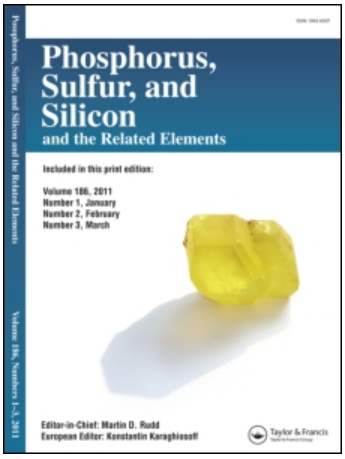

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ORGANOPHOSPHORUS COMPOUNDS AS POTENTIAL FUNGICIDES. PART II.[1] AMINOALKANE-, GUANIDINOALKANE-, AND THIOUREIDOALKANE-PHOSPHONIC ACIDS: PREPARATION, SPECTROSCOPY, AND FUNGICIDAL ACTIVITY

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A range of α-amino-, ω-amino-, α-guanidino-, and ω-guanidinoalkanephosphonic acids has been prepared for the purpose of studying their spectroscopic features and fungicidal activity. In addition, α-thioureido-octanephosphonic acid and thioureylene-1,1-bis(1-octanephosphonic acid) were isolated during the preparation of α-guanidino-octanephosphonic acid. ^{31}P, ^{1}H, and ^{13}C nmr spectral data which were obtained for solutions of the amino- and guanidino-compounds in D_2O or D_2O/D_2SO_4, and for the thioureido compounds in DMSO-d_6, are discussed together with previously reported data for the aminophosphonic types. FAB mass spectrometry generally gives strong pseudomolecular ions $[MH]^+$ for the zwitterionic amino- and guanidino-compounds with relatively simple fragmentations. Fungicidal activity of the α-aminophosphonic acids was found to be greater than for the ω-amino compounds, with maximum activity at a chain length of three carbon atoms when used as a seed dressing for the control of *Drechslera* spp. Moderately good activity was shown by the thioureido compounds against a number of fungal organisms in vitro but the guanidino-compounds exhibited low activity.

Key words: Organophosphorus; fungicides; aminophosphonic acids; guanidinophosphonic acids; NMR spectroscopy; FAB mass spectrometry.

INTRODUCTION

In the course of our investigations into the fungicidal activity of guanidine derivatives,[2] including the *N*-(ω-guanidinoalkyl)aminoalkanephosphonic acids and their aminophosphonic precursors,[1,3] we also carried out a systematic study of the fungicidal activity of simple α- and ω-aminoalkanephosphonic acids and related compounds and found that certain members of the α-amino series had useful potential as agricultural fungicides, particularly as seed-dressing agents for the control of *Drechslera teres* and other pathogens of cereal crops.[4] Detailed studies of the biological and environmental effects of α-aminopropanephosphonic acid (**1**, R = Et) (ampropylfos)[5] have furthermore shown this compound to have extremely low mammalian toxicity (LD_{50} in excess of 5000 mg kg^{-1}) and to have no obviously deleterious effects.[6] In this paper we report our studies on the preparation, spectroscopy, and fungicidal activity of α- and ω-aminoalkanephosphonic acids (**1**, **2**),

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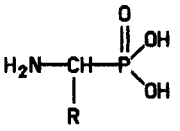

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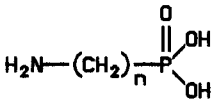

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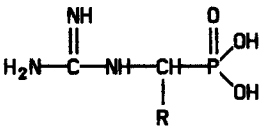

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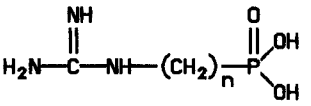

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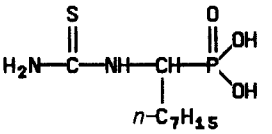

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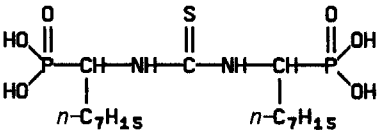

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α- and ω-guanidinoalkanephosphonic acids (**3**, **4**), and some related thioureido derivatives (**5**, **6**).

