acetic acid (10 cm^3). Concentrated hydrochloric acid (50 cm^3) was then added and the mixture was heated under reflux (6 h) and allowed to cool. The aqueous phase was separated off and washed with benzene (20 cm^3) and the volatile components were distilled off from the organic layer on a rotary evaporator. The viscous residue was dissolved in methanol (40 cm^3) and propylene oxide added until the pH was 6. The precipitate was filtered off, washed with acetone (20 cm^3) and recrystallised from water-methanol. Drying in a vacuum oven at 60 ^oC gave 1-aminoethanephosphonic acid (3.4 g, 54.4%) as a fine white crystalline solid, m.p. 273-275 ^oC (lit. m.p. 272-274 ^oC),[20] m/z (FAB, %) 494 (M+4G+1, 2.1), 402 (M+3G+1, 5.0), 310 (M+2G+1, 13.5), 251 (2M+1, 7.3), 218 (M+G+1, 89.0), 126 (M+1, 100.0), 115 (21.4), 100 (14.9), 99 (14.7), 95 (10.3).

6.4 PREPARATION OF 1-AMINOPROPANEPHOSPHONIC ACID

Method (a)

Ethyl carbamate (4.45 g, 50 mmol), triphenyl phosphite (15.5 g, 50 mmol), and propanal (4.06 g, 70 mmol) were heated under reflux (1 h) with glacial acetic acid (10 cm^3). Concentrated hydrochloric acid (50 cm^3) was added and the mixture was heated under reflux (6 h) and allowed to cool. The aqueous phase was separated and washed with benzene (20 cm^3) and the volatile components were distilled off on a rotary evaporator. The viscous residue was dissolved in methanol (40 cm^3) and propylene oxide added until the pH was 6. The precipitate was filtered off, washed with acetone (20 cm^3) and recrystallised from water-methanol. After drying in a vacuum oven at 60 ^oC 1-aminopropanephosphonic acid (4.2 g, 60.4%) was obtained as a fine white crystalline solid, m.p. 264-266 ^oC (lit. m.p. 264-266 ^oC),[20] (Found: C, 25.7; H, 7.2; N, 9.9. Calc. for $C_3H_{10}NO_3P$: C, 25.9; H, 7.2; N, 10.1%); ^1H (D_2O/D_2SO_4) 1.11 (3H, t, $\underline{CH_3}$, $^3J_{HCCH}$ 7.4 Hz), 1.25-1.65 (2H, br m, $\underline{CH_2}$), 3.54 (1H, m, $\underline{CH}$); ^{13}C (D_2O/D_2SO_4) 12.6 (d, $\underline{CH_3}$, $^3J_{PCCC}$ 8.8 Hz), 24.2 (s, $\underline{C}H_2$), 52.9 (d, P$\underline{C}$H, $^1J_{PC}$ 153.9 Hz); ^{13}C (SFORD) 12.6 (d of q), 24.2 (t), 52.9 (d of d); ^{31}P (D_2O/D_2SO_4) 18.5 (br s); m/z (FAB, %) 418 (3M+1, 6.4), 359 (5.2), 321 (4.2), 279 (2M+1, 53.1), 232 (M+G+1, 6.4), 199 (13.4), 140 (M+1, 100), 125 (4.6), 124 (2.9), 100 (15.7).

6.5 PREPARATION OF 1-AMINO-OCTANEPHOSPHONIC ACID

Method (a)

Ethyl carbamate (4.45 g, 50 mmol), triphenyl phosphite (15.5 g, 50 mmol) and octanal (9.0 g, 70 mmol) were heated under reflux (1 h) with glacial acetic acid (10 cm^3). Concentrated hydrochloric acid (50 cm^3) was then added, the mixture was heated under reflux (6 h) and allowed to cool. The aqueous phase was separated and washed with benzene (20 cm^3) and the volatile components were distilled off on a rotary evaporator. The viscous residue was dissolved in methanol (40 cm^3) and propylene oxide was added until the pH was 6. The precipitate was filtered off, washed with acetone (20 cm^3) and recrystallised from water-methanol. Drying in a vacuum oven at 60 ^oC gave 1-amino-octanephosphonic acid (0.5 g, 5.2%) as a fine white crystalline solid, m.p. 269-270 ^oC, (Found: C, 45.2; H, 9.3; N, 6.8; $C_8H_{20}NO_3P$ requires: C, 45.9; H, 9.6; N, 6.7%); ^{13}C (D_2O/D_2SO_4) 16.3 (s, $\underline{CH_3}$), 24.8 (s), 25.7 (d, $PCHCH_2\underline{C}H_2$, $^3J_{PCCC}$ 15.1 Hz), 30.5, 31.0, 31.3 and 34.0 (singlets), 51.0 (d, $P\underline{C}H$, $^1J_{PC}$ 153.2 Hz); m/z (FAB, %) 419 (2M+1, 11.9), 210 (M+1, 19.5), 130 (34.8), 109 (9.3), 108 (100), 106 (9.3), 110 (6.6).

Method (b)

Octanal (9.6 g, 75 mmol) was added over 20 min to a solution consisting of ethyl carbamate (4.45 g, 50 mmol), phosphorus trichloride (6.87 g, 50 mmol) and glacial acetic acid (10 cm^3). The solution was then heated under reflux (40 min) and allowed to cool. Concentrated hydrochloric acid (50 cm^3) was added and the mixture was heated under reflux (0.5 h) and allowed to cool. The aqueous layer was separated, treated with animal charcoal and the volatile components were distilled off on a rotary evaporator. The resultant viscous residue was dissolved in methanol (40 cm^3) and propylene oxide was added until the pH reached 6. The precipitate was filtered off, washed with acetone (20 cm^3) and recrystallised from methanol/water. After drying in a vacuum oven at 60 ^oC 1-amino-octanephosphonic acid (0.4 g, 3.8%) was obtained as a fine white crystalline solid, m.p. 269-270 ^oC.

6.6 ATTEMPTED PREPARATION OF 1-AMINO-OCTANEPHOSPHONIC ACID

Ethyl carbamate (8.9 g, 100 mmol), octanal (12.9 g, 100 mmol), and acetic acid (5 cm^3) were heated under reflux (0.5 h) in benzene; however, no water was seen to collect in the Dean and Stark head. Phosphorus trichloride (13.7 g, 100 mmol) was added to this solution dropwise and water (1.55 cm^3, 86%) was collected in the Dean and Stark head. Concentrated hydrochloric acid

(50 cm^3) and water (40 cm^3) were then added to the resultant solution and this mixture was heated under reflux (0.5 h) and allowed to cool. The aqueous layer was separated, treated with charcoal (0.5 g) and the solvents were distilled off on a rotary evaporator to leave a white residue (6 g). This was dissolved in methanol (50 cm^3) and propylene oxide was added until the pH was 6. The precipitate so formed was filtered off and washed with diethyl ether (20 cm^3) to yield a white solid (0.2 g) m.p. 270 ^{o}C (decomp), (Found: C, 13.0; H, 4.7; N, 8.4. Calc. $C_8H_{20}NO_3P$ requires: C, 45.9; H, 9.6; N, 6.7%).

6.7 PREPARATION OF 1-GUANIDINOETHANEPHOSPHONIC ACID

A mixture of thiourea (15.2 g, 200 mmol), triphenyl phosphite (62.0 g, 200 mmol), glacial acetic acid (2 cm^3), and toluene (30 cm^3) was heated to 80 ^oC. Ethanal (8.8 g, 200 mmol) was then added over 0.5 h and the solution heated under reflux (0.25 h). Water (15 cm^3) and methyl cyanide (20 cm^3) were added and the solution heated under reflux (2 h). Water (50 cm^3) was then added and the solution allowed to cool. The organic layer was separated and the volatile components were distilled off from the aqueous layer on a rotary evaporator. The oily residue was dissolved in methanol (50 cm^3), methyl iodide (12.5 cm^3) was added and the mixture was heated under reflux (6 h). After cooling, methanol (50 cm^3) was added and ammonia gas passed through the stirred solution (4 h). The precipitate was filtered off and dissolved in water (100 cm^3) and methanol (30 cm^3). The resultant solution was acidified with glacial acetic acid and then concentrated on a rotary evaporator to ca. 40 cm^3, and stored at 4 ^oC. The crystals that formed were filtered off, washed with methanol (20 cm^3), and dried in a vacuum oven at 60 ^oC to yield 1-guanidinoethanephosphonic acid (5.7 g, 17%) as a fine white crystalline solid, m.p. 285-286 ^oC (lit. m.p. 286-287 ^oC),[38] (Found: C, 21.7; H, 6.1; N, 24.7; P, 18.3. Calc. for $C_3H_{10}N_3O_3P$: C, 21.6; H, 6.0; N, 25.1; P, 18.6%); ^1H (D_2O/D_2SO_4) 1.49 (3H, d of d, $\underline{CH_3}$, $^3J_{PCCH}$ 17.1 Hz, $^3J_{HCCH}$ 7.3 Hz), 4.01 (1H, overlapping

d of q, PCH, $^{3}J_{HCCH}$ 7.1 Hz), ^{13}C ($D2O/D_2SO_4$) 17.3 (s, CH_3), 48.2 (d, PCH, $^{1}J_{PC}$ 158.1 Hz), 159.6 (d, $NHC(:NH)NH_2$, $^{3}J_{PCNC}$ 4.4 Hz); ^{13}C (SFORD) 17.0 (q), 47.9 (d of d), 159.2 (d); ^{31}P (D_2O/D_2SO_4) 23.1 (overlapping d of q, $^{3}J_{HCCP}$ 17.0 Hz, $^{2}J_{HCP}$ 12.8 Hz); m/z (FAB, %) 260 (M+G+1, 13.1), 168 (M+1, 100.0), 127 (20.9), 153 (2.9), 152 (6.7), 151 (1.8), 111 (3.1), 110 (18.4), 109 (1.2), 100 (11.1), 99 (13.9).

6.8 PREPARATION OF 1-GUANIDINOPROPANEPHOSPHONIC ACID ACETATE

A mixture of thiourea (15.2 g, 200 mmol), triphenyl phosphite (62.0 g, 200 mmol), glacial acetic acid (2 cm^3), and toluene (30 cm^3) was heated to 80 ^{o}C. Propanal (11.6 g, 200 mmol) was then added over 0.5 h and the solution heated under reflux (0.25 h). Water (15 cm^3) and methyl cyanide (20 cm^3) were added and the solution heated under reflux (2 h). Water (50 cm^3) was then added and the solution was allowed to cool. The organic layer was separated and the volatile components were distilled off from the aqueous layer on a rotary evaporator. The oily residue was dissolved in methanol (50 cm^3), methyl iodide (12.5 cm^3) was added and the mixture was heated under reflux (6 h). After cooling, methanol (50 cm^3) was added and ammonia gas passed through the stirred solution (4 h) to give a precipitate that was filtered off and dissolved in water (100 cm^3) and methanol (30 cm^3). The resultant solution was acidified with glacial acetic acid,

concentrated on a rotary evaporator to ca. 40 cm^3, and stored at 4 ^oC. The crystals that formed were filtered off, washed with methanol (20 cm^3), and dried in a vacuum oven at 60 ^oC to yield 1-guanidinopropanephosphonic acid acetate (6.0 g, 12.5%) as a fine white crystalline solid, m.p. 289 ^oC. (Found: C, 29.4; H, 6.5; N, 17.6; P, 12.8. $C_6H_{16}N_3PO_5$ requires: C, 29.9; H, 6.6; N, 17.4; P, 12.8%); ^1H (D_2O/D_2SO_4) 1.03 (3H, t, CH_3CH_2, $^3J_{HCCH}$ 7.4 Hz), 1.67 (2H, m, CH_3CH_2,), 2.12 (3H, s, CH_3COO), 3.67 (1H, m, $PCHCH_2$,); ^{13}C (D_2O/D_2SO_4) 12.8 (d, CH_3CH_2, $^3J_{PCCC}$ 13.3 Hz), 23.4 (s, CH_3COO), 25.2 (s, CH_3CH_2), 54.4 (d, PCH, $^1J_{PC}$ 155.1 Hz), 160.2 (d, $NHC(:NH)NH_2$, $^3J_{PCNC}$ 4.4 Hz), 180.4 (s, C(O)O). ^{31}P (D_2O/D_2SO_4) 22.1 (overlapping d of t, $^3J_{HCCP}$ 7.9 Hz, $^2J_{HCP}$ 13.5 Hz); $^{15}N-\{^1H\}^{bb}$ ($H_2O/D_2O/D_2SO_4$) -301.5 (s, PCH_2NH),-312.4 (s, $C(NH_2)_2$); ^{15}N ($H_2O/D_2O/D_2SO_4$) -301.6 (d, PCH_2NH, ^1J_H 4.7 Hz), -312.5 (m, $C(NH)_2$); T.G.A.: weight loss 66 mg at 190-260 ^oC (Calc. 68.4 mg for loss of CH_3CO_2H).

A repeat experiment gave 1-guanidinopropanephosphonic acid as the acetate salt (6.3 g, 13.1%) which was converted to the free zwitterionic form by dissolving in the minimum quantity of hot aqueous methanol (50:50), adding a few drops of acetone and storing the solution at 4 ^oC for several days. The crystals that formed were filtered off, washed with methanol (20 cm^3) and dried in a vacuum oven at 60 ^oC to yield 1-guanidinopropanephosphonic acid (4.1 g, 86.7%) as

a fine white crystalline solid, m.p. 303 °C (lit. m.p. 296-298 °C),[38] (Found: C, 26.7; H, 6.8; N, 23.4; P, 16.5. Calc. for $C_4H_{12}N_3O_3P$: C, 26.5; H, 6.6; N, 23.2; P, 17.1%); ^1H (D_2O/D_2SO_4) 1.03 (3H, t, $\underline{CH_3}$, $^3J_{HCCH}$ 7.3 Hz), 1.66 {1H, m, PCH$\underline{CH(a)}$}, 1.98 {1H, m, PCH$\underline{CH(b)}$}, 3.80 (1H, P$\underline{CH}$, overlapping d of d of doublets); ^1H (220 MHz spin decoupled) 1.66 (3.80 collapsed to a d of doublets), 1.98 (3.80 collapsed to a d of doublets); ^1H (80 MHz spin decoupled) 1.80 (3.80 collapsed to a d); ^{13}C (D_2O/D_2SO_4) 12.7 (d, $\underline{CH_3}$, $^3J_{PCCC}$ 13.3 Hz), 25.1 (s, $CH_3\underline{CH_2}$), 54.1 (d, P$\underline{CH}$, $^1J_{PC}$ 158.1 Hz), 159.9 (d, NH$\underline{C}$(:NH)NH_2, $^3J_{PCNC}$ 3.7 Hz); ^{13}C (SFORD) 12.7 (q), 25.1 (t), 54.1 (d of d); ^{31}P (D_2O/D_2SO_4) 22.8 (d of t, $^3J_{HCCP}$ 8.1 Hz, $^2J_{HCP}$ 12.6 Hz); m/z (FAB, %) 274 (M+G+1, 1.0), 182 (M+1, 100.0), 154 (3.4), 125 (1.8), 123 (0.1), 102 (5.0), 101 (23.4), 100 (30.1).

6.9 PREPARATION OF 1-GUANIDINO-OCTANEPHOSPHONIC ACID

A mixture of thiourea (15.2 g, 200 mmol), triphenyl phosphite (62.0 g, 200 mmol), glacial acetic acid (2 cm^3), and toluene (30 cm^3) was heated to 80 °C. Octanal (25.6 g, 200 mmol) was then added over 0.5 h and the solution was heated under reflux (0.25 h). Water (15 cm^3) and methyl cyanide (20 cm^3) were added and the solution heated under reflux (2 h). Water (50 cm^3) was then added and the solution was allowed to cool. The organic layer was separated off and the volatile

components were distilled off from the aqueous layer on a rotary evaporator. The oily residue was dissolved in methanol (50 cm^3), methyl iodide (12.5 cm^3) was added and the mixture was heated under reflux (6 h). After cooling, methanol (50 cm^3) was added and ammonia gas was passed through the stirred solution (4 h), to give a precipitate which was filtered off and dissolved in water (100 cm^3) and methanol (30 cm^3). The resultant solution was acidified with glacial acetic acid, concentrated on a rotary evaporator to ca. 40 cm^3, and stored at 4 ^oC. The crystals that formed were filtered off, washed with methanol (20 cm^3) and dried in a vacuum oven at 60 ^oC to yield 1-guanidino-octanephosphonic acid (0.21 g, 0.4%) as a fine white crystalline solid, m.p. 314 ^oC (Found: C, 43.0; H, 8.6; N, 15.6. $C_9H_{23}N_3O_3P$ requires: C, 42.9; H, 9.1; N, 16.7%); ^1H (D_2O/D_2SO_4) 0.84 (3H, br t, CH_3, $^3J_{HCCH}$ 4.9 Hz), 1.0-2.3 (12H, br m, $CH_3(CH_2)_6$), 3.8 (m, $CHNHC(:NH)NH_2$); ^{13}C (D_2O/D_2SO_4) 16.1 (s, CH_3), 24.4 (s), 27.5 (d, $PCHCH_2CH_2$, $^3J_{PCCC}$ 13.4 Hz), 30.5, 30.9, 31.0 (singlets), 52.3 (d, PCH, $^1J_{PC}$ 160.5 Hz), 159.5 (d, $NHC(:NH)NH_2$, $^3J_{PCNC}$ 4.4 Hz); ^{31}P (D_2O/D_2SO_4) 26.1 (br s); m/z (FAB, %) 503 (2M+1, 7.5), 344 (M+G+1, 2.6), 252 (M+1, 100.0), 237 (3.9), 235 (3), 172 (37.1), 170 (32.5), 128 (12.8), 126 (1.6).

6.10 PREPARATION OF 1-THIOUREIDO-OCTANEPHOSPHONIC ACID

A mixture of thiourea (15.2 g, 200 mmol), triphenyl phosphite (62.0 g, 200 mmol), glacial acetic acid (2 cm^3), and toluene (30 cm^3) was heated to 80 ^oC. Octanal (25.6 g, 200 mmol) was then added over 0.5 h and the solution heated under reflux (0.25 h). Water (15 cm^3) and methyl cyanide (20 cm^3) were added and the solution heated under reflux (2 h). Water (50 cm^3) was then added and the solution was allowed to cool. The organic layer was separated and the volatile components were distilled off from the aqueous layer under reduced pressure to leave a clear yellow viscous oil (ca. 90 g). The above reaction scheme was repeated five times and the oily residues combined (ca. 540 g). After several weeks the oil was dissolved in the minimum volume of diethyl ether and the solid that had formed was filtered off, washed with diethyl ether (3x50 cm^3), and recrystallised from diethyl ether to yield 1-thioureido-octanephosphonic acid (10.2 g, 3.2%) as a white waxy solid, m.p. 166-168 ^oC, (Found: C, 40.5; H, 7.9; N, 10.9; P, 11.3; S, 10.5. $C_9H_{21}N_2O_3PS$ requires: C, 40.3; H, 7.8; N, 10.5; P, 11.6; S, 11.9%); ^1H (DMSO-d_6) 0.86 (3H, t, CH_3, $^3J_{HCCH}$ 5.4 Hz), 1.0-2.1 (12H, br m, $PCH(CH_2)_6CH_3$), 4.5 (1H, br m, PCH), 7.1 (2H, br s, $C(:S)NH_2$, exchanged with D_2O), 7.6 (1H, d, PCHNH, ^3J 9.3 Hz, exchanged with D_2O), 9.7 (2H, br s, $(HO)_2P$); ^{13}C (DMSO-d_6), 13.9 (s, CH_3), 22.0 (s), 25.2 (d, $PCHCH_2CH_2$, $^3J_{PCCC}$ 11 Hz), 28.6 (s), 29.0 (s), 30.4 (s), 31.2 (s),

51.5 (d, PCH, $^{1}J_{PC}$ 151.5 Hz), 183.8 (d, NHC(:S)NH_2, $^{3}J_{PCNC}$ 8.8 Hz); ^{31}P (CD_3OD) 21.0 (br s); m/z (FAB, %) 537 (2M+1, 1.1), 269 (M+1, 43.4), 254 (1.8), 237 (46.0), 222 (3.7), 193 (3.4), 170 (6.8), 155 (15.9), 128 (M-32, 100)

6.11 PREPARATION OF N,N'-BIS-{1-(DIHYDROXYPHOSPHINYL)-OCTYL}-THIOUREA

A mixture of thiourea (15.2 g, 200 mmol), triphenyl phosphite (62.0 g, 200 mmol), glacial acetic acid (2 cm^3), and toluene (30 cm^3) was heated to 80 °C. Octanal (25.6 g, 200 mmol) was then added over 0.5 h and the solution was heated under reflux (0.25 h). Water (15 cm^3) and methyl cyanide (20 cm^3) were added and the solution heated under reflux (2 h). Water (50 cm^3) was then added and the solution was allowed to cool. The aqueous layer was separated and the volatile components were distilled off from the organic layer on a rotary evaporator; phenol (ca. 40 g) was then distilled off under reduced pressure to leave a clear yellow oil. The above reaction scheme was repeated five times and the oils combined. Acetone (500 cm^3) was added and the solution left to stand. After several weeks the solid formed was filtered off, and was washed with diethyl ether (4x100 cm^3). It was recrystallised from water, washed with acetone (100 cm^3) and dried in a vacuum oven at 60 °C to yield N,N'-bis-{1-(dihydroxyphosphinyl)octyl}-thiourea (4.4 g, 0.8%) as a fine white waxy solid, m.p. 263 °C,

51.5 (d, P<u>C</u>H, $^{1}J_{PC}$ 151.5 Hz), 183.8 (d, NH<u>C</u>(:S)NH_2, $^{3}J_{PCNC}$ 8.8 Hz); ^{31}P (CD_3OD) 21.0 (br s); m/z (FAB, %) 537 (2M+1, 1.1), 269 (M+1, 43.4), 254 (1.8), 237 (46.0), 222 (3.7), 193 (3.4), 170 (6.8), 155 (15.9), 128 (M-32, 100)

6.11 PREPARATION OF N,N'-BIS-{1-(DIHYDROXYPHOSPHINYL)-OCTYL}-THIOUREA

A mixture of thiourea (15.2 g, 200 mmol), triphenyl phosphite (62.0 g, 200 mmol), glacial acetic acid (2 cm^3), and toluene (30 cm^3) was heated to 80 ^{o}C. Octanal (25.6 g, 200 mmol) was then added over 0.5 h and the solution was heated under reflux (0.25 h). Water (15 cm^3) and methyl cyanide (20 cm^3) were added and the solution heated under reflux (2 h). Water (50 cm^3) was then added and the solution was allowed to cool. The aqueous layer was separated and the volatile components were distilled off from the organic layer on a rotary evaporator; phenol (<u>ca.</u> 40 g) was then distilled off under reduced pressure to leave a clear yellow oil. The above reaction scheme was repeated five times and the oils combined. Acetone (500 cm^3) was added and the solution left to stand. After several weeks the solid formed was filtered off, and was washed with diethyl ether (4x100 cm^3). It was recrystallised from water, washed with acetone (100 cm^3) and dried in a vacuum oven at 60 ^{o}C to yield <u>N,N'-bis-{1-(dihydroxyphosphinyl)octyl}-thiourea</u> (4.4 g, 0.8%) as a fine white waxy solid, m.p. 263 ^{o}C,

(Found: C, 44.1; H, 8.6; S, 6.7; P, 12.6. $C_{17}H_{38}N_2O_6P_2S$ requires: C, 44.3; H, 8.3; S, 7.0; P, 13.5%); ^1H (DMSO-d_6) 0.85 (6H, br t, $\underline{CH_3}$, $^3J_{HCCH}$ 4.5 Hz), 1.0-2.2 (24H, br m, PCH($\underline{CH_2}$)$_6$), 4.6 (2H, br m, P$\underline{CH}$), 7.0 (4H, br s, $\underline{(HO)_2}$P, exchanged with D_2O), 8.0 (2H, d, PCH$\underline{NH}$, ^3J 10 Hz, exchanged with D_2O); ^{13}C (DMSO-d_6) 13.8 (s, $\underline{C}H_3$), 22.1 (s), 25.4 (d, PCHCH$_2\underline{C}H_2$, $^3J_{PCCC}$ 12.5 Hz), 28.9, 29.0, 30.6 and 31.2 (singlets), 51.4 (d, P$\underline{C}H_2$, $^1J_{PC}$ 150.7 Hz), 184.0 (t, NH$\underline{C}$(:S)NH, $^3J_{PCNC}$ 7.0 Hz); $^{31}P-\{^1H\}^{bb}$ (DMSO-d_6) 20.5; m/z (FAB, %) 462 (1.4), 461 (M+1, 6.4), 429 (3.0), 379 (2.1), 267 (1.6), 252 (1.7), 251 (1.4), 170 (3.5), 169 (1.3), 129 (10.2), 128 (100.0), 126 (14.1), 115 (13.0), 110 (13.6).

6.12 PREPARATION OF N-HYDROXY-1-AMINO-OCTANEPHOSPHONIC ACID

Octanaldoxime (10 g, 69.9 mmol) and diethyl phosphite (9.6 g, 69.6 mmol) were heated at 130 ^{o}C (1 h). The volatile components (7.9 g) were distilled off under reduced pressure to leave a dark tarry residue. Concentrated hydrochloric acid (70 cm^3), and ethanol (100 cm^3) were added and the solution was heated under reflux (8 h). The aqueous layer was separated, filtered through kieselguhr and the volatile components were distilled off on a rotary evaporator. The resultant residue was dissolved in methanol (30 cm^3) and propylene oxide was added until the pH was 6. The precipitate (0.5 g, 3.2% after drying) that formed was recrystallised from ethanol/water, washed with acetone (50 cm^3), and dried in a vacuum oven at 60 ^{o}C to yield N-hydroxy-1-amino-octanephosphonic acid (0.1 g, 0.7%) as a fine white crystalline solid, m.p. 267 ^{o}C, (Found: C, 43.5; H, 9.2; N, 6.0. $C_8H_{20}NO_4P$ requires: C, 42.7; H, 8.9; N, 6.2%); ^{1}H (CF_3COOH) 0.55-2.55 (15H, br m, C_7H_{15}), 3.85 (1H, br, PCH), 7.25 (2H, br, CHNH(OH), exchanged with D_2O); ^{13}C (CF_3COOD) 14.4 (s, CH_3), 24.2 (s), 28.2 (d, $PCHCH_2CH_2$, $^{3}J_{PCCC}$ 7.6 Hz), 30.7 (s), 33.4 (s), 53.4 (d, PCH, $^{1}J_{PC}$ 153.5 Hz).

6.13 PREPARATION OF 1-AMINOETHANE-1,1-DIPHOSPHONIC ACID

Acetamide (11.8 g, 200.0 mmol), phosphorous acid (32.8 g, 400.0 mmol) and acetic anhydride (20.4 g, 200.0 mmol) were heated under reflux (2 h) and then in a bath at 170-180 ^{o}C (1 h) during which time the volatile components were allowed to distil off. The residue was cooled, heated until boiling with 6M hydrochloric acid (150 cm^3), and then cooled and filtered. The volatile components were distilled off from the filtrate on a rotary evaporator. Acetone (200 cm^3) was added and the precipitate that formed was filtered off and heated under reflux (10 min) in water (200 cm^3). After cooling, the solid was filtered off and added to a solution of potassium hydroxide (15.5 g, 276.3 mmol) in water (30 cm^3). The resulting solution was heated to boiling and then acidified until pH 1 with concentrated hydrochloric acid and allowed to cool overnight. The crystals that formed were filtered off, washed with water (3x50 cm^3) and methanol (2x50 cm^3), and dried in a vacuum oven at 60 ^{o}C to yield 1-aminoethane-1,1-diphosphonic acid (17.9 g, 43.6%) as a fine white crystalline solid, m.p. 280-281 ^{o}C (lit. m.p. 277 ^{o}C),[55] (Found: C, 11.8; H, 4.4; N, 6.8; P, 30.1. Calc. for $C_2H_9NO_6P_2$: C, 11.7; H, 4.4; N, 6.8; P, 30.2%); ^{1}H (NaOH/D_2O) 1.3 (t, $\underline{CH_3}$, $^{3}J_{PCCH}$ 14 Hz); ^{13}C (NaOH/D_2O) 23.9 (t, $\underline{CH_3}$, $^{2}J_{PCC}$ 2.9 Hz), 57.6 (t, $CH_3\underline{C}NH_2$, $^{1}J_{PC}$ 124.3 Hz); m/z (FAB, %) 411 (2M+1, 3.4), 391 (M+2G+2, 13.6), 390 (M+2G+1, 6.9), 381 (3.8), 359

(4.7), 300 (M+G+3, 5.6), 298 (21.8), 208 (M+3, 5.4), 207 (M+2, 51.1), 206 (M+1, 15.3), 164 (6.5), 158 (3.4), 124 (1.5), 122 (2.3), 115 (100), 110 (20.2).

6.14 ATTEMPTED GUANIDATION OF 1-AMINOETHANE-1,1-DIPHOSPHONIC ACID

Method (a): Under acid conditions

1-Aminoethane-1,1-diphosphonic acid (4.1 g, 20.0 mmol) and S-methylisothiouronium chloride (2.53 g, 20.0 mmol) were heated under reflux (4 h) in 6M hydrochloric acid (50 cm^3). The reaction mixture was allowed to cool and the hydrochloric acid distilled off on a rotary evaporator. Water (30 cm^3) was added and the precipitate filtered off and recrystallised from water-acetone to yield unreacted 1-aminoethane-1,1-diphosphonic acid (1.9 g, 46.3%), m.p. 268-269 ^oC, (lit. m.p. 277 ^oC),[55] (Found: C, 11.4; H, 4.0; N, 7.0. Calc. for $C_2H_9NO_6P_2$: C, 11.7; H, 4.4; N, 6.8%).

Method (b): Under basic conditions

1-Aminoethane-1,1-diphosphonic acid (2.5 g, 12.2 mmol), S-methylisothiouronium chloride (3.1 g, 24.5 mmol) and potassium hydroxide (4.12 g, 73.4 mmol) were dissolved in water (7 cm^3) and heated at 55 ^oC (4 h). Water (15 cm^3) was added and the solution acidified until pH 1 with concentrated hydrochloric acid. The volatile components were distilled off on a rotary evaporator and cold water (20 cm^3) was added to the solid residue. The insoluble material was filtered off, washed with methanol (20 cm^3), and dried in a vacuum oven at 60 ^oC to yield unreacted 1-aminoethane-1,1-diphosphonic acid (1.9 g, 76.0%) as a fine white crystalline solid, m.p. 275 ^oC (lit. m.p. 277 ^oC),[55] whose I.R. spectrum was identical to that of the starting material.

6.15 ATTEMPTED CONDENSATION OF ACETYLGUANIDINIUM CHLORIDE AND PHOSPHOROUS ACID IN ACETIC ANHYDRIDE

Acetylguanidinium chloride (10.0 g, 72.7 mmol) was dissolved in butan-1-ol (100 cm^3) and a solution of sodium (1.67 g, 72.6 mmol) in butan-1-ol (100 cm^3) added. The precipitate so formed was filtered off and the butan-1-ol distilled off on a rotary evaporator. Acetic anhydryde (10.5 g, 102.9 mmol) and phosphorus acid (11.93 g, 145.5 mmol) were then added and the resultant solution

heated under reflux (4 h). The volatile components were then distilled off under reduced pressure to leave a clear viscous oil. ^1H (D_2O) 2.25 (s, $\underline{CH_3}C(:O)NH$).

6.16 ATTEMPTED CONDENSATION OF ACETYLGUANIDINIUM CHLORIDE WITH PHOSPHOROUS ACID AND PHOSPHORUS TRICHLORIDE

Acetylguanidinium chloride (4.0 g, 29.1 mmol) and phosphorous acid (3.6 g, 43.9 mmol) were dissolved in chlorobenzene (17 cm^3) and heated to 100 ^oC. Phosphorus trichloride (7.0 g, 50.9 mmol) was then added drowise over 15 min and the resultant solution heated at 110 ^oC (1 h) and allowed to cool. The liquid was decanted off and water (40 cm^3) added to the residue and the mixture was heated to reflux and allowed to cool. The solid was filtered off, washed with acetone (20 cm^3), then diethyl ether (20 cm^3) and dried in a vacuum oven at 60 ^oC to yield an orange solid (0.6 g) m.p. >340 ^oC (decomp). The washings, filtrate and decanted liquors were each evaporated to dryness and their proton nmr recorded. In each case the only signal present was a singlet at *ca.* 2.3 ppm due to the $\underline{CH_3}C(:O)NH$ group.

6.17 ATTEMPTED CONDENSATION OF DODECANOYLGUANIDINIUM CHLORIDE WITH PHOSPHOROUS ACID AND PHOSPHORUS TRICHLORIDE

Dodecanoylguanidinium chloride (1.5 g, 5.4 mmol) and phosphorous acid (1.0 g, 12.2 mmol) were dissolved in 1,1,2,2-tetrachloroethane (10 cm^3) while phosphorus trichloride (1.5 g, 10.9 mmol) dissolved in 1,1,2,2-tetrachloroethane (5 cm^3) was added over 5 min. This mixture was heated at 120 ^oC (1.5 h), then under reflux (2 h) and allowed to cool. 1,1,2,2-Tetrachloroethane (20 cm^3) was then added and the orange solid was filtered off. It was washed with ethanol (50 cm^3) and dried in a vacuum oven at 70 ^oC (3 h) to yield an orange solid (0.7 g) m.p. >300 ^oC, (Found: C, 32.4; H, 6.3; N, 8.8; P, 27.0%); m/z (FAB, %) 388 (2.1), 306 (4.6), 243 (18.5), 242 ($C_{11}H_{23}C(O)NHC(:NH)NH_2$+1, 100), 240 (19.0), 191 (12.0), 114 (10.8), 101 (9.6), 99 (9.6); $^{31}P-\{^1H\}^{bb}$ (DMSO-d_6) -0.5.

This orange solid (0.5 g) was dissolved in hot methanolic potassium hydroxide solution (150 cm^3, 20%) and hot water (150 cm^3) was added. The solution was filtered to remove the insoluble materials and the filtrate acidified to pH 1 with concentrated hydrochloric acid. The precipitate formed on standing was filtered off and dried in a vacuum oven to yield dodecanoylguanidinium chloride (0.1 g) as a white waxy solid,. (Found: C, 54.4; H, 9.7; N, 13.8. $C_{13}H_{28}ClN_3O$ requires: C, 56.2; H, 10.1; N, 15.1%).

6.18 PREPARATION OF AMINOMETHANEPHOSPHONIC ACID

Triethyl phosphite (13.5 g, 81.3 mmol) and N-bromomethylphthalimide (19.5 g, 81.2 mmol) were heated at 170 °C (2 h) during which time the evolved ethyl bromide (8.1 g, 91.4%) was collected.[159] Concentrated hydrochloric acid (150 cm^3) was added to the solution which was then heated under reflux (10 h) and allowed to cool overnight. The precipitated phthalic acid was filtered off and the volatile components were removed from the filtrate on a rotary evaporator. The residue was dissolved in methanol (20 cm^3) and propylene oxide (*ca.* 400 cm^3) was added until the pH reached 6. The precipitated crude aminomethanephosphonic acid was filtered off and recrystallised twice from water-ethanol, washing with methanol (20 cm^3) after each crystallisation. Drying in a vacuum oven at 70 °C gave aminomethanephosphonic acid (6.1 g, 67.6%) as a fine white crystalline solid, m.p. 328 °C (lit. m.p. 325-330 °C),[77] (Found: C, 10.1; H, 5.1; N, 12.6; P, 27.8. Calc. for CH_6NO_3P: C, 10.8; H, 5.4; N, 12.6; P, 27.9%); ^1H (D_2O) 3.10 (d, PCH_2, $^2J_{PCH}$ 12.2 Hz); ^1H (D_2O/D_2SO_4) 3.42 (d, PCH_2, $^2J_{PCH}$ 13.2 Hz); ^{13}C (D_2O) 41.3 (d, PCH_2, $^1J_{PC}$ 141.9 Hz); ^{13}C (D_2O/D_2SO_4) 37.6 (d, PCH_2, $^1J_{PC}$ 149.9 Hz); ^{31}P (D_2O) 11.0 (t, $^2J_{HCP}$, 12.2 Hz); $^{31}P-\{^1H\}^{bb}$ (D_2O/D_2SO_4) 15.4; m/z (FAB, %) 296 (M+2G+1, 7.7), 223 (2M+1, 2.1), 204 (M+G+1, 48.3), 112 (M+1, 100.0), 95 (18.2), 30 (35).

6.19 PREPARATION OF 2-AMINOETHANEPHOSPHONIC ACID

Triethyl phosphite (16.7 g, 100.5 mmol) and N-(2-bromoethyl)phthalimide (24.7 g, 97.3 mmol) were heated at 180 °C (3 h) while the evolving ethyl bromide (10.3 g, 97%) was collected.[159] Concentrated hydrochloric acid (150 cm^3) was added to the solution which was then heated under reflux (8 h) and allowed to cool overnight. The precipitated phthalic acid was filtered off and the solvents removed from the filtrate on a rotary evaporator. The resulting viscous residue was dissolved in methanol (30 cm^3) and propylene oxide (ca. 400 cm^3) was added until the pH reached 6 when a pale yellow oil separated. The mixture was stored at -18 °C for several days during which time the oil crystallised. The supernatant layer was decanted off and the crystals washed with methanol (2x50 cm^3). The crude product was recystallised from cold water-methanol, washed with methanol (50 cm^3) and dried in a vacuum oven at 70 °C (3 h) to yield 2-aminoethane-phosphonic acid (6.7 g, 55.1%) as a fine white crystalline solid, m.p. 272-273 °C, (lit. m.p. 274-276 °C),[80] (Found: C, 19.3; H, 6.4; N, 11.2; P, 24.5. Calc. for $C_2H_8NO_3P$: C, 19.2; H, 6.4; N, 11.2; P, 24.8%); ^1H (D_2O) 1.95 (2H, overlapping d of t, PCH_2, $^3J_{HCCH}$ 8.0 Hz, $^2J_{PCH}$ 17.8 Hz), 3.0-3.3 (2H, m, CH_2NH_2); ^{13}C (D_2O) 28.9 (d, PCH_2, $^1J_{PC}$ 131.6 Hz), 38.5 (s, CH_2NH_2); ^{13}C (D_2O/D_2SO_4) 27.3 (d, PCH_2, $^1J_{PC}$ 139.0 Hz), 37.9 (s, CH_2NH_2); ^{31}P (D_2O) 18.8 (overlapping t of t); $^{31}P-\{^1H\}^{bb}$ (D_2O/D_2SO_4) 26.5

(overlapping t of t); m/z (FAB, %) 402 (M+3G+1, 2.0), 310 (M+2G+1, 8.1), 251 (2M+1, 4.8), 218 (M+G+1, 34.5), 126 (M+1, 100), 111 (6.6), 110 (3.7), 109 (2.5), 100 (2.0), 99 (1.5).

6.20 PREPARATION OF 3-AMINOPROPANEPHOSPHONIC ACID

Triethyl phosphite (17.5 g, 105.3 mmol) and N-(bromopropyl)phthalimide (25.7 g, 95.9 mmol) were heated at 160-180 ^{o}C (3 h) during which time the evolving ethyl bromide (8.1 g, 77.5%, identified by nmr) was collected in the apparatus described.[159] Concentrated hydrochloric acid (150 cm^3) was then added and the solution was heated under reflux (8 h) and and allowed to cool overnight. The precipitated phthalic acid was filtered off and the volatile components were distilled off from the filtrate on a rotary evaporator. The residual oil was dissolved in methanol (30 cm^3) and propylene oxide (ca. 400 cm^3) was added until the pH reached 6. The precipitate was filtered off and recrystallised from water-ethanol, washed with methanol (30 cm^3) and dried in a vacuum oven at 70 ^{o}C to yield 3-aminopropanephosphonic acid (6.6 g, 49.5%) as a fine white crystalline solid, m.p. 278 ^{o}C (lit. m.p. 274 ^{o}C),[13] (Found: C, 25.9; H, 7.0; N, 10.5; P, 21.8. Calc. for $C_3H_{10}NO_3P$: C, 25.9; H, 7.2; N, 10.1; P, 22.3%); ^{1}H (D_2O) 1.53-1.96 (4H, br m, PCH_2CH_2), 3.08 (2H, br t, CH_2NH_2, $^{3}J_{HCCH}$ 6.3 Hz); ^{1}H (D_2O/D_2SO_4) 1.98 (4H, m, PCH_2CH_2), 3.15 (2H, br m, CH_2NH_2); ^{13}C (D_2O) 24.4 (d,

$PCH_2\underline{C}H_2$, $^2J_{PCC}$ 4.3 Hz), 27.9 (d, $P\underline{C}H_2$, $^1J_{PC}$ 135.5 Hz), 43.1 (d, $\underline{C}H_2NH_2$, $^3J_{PCCC}$ 17.7 Hz); ^{13}C (D_2O/D_2SO_4) 23.0 (d, $PCH_2\underline{C}H_2$, $^2J_{PCC}$ 4.7 Hz), 25.8 (d, $P\underline{C}H_2$, $^1J_{PC}$ 137.7 Hz), 42.9 (d, $\underline{C}H_2NH_2$, $^3J_{PCCC}$ 20.3 Hz); ^{31}P (D_2O) 23.7 (br s); ^{31}P (D_2O/D_2SO_4) 31.1 (br s); m/z (FAB, %) 324 (M+2G+1, 7.2), 279 (2M+1, 3.7), 232 (M+G+1, 23.2), 140 (M+1, 100), 123 (11.7), 115 (6.0).

6.21 PREPARATION OF 4-AMINOBUTANEPHOSPHONIC ACID

Triethyl phosphite (6.5 g, 39.2 mmol) and N-(4-bromobutylphthalimide) (10.0 g, 35.5 mmol) were heated at 180-190 ^oC (4 h) while the evolving ethyl bromide (3.21 g, 83%, identified by nmr) was collected in the apparatus described.[159] The reaction mixture was allowed to cool and light petroleum (b.p. 40-60 ^oC) (30 cm^3) was added. The mixture was vigorously shaken, allowed to stand, and the petroleum layer decanted off. Concentrated hydrochloric acid (150 cm^3) was then added and the solution heated under reflux (8 h), and allowed to cool overnight. The precipitated phthalic acid (5.6 g, 95% after drying) was filtered off and the volatile components distilled off from the filtrate on a rotary evaporator. The residual oil was dissolved in methanol (20 cm^3) and propylene oxide (ca. 400 cm^3) was added until the pH was 6. The precipitate was filtered off, and recrystallised from water-methanol, washed with methanol (30 cm^3) and dried in a vacuum oven at 60 ^oC (3 h) to

yield 4-aminobutanephosphonic acid (3.7 g, 68.2%) as a fine white crystalline solid, m.p. 275 ^{o}C (lit. m.p. 133-134 ^{o}C),[65] (Found: C, 30.1; H, 7.8; N, 9.0; P, 20.3. Calc. for $C_4H_{12}NO_3P$: C, 31.4; H, 7.8; N, 9.1; P, 20.3%); ^{1}H (D_2O) 1.66 (6H, br m, $P(\underline{CH_2})_3CH_2$), 3.01 (2H, br t, $\underline{CH_2}NH_2$); ^{13}C (D_2O) 23.0 (d, $PCH_2\underline{C}H_2$, $^{2}J_{PCC}$ 4.4 Hz), 30.0 (d, $P\underline{C}H_2$, $^{1}J_{PC}$ 133.8 Hz), 30.7 (d, $P(CH_2)_2\underline{C}H_2$, $^{3}J_{PCCC}$ 16.9 Hz), 42.0 (s, $\underline{C}H_2NH_2$); ^{13}C (D_2O/D_2SO_4) 21.3 (d, $PCH_2\underline{C}H_2$, $^{2}J_{PCC}$ 4.7 Hz), 27.5 (d, $P\underline{C}H_2$, $^{1}J_{PC}$ 135.0 Hz), 29.8 (d, $P(CH_2)_2\underline{C}H_2$, $^{3}J_{PCCC}$ 17.0 Hz), 42.2 (s, $\underline{C}H_2NH_2$); ^{31}P (D_2O) 25.9 (br s); ^{31}P (D_2O/D_2SO_4) 34.5 (br m); m/z (FAB, %) 338 (M+2G+1, 2.3), 307 (2M+1, 13.8), 246 (M+G+1, 12.9), 154 (M+1, 100.0), 137 (16.4), 111 (2.5), 110 (0.9).

6.22 PREPARATION OF 6-AMINOHEXANEPHOSPHONIC ACID

N-(6-Chlorohexyl)phthalimide (14.0 g, 53 mmol) and triethyl phosphite (8.75 g, 53 mmol) were heated at 160 ^{o}C (5.5 h). The volatile components boiling at 44 ^{o}C at 0.4 mm Hg were distilled off and the residue allowed to cool. More triethyl phosphite (4.6 g, 23 mmol) was added and the mixture heated again at 160 ^{o}C (2.5 h). The volatile components were then distilled off. Glacial acetic acid (60 cm^3), 48% hydrobromic acid (130 cm^3) and water (20 cm^3) were added to the residue and the resulting solution was heated under reflux (8 h). The volatile components were distilled off on a rotary evaporator and the residue was dissolved in methanol (15 cm^3). Propylene

oxide was added until the pH reached 6 and the precipitate so formed was filtered off, washed with methanol (20 cm^3) and dried (4.4 g, 45.8% after drying). It was then recrystallised twice from water-methanol, washed with methanol (20 ^oC) after each crystallisation and dried in a vacuum oven at 60 ^oC to yield 6-aminohexanephosphonic acid (2.6 g, 27.1%) as a fine white crystalline solid, m.p. 274 ^oC, (Found: C, 39.4; H, 8.6; N, 7.9; P, 17.2. $C_6H_{16}NO_3P$ requires: C, 39.8; H, 8.8; N, 7.7; P, 17.1%); ^1H (D_2O) 1.2-2.1 (10H, br, $P(CH_2)_5$), 2.95 (2H, t, CH_2NH, $^3J_{HCCH}$ 6.0 Hz); ^{13}C (D_2O) 25.5 (PCH_2CH_2, $^2J_{PCC}$ 4.4 Hz), 27.8 (s, $P(CH_2)_3CH_2$), 29.2 (s, $CH_2CH_2NH_2$), 30.4 (d, PCH_2, $^1J_{PC}$ 133.1 Hz), 32.1 (d, $P(CH_2)_2CH_2$, $^3J_{PCCC}$ 16.2 Hz), 42.3 (s, CH_2NH_2); ^{13}C (D_2O/D_2SO_4) 23.5 (d, PCH_2CH_2, $^2J_{PCC}$ 5.3 Hz), 27.2 (d, PCH_2, 132.2 Hz), 27.6 (s, $P(CH_2)_3CH_2$), 29.3 (s, $CH_2CH_2NH_2$), 31.5 (d, $P(CH_2)_2CH_2$, $^3J_{PCCC}$ 17.0 Hz), 43.9 (s, CH_2NH_2); ^{31}P (D_2O) 26.7 (br s); $^{31}P\{^1H\}$ (D_2O/D_2SO_4) 33.3; m/z (FAB, %) 366 (M+2G+1, 2.4), 363 (2M+1, 7.8), 274 (M+G+1, 8.5), 182 (M+1, 100.0), 165 (1.4), 102 (53.6), 100 (14.6).

6.23 PREPARATION OF 8-AMINO-OCTANEPHOSPHONIC ACID

N-(8-Bromo-octyl)phthalimide (8.0 g, 23.7 mmol) and triethyl phosphite (4.3 g, 25.9 mmol) were heated together at 170 ^{o}C (4 h) while the evolving ethyl bromide (1.8 g, 68%) was collected in the apparatus described.[159] Concentrated hydrochloric acid (300 cm 3) was then added to the solution which was heated under reflux (8 h) and then allowed to cool. Water (50 cm^3) was added and the phthalic acid (3.5 g, 89% after drying) was filtered off. The volatile materials were distilled off from the filtrate on a rotary evaporator and the residue dissolved in methanol (50 cm^3). Propylene oxide was added until the pH was 6, and the resultant precipitate was filtered off and washed with acetone (50 cm^3). It was recrystallised from water-methanol, washed with methanol (40 cm^3) and dried in a vacuum oven at 60 ^{o}C to yield 8-amino-octane-phosphonic acid (2.8 g, 56.6%) as a fine white crystalline solid, m.p. 254-255 ^{o}C, (Found: C, 45.5; H, 9.3; N, 7.8. $C_8H_{20}NO_3P$ requires: C, 45.9; H, 9.6; N, 6.7%); ^{1}H (D_2O/D_2SO_4) 1.03-2.23 (14H, br m, $P(CH_2)_7$), 3.06 (2H, t, CH_2NH_2, $^{3}J_{HCCH}$ 7.1 Hz); ^{13}C (D_2O/D_2SO_4) 23.9 (d, PCH_2CH_2, $^{2}J_{PCC}$ 5.4 Hz), 27.6 (d, PCH_2, $^{1}J_{PC}$ 132.2 Hz), 28.1 (s), 29.4 (s), 30.5 (s), 32.0 (d, $P(CH_2)_2CH_2$, $^{3}J_{PCCC}$ 17.0 Hz), 43.3 (s, CH_2NH_2); ^{31}P (D_2O/D_2SO_4) 39.0 (br m); m/z (FAB, %) 419 (2M+1, 2.4), 394 (1.5), 302 (6.7), 222 (2.0), 211 (4.4), 210 (M+1, 100), 209 (2.2), 208 (2.2), 130 (10.6), 128 (3.3).