RESULTS AND DISCUSSION

Preparations of α- and ω-Aminoalkanephosphonic Acids

Numerous methods have been reported for the preparation of α-aminoalkanephosphonic acids (**1**).[7] In our present studies we found it convenient to use the one-pot procedure of Oleksyszyn and Tyka,[8] in which a mixture of triphenyl phosphite, an aldehyde or ketone, and either ethyl or benzyl carbamate is heated under reflux in glacial acetic acid, followed by hydrolysis of the intermediate diphenyl *N*-alkoxycarbonyl-α-aminoalkanephosphonate.[9] The yields obtained by this method are sometimes poor but the procedure is simple and pure products were easily obtainable after recrystallisation.

ω-Aminophosphonic acids (**2**) were obtained by interaction of the appropriate *N*-(ω-halogenoalkyl)phthalimides with triethyl phosphite and hydrolysis of the so-formed ω-phthalimidoalkylphosphonates.[10–12] For the lower members of the series (**2**, n = 1, 2, 3, and 4) the readily available *N*-(ω-bromoalkyl)phthalimides were employed as starting materials. For the preparation of higher members, *N*-(6-chlorohexyl)phthalimide, *N*-(8-bromo-octyl)phthalimide, and *N*-(11-bromoundecyl)phthalimide were first obtained by the interaction of potassium phthalimide with 6-chlorohexanol, 8-chloro-octanol, and 11-bromoundecanol respectively, and subsequent replacement of the ω-hydroxy group by halogen.

Preparations of α- and ω-Guanidinoalkanephosphonic Acids

The α- and ω-guanidinophosphonic acids (**3**, **4**) are less well known than the aminophosphonic acids and are referred to in only a few publications.[13–15] In the α-substituted series, the four homologues that have been reported (**3**, R = Me, Et, Pr, Pr^i)[13] were prepared in low yield by the interaction of triphenyl phosphite with an aldehyde and thiourea in acetic acid/toluene, followed by sequential treatment of the intermediate thioureidophosphonic acid with methyl iodide, ammonia, and acetic acid. We similarly obtained low yields of products (**3**, R = Me, Et, *n*-C_7H_{15}) by this procedure and the final products crystallised slowly. In the case of α-guanidinopropanephosphonic acid (**3**, R = Et), the first product to separate was not the free compound as reported[13] but the mono acetate; the free compound was, however, obtained by recrystallisation from aqueous ethanol to which a few drops of acetone had been added. Separation of ω-guanidino-octylphosphonic acid (**3**, R = *n*-C_7H_{15}) was particularly slow and the final yield that could be obtained in crystalline form amounted to less than 1%. In this case, one cause of the low yield appears to be the increased solubility of the long-chain ureido intermediate in organic solvents; this intermediate therefore remains largely in the organic layer at the stage at which the aqueous layer is separated for further work up. In separate experiments, both 1-thioureido-octanephosphonic acid (**5**) and thioureylene-*N*,*N*′-bis-(1-octanephosphonic acid) (**6**) were isolated in pure form from the organic layer as waxy solids, the latter showing that thiourea had undergone reaction at both nitrogen atoms. Crystallization of the thioureido and thioureylene derivatives was also extremely slow, and the compounds were isolated in only low yields.

Attempts to prepare the α-guanidinoalkanephosphonic acids by reaction of the α-amino compounds with *S*-methylisothiouronium chloride failed, whereas reaction with *S*-ethylisothiouronium bromide has been reported to be successful.[13] Although steric hindrance may be a factor in making reaction at the α-position difficult, the reason for this discrepancy remains uncertain.

The only ω-guanidinoalkanephosphonic acids to have been reported previously are the first three members of the series (**4**, *n* = 1, 2, or 3).[14,15] Analytical data were given only for **4** (*n* = 1) as the monosodium salt dihydrate[14] and for **4** (*n* = 2) as the sesquihydrate[15]; no spectroscopic data were given. In the present studies, the anhydrous ω-guanidinoalkanephosphonic acids (**4**, *n* = 1, 2, 3, 4, 6, 8) were prepared in good yields from the corresponding ω-amino acids by interaction with *S*-methylisothiouronium chloride under alkaline conditions, followed by work up as previously described.[1]