6.24 PREPARATION OF 11-AMINO-UNDECANEPHOSPHONIC ACID

N-(11-Bromo-undecyl)phthalimide (11.0 g, 28.9 mmol) and triethyl phosphite (5.5 g, 33.1 mmol) were heated together at 180-200 ^{o}C (4 h) while the evolving ethyl bromide (2.8 g, 88.9%) was collected in the apparatus described.[159] Concentrated hydrochloric acid (300 cm^3) and acetic acid (100 cm^3) were then added and the solution was heated under reflux (8 h) and then allowed to cool. The solution was concentrated (to *ca.* 50 cm^3) on a rotary evaporator and the precipitated phthalic acid filtered off. The filtrate was then evaporated until dry on a rotary evaporator and the residue dissolved in methanol (50 cm^3). Propylene oxide was added until the pH was 6, and the resultant precipitate was filtered off and washed with acetone (2x20 cm^3). It was recrystallised from water, washed with methanol (40 cm^3) and dried in a vacuum oven at 60 ^{o}C (3 h) to yield **11-amino-undecanephosphonic acid** (4.4 g, 60.7%) as a fine white crystalline solid, m.p. 256 ^{o}C; ^{1}H (D_2O/D_2SO_4) 1.08-2.22 (20H, br m, $P(CH_2)_{10}$), 3.05 (2H, t, CH_2NH_2, $^{3}J_{HCCH}$ 6.6 Hz); ^{13}C (D_2O/D_2SO_4) 23.8 (d, PCH_2CH_2, $^{2}J_{PCC}$ 6 Hz), 27.5 (d, PCH_2, $^{1}J_{PC}$ 139.0 Hz), 28.3, 29.5, 31.3, 31.8 and 32.7 {singlets, $P(CH_2)_2(CH_2)_8$)}, 43.5 (CH_2NH_2); ^{31}P (D_2O/D_2SO_4) 41.2 (br m); m/z (FAB, %) 252 (M+1, 100.0), 250 (24.0), 234 (3.4), 172 (5.0), 170 (8.8), 156 (2.0), 142 (2.9), 128 (3.0), 110 (2.9), 109 (2.1), 96 (3.4).

6.25 PREPARATION OF O,O-DIETHYL 4-PHTHALIMIDOBUTANEPHOSPHONATE

Triethyl phosphite (6.4 g, 38.5 mmol) and N-(4-bromobutylphthalimide) (9.9 g, 35.0 mmol) were heated at 170 ^{o}C (3 h) while the evolving ethyl bromide (3.1 g, 81%, identified by nmr) was collected in the apparatus described.[159] The reaction mixture was allowed to cool and light petroleum (b.p. 40-60 ^{o}C)(20 cm^{3}) was added. The mixture was vigorously shaken, allowed to stand, and the petroleum layer decanted off. The oily residue was dissolved in diethyl ether (20 cm^{3}) and stored at -18 ^{o}C for five days. The solid that formed was filtered off (the filtrate was used for the preparation of 4-guanidinobutanephosphonic acid in 38% yield), washed with light petroleum (b.p. 40-60 ^{o}C)(20 cm^{3}) and recrystallised from diethyl ether/light petrol. It was dried in a vacuum oven at room temperature to yield O,O-diethyl 4-phthalimidobutanephosphonate (3.4 g, 28.7%) as a white crystalline solid, m.p. 67-71 ^{o}C, (Found: C, 57.3; H, 6.5; N, 3.7; P, 9.0; M^{+} 339.1234. $C_{16}H_{22}NO_5P$ requires: C, 56.6; H, 6.5; N, 4.1; P, 9.1%; M^{+} 339.1233). ^{1}H ($CDCl_3$) 1.31 (6H, t, $\underline{CH_3}CH_2O$, $^{3}J_{HCCH}$ 7.1 Hz), 1.71 (6H, br m, $P(\underline{CH_2})_3$), 3.70 (2H, t, $\underline{CH_2}N$, $^{3}J_{HCCH}$ 6.5 Hz), 4.09 (4H, overlapping d of q, $\underline{CH_2}O$), 7.78 (4H, m, aromatic); ^{13}C ($CDCl_3$) 16.5 (d, $\underline{C}H_3$, $^{3}J_{POCC}$ 6.1 Hz), 19.9 (d, $PCH_2\underline{C}H_2$, $^{2}J_{PCC}$ 3.0 Hz), 25.7 (d, $P\underline{C}H_2$, $^{1}J_{PC}$ 160.5 Hz), 28.8 (d, $P(CH_2)_2\underline{C}H_2$, $^{3}J_{PCCC}$ 4.9 Hz), 37.3 (s, $\underline{C}H_2N$), 61.5 (d, $\underline{C}H_2O$, $^{2}J_{POC}$ 6.7 Hz), 123.3 (s, $\underline{C_3}$ aromatic), 132.3 (s, $\underline{C_1}$

aromatic), 134.1 (s, C_2 aromatic), 168.4 (s, C=O); ^{31}P ($CDCl_3$) 31.4 (br s); m/z (%) 339 (M^+, 11.7), 179 (62.4), 166 (88.2), 165 (86.5), 160 (9 5.6), 152 (100.0), 139 (19.0), 138 (53.2), 130 (42.5), 125 (71.6), 123 (21.0), 111 (26.5), 108 (19.5).

6.26 REACTION OF O,O-DIETHYL 2-BROMOETHANEPHOSPHONATE WITH GUANIDINE

Sodium (2.3 g, 100.0 mmol) was dissolved in butan-1-ol (50 cm^3). The solution was added to a boiling solution of guanidine hydrochloride (9.55 g, 100.0 mmol) in butan-1-ol (200 cm^3) and the mixture heated under reflux (10 min). Sodium chloride (5.4 g, 92.3% after drying) was filtered off, the filtrate was heated under reflux, and O,O-diethyl 2-bromoethanephosphonate (12.25 g, 0.05 mmol) dissolved in butan-1-ol (25 cm^3) was added over 30 min. The mixture was heated under reflux (2 h), and allowed to cool. The butan-1-ol was distilled off on a rotary evaporator and concentrated hydrochloric acid (100 cm^3) added to the residue. The solution was heated under reflux (8 h), cooled, and the volatile components were distilled off on a rotary evaporator. The viscous residue was dissolved in ethanol (50 cm^3) and propylene oxide (10 cm^3) added. The sticky precipitate so formed was dissolved in water and applied to an ion-exchange column (Dowex $50H^+$). The column was first washed with water until neutral, then eluted with 4N ammonia solution (400 cm^3). The volatiles were distilled off on a rotary evaporator, the residue was dissolved in water (40 cm^3), and dilute hydrochloric acid was added until pH 4. A few drops of acetone were then added and the solution left to crystallise. The crystals that formed were filtered off, washed with ethanol (20 cm^3) and then diethyl ether (20 cm^3), and dried in a

vacuum oven at 60 °C to yield a fine white crystalline solid, (0.7 g) m.p. 230-231 °C identified as a mixture of 2-guanidinoethanephosphonic acid and 1,1-{2-(dihydroxyphosphinyl)ethyl}-guanidine. ^{13}C (D_2O) {relative intensities, %} 28.1 (d, PCH_2, $^1J_{PC}$ 130.2 Hz) {14.0}, 29.8 (d, PCH_2, $^1J_{PC}$ 132.9 Hz) {7.0}, 39.3 (s, $CH_2NHC(:NH)NH_2$) {5.5}, 46.4 (s, $CH_2CH_2NC(:NH)NH_2$) {14.5}, 158.2 (s, $NHC(:NH)NH_2$) {1}, 158.9 (s, $NC(:NH)NH_2$) {2.5}; $^{31}P-\{^1H\}^{bb}$ (D_2O) 21.9 (s), 22.7 (s); $^{31}P-\{^1H\}^{bb}$ (D_2O/D_2SO_4) 27.4 (s, 76%), 28.3 (s, 24%); m/z (FAB, %) 369 (M+G+2, 23.3), 278 (13.0), 277 (M+2, 100.0), 276 (M+1, 43.4), 275 (11.9), 219 (23.5), 211 (31.8), 195 (5.1), 191 (25.3), 187 (19.6), 18.6 (83.8), 183 (27.1), 182 (5.4), 181 (1.7), 177 (11.4), 168 (16.0), 167 (16.2), 137 (5.0), 115 (20.0), 111 (26.0), 109 (9.4), 107 (5.8), 100 (10.6), 99 (15.9), 94 (62.0).

6.27 PREPARATION OF GUANIDINOMETHANEPHOSPHONIC ACID

Aminomethanephosphonic acid (3.0 g, 27.0 mmol), S-methylisothiouronium chloride (6.84 g, 54.1 mmol), and potassium hydroxide (6.06 g, 108.0 mmol) 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 until pH 2 with concentrated hydrochloric acid and the volatile components distilled off on a rotary evaporator. Methanol (100 cm^3) was then added to the residue and the potassium chloride (6.7 g, 83.1% after

drying) was filtered off. Propylene oxide (ca. 400 cm^3) was added to the filtrate until the pH was 6. The supernatant liquors were decanted off and the residue was washed with methanol (200 cm^3). The crude guanidinomethanephosphonic acid was recrystallised from water-methanol, washed with methanol (20 cm 3) and dried in a vacuum oven at 70 °C to yield guanidinomethanephosphonic acid (2.9 g, 70.1%) as a fine white crystalline solid, m.p. 331-332 °C, (Found: C, 15.6; H, 5.2; N, 28.0; P, 20.2. $C_2H_8N_3O_3P$ requires: C, 15.7; H, 5.2; N, 27.5; P, 20.3%); ^1H (D_2O) 3.35 (d, $P\underline{C}H_2$, $^2J_{PCH}$ 12.2 Hz); ^{13}C (D_2O) 42.6 (d, $P\underline{C}H_2$, $^1J_{PC}$ 145.2 Hz), 160.6 (d, $NH\underline{C}(:NH)NH_2$, $^3J_{PCNC}$ 5.5 Hz); ^{13}C (D_2O/D_2SO_4) 41.2 (d, $P\underline{C}H_2$, $^1J_{PC}$ 149.9 Hz), 160.2 (d, $NH\underline{C}(:NH)NH_2$, $^3J_{PCNC}$ 4.1 Hz); ^{31}P (D_2O) 14.2 (t, $^2J_{HCP}$ 11.8 Hz); $^{31}P-\{^1H\}^{bb}$ (D_2O/D_2SO_4) 19.0; m/z (FAB, %) 238 (M+2G+1, 3.0), 307 (2M+1, 5.5), 246 (M+G+1, 12.8), 154 (M+1, 100.0), 137 (4.6), 127 (6.6), 115 (4.2), 97 (1.8), 95 (2.5).

6.28 PREPARATION OF 2-GUANIDINOETHANEPHOSPHONIC ACID

2-Aminoethanephosphonic acid (4.0 g, 32.0 mmol), S-methylisothiouronium chloride (8.1 g, 64.0 mmol), and potassium hydroxide (7.2 g, 128.3 mmol) were dissolved in water (15 cm^3) and heated at 60 °C (4 h) whilst the evolving methanethiol was collected in potassium permanganate traps. The resultant solution was acidified until pH 2 with concentrated hydrochloric acid and the

solvents removed on a rotary evaporator. Methanol (100 cm^3) was added to the residue and the precipitated potassium chloride (8.2 g, 85.6% after drying) was filtered off. Propylene oxide (ca. 400 cm^3) was added to the filtrate until the pH reached 6 when a colourless oil separated. The mixture was stored at -18 ^oC for several days during which time the oil crystallised. The supernatant liquors were decanted off and the residue was recrystallised from cold water-ethanol, washed with ethanol (50 cm^3), and dried in a vacuum oven at 70 ^oC to yield 2-guanidinoethanephosphonic acid (2.6 g, 48.6%) as a fine white crystalline solid, m.p. 228-229 ^oC, (lit. m.p. 228 ^oC),[60] (Found: C, 21.6; H, 6.0; N, 23.9; P, 18.2. Calc. for $C_3H_{10}N_3O_3P$: C, 21.6; H, 6.0; N, 25.1; P, 18.6%); ^1H (D_2O) 1.90 (2H, overlapping d of t, PCH_2, $^3J_{HCCH}$ 7.8 Hz, $^2J_{PCH}$ 17.1 Hz), 3.2-3.7 (2H, m, CH_2NH); ^{13}C (D_2O) 30.4 (d, PCH_2, $^1J_{PC}$ 131.6 Hz), 39.8 (s, CH_2NH), 159.6 (s, $NHC(:NH)NH_2$); ^{13}C (D_2O/D_2SO_4) 29.1 (d, PCH_2, $^1J_{PC}$ 136.3 Hz), 39.1 (d, CH_2NH, $^2J_{PCC}$ 2.7 HZ), 160.2 (s, $NHC(:NH)NH_2$); ^{31}P (D_2O) 20.6 (overlapping t of t); ^{31}P (D_2O/D_2SO_4) 28.8 (overlapping t of t); m/z (FAB, %) 502 (3M+1, 2.2), 352 (M+2G+1, 1.6), 335 (2M+1, 18.8), 260 (M+G+1, 7.9), 168 (M+1, 100.0), 152 (4.7), 151 (4.8), 126 (2.3), 111 (1.1), 110 (1.9), 109 (3.2).

6.29 PREPARATION OF 3-GUANIDINOPROPANEPHOSPHONIC ACID

3-Aminopropanephosphonic acid (2.2 g, 15.8 mmol), S-methylisothiouronium chloride (4.0 g, 31.6 mmol), and potassium hydroxide(3.55 g, 63.3 mmol) were dissolved in water (15 cm^3) and heated at 60 ^oC (4 h). The solution was allowed to cool and acidified to pH 2 with concentrated hydrochloric acid. The volatile components were distilled off using a rotary evaporator. Methanol (30 cm^3), was added to the viscous residue and the insoluble potassium chloride (3.9 g, 82.6% after drying) was filtered off. Propylene oxide (ca. 400 cm^3) was then added to the filtrate until the pH reached 6 when a sticky precipitate was obtained. The supernatant liquors were decanted off and this material was recrystallised from water-ethanol, washed with methanol (30 cm^3) and dried in a vacuum oven at 70 ^oC (6 h) to yield 3-guanidinopropanephosphonic acid (2.3 g, 80.3%) as a fine white crystalline solid, m.p. 278 ^oC, (Found: C, 26.5; H, 6.7; N, 23.0; P, 17.1. $C_4H_{12}N_3O_3P$ requires: C, 26.5; H, 6.6; N, 23.2; P, 17.1%); ^1H (D_2O) 1.54-1.94 (4H, m, $PCH_2\underline{CH_2}$), 3.28 (2H, t, $\underline{CH_2}NHC(:NH)NH_2$, $^3J_{HCCH}$ 6.6 Hz); ^{13}C (D_2O) 25.7 (d, $PCH_2\underline{CH_2}$, $^2J_{PCC}$ 4.1 Hz), 27.7 (d, $P\underline{CH_2}$, $^1J_{PC}$ 134.3 Hz), 44.6 (d, $\underline{CH_2}NH$, $^3J_{PCCC}$ 17.0 Hz), 159.8 (s, $NH\underline{C}(:NH)NH_2$); ^{13}C (D_2O/D_2SO_4) 24.1 (d, $PCH_2\underline{CH_2}$, $^2J_{PCC}$ 4.1 Hz), 25.6 (d, $P\underline{CH_2}$, $^1J_{PC}$ 137.0 Hz), 44.2 (d, $P(CH_2)_2\underline{CH_2}$, $^3J_{PCCC}$ 19.7 Hz), 159.6 (s, $NH\underline{C}(:NH)NH_2$); ^{31}P (D_2O) 24.7 (br m); ^{31}P (D_2O/D_2SO_4) 38.6 (br m); m/z (FAB, %) 366 (M+3G+1,

1.1), 363 (2M+1, 2.6), 274 (M+G+1, 4.2), 182 (M+1, 100.0), 167 (2.0), 152 (3.2), 125 (2.6), 123 (2.0), 110 (2.6), 102 (3.3), 101 (2.6), 100 (6.3).

6.30 PREPARATION OF 4-GUANIDINOBUTANEPHOSPHONIC ACID

4-Aminobutanephosphonic acid (2.1 g, 13.7 mmol) S-methylisothiouronium chloride (3.5 g, 27.7 mmol), and potassium hydroxide (3.1 g, 55.2 mmol) were dissolved in water (8 cm^3) and heated at 60 ^oC (4 h) whilst the evolving methanethiol was collected in potassium permanganate traps. The solution was acidified to pH 2 with concentrated hydrochloric acid and the volatile components were then distilled off on a rotary evaporator. Methanol (30 cm^3) was added to the residue and the insoluble potassium chloride (3.6 g, 87% after drying) was filtered off. Propylene oxide (ca. 400 cm^3) was then added to the filtrate until the pH was 6, to yield a sticky precipitate. The supernatant liquors were decanted off and the residue was recrystallised from water-ethanol, washed with methanol (30 cm^3), and dried in a vacuum oven at 70 ^oC (3 h) to yield 4-guanidinobutanephosphonic acid (1.8 g, 67.3%) as a fine white crystalline solid, m.p. 265-266 ^oC, (Found: C, 30.1; H, 7.0; N, 21.3; P, 15.9. $C_5H_{14}N_3O_3P$ requires: C, 30.8; H, 7.2; N, 21.5; P, 15.9%); ^1H (D_2O/D_2SO_4) 1.34-2.20 (6H, m, $P(CH_2)_3$), 3.21 (2H, t, $CH_2NHC(:NH)NH_2$, $^3J_{HCCH}$ 6.1 Hz); ^{13}C (D_2O) 23.2 (d, PCH_2CH_2, $^2J_{PCC}$ 4.4 Hz), 30.1 (d, PCH_2, $^1J_{PC}$ 133.3 Hz),

31.9 (d, $P(CH_2)_2\underline{C}H_2$, $^3J_{PCCC}$ 16.2 Hz), 43.7 (s, $\underline{C}H_2NH$), 159.9 (s, $NH\underline{C}(:NH)NH_2$); ^{13}C (D_2O/D_2SO_4) 21.7 (d, $PCH_2\underline{C}H_2$, $^2J_{PCC}$ 4.7 Hz), 27.9 (d, $P\underline{C}H_2$, $^1J_{PC}$ 135.0 Hz), 31.3 (d, $P(CH_2)_2\underline{C}H_2$ $^3J_{PCCC}$ 16.3 Hz), 43.8 (s, $\underline{C}H_2NH$), 159.8 (s, $NH\underline{C}(:NH)NH_2$); ^{31}P (D_2O) 25.7 (br s); ^{31}P (D_2O/D_2SO_4) 35.2 (br m); $^{15}N-\{^1H\}^{bb}$ (D_2O/H_2O) -299.4 (s, $\underline{NH}C$), -313.8 (s, $C(:\underline{NH})NH_2$); m/z (FAB, %) 391 (2M+1, 3.2), 288 (M+G+1, 6.5), 223 (131+G, 5.0), 196 (M+1, 100.0), 181 (2.1), 139 (6.9), 137 (8.7), 131 (20.5), 116 (6.4), 115 (5.2), 114 (5.1), 100 (2.5).

6.31 PREPARATION OF 6-GUANIDINOHEXANEPHOSPHONIC ACID

6-Aminohexanephosphonic acid (1.0 g, 5.52 mmol), S-methylisothiouronium chloride (1.48 g, 11.7 mmol), and potassium hydroxide (1.0 g, 17.8 mmol) were dissolved in water (6 cm^3) and heated at 50-55 ^oC (4 h) whilst the evolving methanethiol was collected in potassium permanganate traps. The solution was allowed to cool, methanol (50 cm^3) was added, and the solution acidified to pH 2 with concentrated hydrochloric acid. The precipitated potassium chloride (0.9 g, 67.7%, after drying) was filtered off and the volatile components distilled off on a rotary evaporator. The residue was dissolved in methanol (30 cm^3) and more potassium chloride (0.2 g, 15.0%, after drying) was filtered off. Propylene oxide (ca. 400 cm^3) was added to the filtrate until the pH reached 6 which gave a sticky white precipitate. The supernatant liquors were decanted off from it and the

residue dissolved in hot water (25 cm^3). Methanol (50 cm^3) and acetone (40 cm^3) were then added and the resultant solution was left to stand. The crystals that formed were filtered off, washed with acetone (15 cm^3) and dried in a vacuum oven at 70 ^oC (3 h) to yield 6-guanidinohexanephosphonic acid (0.7 g, 56.8%) as a fine white crystalline solid, m.p. 280-282 ^oC, (Found: C, 36.5; H, 8.2; N, 18.8; P, 13.9. $C_7H_{18}N_3O_3P$ requires: C, 37.7; H, 8.1; N, 18.8; P, 13.9%); ^1H (D_2O) 1.1-1.7 (10H, br m, $P(CH_2)_5$), 3.2 (2H, t, CH_2NH, $^3J_{HCCH}$ 6.3 Hz); ^{13}C (D_2O) 25.7 (d, PCH_2CH_2, $^2J_{PCC}$ 4.3 Hz), 28.1 (s, $P(CH_2)_3CH_2$), 30.5 (s, $P(CH_2)_4CH_2$), 30.5 (d, PCH_2, $^1J_{PC}$ 133.1 Hz) 32.4 (d, $P(CH_2)_2CH_2$, $^3J_{PCCC}$ 16.5 Hz), 159.8 (s, $NHC(:NH)NH_2$); ^{31}P (D_2O) 27.1 (br s); $^{31}P-\{^1H\}^{bb}$ (D_2O/D_2SO_4) 33.2; m/z (FAB, %) 447 (2M+1, 2.5), 408 (M+2G+1, 0.7), 316 (M+G+1, 2.8), 277 (9.9), 224 (M+1, 100.0), 223 (5.5), 209 (3.4), 186 (6.0), 167 (17.5), 165 (8.0), 144 (16.5), 142 (16.2), 140 (1.4), 128 (4.6), 114 (3.7), 100 (5.5).

6.32 PREPARATION OF 8-GUANIDINO-OCTANEPHOSPHONIC ACID

8-Amino-octanephosphonic acid (2.0 g, 9.56 mmol), S-methylisothiouronium chloride (2.4 g, 19.0 mmol) and potassium hydroxide (21.5 g, 38.3 mmol) were dissolved in water (20 cm^3) and heated (4 h) in an oil bath at 70 ^oC. Concentrated hydrochloric acid was then added until pH 1 and the volatile components were then distilled off on a

rotary evaporator. Methanol (100 cm^3) was added and the insoluble potassium chloride (2.3 g, 80.5% after drying) was filtered off. Propylene oxide (ca. 400 cm^3) was then added to the filtrate until the pH was 6, and the white precipitate that formed was filtered off and washed with acetone (50 cm^3). It was recrystallised from water (ca. 600 cm^3), washed with acetone (3x30 cm^3), and dried in a vacuum oven at 60 °C (5 h) to yield 8-guanidino-octanephosphonic acid (1.8 g, 75.0%) as a fine white crystalline solid, m.p. 261 °C, (Found: C, 43.1; H, 8.6; N, 15.6; P, 11.9. $C_9H_{22}N_3O_3P$ requires: C, 43.0; H, 8.8; N, 16.7; P, 12.3%); ^1H (D_2O/D_2SO_4) 1.03-2.23 (14H, br m, $P(CH_2)_7$), 3.15 (2H, t, $CH_2NHC(:NH)NH_2$, $^3J_{HCCH}$ 6.3 Hz); ^{13}C (D_2O/D_2SO_4) 23.9 (d, $PCH_2\underline{C}H_2$, $^2J_{PCC}$ 5.4Hz), 27.7 (d, $P\underline{C}H_2$, $^1J_{PC}$ 132.9Hz), 28.5 (s), 30.5 (s), 32.0 (d, $P(CH_2)_2\underline{C}H_2$, $^3J_{PCCC}$ 17.0Hz), 44.4 ($\underline{C}H_2NH$), 159.5 (s, $NH\underline{C}(:NH)NH_2$); ^{31}P (D_2O/D_2SO_4) 39.3 (br m); m/z (FAB, %) 342 (M+G+1, 1.1), 252 (M+1, 100), 250 (15.7), 236 (3.6), 235 (2.4), 234 (5.0), 172 (24.7), 170 (35.4), 156 (10.3), 142 (11.0), 128 (13.2), 114 (10.3), 100 (12.0).

6.33 PREPARATION OF 1-HYDROXYOCTANEPHOSPHONIC ACID

Phosphorus trichloride (82.5 g, 600 mmol) was added dropwise to octanal (64.0 g, 500 mmol) so that the temperature did not rise above 35 ^{o}C. After addition was complete the mixture was stirred at room temperature (2 h). Glacial acetic acid (90.0 g, 1500 mmol) was added so that the temperature did not rise rise above 35 ^{o}C and the resultant mixture was stirred overnight. The solution that formed was poured into ice/water ca. 1200 g, shaken vigorously, and concentrated on a rotary evaporator (ca. 200 cm^3). The crude phosphonic acid was filtered off, washed with diethyl ether (2x50 cm^3), recrystallised twice from methanol/water, washed with diethyl ether (3x50 cm^3) and dried in a vacuum oven at 60 ^{o}C to yield 1-hydroxyoctanephosphonic acid (16.8 g, 16%) as a white waxy solid, m.p. 150-155 ^{o}C, (Found: C, 45.7; H, 9.1; P, 14.6. $C_8H_{19}O_4P$ requires: C, 45.7; H, 9.1; P, 14.8%); ^{1}H (DMSO-d_6) 0.5-1.8 (15H, br, C_7H_{15}), 3.35 (1H, br t, PCH), 8.0 (3H, br, $(HO)_2P$ and CH(OH), exchanged with D_2O); ^{13}C (DMSO-d_6) 13.8 (s, CH_3), 22.0 (s), 25.5 (d, $PCHCH_2CH_2$, $^{3}J_{PCCC}$ 13.3 Hz), 28.7 (s), 28.8 (s), 31.3 (s), 67.0 (d, PCH, $^{1}J_{PC}$ 161.8 Hz); ^{13}C (SFORD) 67.0 (d of d); ^{31}P (DMSO-d_6) 22.6 (br m); m/z (FAB, %) 421 (2M+1, 40.4), 403 (6.9), 303 (M+G+1, 6.0), 211 (M+1, 100.0), 193 (12.5), 129 (27.3), 109 (6.8).

6.33 PREPARATION OF 1-HYDROXYOCTANEPHOSPHONIC ACID

Phosphorus trichloride (82.5 g, 600 mmol) was added dropwise to octanal (64.0 g, 500 mmol) so that the temperature did not rise above 35 ^{o}C. After addition was complete the mixture was stirred at room temperature (2 h). Glacial acetic acid (90.0 g, 1500 mmol) was added so that the temperature did not rise rise above 35 ^{o}C and the resultant mixture was stirred overnight. The solution that formed was poured into ice/water *ca.* 1200 g, shaken vigorously, and concentrated on a rotary evaporator (*ca.* 200 cm^3). The crude phosphonic acid was filtered off, washed with diethyl ether (2x50 cm^3), recrystallised twice from methanol/water, washed with diethyl ether (3x50 cm^3) and dried in a vacuum oven at 60 ^{o}C to yield 1-hydroxyoctanephosphonic acid (16.8 g, 16%) as a white waxy solid, m.p. 150-155 ^{o}C, (Found: C, 45.7; H, 9.1; P, 14.6. $C_8H_{19}O_4P$ requires: C, 45.7; H, 9.1; P, 14.8%); ^{1}H (DMSO-d_6) 0.5-1.8 (15H, br, C_7H_{15}), 3.35 (1H, br t, PCH), 8.0 (3H, br, $(HO)_2P$ and CH(OH), exchanged with D_2O); ^{13}C (DMSO-d_6) 13.8 (s, CH_3), 22.0 (s), 25.5 (d, $PCHCH_2CH_2$, $^3J_{PCCC}$ 13.3 Hz), 28.7 (s), 28.8 (s), 31.3 (s), 67.0 (d, PCH, $^1J_{PC}$ 161.8 Hz); ^{13}C (SFORD) 67.0 (d of d); ^{31}P (DMSO-d_6) 22.6 (br m); m/z (FAB, %) 421 (2M+1, 40.4), 403 (6.9), 303 (M+G+1, 6.0), 211 (M+1, 100.0), 193 (12.5), 129 (27.3), 109 (6.8).

6.34 PREPARATION OF 1-CHLORO-OCTANEPHOSPHONIC ACID

Method (a): From phosphorus trichloride and octanal

Phosphorus trichloride (137.5 g, 1000 mmol) was added dropwise to octanal (64.0 g, 500 mmol) so that the temperature did not rise above 35 ^{o}C. After addition was complete the mixture was stirred at room temperature (2.5 h). Glacial acetic acid (90.0 g, 1500 mmol) was added so that the temperature did not rise above 35 ^{o}C and the resultant mixture was stirred overnight. The solution that formed was poured into diethyl ether (300 cm^3) and cooled in an ice bath. Water was added dropwise (so that the temperature did not rise above 10 ^{o}C) until the evolution of gas ceased. The mixture was transferred to a separating funnel, the aqueous layer discarded and the organic layer washed with water (2x100 cm^3) and dried ($MgSO_4$). The volatile components were distilled off on a rotary evaporator and the oily residue triturated with light petroleum (b.p. 60-80 ^{o}C)(ca. 500 cm^3). The solid that formed on standing was filtered off, washed with diethyl ether (2x50 cm^3), and dried in a vacuum oven at 60 ^{o}C to yield 1-chloro-octanephosphonic acid (22.7 g, 19.9%) as a white waxy solid, m.p. 149-150 ^{o}C, (Found: P, 13.5. $C_8H_{18}ClO_3P$ requires: P, 13.5%); ^{1}H (DMSO-d_6) 0.5-1.8 (15H, br, C_7H_{15}), 3.9 (1H, br t, PCH), 6.18 (2H, br s, $P(OH)_2$, exchanged with D_2O); ^{13}C (DMSO-d_6) 13.9 (s, CH_3), 22.0 (s), 25.5 (d, $PCHCH_2CH_2$, $^{3}J_{PCCC}$ 6.1 Hz), 28.6

(s), 29.3 (s), 30.8 (s), 31.3 (s), 74.9 (d, PCHCl, $^{1}J_{PC}$ 158.8 Hz); ^{31}P (DMSO-d_6) 20.4 (br s).

Method (b): From 1-hydroxyoctanephosphonic acid and thionyl chloride

1-Hydroxyoctanephosphonic acid (12.5 g, 59.5 mmol) and thionyl chloride (83.0 g, 697.5 mmol) were heated under reflux (4.5 h). The excess of thionyl chloride was then distilled off under reduced pressure. The residual oil was dissolved in diethyl ether (150 cm^3), and washed with sodium bicarbonate solution (5%) until neutral. The organic layer was then washed with hydrochloric acid (100 cm^3), water (100 cm^3) and dried ($MgSO_4$). The diethyl ether was distilled off on a rotary evaporator and the residual oil triturated with light petroleum (b.p. 60-80 ^{o}C)(150 cm^3). The solid formed was filtered off, washed with diethyl ether (20 cm^3) and dried in a vacuum oven at 60 ^{o}C to yield 1-chloro-octanephosphonic acid (5.5 g, 40.1%) as a white waxy solid, m.p. 148-149 ^{o}C with identical ^{1}H and ^{13}C nmr spectra to that of the product obtained above.

Method (c): From 1-chloro-octanephosphonyl dichloride

1-Chloro-octanephosphonyl dichloride (3.2 g, 12.0 mmol) was poured into iced water (150 cm^3) and shaken vigorously and the water was distilled off on a rotary evaporator. The residual oil was triturated with light petroleum (b.p. 60-80 ^oC) and the resultant precipitate was washed with diethyl ether (40 cm^3) and dried in a vacuum oven at 60 ^oC to yield 1-chloro-octanephosphonic acid (2.2 g, 80%) as a white waxy solid, m.p. 148-150 ^oC with identical ^1H and ^{13}C nmr spectra to those for the products obtained above.

6.35 PREPARATION OF 1-CHLORO-OCTANEPHOSPHONYL DICHLORIDE

1-Hydroxyoctanephosphonic acid (20.3 g, 96.6 mmol) and phosphorus pentachloride (60.4 g, 289.7 mmol) were heated under reflux (3 h). The phosphorus oxychloride that formed was distilled off under reduced pressure and the residual oil was distilled to yield 1-chloro-octane-phosphonyl dichloride (17.4 g, 67.8%) as a colourless free running oil, b.p. 140 ^oC at 4 mm Hg, n_D^{23}1.4713 (Found: C, 36.0; H, 6.1; easily hydrolysing Cl, 26.5. $C_8H_{16}Cl_3OP$ requires: C, 36.3; H, 5.7; easily hydrolysing Cl, 26.7%); I.R. (thin film) 1290 cm^{-1}, (P=O).

6.36 PREPARATION OF CHLOROMETHANEPHOSPHONYL DICHLORIDE

Seven sealed glass tubes each containing paraformaldehyde (5.0 g, 166.7 mmol) and phosphorus trichloride (36.2 g, 26.3 mmol) were heated (19 h) at 240 ^{o}C. After cooling, the contents of all the tubes were combined and the unreacted phosphorus trichloride was distilled off under reduced pressure. The resultant brown liquid was distilled through a 10 cm Vigreux column and the fraction boiling at 58-61 ^{o}C at 0.03 mm Hg was collected and redistilled to yield chloromethanephosphonyl dichloride (105.5 g, 54%) as a colourless free-running oil, b.p. 65 ^{o}C at 0.02 mm Hg (lit. b.p. 77-78 ^{o}C at 10 mm Hg).[92]

6.37 PREPARATION OF CHLOROMETHANEPHOSPHONIC ACID

Chloromethanephosphonyl dichloride (42.2 g, 251.9 mmol) was poured into water (100 cm^3) and the volatile components distilled from the resulting solution on a rotary evaporator. The residue was dissolved in diethyl ether (300 cm^3) and the solution dried ($MgSO_4$). The diethyl ether was distilled off on a rotary evaporator and the residue was dried in a vacuum oven at 35 ^{o}C (7 h) and then over phosphorus pentoxide in a desiccator to yield chloromethanephosphonic acid (29.5 g, 90%) as a fine white crystalline solid, m.p. 89 ^{o}C, (lit. m.p.89-90 ^{o}C),[160] (Found: C, 9.2; H, 3.3. Calc. for CH_4ClO_3P: C, 9.2; H, 3.1%); ^{1}H (DMSO-d_6) 3.6 (2H, d, $\underline{PCH_2}$, $^2J_{PCH}$ 10.0 Hz), 11.4

6.36 PREPARATION OF CHLOROMETHANEPHOSPHONYL DICHLORIDE

Seven sealed glass tubes each containing paraformaldehyde (5.0 g, 166.7 mmol) and phosphorus trichloride (36.2 g, 26.3 mmol) were heated (19 h) at 240 °C. After cooling, the contents of all the tubes were combined and the unreacted phosphorus trichloride was distilled off under reduced pressure. The resultant brown liquid was distilled through a 10 cm Vigreux column and the fraction boiling at 58-61 °C at 0.03 mm Hg was collected and redistilled to yield chloromethanephosphonyl dichloride (105.5 g, 54%) as a colourless free-running oil, b.p. 65 °C at 0.02 mm Hg (lit. b.p. 77-78 °C at 10 mm Hg).[92]

6.37 PREPARATION OF CHLOROMETHANEPHOSPHONIC ACID

Chloromethanephosphonyl dichloride (42.2 g, 251.9 mmol) was poured into water (100 cm^3) and the volatile components distilled from the resulting solution on a rotary evaporator. The residue was dissolved in diethyl ether (300 cm^3) and the solution dried ($MgSO_4$). The diethyl ether was distilled off on a rotary evaporator and the residue was dried in a vacuum oven at 35 °C (7 h) and then over phosphorus pentoxide in a desiccator to yield chloromethanephosphonic acid (29.5 g, 90%) as a fine white crystalline solid, m.p. 89 °C, (lit. m.p.89-90 °C),[160] (Found: C, 9.2; H, 3.3. Calc. for CH_4ClO_3P: C, 9.2; H, 3.1%); ^1H (DMSO-d_6) 3.6 (2H, d, $P\underline{CH_2}$, $^2J_{PCH}$ 10.0 Hz), 11.4

(2H, s, P(OH)$_2$, exchanged with D_2O); ^1H (D_2O) 3.64 (d, PCH$_2$, $^2J_{PCH}$ 10.0 Hz); ^{13}C (D_2O) 37.2 (d, PCH$_2$, $^1J_{PC}$ 159.6 Hz); ^{31}P (D_2O) 17.2 (t, $^2J_{HCP}$ 9.9 Hz),

6.38 ATTEMPTED CONDENSATION OF 1-CHLORO-OCTANEPHOSPHONIC ACID AND GUANIDINE

Sodium metal (1.20 g, 52.2 mmol) was dissolved in butan-1-ol (50 cm^3). The solution was added to a boiling solution of guanidine hydrochloride (5.01 g, 52.5 mmol) in butan-1-ol (150 cm^3) and the mixture was heated under reflux (10 min). Sodium chloride was filtered off, the filtrate was heated under reflux, and 1-chloro-octanephosphonic acid (3.0 g, 13.1 mmol) was added over 20 min. The mixture was then heated under reflux (3 h), and allowed to cool. The precipitate was filtered off, washed with acetone (30 cm^3), recrystallised from water-acetone, and dried in a vacuum oven at 60 ^oC to yield the guanidinium salts of 1-chloro-octanephosphonic acid (4.4 g) as a white crystalline solid, m.p. 235 ^oC; ^{13}C (D_2O) 16.4 (s, CH$_3$), 25.2 (s), 29.4 (d, PCHCH$_2$CH$_2$, $^3J_{PCCC}$ 6.6 Hz), 31.9 (s), 32.6 (s), 33.3 (s), 34.6 (s), 77.5 (d, PCH, $^1J_{PC}$ 150.8 Hz), 161.0 (s, NH$_2$C(:NH)NH$_2$); ^{31}P (D_2O) 18.8 (br s).

D_2SO_4 (ca. 5 cm^3) was then added to the nmr solution to give a precipitate which was filtered off dried in a vacuum oven at 60 °C, and identified as 1-chloro-octanephosphonic acid; ^{13}C (DMSO-d_6) 13.9 (s, CH_3), 22.1 (s), 25.2 (d, $PCHCH_2\underline{C}H_2$, $^3J_{PCCC}$ 9.6 Hz), 28.6 (s), 29.3 (s), 30.9 (s), 31.3 (s), 75.1 (d, $P\underline{C}H$, $^1J_{PC}$ 158.1 Hz). The filtrate contained the guanidinium ion; ^{13}C (D_2O/D_2SO_4) 160.7 (s).

6.39 ATTEMPTED CONDENSATION OF CHLOROMETHANEPHOSPHONIC ACID AND GUANIDINE

Sodium metal (4.58 g, 199.1 mmol) was stirred in butan-1-ol (150 cm^3) until all dissolved. Guanidine hydrochloride (19.0 g, 199.2 mmol) was then added, the mixture was heated under reflux (10 min), and the precipitated sodium chloride filtered off. The filtrate was heated under reflux and chloromethanephosphonic acid (5.2 g, 39.8 mmol) dissolved in butan-1-ol (50 cm^3) was added dropwise over 20 min. The resultant mixture was heated under reflux (3.5 h) and the precipitate that formed was filtered off from the hot mixture, recrystallised from water-ethanol, washed with ethanol (30 cm^3), and dried in a vacuum oven at 60 °C to yield <u>bis-guanidinium chloromethanephosphonate</u> (5.9 g, 62%) as a fine white crystalline solid, m.p. 202-203 °C, (Found: C, 14.3; H, 5.7; P, 12.3. $C_3H_{14}ClN_6O_3P$ requires: C, 14.5; H, 5.6; P, 12.5%); ^1H (D_2O) 3.2 (d, $P\underline{CH_2}Cl$, $^2J_{PCH}$ 9 Hz);

^{13}C (D_2O) 41.2 (d, P$\underline{CH_2}$Cl, $^1J_{PC}$ 136.8 Hz), 161.0 (s, NHC(:NH)NH_2); m/z (FAB, %) 438 (2.0), 308 (3.0), 251 (11.8), 249 (M+1, 38.7), 244 (2 guanidine+G+1, 1.4), 228 (6.0), 214 (3.9), 190 (M-guanidine+1, 17.3), 155 (10.7), 152 (guanidine+G+1, 100), 119 (2 guanidine+1, 75.7).

6.40 ATTEMPTED CONDENSATION OF CHLOROMETHANEPHOSPHONIC ACID AND DODECYLGUANIDINE

Chloromethanephosphonic acid (1.0 g, 7.7 mmol) and dodecylguanidine (6.9 g, 30.3 mmol) were dissolved in butan-1-ol (100 cm^3) and heated under reflux (3 h) and allowed to cool. Acetone (200 cm^3) was added to the clear solution and the precipitate that was formed was filtered off. It was recrystallised from methanol/acetone and dried in a vacuum oven at room temperature to yield dodecylguanidinium chloromethanephosphonate (2.5 g, 91.3%) as a fine white solid, m.p. 140-141 ^oC, (Found: C, 46.7; H, 8.7; N, 11.8. $C_{14}H_{33}ClN_3O_3P$ requires: C, 47.0; H, 9.2; N, 11.8%); ^{13}C (pyridine-d_5) 14.3 (s, $\underline{CH_3}$), 23.0, 27.7, 29.8, 30.2 and 31.2 (singlets, $CH_3(\underline{CH_2})_{10}$), 41.0 (d, P$\underline{CH_2}$, $^1J_{PC}$ 135.6 Hz), 42.3 (s, $\underline{CH_2}$NHC(:NH)NH_2), 159.4 (s, NH$\underline{C}$(:NH)NH_2); $^{31}P-\{^1H\}^{bb}$ (DMSO-d_6) 9.1.

6.41 ATTEMPTED CONDENSATION OF 1-CHLORO-OCTANEPHOSPHONIC ACID AND 1,8-DIAMINO-OCTANE

1-Chloro-octanephosphonic acid (6.4 g, 28.0 mmol) and 1,8-diamino-octane (19.5 g, 135.4 mmol) were heated under reflux (22 h) in pyridine (350 cm^3) and allowed to cool. The solid was filtered off and washed with ethanol (50 cm^3). It was then successively heated to reflux and filtered off while still hot from water (200 cm^3), ethanol (300 cm^3), and ethanol (400 cm^3). It was then washed with diethyl ether (40 cm^3) and dried in a vacuum oven at 60 ^oC to yield the octane-1,8-diammonium 1-chloro-octanephosphonate (6.5 g, 62.3%) as a fine white crystalline solid, m.p. 159-161 ^oC, (Found: C, 51.9; H, 10.7; N, 7.6. $C_{16}H_{38}ClNO_3P$ requires: C, 51.5; H, 10.2; N, 7.5%); ^1H (D_2O/D_2SO_4) 0.5-1.9 (27H, br overlapping signals, C_7H_{15} and $NH_2CH_2(CH_2)_6$), 2.6 (4H, br s, $NHCH_2(CH_2)_6CH_2$), 3.9 (1H, br s, PCH); ^{13}C (D_2O/D_2SO_4) 16.0 (s, CH_3), 24.6, 26.7, 30.7, 31.8 and 33.6 ($CH_3(CH_2)_6$), 70.2 (d, PCH, $^1J_{PC}$ 155.2 Hz), 27.6, 29.1 and 30.4 (singlets, $NHCH_2(CH_2)_6$), 43.8 (s, $NH_2CH_2(CH_2)_6CH_2$); $^{31}P-\{^1H\}^{bb}$ (D_2O/D_2SO_4) 27.6.

6.42 ATTEMPTED CONDENSATION OF CHLOROMETHANEPHOSPHONIC ACID WITH 1,8-DIAMINO-OCTANE IN PYRIDINE

Chloromethanephosphonic acid (3.0 g, 23.0 mmol) and 1,8-diamino-octane (16.6 g, 115.3 mmol) were heated under reflux (20 h) in pyridine (250 cm^3) and the mixture allowed to cool. The precipitate was filtered off, washed with ethanol (2x250 cm^3) and recrystallised from water-ethanol. The recrystallised solid was washed with ethanol (100 cm^3) and dried in a vacuum oven at 60 ^oC to yield octane-1,8-diammonium chloromethanephosphonate (5.3 g, 84%) as a fine white crystalline solid m.p. 212 ^oC, (Found: C, 38.5; H, 8.4; N, 10.2. $C_9H_{24}N_2ClO_3P$ requires: C, 39.3; H, 8.7; N, 10.2%). ^{13}C (D_2O/D_2SO_4) 28.2, 29.5 and 30.7 (singlets, $NHCH_2\underline{(CH_2)_6}$), 41.0 (d, $P\underline{CH_2}Cl$, $^1J_{PC}$ 137.3 Hz), 42.5 (s, $NH_2\underline{CH_2}(CH_2)_6\underline{CH_2}NH_2$); $^{31}P-\{^1H\}^{bb}$ (D_2O/D_2SO_4) 12.1 (s).

6.43 PREPARATION OF N-(2-AMINOETHYL)AMINOMETHANE-PHOSPHONIC ACID MONOHYDRATE

Chloromethanephosphonic acid (15.0 g, 114.9 mmol) and 1,2-diaminoethane (41.4 g, 688.8 mmol) were dissolved in water (100 cm^3) and heated under reflux (20 h). The water and excess diamine were then distilled off on a rotary evaporator and the resultant viscous yellow residue was dissolved in water (20 cm^3). Ethanol (1200 cm^3) was added with vigorous stirring and the precipitate that

formed was washed with ethanol (3x100 cm^3). It was dissolved in water (100 cm^3) and hot ethanol (300 cm^3) was added all at once to the solution. After cooling, the precipitate was filtered off, washed with ethanol (2x100 cm^3) and recrystallised from water-ethanol. It was then washed with ethanol (2x100 cm^3) and dried in a vacuum oven at 70 °C (1 h), powdered in a mortar and pestle and dried for a further two hours to yield N-(2-aminoethyl)-aminomethanephosphonic acid monohydrate (12.6 g, 63.8%) as a fine white crystalline solid, m.p. 248-250 °C (lit. m.p. 251-253 °C),[97] (Found: C, 20.3; H, 7.2; N, 15.7. Calc. for $C_3H_{13}N_2O_4P$: C, 20.9, H, 7.6; N, 16.3%); ^1H (D_2O) 3.03 (2H, d, PCH_2, $^2J_{PCH}$ 12 Hz); ^1H (D_2O/D_2SO_4) 3.64-3.88 (m, $CH_2NH(CH_2)_2$); ^{13}C (D_2O/D_2SO_4) 39.2 (s, CH_2NH_2), 46.2 (d, PCH_2; $^1J_{PC}$ 135.3 Hz), 50.2 (d, $NHCH_2$, $^3J_{PCNC}$ 4.4 Hz); ^{13}C (D_2O) 39.2 (s, CH_2NH_2), 48.9 (d, PCH_2, $^1J_{PC}$ 130.1 Hz), 49.9 (d, $NHCH_2$, $^3J_{PCNC}$ 8.8 Hz); ^{31}P (D_2O) 7.9 (t, $^2J_{HCP}$ 11.8 Hz); ^{31}P (D_2O/D_2SO_4) 12.7 (t, $^2J_{HCP}$ 14.0 Hz), ^{15}N (D_2O/H_2O) -348.0 (NH_2), -354.4 (NH); m/z (FAB, %) 431 (M+3G+1, 0.4), 403 (2M+G+1, 2.6), 339 (M+2G+1, 1.6), 309 (2M+1, 26.7), 247 (M+G+1, 7.1), 277 (26.1), 155 (M+1, 100.0), 149 (3.8), 148 (1.1), 147 (3.4), 133 (32.6), 117 (14.5), 115 (15.8), 103 (30.7).

6.44 PREPARATION OF N-(4-AMINOBUTYL)AMINOMETHANE-PHOSPHONIC ACID MONOHYDRATE

Chloromethanephosphonic acid (7.0 g, 53.6 mmol) and 1,4-diaminobutane (30.0 g, 340.0 mmol) were dissolved in water (200 cm^3) and heated under reflux (20 h). The water was then distilled off on a rotary evaporator. Acetone (110 cm^3) was added and the insoluble material was filtered off and washed with acetone (2x70 cm^3). This solid residue (9.8 g, 91% after drying) was heated under reflux (5 min) in ethanol (100 cm^3) and allowed to cool. The undissolved solid was filtered off, washed with ethanol (3x100 cm^3) and recrystallised from water-ethanol. After washing with ethanol (2x100 cm^3) this solid was dried in a vacuum oven at 70 ^oC (3 h) to yield N-(4-aminobutyl)aminomethanephosphonic acid monohydrate (6.2 g, 57.8%) as a fine white crystalline solid, m.p. 258 ^oC, (Found: C, 29.8; H, 8.3; N, 13.0; P, 14.7. $C_5H_{17}N_2O_3P$ requires: C, 30.0; H, 8.5; N, 14.0; P, 15.5%); ^1H (D_2O/D_2SO_4) 1.82 (4H, m, $NHCH_2(CH_2)_2$), 3.12 (2H, t, CH_2NH_2, $^3J_{HCCH}$ 6.3 Hz), 3.28 (2H, t, $NHCH_2$, $^3J_{HCCH}$ 6.8 Hz), 3.45 (2H, d, PCH_2, $^2J_{PCH}$ 14.1 Hz); ^{13}C (D_2O/D_2SO_4) 24.8 (s, $CH_2CH_2NH_2$), 26.2 (s, $NHCH_2CH_2$), 41.9 (s, CH_2NH_2), 45.4 (d, PCH_2, $^1J_{PC}$ 147.8 Hz), 51.9 (d, $NHCH_2$ $^3J_{PCNC}$ 8.2 Hz); ^{31}P (D_2O/D_2SO_4) 13.6 (t, $^2J_{HCP}$ 14.0 Hz); ^{31}P (D_2O) 7.2 (t, $^2J_{HCP}$ 11.8 Hz); m/z (FAB, %) 459 (M+3G+1, 2.5), 457 (2M+G+1, 2.3), 367 (M+2G+1, 4.2), 365 (2M+1, 11.7), 183 (M+1, 100), 182 (10.3), 122 (4.6), 102 (5.4), 101 (2.5).