In all cases, products were characterized by ^1H, ^{13}C, and ^{31}P nmr spectroscopy, and by fast-atom bombardment mass spectrometry as discussed below. A preliminary report of these studies has been made elsewhere.[16]

Characterization by NMR Spectroscopy

The nmr spectra of aminophosphonic acids and guanidinophosphonic acids are pH-dependent, chemical shifts and coupling constants varying with the state of protonation of the species under investigation.[17] Nevertheless, for the purposes of structural characterization, the ranges within which chemical shifts and coupling constants can be expected to fall are clear and there are uniform patterns that can

be recognized. In the present studies, either D_2O or D_2O/D_2SO_4 was used as solvent according to the solubility characteristics of the compound studied. ^{31}P and ^{13}C nmr data are given in Tables I and II for the aminophosphonic acids and in Tables III and IV for the guanidino compounds. Data for certain of the aminophosphonic acids have been given previously[17-21] as noted in the footnotes to Tables I and II and are generally in accord with the values that we have found under similar conditions. Small variations that occur may be attributable to the influence of differences in concentration. There are no previous reports of nmr data for the guanidinophosphonic acids.

^1H nmr data for both the amino[22] and guanidino derivatives appear in the experimental section but are less useful than ^{13}C nmr data for the purpose of routine characterization because of their complexity, except for the lower members of the series. Thus, aminomethanephosphonic acid (**2**, $n = 1$) and guanidinomethane phosphonic acid (**4**, $n = 1$) exhibit simple doublets in D_2O at δ_H 3.1 and 3.35 respectively, with coupling constants $^2J_{PH} = 12.2$ Hz for both. In the cases of α-aminoethanephosphonic acid (**1**, R = Me) and α-guanidinoethanephosphonic acid (**3**, R = Me) the terminal methyl groups appear as doublets of doublets at δ_H 1.3–1.5 ppm ($^3J_{HH}$ = 7–8 Hz, $^3J_{PH}$ = 16–17 Hz), whilst the α-CH signal appears as a multiplet due to overlap of the component lines of a doublet of quartets. In the higher alkyl derivatives the β-CH_2 protons are non-equivalent because of the chiral α-carbon atom. Coupling between these protons, phosphorus, and the protons on C_α and C_γ gives rise theoretically, therefore, to a 64-line signal for the β-methylene protons of α-aminopropanephosphonic acid or a 48-line signal for the higher alkyl homologues. In all cases complex multiplets are normally observed. The α-CH proton couples separately to each of the β-CH_2 protons as well as to phosphorus and gives rise to a doublet of doublet of doublets, although overlap may cause the appearance of a seven-line signal.[23]

In the ω-amino and ω-guanidino series the methylene protons adjacent to the terminal amino group give rise to the expected triplet ($^1J_{HCCH}$ = 6–7 Hz) at about 3–3.3 ppm. No significant change occurs on acidification, thus confirming that the compounds exist in the zwitterionic form in D_2O. The α-methylene protons (adjacent to phosphorus) appear as distinct doublets of triplets at δ_H 1.9–1.95 in both 2-aminoethanephosphonic acid and 2-guanidinoethanephosphonic acid, with similar coupling constants for both ($^3J_{HH}$ = ca. 8 and $^2J_{PH}$ = 17–18 Hz). For higher members of the series there is generally extensive overlap of methylene proton signals, including those of the CH_2 group adjacent to phosphorus.

^{31}P nmr chemical shifts for the α-aminoalkanephosphonic acids all lie within the range 13.5–14.5 in D_2O but more downfield to ca. 18 ppm in the presence of an excess of D_2SO_4 as the phosphonic acid group becomes fully protonated. It is important to note that the ^{31}P chemical shift also moves downfield in alkaline conditions, as shown by the values (δ_P 20.9–22.0) reported for solutions of five members of the series (**1**, R = Me, Et, Pr^i, Bu, Pe) in KOH/H_2O.[18] Similar variations have previously been observed for aminomethanephosphonic acid, for which δ_P moves upfield from 14.45 for the fully protonated form, through 11.02 and 9.20 for the first and second deprotonations, and then downfield again to 19.13 as the third deprotonation occurs.[17] This large downfield shift, which accompanies deprotonation of nitrogen, was attributed to a change from a cyclic structure which