6.45 PREPARATION OF N-(6-AMINOHEXYL)AMINOMETHANE-PHOSPHONIC ACID MONOHYDRATE

Chloromethanephosphonic acid (6.5 g, 49.8 mmol) and 1,6-diaminohexane (34.8 g, 299.5 mmol) were dissolved in water (130 cm^3) and heated under reflux (20 h). The volatiles were then distilled off on a rotary evaporator and the solid residue heated under reflux (5 min) in ethanol (250 cm^3). After cooling, the undissolved solid (10.4 g, 95% after drying) was filtered off, washed with ethanol (3x100 cm^3) and recrystallised from water-ethanol. It was washed with ethanol (2x100 cm^3) and dried in a vacuum oven at 60 ^oC (3 h) to yield N-(6-aminohexyl)-aminomethanephosphonic acid monohydrate (6.2 g, 54.6%) as a fine white crystalline solid, m.p. 235 ^oC, (Found: C, 36.1; H, 9.3; N, 12.2. $C_7H_{21}N_2O_4P$ requires: C, 36.8, H, 9.2; N, 12.3%); ^1H ($D2O/D_2SO_4$) 1.48 (4H, br s, $NH(CH_2)_2\underline{(CH_2)_2}$), 1.75 (4H, br m, $NHCH_2\underline{CH_2}(CH_2)_2\underline{CH_2}$), 3.06 (2H, t, $\underline{CH_2}NH_2$, $^3J_{HCCH}$ 7.9 Hz), 3.25 (2H, t, $NH\underline{CH_2}$, $^3J_{HCCH}$ 7.7 Hz), 3.50 (2H, d, $P\underline{CH_2}$, $^2J_{PCH}$ 14.1 Hz); ^1H (D_2O) 1.44 (4H, br s, $NH(CH_2)_2\underline{CH_2CH_2}(CH_2)_2NH$), 1.72 (4H, br m, $NHCH_2\underline{CH_2}(CH_2)_2\underline{CH_2}$), 2.97 (d, $P\underline{CH_2}$, $^2J_{PCH}$ 12.3 Hz), 3.02 (t, $\underline{CH_2}NH_2$, $^3J_{HCCH}$ 7.9 Hz) 3.18 (2H, t, $NH\underline{CH_2}$, $^3J_{HCCH}$ 7.7 Hz); ^{13}C ($D2O/D_2SO_4$) 27.6 (s, $\underline{(CH_2)_3}CH_2NH_2$), 29.2 (s, $NHCH_2\underline{CH_2}$), 43.1 (s, $\underline{CH_2}NH_2$), 45.7 (d, $P\underline{CH_2}$, $^1J_{PC}$ 148.5), 53.0 (d, $NH\underline{CH_2}$, $^3J_{PCNC}$ 7.7 Hz); ^{31}P (D_2O) 7.6 (t, $^2J_{HCP}$ 11.4 Hz); ^{31}P (D_2O/D_2SO_4) 14.1 (t, $^2J_{HCP}$ 14.3 Hz); m/z (FAB, %) 421 (2M+1, 2.8), 211 (M+1, 100.0), 196 (1.6), 195

(1.8), 194 (1.6), 192 (8.1), 129 (34.1), 117 (15.0), 114 (5.5), 113 (4.1), 112 (35.6), 110 (18.1), 98 (48.0), 96 (10.2); T.G.A.: weight loss 14 mg at 140-180 ^{o}C from 0.1775 g (Calc. loss for 1 molecule of water of crystallisation: 14 mg, 100%).

6.46 PREPARATION OF N-(8-AMINO-OCTYL)AMINOMETHANE-PHOSPHONIC ACID MONOHYDRATE

Chloromethanephosphonic acid (7.5 g, 57.5 mmol) and 1,8-diamino-octane (50.0 g, 346.6 mmol) were dissolved in water (110 cm^3) and heated under reflux (20 h). The volatiles were then distilled off on a rotary evaporator and the solid residue heated under reflux (5 min) in ethanol (250 cm^3). After cooling, the undissolved solid (13.3 g, 90% after drying) was filtered off, washed with ethanol (3x100 cm^3) and recrystallised from water-ethanol. It was washed with ethanol (2x100 cm^3) and dried in a vacuum oven at 60 ^{o}C (3 h) to yield N-(8-amino-octyl)-aminomethanephosphonic acid monohydrate (8.4 g, 64.1%) as a fine white crystalline solid, m.p. 242 ^{o}C, (Found: C, 42.0; H, 9.3; N, 11.1. $C_9H_{25}N_2O_4P$ requires: C, 42.2; H, 9.8; N, 11.0%); ^{1}H (D_2O/D_2SO_4) 1.37 (8H, br s, $NH(CH_2)_2\underline{(CH_2)_4}$), 1.72 (4H, br m, $NHCH_2\underline{CH_2}(CH_2)_4\underline{CH_2}$), 3.04 (2H, t, $\underline{CH_2}NH_2$, $^{3}J_{HCCH}$ 7.7 Hz), 3.22 (2H, t, $NHCH_2$, $^{3}J_{HCCH}$ 7.7 Hz), 3.43 (2H, d, PCH_2, $^{2}J_{PCH}$ 13.6 Hz); ^{13}C (D_2O/D_2SO_4) 27.9, 28.1, 29.4, 30.4 (singlets, $NHCH_2\underline{(CH_2)_6}$), 42.6 (s, $\underline{CH_2}NH_2$), 45.7 (d, PCH_2, $^{1}J_{PC}$ 146.5 Hz), 52.6 (d, $NHCH_2$, $^{3}J_{PCNC}$ 7.5 Hz), ^{13}C (D_2O) 28.1,

29.4, 30.6, (singlets, $NHCH_2\underline{(CH_2)_6}$), 42.3 (s, $\underline{C}H_2NH_2$), 48.6 (d, $P\underline{C}H_2$, $^1J_{PC}$ 128.2 Hz), 52.4 (d, $NH\underline{C}H_2$, $^3J_{PCNC}$ 6.1 Hz); ^{31}P (D_2O) 8.7 (t, $^2J_{HCP}$ 11.4 Hz), ^{31}P ($D2O/D_2SO_4$) 13.5 (t, $^2J_{HCP}$ 13.8 Hz), m/z (FAB, %) 331 (M+G+1, 2.5), 239 (M+1, 100.0), 223 (2.4), 222 (2.2), 170 (3.1), 169 (7.6), 168 (3.2), 158 (9.4), 157 (85.9), 145 (13.5), 141 (3.8), 140 (9.7), 138 (9.0).

6.47 PREPARATION OF N-(8-AMINO-OCTYL)-2-AMINOETHANE-PHOSPHONIC ACID MONOHYDRATE

O,O-Diethyl 2-bromoethanephosphonate (15.3 g, 62.4 mmol) and 1,8-diamino-octane (54.0 g, 375.0 mmol) were dissolved in water (250 cm^3) and heated under reflux (5 h). The volatiles were distilled off on a rotary evaporator and the unreacted diamine (ca. 35 g) was then distilled off under reduced pressure. Concentrated hydrochloric acid (280 cm^3) was added to the glassy residue and the resultant solution heated under reflux (8 h). After cooling, the volatile components were distilled off on a rotary evaporator and the oily residue dissolved in methanol (75 cm^3). Propylene oxide (ca. 400 cm^3) was added until the pH reached 6 and the precipitate so formed was filtered off, heated under reflux (5 min) in ethanol (250 cm^3) and allowed to cool overnight. The solid that precipitated was dried in a vacuum oven to yield the crude product (10.2 g, 60.5%). It was recrystallised from water-ethanol, washed with ethanol (2x50 cm^3) and dried in

a vacuum oven at 60 ^{o}C (3 h) to yield N-(8-amino-octyl)-2-aminoethanephosphonic acid monohydrate (5.9 g, 35%) as a fine white crystalline solid, m.p. 210 ^{o}C, (Found: C, 43.9; H, 9.4; N, 9.8. $C_{10}H_{27}N_2O_4P$ requires: C, 44.4; H, 10.0; N, 10.4%); ^{1}H (D_2O/D_2SO_4) 1.36 (8H, s, $NH(CH_2)_2(CH_2)_4$), 1.70 (4H, br m, $NHCH_2CH_2(CH_2)_4CH_2$), 2.33 (2H, d of t, PCH_2, $^{2}J_{PCH}$ 22 Hz, $^{3}J_{HCCH}$ 8 Hz), 3.09 (4H, overlapping d of t, CH_2NH_2, $NHCH_2$), 3.37 (2H, overlapping d of t, PCH_2CH_2); ^{13}C (D_2O/D_2SO_4) 22.5 (half of a doublet, PCH_2), 28.1, 29.4, 30.5 (singlets, $NHCH_2(CH_2)_6$), 43.5 (s, CH_2NH_2), 44.9 (s, PCH_2CH_2), 51.4 (s, $NHCH_2$); ^{31}P (D_2O) 18.4 (overlapping t of t); ^{31}P ($D2O/D_2SO_4$) 27.9 (overlapping t of t); m/z (FAB, %) 505 (2M+1, 4.1), 345 (M+G+1, 1.4), 254 (15.1), 253 (M+1, 100.0), 236 (2.6), 171 (3.0), 145 (2.9), 143 (2.9), 138 (7.2), 126 (4.0), 114 (1.8), 100 (1.6).

6.48 PREPARATION OF N-(10-AMINODECYL)AMINOMETHANE-PHOSPHONIC ACID MONOHYDRATE

Chloromethanephosphonic acid (5.5 g, 42.1 mmol) and 1,10-diaminodecane (44.0 g, 255.4 mmol) were dissolved in water (200 cm^3) and heated under reflux (20 h). The volatiles were then distilled off on a rotary evaporator and the solid residue was heated under reflux (5 min) in ethanol (300 cm^3). After cooling, the undissolved solid (11.4 g, 87% after drying) was filtered off, washed with ethanol (2x100 cm^3) and recrystallised from water-ethanol. It was washed methanol (100 cm^3) and dried in a vacuum oven at 60 ^oC (3 h), to yield N-(10-aminodecyl)amino-methanephosphonic acid monohydrate (7.4 g, 61.8%) as a fine white crystalline solid, m.p. 238 ^oC, (Found: C, 46.4; H, 9.6; N, 9.3. $C_{11}H_{29}N_2O_4P$ requires: C, 46.5; H, 10.2; N, 9.9%); ^1H (D_2O/D_2SO_4) 1.31 (12H, br s, $NH(CH_2)_2(CH_2)_6$), 1.71 (4H, br m, $NHCH_2CH_2(CH_2)_6CH_2$), 3.05 (2H, t, CH_2NH_2, $^3J_{HCCH}$ 7.4 Hz), 3.22 (2H, t, $NHCH_2$, $^3J_{HCCH}$ 7.8 Hz), 3.46 (2H, d, PCH_2, $^2J_{PCH}$ 14.4 Hz); ^{13}C (D_2O/D_2SO_4) 27.6, 27.8, 29.1, 30.4 and 30.6 (singlets, $(CH_2)_8CH_2NH_2$), 42.9 (s, CH_2NH_2), 45.2 (d, PCH_2, $^1J_{PC}$ 148.5 Hz), 52.9 (d, $NHCH_2$, $^3J_{PCNC}$ 6.8 Hz); ^{31}P (D_2O) 7.4 (t, $^2J_{HCP}$ 11.8 Hz); ^{31}P (D_2O/D_2SO_4) 14.2 (t, $^2J_{HCP}$ 14.0 Hz); m/z (FAB, %) 267 (M+1, 36.7), 252 (1.7), 251 (2.0), 250 (1.6), 198 (3.5), 197 (13.6), 185 (100.0), 183 (10.9), 168 (8.2), 156 (10.8), 154 (10.4).

6.48 PREPARATION OF N-(10-AMINODECYL)AMINOMETHANE-PHOSPHONIC ACID MONOHYDRATE

Chloromethanephosphonic acid (5.5 g, 42.1 mmol) and 1,10-diaminodecane (44.0 g, 255.4 mmol) were dissolved in water (200 cm^3) and heated under reflux (20 h). The volatiles were then distilled off on a rotary evaporator and the solid residue was heated under reflux (5 min) in ethanol (300 cm^3). After cooling, the undissolved solid (11.4 g, 87% after drying) was filtered off, washed with ethanol (2x100 cm^3) and recrystallised from water-ethanol. It was washed methanol (100 cm^3) and dried in a vacuum oven at 60 ^oC (3 h), to yield N-(10-aminodecyl)amino-methanephosphonic acid monohydrate (7.4 g, 61.8%) as a fine white crystalline solid, m.p. 238 ^oC, (Found: C, 46.4; H, 9.6; N, 9.3. $C_{11}H_{29}N_2O_4P$ requires: C, 46.5; H, 10.2; N, 9.9%); ^1H (D_2O/D_2SO_4) 1.31 (12H, br s, $NH(CH_2)_2(\underline{CH_2})_6$), 1.71 (4H, br m, $NHCH_2\underline{CH_2}(CH_2)_6\underline{CH_2}$), 3.05 (2H, t, $\underline{CH_2}NH_2$, $^3J_{HCCH}$ 7.4 Hz), 3.22 (2H, t, $NHCH_2$, $^3J_{HCCH}$ 7.8 Hz), 3.46 (2H, d, PCH_2, $^2J_{PCH}$ 14.4 Hz); ^{13}C (D_2O/D_2SO_4) 27.6, 27.8, 29.1, 30.4 and 30.6 (singlets, $(\underline{CH_2})_8CH_2NH_2$), 42.9 (s, $\underline{CH_2}NH_2$), 45.2 (d, $P\underline{C}H_2$, $^1J_{PC}$ 148.5 Hz), 52.9 (d, $NH\underline{C}H_2$, $^3J_{PCNC}$ 6.8 Hz); ^{31}P (D_2O) 7.4 (t, $^2J_{HCP}$ 11.8 Hz); ^{31}P (D_2O/D_2SO_4) 14.2 (t, $^2J_{HCP}$ 14.0 Hz); m/z (FAB, %) 267 (M+1, 36.7), 252 (1.7), 251 (2.0), 250 (1.6), 198 (3.5), 197 (13.6), 185 (100.0), 183 (10.9), 168 (8.2), 156 (10.8), 154 (10.4).

6.49 PREPARATION OF N-(12-AMINODODECYL)AMINOMETHANE-PHOSPHONIC ACID MONOHYDRATE

Chloromethanephosphonic acid (15.1 g, 115.7 mmol) and 1,12-diaminododecane (100.0 g, 499.1 mmol) were dissolved in water (160 cm^3) and heated under reflux (20 h). The volatiles were then distilled off on a rotary evaporator and the solid residue was heated under reflux (5 min) in ethanol (250 cm^3) and allowed to cool. The precipitate was filtered off, washed with ethanol (3x100 cm^3) and recrystallised from water-ethanol. It was washed with ethanol (2x100 cm^3) and dried in a vacuum oven at 60 ^oC (3 h) to yield N-(12-aminododecyl)aminomethane-phosphonic acid monohydrate (13.5 g, 51.8%) as a fine white crystalline solid, m.p. 234 ^oC, (Found: C, 49.9; H, 10.0; N, 9.0. $C_{13}H_{33}N_2O_4P$ requires: C, 50.0; H, 10.6; N, 9.0%); ^1H ($D2O/D_2SO_4$) 1.29 (16H, s, $NH(CH_2)_2(CH_2)_8$), 1.71 (4H, br m, $NHCH_2CH_2(CH_2)_8CH_2$), 3.05 (2H, CH_2NH_2, $^3J_{HCCH}$ 7.7 Hz), 3.22 (2H, t, $NHCH_2$, $^3J_{HCCH}$ 7.7 Hz), 3.52 (2H, d, PCH_2, $^2J_{PCH}$ 13.2 Hz); ^{13}C ($D2O/D_2SO_4$) 28.2, 29.4, 30.9, 31.2 (singlets, $NHCH_2(CH_2)_{10}$), 43.3 (s, CH_2NH_2), 45.4 (d, PCH_2, $^1J_{PC}$ 150.1 Hz), 53.4 (d, $NHCH_2$, $^3J_{PCNC}$ 7.3 Hz); ^{31}P (D_2O) 7.4 (t, $^2J_{HCP}$ 11.2 Hz), ^{31}P ($D2O/D_2SO_4$) 14.8 (t, $^2J_{HCP}$ 14.0 Hz); m/z (FAB, %) 387 (M+G+1, 0.5), 295 (M+1, 66.8), 279 (2.5), 225 (22.0), 224 (3.6), 214 (17.1), 213 (100.0), 201 (38.2), 200 (3.5), 199 (8.1), 198 (4.9), 184 (14.2), 182 (10.1), 170 (7.6), 168 (6.2).

6.50 PREPARATION OF N-(13-AMINO-7-AZATRIDECYL)-AMINOMETHANEPHOSPHONIC ACID MONOHYDRATE

Chloromethanephosphonic acid (6.3 g, 48.3 mmol) and and 1,13-diamino-7-azatridecane (62.1 g, 288.8 mmol) were dissolved in water (150 cm^3) and heated under reflux (20 h). The water was then distilled off on a rotary evaporator, acetone (150 cm^3) was added, and the mixture was left to stand overnight. The solid that formed was filtered off, washed with acetone (2x50 cm^3) and dried in a vacuum oven at 60 ^oC (3 h) to yield N-(13-amino-7-azatridecyl)aminomethanephosphonic acid monohydrate (15.2 g, 96.3%) as a fine white crystalline solid, m.p. 183-184 ^oC; ^{13}C (D_2O/D_2SO_4) 27.7, 28.0 and 29.2 (singlets, $(CH_2)_4CH_2NHCH_2(CH_2)_4$), 43.2 (s, CH_2NH_2), 45.6 (d, PCH_2, $^1J_{PC}$ 150.5 Hz), 50.9 (s, CH_2NHCH_2), 53.3 (d, $NHCH_2$, $^3J_{PCNC}$ 8.8 Hz); ^{31}P (D_2O/D_2SO_4) 14.9 (br t); m/z (FAB, %) 310 (M+1, 2.9), 228 (1.8), 216 (10.4), 214 (1.7), 199 (2.8), 197 (13.4), 152 (11.1), 148 (10.0), 140 (10.6), 138 (17.0), 126 (27.4), 122 (22.0), 112 (66.9), 110 (36.2), 108 (25.8), 100 (27.1), 98 (100.0), 96 (55.4), 94 (29.2), 93 (28.1).

6.51 REACTION OF N-(2-AMINOETHYL)AMINOMETHANEPHOSPHONIC ACID AND S-METHYLISOTHIOURONIUM CHLORIDE TO YIELD 1-PHOSPHONOMETHYL-2-IMINOIMIDAZOLIDINE

N-(2-Aminoethyl)aminomethanephosphonic acid monohydrate (3.3 g, 19.2 mmol), S-methylisothiouronium chloride (5.5 g, 43.5 mmol), and potassium hydroxide (4.8 g, 85.5 mmol) were dissolved in water (15 cm^3) and heated at 60 ^oC (4 h). After cooling, concentrated hydrochloric acid was added until pH 1 and the volatile components were distilled off on a rotary evaporator. The oily residue was dissolved in methanol (100 cm^3) and the insoluble potassium chloride (6.3 g, 98.7% after drying) was filtered off. The solution was concentrated to *ca.* 50 cm^3 and propylene oxide (*ca.* 400 cm^3) was added until the pH was 6. The precipitate so formed was washed with methanol (20 cm^3) and recrystallised from water-methanol. The crystals that formed were washed with methanol (30 cm^3) and dried in a vacuum oven at 70 ^oC (3 h) to yield 1-phosphonomethyl-2-iminoimidazolidine (1.7 g, 49.5%) as a fine white crystalline solid, m.p. 345-349 ^oC, (Found: C, 25.7; H, 5.7; N, 23.4. $C_4H_{10}N_3O_3P$ requires: C, 26.8; H, 5.6; N, 23.5%); ^1H (D_2O) 3.48 (d, PCH_2, $^2J_{HCP}$ 10.8 Hz), 3.75 (m, $N(CH_2)_2NH$); ^1H (D_2O/D_2SO_4) 3.55 (d, PCH_2, $^2J_{PCH}$ 10.7 Hz), 3.66-3.84 (m, $N(CH_2)_2NH$); ^{13}C (D_2O) 43.7 (s, CH_2NH), 46.0 (d, PCH_2, $^1J_{PC}$ 147.4 Hz), 52.5 (s, NCH_2), 162.0 (d, $NHC(:NH)NH_2$, $^3J_{PCNC}$ 2.2 Hz); ^{13}C (D_2O/D_2SO_4) 43.9 (s, CH_2NH), 44.4 (d, PCH_2, $^1J_{PC}$

157.3 Hz), 52.5 (s, $N\underline{C}H_2CH_2$), 160.8 (d, $NH\underline{C}(:NH)NH_2$, $^3J_{PCNC}$ 2.0 Hz); ^{31}P (D_2O) 13.4 (t, $^2J_{HCP}$ 10.5 Hz), $^{31}P-\{^1H\}^{bb}$ (D_2O/D_2SO_4) 19.8; m/z (FAB, %) 456 (M+3G+1, 1.2), 364 (M+2G+1, 3.0), 272 (M+G+1, 12.6), 181 (5.3), 180 (M+1, 100.0), 179 (5.9), 127 (3.3), 110 (3.2), 100 (8.2), 99 (10.4), 98 (6.0).

The following guanidinophosphonic acids were found to give inconsistent and variable analysis. Some of the compounds were found to analyse as monohydrates whilst others appeared to be dihydrates. Thermogravimetric analysis confirmed the presence of one molecule of water but did not rule out the possibility of a second molecule of water since the compounds rapidly decomposed after this initial weight loss.

As the aminophosphonic acid precursors were found to be monohydrates we have reported these guanidinophosphonic acids also as monohyrates and calculated the yields as such.

6.52 PREPARATION OF N-(4-GUANIDINOBUTYL)AMINOMETHANE-PHOSPHONIC ACID MONOHYDRATE

N-(4-Aminobutyl)aminomethanephosphonic acid monohydrate (3.8 g, 19.0 mmol), S-methylisothiouronium chloride (4.8 g, 37.9 mmol), and sodium hydroxide (3.04 g, 76.0 mmol) were dissolved in water (50 cm^3) and heated in an oil bath at 70 ^oC (4 h). The clear solution was then acidified to pH 1 with concentrated hydrochloric acid and the volatile components were distilled off on a rotary evaporator. The oily residue was dissolved in methanol (100 cm^3) and the precipitated sodium chloride (3.7 g, 86.2% after drying) was filtered off. Propylene oxide (ca. 300 cm^3) was then added to the filtrate until the pH was 6, yielding a sticky white precipitate. The supernatant liquors were decanted off and the residue dissolved in the minimum of cold water. Acetone was added dropwise to this solution until it just became opaque; a few drops of water were then added to clear the solution which was stored at 4 ^oC for several days. The crystals that formed were filtered off, washed with acetone (2x20 cm^3) and dried in a vacuum oven at 60 ^oC (3 h) to yield N-(4-guanidinobutyl)aminomethanephosphonic acid monohydrate (2.9 g, 63.1%) as a fine white crystalline solid, m.p. 160-161 ^oC; ^1H (D_2O/D_2SO_4) 1.80 (4H, m, $NHCH_2(CH_2)_2$), 3.27 (4H, two overlapping triplets, $NHCH_2(CH_2)_2CH_2$), 3.43 (2H, d, PCH_2, $^2J_{PCH}$ 13.8 Hz); ^1H (D_2O) 1.74 (4H, br m, $NHCH_2(CH_2)_2$), 3.02 (2H, d, PCH_2,

$^{2}J_{PCH}$ 12.0 Hz), 3.26 (4H, two overlapping triplets, $NHC\underline{H_2}(CH_2)_2C\underline{H_2}$); ^{13}C (D_2O/D_2SO_4) 25.1 (s, $\underline{C}H_2CH_2NH$), 27.4 (s, $NHCH_2\underline{C}H_2$), 43.1 (s, $\underline{C}H_2NHC(:NH)NH_2$), 45.4 (d, $P\underline{C}H_2$, $^{1}J_{PC}$ 147.2 Hz), 51.9 (d, $NH\underline{C}H_2$, $^{3}J_{PCNC}$ 7.5 Hz), 159.3 (s, $NH\underline{C}(:NH)NH_2$); ^{31}P (D_2O/D_2SO_4) 13.3 (t, $^{2}J_{HCP}$ 13.3 Hz); ^{31}P (D_2O) 7.8 (t, $^{2}J_{HCP}$ 11.8 Hz); m/z (FAB, %) 225 (M+1, 100.0), 207 (14.8), 168 (4.7), 143 (9.5), 115 (42.3), 114 (12.8), 112 (5.0), 100 (4.6).

6.53 PREPARATION OF N-(6-GUANIDINOHEXYL)AMINOMETHANE-PHOSPHONIC ACID MONOHYDRATE

N-(6-Aminohexyl)aminomethanephosphonic acid monohydrate (6.1 g, 26.7 mmol), S-methylisothiouronium chloride (6.3 g, 49.8 mmol), and sodium hydroxide (4.15 g, 103.7 mmol) were dissolved in water (50 cm^3) and heated in an oil bath at 60 ^{o}C (4 h). The clear solution was then acidified to pH 1 with concentrated hydrochloric acid and the volatile components were distilled off on a rotary evaporator. The oily residue was dissolved in methanol (50 cm^3) and the precipitated sodium chloride (4.3 g, 72.1% after drying) was filtered off. Propylene oxide (ca. 400 cm^3) was then added to the filtrate until the pH was 6, which resulted in the formation of a sticky white precipitate. The supernatant liquors were decanted off and the residue dissolved in cold water (50 cm^3). Acetone was added dropwise to this solution until it just became opaque; a few drops of water were then added to clear the

solution which was stored at 4 ^{o}C for several days. The crystals that formed were filtered off, washed with acetone (2x20 cm^{3}) and dried in a vacuum oven at 60 ^{o}C (3 h) to yield N-(6-guanidinohexyl)aminomethanephosphonic acid monohydrate (4.3 g, 59.5%) as a fine white crystalline solid, m.p. 182 ^{o}C; ^{1}H (D_2O/D_2SO_4) 1.42 (4H, br m, $NH(CH_2)_2(\underline{CH_2})_2$), 1.74 (4H, br m, $NHCH_2\underline{CH_2}(CH_2)_2\underline{CH_2}$), 3.21 (4H, m, $NH\underline{CH_2}(CH_2)_4\underline{CH_2}NH$), 3.46 (2H, d, $P\underline{CH_2}$, $^{2}J_{PCH}$ 14.0 Hz); ^{1}H (D_2O) 1.42 (4H, br s, $NH(CH_2)_2(\underline{CH_2})_2$), 1.79 (4H, two overlapping triplets, $NHCH_2\underline{CH_2}(CH_2)_2\underline{CH_2}$), 3.01 (2H, d, $P\underline{CH_2}$, $^{2}J_{PCH}$ 12.0 Hz), 3.20 (4H, two overlapping triplets, $NH\underline{CH_2}(CH_2)_4\underline{CH_2}$); ^{13}C ($D_2O/D_2SO_4$) 27.6, 27.7 and 30.0 (singlets, $NHCH_2(\underline{CH_2})_4$), 43.8 (s, $\underline{CH_2}NHC(:NH)NH_2$), 45.3 (d, $P\underline{CH_2}$, $^{1}J_{PC}$ 149.9 Hz), 52.9 (d, $NH\underline{CH_2}$, $^{3}J_{PCNC}$ 7.5 Hz), 159.1 (s, $NH\underline{C}(:NH)NH_2$); ^{31}P (D_2O/D_2SO_4) 14.6 (t, $^{2}J_{HCP}$ 14.0 Hz); m/z (FAB, %) 253 (M+1, 100), 238 (9.2), 196 (56.9), 171 (29.7), 144 (36.2), 142 (14.5), 114 (74.7), 100 (3.1); T.G.A.: weight loss 6.5 mg at 110-160 ^{o}C from 0.1028 g, (Calc. loss for 1 molecule of water of crystallisation 6.85 mg, 95%).

6.54 PREPARATION OF N-(8-GUANIDINO-OCTYL)AMINOMETHANE-PHOSPHONIC ACID MONOHYDRATE

N-(8-Amino-octyl)aminomethanephosphonic acid monohydrate (5.6 g, 21.9 mmol), S-methylisothiouronium chloride (5.53 g, 43.7 mmol), and potassium hydroxide (4.9 g, 87.3 mmol) were dissolved in water (50 cm^3) and heated in an oil bath at 60 ^oC (4 h). The clear solution was then acidified to pH 1 with concentrated hydrochloric acid and the volatile components were distilled off on a rotary evaporator. The oily residue was dissolved in methanol (50 cm^3) and the precipitated potassium chloride (5.9 g, 80.3% after drying) was filtered off. Propylene oxide (ca. 400 cm^3) was then added to the filtrate until the pH was 6, yielding a sticky white precipitate. The supernatant liquors were decanted off and the residue dissolved in cold water (50 cm^3). Acetone was added dropwise to this solution until it just became opaque; a few drops of water were then added to clear the solution which was stored at 4 ^oC for several days. The crystals that formed were filtered off, washed with acetone (2x20 cm^3) and dried in a vacuum oven at 60 ^oC (3 h) to yield N-(8-guanidino-octyl)aminomethanephosphonic acid monohydrate (3.9 g, 60.0%) as a fine white crystalline solid, m.p. 171 ^oC; ^1H (D_2O/D_2SO_4) 1.32 (8H, br s, $NH(CH_2)_2(CH_2)_4$), 1.51 (2H, br m, $CH_2CH_2NHC(:NH)NH_2$), 1.70 (2H, br m, $NHCH_2CH_2$), 3.11 (4H, m, $NHCH_2(CH_2)_6CH_2$), 3.39 (2H, d, PCH_2, $^2J_{PCH}$ 13.5 Hz); ^1H (D_2O) 1.37 (8H, br s,

$NH(CH_2)_2(\underline{CH_2})_4$), 1.78 (4H, br m, $NHCH_2\underline{CH_2}(CH_2)_4\underline{CH_2}$), 3.03 (2H, d, $P\underline{CH_2}$, $^2J_{PCH}$ 12.0 Hz), 3.20 (4H, two overlapping t, $NH\underline{CH_2}(CH_2)_6\underline{CH_2}$); ^{13}C (D_2O/D_2SO_4) 27.6, 27.9 and 30.2 (singlets, $NHCH_2(\underline{CH_2})_6$), 43.8 (s, $\underline{CH_2}NHC(:NH)NH_2$), 45.2 (d, $P\underline{CH_2}$, $^1J_{PC}$ 149.9 Hz), 53.1 (d, $NH\underline{CH_2}$, $^2J_{PCC}$ 8.1 Hz), 159.0 (s, $NH\underline{C}(:NH)NH_2$); ^{13}C (D_2O) 28.1, 28.2, 30.6 and 30.8 (singlets, $NHCH_2(\underline{CH_2})_6$), 44.1 (s, $\underline{CH_2}NHC(:NH)NH_2$), 48.0 (d, $P\underline{CH_2}$, $^1J_{PC}$ 132.2 Hz), 52.5 (d, $NH\underline{CH_2}$, $^3J_{PCNC}$ 6.8 Hz), 159.8 (s, $NH\underline{C}(:NH)NH_2$); ^{31}P (D_2O/D_2SO_4) 13.0 (t, $^2J_{HCP}$ 13.6 Hz); $^{31}P-\{^1H\}^{bb}$ (D_2O) 8.0; m/z (FAB, %) 281 (M+1, 100), 266 (4.9), 224 (12.6), 200 (8.9), 199 (48.6), 172 (17.6), 170 (24.8), 156 (13.1), 142 (28.9), 128 (13.4), 114 (11.2), 100 (14.5); T.G.A.: weight loss 6.5 mg at 110-140 °C from 0.1147 g (Calc. loss for 1 molecule of water of crystallisation: 6.9 mg, 94%).

6.55 PREPARATION OF N-(8-GUANIDINO-OCTYL)-2-AMINOETHANE-PHOSPHONIC ACID MONOHYDRATE

N-(8-Amino-octyl)-2-aminoethanephosphonic acid monohydrate (4.0 g, 14.8 mmol), S-methylisothiouronium chloride (3.75 g, 29.6 mmol), and potassium hydroxide (3.32 g, 59.2 mmol) were dissolved in water (60 cm^3) and heated in an oil bath at 80 °C (4.5 h). The clear solution was then acidified to pH 2 with concentrated hydrochloric acid and the volatile components were distilled off on a rotary evaporator. The oily residue was dissolved in methanol (75 cm^3) and the

precipitated potassium chloride (3.5 g, 79.3% after drying) was filtered off. Propylene oxide (ca. 400 cm^3) was then added to the filtrate until the pH was 6, yielding a sticky white precipitate. The supernatant liquors were decanted off and the residue dissolved in cold water (50 cm^3). Acetone was added dropwise to this solution until it just became opaque; a few drops of water were then added to clear the solution which was stored at 4 ^oC for several days. The crystals that formed were filtered off, washed with acetone (2x30 cm^3) and dried in a vacuum oven at 60 ^oC (3 h) to yield N-(8-guanidinooctyl)-2-aminoethanephosphonic acid monohydrate (2.7 g, 58.4%) as a fine white crystalline solid, m.p. 108 ^oC, (Found: C, 43.1; H, 9.4; N, 17.9. $C_{11}H_{29}N_4O_4P$ requires: C, 42.3; H, 9.3; N, 17.9%); ^1H (D_2O/D_2SO_4) 1.36 (8H, br s, $NH(CH_2)_2(CH_2)_4$), 1.68 (4H, br m, $NHCH_2CH_2(CH_2)_4CH_2$), 2.36 (2H, m, PCH_2), 3.20 (4H, m, $NHCH_2(CH_2)_6CH_2$), 3.40 (2H, m, PCH_2CH_2NH); ^{13}C (D_2O/D_2SO_4) 26.1 (d, PCH_2, $^1J_{PC}$ 139 Hz), 28.1, 28.3, 30.5, 30.6 (singlets, $NHCH_2(CH_2)_6$), 44.2 (s, $CH_2NHC(NH)NH_2$), 44.8 (s, PCH_2CH_2), 51.1 (s, $NHCH_2$), 159.3 (s, $NHC(:NH)NH_2$); ^{31}P (D_2O/D_2SO_4) 26.6 (overlapping t of t); $^{31}P-\{^1H\}^{bb}$ (D_2O) 18.0; m/z (FAB, %) 296 (14.9), 295 (M+1, 100), 293 (11.3), 238 (23.0), 213 (12.6), 187 (15.0), 172 (25.9), 168 (11.0), 158 (19.7), 156 (30.5), 144 (17.7), 130 (15.2), 126 (12.1), 114 (22.7), 109 (14.5), 100 (26.3), 98 (11.2), 97 (17.3).

6.56 PREPARATION OF N-(10-GUANIDINODECYL)AMINOMETHANE-PHOSPHONIC ACID MONOHYDRATE

N-(10-Aminodecyl)aminomethanephosphonic acid monohydrate (4.1 g, 14.4 mmol), S-methylisothiouronium chloride (3.65 g, 28.9 mmol), and sodium hydroxide (2.8 g, 70.0 mmol) were dissolved in water (100 cm^3) and heated in an oil bath at 70 ^oC (4 h). The clear solution was then acidified to pH 1 with concentrated hydrochloric acid and the volatile components were distilled off on a rotary evaporator. The oily residue was dissolved in methanol (100 cm^3) and the precipitated sodium chloride (3.4 g, 83.0% after drying) was filtered off. Propylene oxide (ca. 400 cm^3) was then added to the filtrate until the pH was 6. The solid formed was filtered off and washed with methanol (50 cm^3) (4.2 g, 89% after drying). This crude product was recrystallised by dissolution in the minimum of cold water and adding acetone until the solution just became opaque. A few drops of water were then added to to clear the solution which was then stored at 4 ^oC for several days. The crystals that formed were filtered off, washed with acetone (2x50 cm^3) and dried in a vacuum oven at 60 ^oC (3 h) to yield N-(10-guanidinodecyl)aminomethane-phosphonic acid monohydrate (3.8 g, 80.7%) as a fine white crystalline solid, m.p. 133-134 ^oC. ^1H (D_2O/D_2SO_4) 1.31 (12H, br s, $NH(CH_2)_2(CH_2)_6$), 1.58 (2H, br m, $NHCH_2CH_2$), 1.72 (2H, br m, $(CH_2)_6CH_2CH_2NHC(:NH)NH_2$), 3.20 (4H, t, $NHCH_2(CH_2)_8CH_2$, $^3J_{HCCH}$ 7.0 Hz), 3.50 (2H, d, PCH_2, $^2J_{PCH}$

13.5 Hz); ^{13}C (D_2O/D_2SO_4) 27.9, 28.3, 28.5, 30.6, 30.9, 31.0 and 31.1 (singlets, $NHCH_2\underline{(CH_2)_8}$), 44.1 (s, $\underline{C}H_2NHC(:NH)NH_2$), 45.6 (d, $P\underline{C}H_2$, $^1J_{PC}$ 146.5 Hz), 52.5 (d, $NH\underline{C}H_2$, $^3J_{PCNC}$ 7.5 Hz), 159.5 (s, $NH\underline{C}(:NH)NH_2$). ^{31}P (D_2O/D_2SO_4) 12.9 (t, $^2J_{HCP}$ 13.6 Hz); ^{31}P (D_2O) 8.8 ($^2J_{HCP}$ 10.7 Hz); m/z (FAB, %) 309 (M+1, 100.0), 294 (2.9), 267 (56.6), 252 (7.6), 227 (37.4), 198 (14.5), 186 (10.1), 185 (60.3), 170 (18.6), 156 (11.8), 100 (10.2), 93 (32.1).

6.57 PREPARATION OF N-(12-GUANIDINODODECYL)AMINOMETHANE-PHOSPHONIC ACID MONOHYDRATE

N-(12-Aminododecyl)aminomethanephosphonic acid monohydrate (2.5 g, 8.0 mmol), S-methylisothiouronium chloride (2.03 g, 16.4 mmol), and sodium hydroxide (1.3 g, 38.2 mmol) were dissolved in water (120 cm^3) and heated in an oil bath at 90 ^oC (4 h). The clear solution was then acidified to pH 1 with concentrated hydrochloric acid and the volatile components were distilled off on a rotary evaporator. The oily residue was dissolved in methanol (100 cm^3) and the precipitated sodium chloride (0.9 g, 47.3% after drying) was filtered off. Propylene oxide (ca. 400 cm^3) was then added to the filtrate until the pH was 6. The solid formed was filtered off and washed with methanol (50 cm^3) (2.6 g, 91% after drying). This crude product was recrystallised from water-acetone, washed with acetone (50 cm^3) and dried in a vacuum oven at 60 ^oC (3 h) to yield N-(12-guanidinododecyl)aminomethanephosphonic

acid monohydrate (2.9 g, 66.7%) as a fine white crystalline solid, m.p. 129-130 °C, (Found: C, 48.0; H, 9.3; N, 14.9. $C_{14}H_{35}N_4O_4P$ requires: C, 47.5; H, 9.9; N, 15.9%); ^1H (D_2O/D_2SO_4) 1.29 (16H, $NH(CH_2)_2(CH_2)_8$), 1.60 (2H, m, $NHCH_2CH_2$), 1.74 (2H, m, $(CH_2)_{10}CH_2CH_2NH$), 3.21 (4H, m, $NHCH_2(CH_2)_{10}CH_2$), 3.47 (2H, d, PCH_2, $^2J_{PCH}$ 13.5 Hz); ^{13}C (D_2O/D_2SO_4) 28.0, 28.3, 28.6, 30.6, 30.9, 31.0 and 31.4 (singlets, $NHCH_2(CH_2)_{10}$), 44.4 (s, $CH_2NHC(:NH)NH_2$), 45.6 (d, PCH_2, $^1J_{PC}$ 148.5), 53.7 (d, $NHCH_2$, $^3J_{PCNC}$ 7.5 Hz), 159.4 (s, $NHC(:NH)NH_2$); $^{31}P-\{^1H\}^{bb}$ (D_2O) 8.6; ^{31}P (D_2O/D_2SO_4) 15.1 (t, $^2J_{HCP}$ 13.2 Hz); m/z (FAB, %) 338 (16.4), 337 (M+1, 100), 295 (3.7), 255 (44.2), 226 (13.6), 212 (5.6), 198 (8.7), 184 (6.2), 170 (5.9), 156 (6.5), 142 (7.0), 128 (8.5), 114 (7.9), 100 (9.1).

6.58 PREPARATION OF N-(12-UREIDODODECYL)AMINOMETHANE-PHOSPHONIC ACID MONOHYDRATE

N-(12-Aminododecyl)aminomethanephosphonic acid monohydrate (6.9 g, 22.1 mmol), cyanamide (7.5 g, 178.6 mmol), and potassium hydroxide (3.7 g, 66.0 mmol) were dissolved in water (200 cm^3) and heated under reflux (20 h). The clear solution was then acidified to pH 1 with concentrated hydrochloric acid and the volatile components were distilled off on a rotary evaporator. The oily residue was dissolved in water (100 cm^3) and methanol (100 cm^3); propylene oxide (ca. 600 cm^3) was then added until the pH was 6. The solid formed was filtered off and

washed with water (100 cm^3) then ethanol (100 cm^3). It was then heated under reflux (5 min) in water (50 cm^3) and the solid filtered off while hot. .This solid was washed with ethanol (100 cm^3) and dried in a vacuum oven at 60 ^oC to yield N-(12-ureidododecyl)aminomethanephosphonic acid monohydrate (2.7 g, 34.4%) as a fine white crystalline solid, m.p. 129-130 ^oC, (Found: C, 47.0; H, 9.6; N, 11.9. $C_{14}H_{34}N_3PO_5$ requires: C, 47.3; H, 9.6; N, 11.8%); ^{13}C (D_2O/D_2SO_4) 28.0, 28.3, 30.4, 30.9 and 31.4 (singlets, $NHCH_2\underline{(CH_2)_{10}}$), 44.3 (s, $\underline{CH_2}NHC(:O)NH$), 45.2 (d, PCH_2, $^1J_{PC}$ 152.6 Hz), 53.7 (d, $NHCH_2$, $^3J_{PCNC}$ 10.2 Hz), 162.1 (s, $NHC(:O)NH_2$); m/z (FAB, %) 380 (19.4), 339 (17.0), 338 (M+1, 100.0), 336 (10.3), 286 (14.4), 256 (35.3), 213 (12.0), 128 (1.1), 114 (2.9).

6.59 PREPARATION OF OCTANE-1,8-DIGUANIDINIUM SULPHATE

1,8-Diamino-octane (7.2 g, 50.0 mmol) and S-methylisothiouronium sulphate (14.5 g, 52.1 mmol) were dissolved in water (40 cm^3) and heated under reflux (2 h) while the evolving methanethiol was collected in potassium permanganate traps. Concentrated sulphuric acid (2 cm^3) was added and the solution was concentrated to ca. 20 cm^3 on a rotary evaporator and stored at 4 ^oC overnight. The crystals that formed were filtered off, washed with methanol (2x20 cm^3), and recrystallised from water-ethanol. The recrystallised material was washed with methanol (40 cm^3) and dried in a vacuum oven at 60 ^oC

(4 h) to yield <u>octane-1,8-diguanidinium sulphate</u> (13.5 g, 82.8%) as a fine white crystalline solid, m.p. 282 °C (decomp) (lit. m.p. 280 °C),[9] (Found: C, 35.9; H, 7.9; N, 25.8. Calc. for $C_{10}H_{26}N_6O_4S$: C, 36.8; H, 8.0; N, 25.8%); ^{13}C (D_2O/D_2SO_4) 27.8 (s), 29.9 (s), 30.2 (s), 43.7 (s, <u>C</u>H_2NH), 158.8 (s, NH<u>C</u>(:NH)NH_2); m/z (FAB, %) 327 (M+H_2SO_4+1, 29.6), 229 (M+1, 66.3), 228 (2.9), 172 (100), 170 (12.9), 156 (8.0), 142 (3.9), 128 (6.4), 114 (4.9), 100 (4.3).

6.60 PREPARATION OF 1-DODECYL-2-(DIETHOXYPHOSPHINYL)GUANIDINE

To a solution of dodecylguanidine (10.0 g, 44.0 mmol) in carbon tetrachloride (100 cm^3) was added diethyl phosphite (4.0 g, 29.0 mmol) dissolved in carbon tetrachloride (20 cm^3) in one portion. The solution was stirred (10 min) during which time heat was evolved and the dodine was seen to dissolve. The solvents were distilled off on a rotary evaporator and the residue dissolved in diethyl ether (200 cm^3) and left to stand overnight. The solid that formed was filtered off (2.2 g, 21% after drying), recrystallised from chloroform/diethyl ether and dried in a vacuum oven at 60 ^oC to yield 1-dodecyl-2-(diethoxyphosphinyl)guanidine (1.5 g, 14.3%) as a fine white crystalline solid, m.p. 167-168 ^oC, (Found: C, 53.6; H, 10.1; N, 11.0; P, 8.3; M^+ 363.2662 $C_{17}H_{38}N_3O_3P$ requires: C, 56.1; H, 10.5; N, 11.6; P, 8.6%; M^+ 363.2674); ^1H (DMSO-d_6) 0.7-1.7 (29H, overlapping signals, $C_{11}H_{23}$ and CH_3CH_2O), 3.0 (2H, br s, $CH_2NHC(:NH)NH_2$), 3.67 (4H, overlapping d of q, CH_2O, $^3J_{HCCH}$ 7 Hz, $^3J_{POCH}$ 7 Hz), 7.41 (3H, br, NHC(:NH)NH, exchanged with D_2O); ^{13}C (DMSO-d_6) 13.7 (s, $CH_3(CH_2)_{11}$), 16.5 (d, CH_3CH_2O, $^3J_{POCC}$ 6.1 Hz), 21.9, 26.2, 28.6, 30.0 and 31.2 (singlets, $(CH_2)_{10}CH_2$), 40.9 (s, $CH_2NHC(:NH)NH$), 59.5 (d, CH_2O, $^2J_{POC}$ 6.1 Hz), 157.6 (s, NHC(:NH)NH); ^{31}P (DMSO-d_6) 2.2 (m); m/z (%) 363 (M^+, 42.5), 292 (24.8), 278 (25.0), 264 (37.7), 250 (26.7), 236 (36.8), 223 (25.3), 222 (60.3), 209 (61.2), 179 (61.3), 123 (51.8), 55 (25.7), 51 (26.2), 30 (100.0).

6.61 PREPARATION OF 1-DODECYL-2-(DIMETHOXYPHOSPHINYL)GUANIDINE

To a solution of dodecylguanidine (10.0 g, 44.0 mmol) in carbon tetrachloride (100 cm^3) was added dimethyl phosphite (3.2 g, 29.1 mmol) dissolved in carbon tetrachloride (20 cm^3) in one portion. The solution was then heated under reflux (10 min). The solvents were distilled off on a rotary evaporator and the residue dissolved in diethyl ether (200 cm^3) and left to stand overnight. The solid that formed was filtered off (2.4 g, 24.6% after drying) and dissolved in the minimum of hot chloroform and the insoluble materials were removed by filtration. Recrystallisation from chloroform/diethyl ether followed by drying in a vacuum oven at 45 ^oC gave 1-dodecyl-2-(dimethoxyphosphinyl)guanidine (1.7 g, 17.5%) as a fine white crystalline solid, m.p. 155-156 ^oC; ^{13}C (DMSO-d_6) 13.7 (s, $\underline{CH_3}(CH_2)_{11}$), 22.0, 26.1, 28.5, 28.7, 29.0 and 31.2 (singlets, $CH_3(\underline{CH_2})_{10}$), 40.8 (s, $\underline{C}H_2NHC(:NH)NH$), 51.5 (d, $\underline{C}H_3O$, $^2J_{POC}$ 6.1 Hz), 157.5 (s, $NH\underline{C}(:NH)NH_2$); ^{31}P (DMSO-d_6) 1.8 (m); m/z (%) 226 (M-$(MeO)_2PO$, 5.0), 156 (15.7), 142 (17.4), 128 (35.5), 114 (34.5), 109 (1.6), 100 (44.7), 96 (100), 96 (2.9), 95 (32.6), 87 (31.6), 86 (41.1), 73 (69.4), 72 (59.8), 30 (62.7).

6.62 REACTION OF N,N,N′,N′-TETRAMETHYLPHOSPHORODIAMIC-CHLORIDE WITH DODECYLGUANIDINE

N,N,N,N-Tetramethylphosphorodiamidic chloride (3.0 g, 16.1 mmol) and dodecylguanidine (7.3 g, 32.2 mmol) were dissolved in benzene (300 cm^3) and stirred (2 h) at room temperature. The solid that formed on standing overnight was filtered off and the benzene was distilled from the filtrate on a rotary evaporator. The residue was dissolved in hot diethyl ether (30 cm^3) and left to stand when it gave a solid which was filtered off, dried in a vacuum oven at room temperature, to yield a white solid (0.5 g) identified as a mixture, of dodecylguanidine and 1-dodecyl-2-(N,N,N′,N′-tetramethyl-phosphorodiamido)-guanidine; ^{13}C (DMSO-d_6) 13.9 (s, $\underline{C}H_3(CH_2)_{11}$), 22.1, 22.6, 25.9, 26.1, 28.1, 28.5, 28.7, 29.0 and 31.3 ($CH_3\underline{(CH_2)_{10}}$), 35.8 (d, $\underline{(Me_2N)_2}P$, $^2J_{PNC}$ 4.4 Hz), 40.7 (s, $\underline{C}H_2NHC(:NH)NH_2$), 156.6 (d, $NH\underline{C}(:NH)NH$, $^2J_{PNC}$ 3.4 Hz), 157.3 (s, $NH\underline{C}(:NH)NH_2$); ^{31}P (DMSO-d_6) 16.9 (m).

6.63 PREPARATION OF N,N,N′,N′-TETRAMETHYL-1,3-DIPHENYL-1,3,2,4-DIAZADIPHOSPHETIDINE-2,4-DIAMINE-2,4-DIOXIDE

Aniline (5.0 g, 53.7 mmol) and hexamethylphosphoric triamide (15 cm^3) were heated under reflux (3 h) and the solution then allowed to cool overnight. The solid formed was filtered off, washed with water (2x50 cm^3), recrystallised twice from ethanol/water and dried in a

vacuum oven at 60 °C to yield N,N,N′,N′-tetramethyl-1,3-diphenyl-1,3,2,4-diazadiphosphetidine-2,4-diamine-2,4-dioxide (6.2 g, 63.1%) as a fine white crystalline solid, m.p. 263 °C (lit. m.p. 255-258 °C),[108] (Found: C, 53.6; H, 6.4; N, 16.0. Calc. for $C_{16}H_{22}N_4O_2P_2$: C, 52.8; H, 6.0; N, 15.4%); ^{31}P (DMSO-d_6) -2.7 (br m).

6.64 PREPARATION OF N,N,N′,N′-TETRAMETHYL-1,3-BIS-(2,4-DICHLORO-PHENYL)-1,3,2,4-DIAZADIPHOSPHETIDINE-2,4-DIAMINE-2,4-DIOXIDE

2,4-Dichloroaniline (5.0 g, 30.8 mmol) and hexamethylphosphoric triamide (15 cm^3) were heated under reflux (5 h) and the solution then allowed to cool overnight. The solid that formed was filtered off, washed successively with water (50 cm^3), methanol (50 cm^3), acetone (50 cm^3), and diethyl ether (50 cm^3), and dried in a vacuum oven at 60 °C to yield N,N,N′,N′-tetramethyl-1,3-bis-(2,4-dichlorophenyl)-1,3,2,4-diazadiphosphetidine-2,4-di-amine-2,4-dioxide (4.5 g, 61.1%) as a fine light brown crystalline solid, m.p. 187-188 °C, (Found: C, 38.0; H, 3.7; N, 11.6; P, 11.8; Cl, 26.9; M^+ 499.9655. $C_{16}H_{18}Cl_4N_4O_2P_2$ requires: C, 38.2; H, 3.6; N, 11.2; P, 12.3; Cl, 28.3%; M^+ 499.9659); $^{31}P-\{^1H\}^{bb}$ (DMSO-d_6) 6.4; m/z (%) 504 (M^+, 24.4), 503 (10.3), 502 (M^+, 52.3), 501 (41.4), 500 (M^+, 41.4), 461 (33.7), 459 (80.0), 457 (61.2), 352 (22.3), 252 (49.1), 250 (79.0), 192 (36.2), 190 (56.9), 174 (25.0), 172 (100), 161 (40), 124 (30.4), 90 (25.1), 44 (82.0).