TABLE I

^{31}P and ^{13}C nmr data for α-aminoalkanephosphonic acids $(HO)_2P(O)CH(NH_2)R$[a]

R	solvent	δ_P/ppm	δ_C/ppm (J_{PC}/Hz)		
			C(1)	C(2) [b]	C(3)
Me	D_2O	14.1	47.6 (d, 144.9)	16.5 (s)	-
Me	D_2O/D_2SO_4	17.8	47.0 (d, 155.7)	15.7 (s)	-
Et	D_2O	13.9	53.7 (d, 142.9)	24.8 (s)	13.2 (d, 9.4)
Et	D_2O/D_2SO_4	17.9	52.7 (d, 153.7)	24.2 (s)	12.7 (d, 8.8)
Pr^n	D_2O	14.4	51.8 (d, 143.3)	33.3 (s)	21.2 (d, 9.5)[c]
Pr^n	D_2O/D_2SO_4	18.3	50.8 (d, 151.8)	32.5 (s)	21.4 (d, 9.0)[d]
Bu^n	D_2O	14.1	52.3 (d, 142.4)	31.0 (s)	30.6 (d, 9.1)[e]
Bu^n	D_2O/D_2SO_4	18.4	51.1 (d, 151.8)	30.1 (s)	30.0 (d, 8.7)[f]
Pe^n	D_2O/D_2SO_4	17.4	48.5 (d, 152.6)	30.6 (s)	24.8 (d, 8.6)[g]
n-C_6H_{13}	D_2O/D_2SO_4	18.1	50.7 (d, 152.0)	30.3 (s)	27.6 (d, 8.6)[h]
n-C_7H_{15}	D_2O/D_2SO_4	18.2	51.0 (d, 153.2)	30.5 (s)	28.0 (d, 6.7)[i]

[a] ^{31}P and ^{13}C nmr data have been reported elsewhere for saturated solutions of compounds 1 (R = Me, Et, Pr) in D_2O[43,44] and ^{31}P nmr data for compounds 1 (R = Me, Et, Bu, Pe) in KOH/H_2O.[37] [b] Although these signals were recorded as singlets at 80 MHz, a small coupling ($^2J_{PC}$ 0 - 2 Hz) can sometimes be observed at 250 MHz. [c] Also 15.8 (s). [d] Also 15.7 (s). [e] Also singlets at 24.5, 15.9. [f] Also singlets at 24.3, 15.8. [g] Also singlets at 27.7, 21.7, 13.5. [h] Also singlets at 33.2, 30.6, 24.5, 16.0. [i] Also singlets at δ_C 34.0, 31.3, 31.0, 24.8, 16.2.

may exist in solution for the zwitterionic forms of the *N*-protonated molecule, in which intramolecular hydrogen-bonding occurs between hydrogen of the NH_3^+ group and O^- attached to phosphorus. Similar, but smaller downfield shifts in alkaline solution were also observed for the third deprotonations of 2-aminoethyl- and 3-aminopropyl-phosphonic acids (**2**, $n = 2$ and 3, respectively), in which intramolecular hydrogen-bonding of this type was considered to be weaker.[17] Data for the α-guanidinoalkanephosphonic acids (Table III) are given only for solutions in D_2O/D_2SO_4 because of the low solubility of the compounds in water. In each case, the chemical shift is at lower field by 5–8 ppm than for the corresponding amino compounds under similar conditions (Table I).

TABLE II

^{31}P and ^{13}C nmr data for ω-aminoalkanephosphonic acids $(HO)_2P(O)(CH_2)_nNH_2$[a]