6.65 PREPARATION OF N,N,N',N'-TETRAMETHYL-1,3-BIS-(3,5-DICHLORO-PHENYL)-1,3,2,4-DIAZADIPHOSPHETIDINE-2,4-DIAMINE-2,4-DIOXIDE

3,5-Dichloroaniline (5.0 g, 30.8 mmol) and hexamethylphosphoric triamide (15 cm^3) were heated under reflux (5 h) and the solution then allowed to cool overnight. The solid that formed was filtered off, washed successively with water (50 cm^3), methanol (50 cm^3), acetone (50 cm^3), and diethyl ether (50 cm^3), and dried in a vacuum oven at 60 ^oC to yield N,N,N',N'-tetramethyl-1,3-bis-(3,5-dichlorophenyl)-1,3,2,4-diazadiphosphetidine-2,4-diamine-2,4-dioxide (6.2 g, 82.3%) as a fine light brown crystalline solid, m.p. 285 ^oC, (Found: C, 38.0; H, 3.7; N, 11.2; P, 12.2; Cl, 28.3; M^+ 499.9651. $C_{16}H_{18}Cl_4N_4O_2P_2$ requires: C, 38.2; H, 3.6; N, 11.2; P, 12.3; Cl, 28.3%; M^+ 499.9659); $^{31}P-\{^1H\}^{bb}$ (DMSO-d_6) 4.8; m/z (%) 504 (M^+, 4.0), 503 (1.4), 502 (M^+, 8.3), 501 (1.0), 500 (M^+, 6.6), 461 (1.6), 459 (2.7), 457 (2.1), 352 (1.6), 252 (1.9), 250 (2.8), 192 (5.5), 190 (8.7), 90 (5.1), 44 (100.0).

6.66 PREPARATION OF OCTANALDOXIME

A 1 litre flask was charged with octanal (64.0 g, 500.0 mmol), hydroxylamine hydrochloride (44.0 g, 633.1 mmol) and water (90 cm^3). A solution of sodium carbonate (67.0 g, 632.1 mmol) in water (250 cm^3) was then added through the top of the condenser so that the temperature did not rise above 30 ^oC. After addition was complete the mixture was stirred at room temperature (1 h), and the solid that formed was filtered off, washed with water (25 cm^3) and dissolved in benzene (200 cm^3). The aqueous layer was separated and the organic layer washed with water (25 cm^3) and dried ($MgSO_4$). The solvents were distilled off on a rotary evaporator and the residue dissolved in the minimum quantity of hot light petroleum (b.p. 30-40 ^oC) and stored at -18 ^oC. The resultant crystals were filtered off to yield octanaldoxime (41.2 g, 57.6%) as a fine white waxy solid, m.p. 59 ^oC (lit. m.p. 60 ^oC),[158] (Found: C, 68.3; H, 11.1; N, 9.0. Calc. for $C_8H_{17}NO$: C, 67.1; H, 11.9; N, 9.8%); ^1H ($CDCl_3$) 0.7-1.7 (13H, $\underline{C_6H_{13}}$, br m), 2.3 (2H, $\underline{CH_2}CH$, overlapping d of t), 6.7 and 7.4 (1H, pair of triplets, syn and anti forms, $^3J_{HCCH}$ 6 Hz).

6.67 PREPARATION OF DODECANAMIDE

Dodecanoyl chloride (30.5 g, 14.0 mmol) was dissolved in benzene (150 cm^3) and ammonia gas was passed through the stirred solution (1 h). The benzene was distilled off on a rotary evaporator, the residual solid was shaken with water (200 cm^3) and the crude amide was filtered off. Recrystallisation from methanol/water afforded dodecanamide (17.5 g, 63.0%) as a white waxy solid, m.p. 98 ^oC (lit. m.p. 99 ^oC),[163] (Found: C, 71.9; H, 11.8; N, 6.2. Calc. for $C_{12}H_{25}NO$: C, 72.3, H, 12.5, N, 7.0%).

6.68 PREPARATION OF ACETYLGUANIDINIUM CHLORIDE

Acetyl chloride (20.3 g, 259 mmol) and guanidinium chloride (24.3 g, 254 mmol) were heated at 100 ^oC (2 h) in two sealed glass tubes and then allowed to cool. The tubes were opened after cooling in a Cardice/acetone bath, the solid residue was dissolved in water (100 cm^3), and the volatile components were distilled off on a rotary evaporator. The residue was recrystallised from absolute methanol and dried in a vacuum oven at 60 ^oC to yield acetylguanidinium chloride (24.1 g, 67.9%) as a fine white crystalline solid, m.p. 147 ^oC (lit. m.p. 140-142 ^oC),[57] (Found: C, 26.6; H, 5.9; N, 30.1; Cl, 26.1. Calc. for $C_3H_8ClN_3O$: C, 26.2; H, 5.8; N, 30.5; Cl, 25.8%); ^1H (DMSO-d_6) 2.15 (3H, s, $\underline{CH_3}$), 8.40 (4H, br s, $C(\underline{NH_2})_2$, exchanged with D_2O), 12.05 (1H, br s, C(O)$\underline{NH}$, exchanged

with D_2O); m/z (FAB, %) 378 (6.9), 376 (10.2), 241 ($2M+H^{37}Cl+1$, 23.3), 240 (6.8), 239 ($2M+H^{35}Cl+1$, 63.4), 203 (2M+1, 30.1), 197 (11.2), 161 (6.5), 103 (11.0), 102 (M^+, 100), 101 (2.4).

6.69 PREPARATION OF DODECANOYLGUANIDINIUM CHLORIDE

Dodecanoyl chloride (15.5 g, 70.9 mmol) and guanidinium chloride (3.5 g, 36.6 mmol) were heated at 190 oc (3 h) in two sealed glass tubes. On cooling, the solution solidified and the product was recrystallised from ethanol/ water and dried in a vacuum oven at 50 ^oC to yield dodecanoylguanidinium chloride (6.5 g, 64.0%) as a white crystalline solid, m.p. 138-139 ^oC, (Found: C, 57.3; H, 10.5; N, 13.4; Cl, 12.7. $C_{13}H_{28}ClN_3O$ requires: C, 56.2; H, 10.1; N, 15.1; Cl, 12.8%); ^1H (DMSO-d_6) 0.74-1.67 (21H, br, $C_{10}H_{21}$), 2.41 (2H, t, $CH_2C(O)$, $^3J_{HCCH}$ 6.8 Hz), 8.27 (4H, br s, $C(NH_2)_2$, exchanged with D_2O), 11.73 (1H, br s, C(O)NH, exchanged with D_2O); ^{13}C (DMSO-d_6) 13.8 (s, CH_3), 22.0, 23.7, 28.2, 28.6, 28.8, 28.9, 31.2 (singlets, $CH_3(CH_2)_9CH_2$), 154.9 (s, $NHC(:NH)NH_2$), 175.0 (s, C=O); m/z (FAB, %) 481 (1.0), 243 (14.7), 242 (M+1, 100), 241 (4.6), 240 (11.6), 184 (2.0), 156 (1.2), 128 (2.1), 114 (11.4), 101 (9.3).

6.70 PREPARATION OF O,O-DIETHYL 2-BROMOETHANEPHOSPHONATE

Triethyl phosphite (33.2 g, 200 mmol) and 1,2-dibromoethane (150 g, 798 mmol) were heated at 160 ^{o}C (3 h) while the evolving ethyl bromide (19.6 g, 89.9%) was collected in the apparatus described.[159] The excess 1,2-dibromoethane was distilled off under reduced pressure, and the residue was distilled to yield O,O-diethyl 2-bromoethanephosphonate (33.5 g, 68%) as a colourless free running oil, b.p. 78 ^{o}C at 0.15 mm Hg (lit. b.p. 75 ^{o}C at 1mm Hg),[161] n_D^{26} 1.4525 (lit. n_D^{20} 1.4600),[161] (Found: C, 30.7; H, 5.9. Calc. for $C_6H_{14}BrO_3P$: C, 29.4; H, 5.7%); ^{1}H ($CDCl_3$) 1.34 (6H, t, $\underline{CH_3}$, $^{3}J_{HCCH}$ 7.1 Hz), 2.17-2.61 (2H, m, $P\underline{CH_2}$), 3.39-3.70 (2H, m, $\underline{CH_2}Br$), 4.13 (4H, overlapping d of q, $PO\underline{CH_2}$); ^{13}C ($CDCl_3$) 16.5 (d, $\underline{CH_3}$, $^{3}J_{POCC}$ 5.9 Hz), 23.9 (s, $\underline{CH_2}Br$), 31.0 (d, $P\underline{C}H_2$, $^{1}J_{PC}$ 135.3 Hz), 62.0 (d, $PO\underline{C}H_2$, $^{2}J_{POC}$ 6.6 Hz); ^{13}C (SFORD) 16.3 (d of q), 27.5 (t), 29.1 (d of t), 63.0 (d of t); ^{31}P-{^{1}H}^{bb} ($CDCl_3$) 23.5.

6.71 PREPARATION OF 6-CHLOROHEXAN-1-OL

A three necked flask (1 L) was charged with Hexane-1,6-diol (50.0 g, 423.7 mmol), concentrated hydrochloric acid (480 cm^3), and water (150 cm^3). The mixture was heated in an oil bath at 100 ^{o}C and light petroleum (b.p. 100-120 ^{o}C) was introduced via a glass inlet tube into the bottom of the stirred solution for

sixteen hours (at ca. 1.2 L/h); the upper petrol layer being removed continuously. The petrol extracts were combined and concentrated on a rotary evaporator (ca. 300 cm^3), washed with sodium bicarbonate solution (5%) until neutral, washed with water (100 cm^3) and dried ($MgSO_4$). The solvents were distilled off on a rotary evaporator and the residue distilled through a 10 cm Vigreux column to give the following fractions: (i) a mixture (6.7 g), b.p. 54 °C at 0.18 mm Hg, containing 6-chlorohexan-1-ol (58.5%) and 1,6-dichlorohexane (41.5%)(g.l.c.); (ii), 6-chlorohexan-1-ol (17.7 g, 30.9%) as a colourless free running oil, b.p. 68-72 °C at 0.18 mm Hg, (lit. b.p. 116-117 °C at 19 mm Hg),[162] (Found: C, 53.3; H, 9.8. Calc. for $C_6H_{13}ClO$: C, 52.7; H, 9.5%); ^1H ($CDCl_3$) 1.0-2.1 (8H, br m, $CH_2(CH_2)_4CH_2$), 3.48 (2H, t, CH_2Cl, $^3J_{HCCH}$ 6 Hz), 3.54 (2H,t CH_2OH, $^3J_{HCCH}$ 6 Hz), 2.84-3.70 (1H, CH_2OH, exchanged with D_2O); ^{13}C ($CDCl_3$) 25.1 (s, $CH_2CH_2CH_2Cl$), 26.7 (s, $CH_2CH_2CH_2OH$), 32.5 (s, CH_2CH_2Cl), 32.6 (s, CH_2CH_2OH), 45.0 (s, CH_2Cl), 62.6 (s, CH_2OH); I.R. (thin film) 3620-3010 cm^{-1} (OH); 2930 (s), 2860 (s); m/z (%) 137 (M^+, 1.7), 135 (M^+, 2.7), 119 (12.4), 83 (64.2), 82 (21.3), 67 (21.9), 55 (100.0), 41 (66.7).

6.72 PREPARATION OF N-(6-HYDROXYHEXYL)PHTHALIMIDE

6-Chlorohexan-1-ol (16.3 g, 119.4 mmol) and potassium phthalimide (23.1 g, 124.8 mmol) were heated (3.5 h) in dimethylformamide (100 cm^3) at 110 ^oC. The reaction mixture was allowed to cool and the insoluble materials filtered off. Chloroform (150 cm^3) was added to the filtrate and the resultant solution washed with water (500 cm^3). The aqueous layer was washed with chloroform (2x50 cm^3), and the combined organic layers were washed with 0.2M sodium hydroxide solution (100 cm^3) and then with water (100 cm^3). The solution was concentrated on a rotary evaporator (ca. 100 cm^3), washed with water and dried ($MgSO_4$). The solvents were distilled off on a rotary evaporator and the residue was cooled in Cardice/acetone. Trituration with light petroleum (b.p. 30-40 ^oC)(280 cm^3) gave a fine solid which was filtered off, washed with light petroleum (30 cm^3) and dried in a vacuum oven at room temperature to yield N-(6-hydroxyhexyl)phthalimide (16.3 g, 54.4%) as a white waxy solid, m.p. 44-45 ^oC, (Found: C, 71.4; H, 7.4; N, 5.4. $C_{14}H_{17}NO_3$ requires: C, 68.0; H, 6.9; N, 5.7%); ^1H (DMSO-d_6) 1.0-1.9 (8H, br m, $CH_2(CH_2)_4CH_2$), 3.40-3.55 (2H, two overlapping triplets, NCH_2 and CH_2OH), 4.05 (1H, s, CH_2OH, exchanged with D_2O), 7.82 (4H, s, aromatic); ^{13}C ($CDCl_3$) 25.3 (s, $CH_2(CH_2)_2N$), 26.6 (s, $CH_2(CH_2)_2OH$), 28.6 (s, CH_2CH_2N), 32.6 (s, CH_2CH_2OH), 38.0 (s, CH_2N), 62.7 (s, CH_2OH), 123.3 (s, C_2 aromatic), 132.3 (s, C_1 aromatic),

134.0 (s, C_3 aromatic), 168.7 (s, C=O); I.R. (thin film) 3700-3120 cm^{-1} (OH), 1690 cm^{-1} (C=O).

6.73 PREPARATION OF N-(6-CHLOROHEXYL)PHTHALIMIDE

N-(6-Hydroxyhexyl)phthalimide (15.4 g, 61.4 mmol) and thionyl chloride (50 g, 420.1 mmol) were heated under reflux (3 h). The excess of thionyl chloride was distilled off under reduced pressure and the residue dissolved in chloroform (100 cm^3), washed with water (40 cm^3) and dried ($MgSO_4$). The chloroform was distilled off on a rotary evaporator and the residue solidified on cooling in Cardice/acetone. Petroleum spirit (b.p. 30-40 ^oC)(100 cm^3) was added and the solid was filtered off, washed with light petroleum (30 cm^3), and dried in a vacuum oven at room temperature to yield N-(6-chlorohexyl)phthalimide (14.0 g, 89.9%) as a white waxy solid, m.p. 39 ^oC, ^1H ($CDCl_3$) 1.2-2.1 (8H, br m, $CH_2(CH_2)_4CH_2$), 3.48 and 3.6 (4H, two overlapping triplets, CH_2Cl and CH_2N), 7.7 (4H, s, aromatic); I.R. (thin film) 1720 cm^{-1} (C=O).

6.74 ATTEMPTED PREPARATION OF O,O-DIETHYL 8-BROMO-OCTANEPHOSPHONATE

Triethyl phosphite (15.2 g, 91.5 mmol) and 1,8-dibromo-octane (100.0 g, 367.6 mmol) were heated at 180 °C (2.5 h) while the evolving ethyl bromide (6.96 g, 70.2%) was collected in the apparatus described.[159] The reaction mixture was distilled through a 10 cm Vigreux column to yield a fraction (70 g), b.p. 96 °C at 1mm Hg containing 1,8-dibromo-octane (ca. 95%, g.l.c.). On further distillation the residue decomposed with gas evolution and the contents of the flask polymerised to yield a light brown thermoplastic, rubbery material (8.0 g), m.p. >310 °C.

Similar results were obtained on attempted condensation of triethyl phosphite with 1,10-dibromodecane or 1,12-dibromododecane.

6.75 ATTEMPTED PREPARATION OF N-(8-BROMO-OCTYL)PHTHALIMIDE

1,8-Dibromo-octane (39.7 g, 146.0 mmol) and potassium phthalimide were heated under reflux (7.5 h) in dimethylformamide (150 cm^3) and allowed to cool. The white solid (3.3 g after drying) that fomed was filtered off and chloroform (300 cm^3) added to the filtrate. The resultant solution was successively washed with water (500 and 200 cm^3), 0.1 mol. sodium hydroxide solution (100 cm^3) and water (200 cm^3). The volatile materials were then

distilled off on a rotary evaporator and the residue steam distilled to remove the unreacted 1,8-dibro-octane (600 cm^3 water collected). Petroleum spirit (b.p. 40-60 ^oC, 60 cm^3) was added and the aqueous layer separated. On standing overnight this petrol layer gave a fine white precipitate of 1,8-diphthalimido-octane (0.4 g, 3%) m.p. 110-112 ^oC, (Found: C, 67.6; H, 6.7; N, 6.2. $C_{24}H_{24}N_2O_2$ requires: C, 71.2; H, 6.0; N, 6.9%); ^1H ($CDCl_3$) 1.4 (12H, br s, $NCH_2\underline{(CH_2)_6}$), 3.4 (4H, br t, $\underline{CH_2}N$, $^3J_{HCCH}$ 7 Hz), 7.8 (8H, m, phthalimide).

6.76 PREPARATION OF N-(8-HYDROXYOCTYL)PHTHALIMIDE

1-Chloro-8-hydroxyoctane (28.5 g, 173.3 mmol) and potassium phthalimide (32.1 g, 173.3 mmol) were heated (10 h) in dimethylformamide (60 cm^3) in an oil bath at 110-120 ^oC. After cooling overnight, the white insoluble materials were filtered off and washed with diethyl ether (2x50 cm^3). The filtrate and ether washings were combined and the solvents were distilled off on a rotary evaporator at 90 ^oC. The residue was dissolved in diethyl ether (50 cm^3) and filtered to leave a clear solution which was stored at -18 ^oC overnight. Diethyl ether (100 cm^3) was then added, and the white solid was filtered off, and washed with diethyl ether (2x10 cm^3). The solid was recrystallised from diethyl ether, washed with diethyl ether (2x10 cm^3) and dried in a vacuum oven at room temperature to yield N-(8-hydroxyoctyl)phthalimide

(28.9 g, 60.7%) as a fine white waxy solid, m.p. 50-52 ^{o}C, (Found: C, 69.4; H, 8.0; N, 4.6. $C_{16}H_{21}NO_3$ requires: C, 69.8; H, 7.6; N, 5.1%); ^{1}H (DMSO-d_6) 1.27 (12H, br s, $PCH_2\underline{(CH_2)_6}$), 3.34-3.65 (5H, m, $\underline{NCH_2}$ and $\underline{CH_2}$-OH, OH exchanged with D_2O), 7.86 (4H, s, phthalimide); ^{13}C (DMSO-d_6) 25.5, 26.3, 27.9, 28.6, 28.8, and 32.6 (singlets, $-\underline{(CH_2)_6}-$), 37.4 (s, $\underline{CH_2}N$), 60.8 (s, $\underline{CH_2}OH$), 123.0 (s, $\underline{C_3}$ aromatic), 131.7 (s, $\underline{C_1}$ aromatic), 134.4 (s, $\underline{C_2}$ aromatic), 168.0 (s, C=O); m/z (%) 275 (M^+, 12.3), 161 (39.5), 160 (76.4), 147 (48.3), 104 (46.3), 84 (60.2), 83 (28.0), 77 (43.6), 69 (45.3), 68 (60.3), 67 (73.2), 54 (100.0), 53 (38).

6.77 PREPARATION OF N-(8-BROMO-OCTYL)PHTHALIMIDE

N-(8-Hydroxyoctyl)phthalimide (25.5 g, 92.7 mmol) was dissolved in acetonitrile (150 cm^3) and bromomethylenedimethylammonium bromide (26.1 g, 120.3 mmol) added in one portion with vigorous stirring. When all the reagent had dissolved the reaction mixture was heated under reflux (1 h) and allowed to cool. Some of the acetonitrile (ca. 100 cm^3) was distilled off on a rotary evaporator and water (40 cm^3) was added to the residue. Diethyl ether (400 cm^3) was then added, the aqueous layer was separated and the organic layer was washed with water (2x20 cm^3) and dried ($MgSO_4$). The solvents were distilled off on a rotary evaporator and the residue crystallised from diethyl ether/light petroleum (b.p. 30-40 ^{o}C) to give a

solid which was washed with light petroleum (40 cm^3) and dried in a vacuum oven at room temperature to yield N-(8-bromo-octyl)phthalimide (28.2 g, 90.0%) as a fine white waxy solid, m.p. 46 ^oC, (Found: C, 56.1; H, 5.6. $C_{16}H_{20}BrNO_2$ requires: C, 56.8; H, 5.6%); ^1H ($CDCl_3$) 1.4-1.9 (12H, br m, $(CH_2)_6CH_2Br$), 3.39 (2H, CH_2N, t, $^3J_{HCCH}$ 6.6 Hz), 3.68 (2H, t, CH_2Br, $^3J_{HCCH}$ 7.0 Hz), 7.77 (4H, m, phthalimide); ^{13}C ($CDCl_3$) 28.6, 28.1, 28.6, 29.0, 32.8 (singlets, $(CH_2)_6CH_2Br$), 33.8 (s, CH_2Br), 38.1 (s, CH_2N), 123.3 (s, C_3 aromatic), 132.4 (s, C_1 aromatic), 133.9 s, C_2 aromatic), 168.6 (s, C=O); m/z (%) 339 (M^+,29.9), 337 (M^+,29.6), 161 (65.8), 160 (100.0), 148 (15.1), 130 (16.9), 104 (10.1), 77 (12.4), 76 (12.4).

6.78 PREPARATION OF N-(11-HYDROXYUNDECYL)PHTHALIMIDE

1-Bromo-11-hydroxyundecane (50.6 g, 201.4 mmol) and potassium phthalimide (40.0 g, 215.9 mmol) were heated (11 h) in dimethylformamide (190 cm^3) in an oil bath at 130 ^oC. After cooling, overnight the white insoluble materials (25.1 g, after drying) were filtered off and washed with diethyl ether (2x50 cm^3). The filtrate and the ether washings were combined and the solvents were distilled off on a rotary evaporator at 90 ^oC. The residue was dissolved in diethyl ether (150 cm^3) and filtered to leave a clear solution which was stored at -18 ^oC. The solid that formed was filtered off, washed with diethyl ether (2x100 cm^3), recrystallised from

diethyl ether/light petroleum (b.p. 40-60 ^{o}C) and dried in a vacuum oven at room temperature to yield N-(11-hydroxyundecyl)phthalimide (41.7 g, 65.3%) as a fine white waxy solid, m.p. 68-70 ^{o}C; ^{1}H ($CDCl_3$) 1.0-2.1 (18H, br m, $(CH_2)_9CH_2N$), 2.65 (1H, br s, OH, exchanged with D_2O), 3.4-3.8 (4H, m, CH_2N and CH_2OH), 7.78 (4H, d, phthalimide); ^{13}C ($CDCl_3$) 25.8, 26.9, 28.1, 28.6, 29.2, 29.5 and 32.8 (singlets, $(CH_2)_9CH_2N$), 38.1 (CH_2N), 62.9 (CH_2OH), 123.3 (C_3 aromatic), 132.3 (C_1 aromatic), 134.0 (C_2 aromatic), 168.6 (C=O); m/z (%) 317 (M^+, 7.0), 161 (37.2), 160 (100), 149 (14.5), 133 (15.2), 130 (21.2), 105 (16.4), 104 (23.2), 78 (27.7), 77 (25.5), 60 (46.1), 50 (29.9).

6.79 PREPARATION OF N-(11-BROMOUNDECYL)PHTHALIMIDE

N-(11-Hydroxyundecyl)phthalimide (29.0 g, 91.5 mmol) was dissolved in acetonitrile (300 cm^3) and bromomethylenedimethylammonium bromide (21.2 g, 97.7 mmol) added in one potion with vigorous stirring. Once dissolution of the reagent was complete the reaction mixture was then heated under reflux (2 h) and allowed to cool. Some of the acetonitrile (ca. 200 cm^3) was distilled off on a rotary evaporator and water (120 cm^3) was added to the resultant solution. Diethyl ether (500 cm^3) was then added, the aqueous layer was separated and the organic layer was washed with sodium bicarbonate solution (5%, 70 cm^3); water (2x20 cm^3), and dried ($MgSO_4$). The

solvents were distilled off on a rotary evaporator and the residue was crystallised from diethyl ether/light petroleum (b.p. 40-60 ^{o}C) to give a solid that was washed with light petroleum (3x20 cm^{3}) and dried in a vacuum oven at room temperature to yield N-(11-bromoundecyl)-phthalimide (22.5 g, 64.7%) as a fine white solid, m.p. 61-63 ^{o}C; ^{1}H ($CDCl_3$) 1.28 (18H, br s, $(CH_2)_9CH_2N$), 3.66 (4H, two overlapping t, CH_2N and CH_2Br), 7.77 (4H, m, phthalimide); ^{13}C ($CDCl_3$) 25.8, 26.9, 28.6, 28.7, 29.2, 29.4 and 32.8 (singlets, $(CH_2)_9CH_2N$), 33.9 (CH_2Br), 38.1 (CH_2N), 123.3 (C_3 aromatic), 132.3 (C_1 aromatic), 133.9 (C_2 aromatic), 168.6 (C=O); m/z (%) 381 (M^+, 25.0), 379 (M^+, 30.4), 317 (38.8), 174 (19.8), 162 (19.4), 161 (100), 160 (72.6), 148 (56.3), 130 (30.9), 104 (31.7), 76 (33.2), 55 (50), 41 (58.7).

6.80 PREPARATION OF DODECYLGUANIDINE

A mixture of dodecylguanidinium acetate (28.7 g, 100.0 mmol) and sodium hydroxide (6.0 g, 150.0 mmol) was heated under reflux (15 min) in methanol (50 cm^{3}). The methanol was distilled off on a rotary evaporator and the solid residue shaken with water (100 cm^{3}). The solid was filtered off, washed with acetone (50 cm^{3}) and recrystallised from methanol/acetone to yield dodecylguanidine (19.3 g, 85.0%) as a fine white waxy solid, m.p. 92-94 ^{o}C, (Found: C, 68.7; H, 14.5; N, 19.1; M^+ 227.2375. $C_{13}H_{29}N_3$ requires: C, 68.7; H, 12.8;

N, 18.5%; 227.2361); ^{1}H (DMSO-d_6) 0.7-1.4 (23H, br m, $\underline{C_{11}H_{23}}$), 2.9 (2H, br t, $\underline{CH_2}NH$), 4.9 (4H, s, $\underline{NHC(:NH)NH_2}$); ^{13}C (pyridine-d_5), 14.3 (s, $\underline{CH_3}$), 22.9, 27.6, 29.9, 30.6, 32.2 (singlets, $CH_3\underline{(CH_2)_{10}}CH_2$), 42.8 (s, $\underline{CH_2}NH$), 159.5 (s, $NH\underline{C}(:NH)NH_2$); m/z (FAB, %) 228 (M+1, 100), 226 (21.8), 184 (1.7), 170 (1.5), 156 (1.8), 142 (3.0), 100 (4.0).

6.81 PREPARATION OF BROMOMETHYLENEDIMETHYLAMMONIUM BROMIDE

Bromine (19.2 g, 120.0 mmol) was added dropwise (10 min) to triphenylphosphine (31.5 g, 120 mmol) dissolved in dimethylformamide (109 g, 1493 mmol) during which time the temperature rose to 70 ^{o}C. The solution was cooled in ice and the resultant precipitate filtered off. The solid was washed successively with dimethylformamide (20 cm^3) and diethyl ether (2x40 cm^3) and was dried in a vacuum desiccator to yield bromomethylenedimethylammonium bromide (21.0 g, 80.6%) as a fine white crystalline solid, m.p. 150-151 ^{o}C (decomp) (lit. m.p. 151-152 ^{o}C decomp).[70]

6.82 PREPARATION OF S-METHYLISOTHIOURONIUM CHLORIDE

Barium chloride dihydrate (26.5 g, 108.8 mmol) and S-methylisothiouronium sulphate (30.3 g, 108.8 mmol) were each dissolved in water (150 cm^3) and the solutions combined and heated at 80 ^{o}C (5 min). The insoluble barium sulphate was filtered off and the water was distilled from the filtrate on a rotary evaporator. The solid so formed was recrystallised from water-acetone, washed with acetone (2x50 cm^3) and dried in a vacuum oven at 60 ^{o}C (2 h) to yield S-methylisothiouronium chloride (25.6 g, 93%) as a fine white crystalline solid m.p. 121-123 ^{o}C, (Found: Cl, 27.8. Calc. for $C_2H_7ClN_2S$: Cl, 28.0%).

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APPENDIX

X-RAY CRYSTALLOGRAPHIC DATA FOR 1-GUANIDINOPROPANEPHOSPHONIC ACID

TABLE 1 Fractional atomic coordinates and thermal parameters ($Å^2$)

Atom	x	y	z	U_{iso} or U_{eq}
P(1)	0.4504(2)	0.3864(1)	0.5680(3)	0.027(1)
C(1)	0.2352(9)	0.3910(4)	0.3317(11)	0.030(4)
O(1)	0.4461(7)	0.4639(3)	0.6847(9)	0.033(3)
O(2)	0.4678(7)	0.3048(3)	0.6742(8)	0.036(3)
O(3)	0.6180(6)	0.3925(3)	0.5017(8)	0.034(3)
C(2)	0.0568(10)	0.3877(6)	0.3662(13)	0.039(4)
C(3)	-0.1212(13)	0.4018(6)	0.1750(20)	0.059(6)
N(1)	0.2292(8)	0.3255(3)	0.1883(10)	0.031(3)
C(4)	0.2799(9)	0.3337(4)	0.0405(11)	0.028(4)
N(2)	0.3612(9)	0.4047(4)	0.0173(12)	0.039(4)
N(3)	0.2533(11)	0.2734(4)	-0.0928(14)	0.048(4)

TABLE 2 Fractional atomic coordinates for the hydrogen atoms

Atom	x	y	z	U_{iso} ($Å^2$)
H(1o)	0.489(17)	0.448(7)	0.804(18)	0.17(4)
H(1)	0.249(10)	0.445(5)	0.266(11)	0.04(2)
H(2a)	0.067(12)	0.429(6)	0.464(14)	0.06(3)
H(2b)	0.054(11)	0.341(5)	0.427(13)	0.04(3)
H(3a)	-0.117(12)	0.451(6)	0.086(14)	0.07(3)
H(3b)	-0.230(17)	0.409(7)	0.185(18)	0.15(4)
H(3c)	-0.149(16)	0.383(8)	0.010(19)	0.06(4)
H(1n)	0.187(12)	0.289(6)	0.200(15)	0.03(3)
H(2na)	0.392(12)	0.405(6)	-0.084(15)	0.01(3)
H(2nb)	0.419(14)	0.421(6)	0.147(16)	0.07(4)
H(3na)	0.285(10)	0.276(4)	-0.197(12)	0.04(2)
H(3nb)	0.247(14)	0.241(6)	-0.052(17)	0.05(4)

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

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
P(1)	0.028(1)	0.012(1)	0.040(1)	0.001(1)	0.021(1)	-0.001(1)
C(1)	0.029(3)	0.015(3)	0.044(4)	-0.001(4)	0.022(3)	-0.001(3)
O(1)	0.041(3)	0.013(2)	0.046(4)	-0.003(2)	0.028(3)	-0.001(2)
O(2)	0.041(3)	0.012(2)	0.056(4)	0.011(2)	0.031(3)	0.004(2)
O(3)	0.024(2)	0.022(2)	0.055(3)	-0.001(2)	0.026(2)	0.000(2)
C(2)	0.029(4)	0.032(4)	0.055(5)	-0.003(5)	0.026(4)	0.001(4)
C(3)	0.037(5)	0.059(6)	0.081(8)	0.012(6)	0.029(6)	0.015(4)
N(1)	0.034(3)	0.015(3)	0.046(4)	-0.004(3)	0.025(3)	-0.005(2)
C(4)	0.028(4)	0.019(3)	0.038(4)	-0.001(3)	0.017(4)	-0.000(3)
N(2)	0.048(4)	0.024(3)	0.045(4)	-0.005(3)	0.032(4)	-0.012(3)
N(3)	0.057(4)	0.026(4)	0.063(5)	-0.009(4)	0.044(4)	-0.010(3)

TABLE 4 Bond lengths (Å)

P(1)	-C(1)	1.811(6)	P(1)	-O(1)	1.517(6)
P(1)	-O(2)	1.500(5)	C(1)	-C(2)	1.526(13)
C(1)	-N(1)	1.470(10)	C(2)	-C(3)	1.498(11)
N(1)	-C(4)	1.309(12)	C(4)	-N(2)	1.354(10)
C(4)	-N(3)	1.324(11)	P(1)	-O(3)	1.588(5)
C(1)	-H(1)	1.02(8)	O(1)	-H(1o)	.82(9)
C(2)	-H(2a)	.95(9)	C(2)	-H(2b)	.88(9)
C(3)	-H(3a)	1.04(9)	C(3)	-H(3b)	.90(9)
C(3)	-H(3c)	1.17(9)	N(1)	-H(1n)	.70(9)
N(2)	-H(2na)	.88(9)	N(2)	-H(2nb)	.89(9)
N(3)	-H(3na)	.89(9)	N(3)	-H(3nb)	.60(9)

TABLE 5 Bond angles (°)

O(1)	-P(1)	-C(1)	105.2(3)	O(2)	-P(1)	-C(1)	111.4(3)
O(2)	-P(1)	-O(1)	116.6(4)	C(2)	-C(1)	-P(1)	112.3(6)
N(1)	-C(1)	-P(1)	112.1(4)	N(1)	-C(1)	-C(2)	110.2(6)
C(3)	-C(2)	-C(1)	112.9(9)	C(4)	-N(1)	-C(1)	126.0(6)
N(2)	-C(4)	-N(1)	121.1(7)	N(3)	-C(4)	-N(1)	121.7(7)
N(3)	-C(4)	-N(2)	117.2(9)	O(3)	-P(1)	-O(1)	110.2(3)
O(3)	-P(1)	-O(2)	108.1(3)	O(3)	-P(1)	-C(1)	104.9(3)
H(1)	-C(1)	-P(1)	104(3)	H(1)	-C(1)	-C(2)	113(5)
H(1)	-C(1)	-N(1)	105(5)	H(1o)	-O(1)	-P(1)	104(8)
H(2a)	-C(2)	-C(1)	108(6)	H(2a)	-C(2)	-C(3)	109(5)
H(2b)	-C(2)	-C(1)	110(6)	H(2b)	-C(2)	-C(3)	112(5)
H(2b)	-C(2)	-H(2a)	104(9)	H(3a)	-C(3)	-C(2)	115(4)
H(3b)	-C(3)	-C(2)	118(7)	H(3b)	-C(3)	-H(3a)	104(9)
H(3c)	-C(3)	-C(2)	127(6)	H(3c)	-C(3)	-H(3a)	66(8)
H(3c)	-C(3)	-H(3b)	111(9)	H(1n)	-N(1)	-C(1)	113(9)
H(1n)	-N(1)	-C(4)	121(9)	H(2na)	-N(2)	-C(4)	116(6)
H(2nb)	-N(2)	-C(4)	99(7)	H(2nb)	-N(2)	-H(2na)	134(9)
H(3na)	-N(3)	-C(4)	125(5)	H(3nb)	-N(3)	-C(4)	106(1)
H(3nb)	-N(3)	-H(3na)	124(3)				

TABLE 6 Intermolecular distances (Å)

N(2) ...P(1)	3.65	1	0.0	0.0	-1.0
H(3c) ...P(1)	3.38	1	-1.0	0.0	-1.0
H(2na)...P(1)	2.78	1	0.0	0.0	-1.0
H(3na)...P(1)	3.12	1	0.0	0.0	-1.0
P(1) ...P(1)	3.95	-1	1.0	1.0	1.0
O(1) ...P(1)	3.34	-1	1.0	1.0	1.0
H(1n) ...P(1)	3.28	-2	0.0	1.0	0.0
O(3) ...C(1)	2.70	-1	1.0	1.0	1.0
N(2) ...O(1)	2.94	1	0.0	0.0	-1.0
H(2na)...O(1)	2.13	1	0.0	0.0	-1.0
O(3) ...O(1)	2.55	-1	1.0	1.0	1.0
N(2) ...O(1)	2.93	-1	1.0	1.0	1.0
H(1) ...O(1)	2.69	-1	1.0	1.0	1.0
H(2nb)...O(1)	2.22	-1	1.0	1.0	1.0
N(3) ...O(2)	2.91	1	0.0	0.0	-1.0
H(2na)...O(2)	2.64	1	0.0	0.0	-1.0
H(3na)...O(2)	2.09	1	0.0	0.0	-1.0
O(3) ...O(2)	2.50	-1	1.0	1.0	1.0
C(2) ...O(2)	3.34	-2	0.0	1.0	0.0
C(3) ...O(2)	3.40	-2	0.0	1.0	0.0
N(1) ...O(2)	2.90	-2	0.0	1.0	0.0
H(2b) ...O(2)	2.87	-2	0.0	1.0	0.0
H(1n) ...O(2)	2.23	-2	0.0	1.0	0.0
N(1) ...O(3)	3.10	-1	1.0	1.0	1.0

Table 6 continued

C(4) ...O(3)	3.38	-1	1.0	1.0	1.0
N(2) ...O(3)	3.22	-1	1.0	1.0	1.0
H(1o) ...O(3)	2.93	-1	1.0	1.0	1.0
H(1) ...O(3)	2.78	-1	1.0	1.0	1.0
H(2nb)...O(3)	2.41	-1	1.0	1.0	1.0
N(3) ...O(3)	3.06	2	0.0	-1.0	0.0
H(3nb)...O(3)	2.48	2	0.0	-1.0	0.0
H(1o) ...N(2)	2.30	1	0.0	0.0	1.0
H(3b) ...N(2)	2.88	1	-1.0	0.0	0.0
H(1o) ...N(2)	2.72	-1	1.0	1.0	1.0
H(3a) ...N(2)	2.88	-1	0.0	1.0	0.0
H(2b) ...N(3)	2.94	-2	0.0	1.0	1.0

TABLE 7 Intramolecular distances (Å)

O(3)	...P(1)	3.60	C(2)	...P(1)	2.78
N(1)	...P(1)	2.73	H(1o)	...P(1)	1.89
H(1)	...P(1)	2.28	H(2a)	...P(1)	2.84
H(2b)	...P(1)	2.91	H(1n)	...P(1)	3.02
H(2nb)	...P(1)	3.02	O(1)	...C(1)	2.65
O(2)	...C(1)	2.74	C(3)	...C(1)	2.52
C(4)	...C(1)	2.48	N(2)	...C(1)	2.88
H(2a)	...C(1)	2.04	H(2b)	...C(1)	2.01
H(3a)	...C(1)	2.73	H(3c)	...C(1)	2.90
H(1n)	...C(1)	1.86	H(2nb)	...C(1)	2.41
O(2)	...O(1)	2.57	O(3)	...O(1)	2.62
C(2)	...O(1)	3.16	H(1)	...O(1)	2.77
H(2a)	...O(1)	2.75	C(2)	...O(2)	3.30
N(1)	...O(2)	3.22	H(1o)	...O(2)	2.46
H(2b)	...O(2)	3.00	N(1)	...C(2)	2.46
H(1)	...C(2)	2.14	H(3a)	...C(2)	2.16
H(3b)	...C(2)	2.08	H(3c)	...C(2)	2.39
H(1n)	...C(2)	2.48	N(1)	...C(3)	2.97
H(1)	...C(3)	2.76	H(2a)	...C(3)	2.02
H(2b)	...C(3)	2.01	H(1n)	...C(3)	2.97
N(2)	...N(1)	2.32	N(3)	...N(1)	2.30
H(1)	...N(1)	1.99	H(2b)	...N(1)	2.66
H(3c)	...N(1)	2.82	H(2nb)	...N(1)	2.25
H(3nb)	...N(1)	2.27	H(1)	...C(4)	2.52
H(1n)	...C(4)	1.77	H(2na)	...C(4)	1.91

Table 7 continued

H(2nb)...C(4)	1.74	H(3na)...C(4)	1.98
H(3nb)...C(4)	1.60	N(3) ...N(2)	2.28
H(1) ...N(2)	2.43	H(1n) ...N(2)	2.95
H(3na)...N(2)	2.50	H(3nb)...N(2)	2.75
H(1n) ...N(3)	2.42	H(2na)...N(3)	2.37
H(2nb)...N(3)	2.90		

X-RAY CRYSTALOGRAPHIC DATA FOR

3-GUANIDINOPROPANEPHOSPHONIC ACID

TABLE 1 Fractional atomic coordinates and thermal parameters ($Å^2$)

Atom	x	y	z	U_{iso} or U_{eq}
P	0.3799(2)	0.3774(3)	0.4458(2)	0.045(2)
O(1)	0.4320(4)	0.3944(9)	0.5441(5)	0.058(5)
O(2)	0.2877(4)	0.4117(8)	0.4237(5)	0.058(5)
O(3)	0.4147(4)	0.4941(9)	0.3989(5)	0.055(4)
C(1)	0.3916(6)	0.1497(12)	0.4219(7)	0.049(6)
C(2)	0.3463(6)	0.1029(12)	0.3285(7)	0.052(6)
C(3)	0.3618(6)	-0.0889(12)	0.3101(7)	0.049(6)
N(1)	0.3166(5)	-0.1222(10)	0.2204(6)	0.052(5)
C(4)	0.3225(7)	-0.2678(13)	0.1756(9)	0.086(8)
N(2)	0.3742(5)	-0.4045(10)	0.2264(6)	0.058(6)
N(3)	0.2844(6)	-0.2778(12)	0.0910(6)	0.054(6)

TABLE 2 Fractional atomic coordinates for the hydrogen atoms

Atom	x	y	z	U_{iso} (A^2)
H(11)	0.368(1)	0.066(1)	0.457(1)	0.10
H(12)	0.458(1)	0.124(1)	0.443(1)	0.10
H(21)	0.279(1)	0.122(1)	0.307(1)	0.10
H(22)	0.368(1)	0.189(1)	0.293(1)	0.10
H(31)	0.339(1)	-0.177(1)	0.344(1)	0.10
H(32)	0.429(1)	-0.110(1)	0.332(1)	0.10
Hn(1)	0.273(1)	-0.021(1)	0.182(1)	0.10
H(2)	0.289	0.398	0.494	0.10
H(1n2)	0.379	-0.501	0.197	0.10
H(2n2)	0.376	-0.408	0.289	0.10

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

Atom	U_{11}	U_{22}	U_{33}	U_{23}	U_{13}	U_{12}
P	0.036(1)	0.017(1)	0.081(2)	0.001(1)	0.012(1)	0.001(1)
O(1)	0.058(4)	0.034(4)	0.083(5)	0.001(4)	0.027(4)	-0.005(3)
O(2)	0.038(4)	0.025(4)	0.110(6)	-0.001(4)	0.014(4)	0.006(3)
O(3)	0.044(4)	0.026(4)	0.095(6)	0.010(4)	0.015(4)	0.000(3)
C(1)	0.045(6)	0.013(5)	0.090(9)	0.002(5)	0.017(6)	0.009(4)
C(2)	0.047(6)	0.020(5)	0.087(8)	0.002(5)	0.019(6)	0.005(5)
C(3)	0.050(6)	0.016(5)	0.083(8)	-0.001(5)	0.017(6)	0.006(4)
N(1)	0.055(5)	0.018(4)	0.083(7)	-0.007(4)	0.014(5)	0.010(4)
C(4)	0.070(7)	0.030(6)	0.159(12)	0.001(7)	0.045(8)	0.002(5)
N(2)	0.061(6)	0.016(5)	0.097(7)	0.000(4)	0.017(5)	0.013(4)
N(3)	0.056(6)	0.046(6)	0.062(6)	-0.002(5)	0.008(5)	0.004(5)

TABLE 4 Bond lengths (Å)

P	-O(1)	1.539(8)	P	-O(2)	1.519(8)
P	-O(3)	1.509(9)	P	-C(1)	1.811(10)
C(1)	-C(2)	1.495(15)	C(2)	-C(3)	1.541(14)
C(3)	-N(1)	1.419(14)	N(1)	-C(4)	1.382(16)
C(4)	-N(2)	1.402(13)	C(4)	-N(3)	1.317(18)
O(2)	-H(2)	1.211(9)	C(1)	-H(11)	1.080(18)
C(1)	-H(12)	1.080(15)	C(2)	-H(21)	1.080(16)
C(2)	-H(22)	1.080(18)	C(3)	-H(31)	1.080(18)
C(3)	-H(32)	1.080(16)	N(1)	-Hn(1)	1.080(11)
N(2)	-H(1n2)	.921(9)	N(2)	-H(2n2)	1.069(12)

TABLE 5 Bond angles (°)

O(2)	-P	-O(1)	107.7(5)	O(3)	-P	-O(1)	111.4(4)
O(3)	-P	-O(2)	114.4(4)	C(1)	-P	-O(1)	105.2(4)
C(1)	-P	-O(2)	109.0(4)	C(1)	-P	-O(3)	108.7(6)
C(2)	-C(1)	-P	114.5(6)	C(3)	-C(2)	-C(1)	113.0(8)
N(1)	-C(3)	-C(2)	109.3(8)	C(4)	-N(1)	-C(3)	127.8(8)
N(2)	-C(4)	-N(1)	115(1)	N(3)	-C(4)	-N(1)	123.0(9)
N(3)	-C(4)	-N(2)	121(1)				
H(2)	-O(2)	-P	101.2(4)	H(11)	-C(1)	-P	109(1)
H(12)	-C(1)	-P	108.1(8)	H(12)	-C(1)	-H(11)	109(1)
C(2)	-C(1)	-H(11)	108.2(9)	C(2)	-C(1)	-H(12)	107(1)
H(21)	-C(2)	-C(1)	108(1)	H(22)	-C(2)	-C(1)	109(1)
H(22)	-C(2)	-H(21)	109(1)	C(3)	-C(2)	-H(21)	108.9(9)
C(3)	-C(2)	-H(22)	108(1)	H(31)	-C(3)	-C(2)	109(1)
H(32)	-C(3)	-C(2)	109.8(9)	H(32)	-C(3)	-H(31)	109(1)
N(1)	-C(3)	-H(31)	109.0(9)	N(1)	-C(3)	-H(32)	110(1)
Hn(1)	-N(1)	-C(3)	116(1)	C(4)	-N(1)	-Hn(1)	116(1)
H(1n2)	-N(2)	-C(4)	116(1)	H(2n2)	-N(2)	-C(4)	112(1)
H(2n2)	-N(2)	-H(1n2)	125.6(9)				

TABLE 6 Intermolecular distances (Å)

H(2n2)	...P	3.15	1	0.0	-1.0	0.0
O(1)	...P	3.68	-1	1.0	1.0	1.0
O(3)	...P	3.55	-1	1.0	1.0	1.0
N(3)	...P	3.69	-2	0.0	0.0	0.0
Hn(1)	...P	2.84	-1	0.5	0.5	0.5
O(3)	...O(1)	2.57	-1	1.0	1.0	1.0
N(3)	...O(1)	3.19	-2	0.0	0.0	0.0
N(3)	...O(2)	3.10	-2	0.0	0.0	0.0
N(1)	...O(2)	2.84	-1	0.5	0.5	0.5
Hn(1)	...O(2)	1.86	-1	0.5	0.5	0.5
C(4)	...O(2)	3.33	-1	0.5	0.5	0.5
N(3)	...O(2)	3.02	-1	0.5	0.5	0.5
H(31)	...O(3)	2.79	1	0.0	-1.0	0.0
N(2)	...O(3)	2.86	1	0.0	-1.0	0.0
H(2n2)	...O(3)	1.87	1	0.0	-1.0	0.0
Hn(1)	...O(3)	2.97	-1	0.5	0.5	0.5
N(2)	...H(21)	3.00	-1	0.5	-0.5	0.5
N(1)	...H(31)	2.90	-1	0.5	-0.5	0.5
C(4)	...H(31)	2.75	-1	0.5	-0.5	0.5
N(3)	...H(31)	2.89	-1	0.5	-0.5	0.5
H(2)	...N(3)	1.95	-2	0.0	0.0	1,0

TABLE 7 Intramolecular distances (Å)

H(11)	...P	2.39	H(12)	...P	2.38
C(2)	...P	2.79	H(21)	...P	2.98
H(22)	...P	2.94	H(2)	...P	2.12
O(2)	...O(1)	2.47	O(3)	...O(1)	2.52
C(1)	...O(1)	2.67	H(11)	...O(1)	2.88
H(12)	...O(1)	2.87	H(2)	...O(1)	2.27
O(3)	...O(2)	2.54	C(1)	...O(2)	2.72
H(11)	...O(2)	2.92	C(2)	...O(2)	3.29
H(21)	...O(2)	2.95			
C(1)	...O(3)	2.70	H(12)	...O(3)	2.92
C(2)	...O(3)	3.23	H(22)	...O(3)	2.84
H(21)	...C(1)	2.10	H(22)	...C(1)	2.11
C(3)	...C(1)	2.53	H(31)	...C(1)	2.78
H(32)	...C(1)	2.78	C(2)	...H(11)	2.10
C(3)	...H(11)	2.76	C(2)	...H(12)	2.09
C(3)	...H(12)	2.71	H(31)	...C(2)	2.15
H(32)	...C(2)	2.16	N(1)	...C(2)	2.41
Hn(1)	...C(2)	2.46	C(3)	...H(21)	2.15
N(1)	...H(21)	2.65	C(3)	...H(22)	2.14
N(1)	...H(22)	2.64	Hn(1)	...C(3)	2.13
C(4)	...C(3)	2.52	N(2)	...C(3)	2.86
H(2n2)	...C(3)	2.48	N(1)	...H(31)	2.04
C(4)	...H(31)	2.89	N(2)	...H(31)	2.94
N(1)	...H(32)	2.06	C(4)	...H(32)	2.78

Table 7 continued

N(2)	...H(32)	2.77	N(2)	...N(1)	2.35
N(3)	...N(1)	2.37	H(2n2)	...N(1)	2.47
C(4)	...Hn(1)	2.09	N(3)	...Hn(1)	2.58
H(1n2)	...C(4)	1.98	H(2n2)	...C(4)	2.05
N(3)	...N(2)	2.37	H(1n2)	...N(3)	2.50

I

END