n	solvent	δ_P/ppm	δ_C/ppm (J_{PC}/Hz)		
			C(1)	C(2)	C(3)
1	D_2O	11.0	41.3 (d, 141.9)	-	-
1	D_2O/D_2SO_4	15.4	37.6 (d, 149.9)	-	-
2	D_2O	18.8	28.9 (d, 131.6)	38.5 (s)	-
2	D_2O/D_2SO_4	26.5	27.3 (d, 139.0)	37.9 (s)	-
3	D_2O	23.7	27.9 (d, 135.5)	24.4 (d, 4.3)	43.1 (d, 17.7)
3	D_2O/D_2SO_4	31.1	25.8 (d, 137.7)	23.0 (d, 4.7)	42.9 (d, 20.3)
4	D_2O	25.9	30.0 (d, 133.8)	23.0 (d, 4.4)	30.7 (d, 16.9)[b]
4	D_2O/D_2SO_4	34.5	27.5 (d, 135.0)	21.3 (d, 4.7)	29.8 (d, 17.0)[c]
6	D_2O	26.7	30.4 (d, 133.1)	25.5 (d, 4.4)	32.1 (d, 16.2)[d]
6	D_2O/D_2SO_4	33.3	27.2 (d, 132.2)	23.5 (d, 5.3)	31.5 (d, 17.0)[e]
8	D_2O/D_2SO_4	39.0	27.6 (d, 132.2)	23.9 (d, 5.4)	32.0 (d, 17.0)[f]
11	D_2O/D_2SO_4	41.2	27.5 (d, 139.0)	23.8 (d, 6.0)	32.3 (d, 18.1)[g]

[a] Data have also been reported for saturated solutions of compounds 2 (n = 1, 2, 3, and 4) in D_2O[43,44] and for compounds 2 (n = 1, 2, and 3) at a range of acidities (pD) from 2 - 11.[35] [b] Also singlet at 42.0. [c] Also singlet at 42.2. [d] Also singlets at 29.2, 42.3. [e] Also singlets at 29.3, 43.9. [f] Also singlets at 28.1, 29.4, 30.5, 43.4. [g] Also singlets at 28.3, 29.5, 31.3, 43.5 (some signals coinciding).

^{31}P chemical shifts of the ω-aminoalkanephosphonic acids move downfield significantly as the chain length increases, varying (in D_2O) from 11.0 for aminomethanephosphonic acid (**2**, n = 1) to 26.7 ppm for ω-aminohexanephosphonic acid (**2**, n = 6) (Table II). Acidification by an excess of D_2SO_4 caused a downfield shift of 4.4 ppm for aminomethanephosphonic acid and of ca. 7–9 ppm for higher homologues (**2**, n = 2–6). For ω-amino-octyl- and ω-aminoundecyl-phosphonic acids, which are sufficiently soluble only in the presence of D_2SO_4, the chemical shifts are still further downfield at 39.0 and 41.2 ppm respectively. This continuing decrease in phosphorus shielding as the chain length increases is in accord with a gradual decrease in the extent of intramolecular hydrogen-bonding as the amino and phosphonic groups become further separated[17] and suggests that some residual interaction still occurs up to a chain length of C_{11} at least.

TABLE III

^{31}P and ^{13}C nmr data for α-guanidinoalkanephosphonic acids $(HO)_2P(O)CHRNHC(:NH)NH_2$

R	solvent	δ_P/ppm	δ_C/ppm (J_{PC}/Hz)			
			C(1)	C(2)	C(3)	
Me	D_2O/D_2SO_4	23.1	48.2 (d, 158.1)	17.3 (s)	-	[a]
Et	D_2O/D_2SO_4	22.8	54.1 (d, 158.1)	25.1 (s)	12.7 (d, 13.3)	[b]
n-C_7H_{15}	D_2O/D_2SO_4	26.1	52.3 (d, 160.5)	30.5 (s)	27.5 (d, 13.4)	[c]

[a] δ_C 159.6 [d, NHC(:NH)NH_2, $^3J_{PCNC}$ 4.4 Hz]. [b] δ_C 159.9 [d, NHC(:NH)NH_2, $^3J_{PCNC}$ 3.7 Hz]. [c] δ_C 159.5 [d, NHC(:NH)NH_2, $^3J_{PCNC}$ 4.4 Hz]. Also singlets at 24.4, 30.9, 31.0, 16.1.

The ^{13}C nmr spectra of the α-amino-, ω-amino-, α-guanidino-, and ω-guanidinoalkanephosphonic acids all exhibit one-bond coupling to phosphorus within the range $^1J_{PC}$ 130–155 Hz, small coupling (not always observable) to the β-carbon atom ($^2J_{PC}$ 0–6 Hz), and a larger three-bond coupling to the γ-position of $^3J_{PC}$ = 9–13 Hz for the α-substituted compounds and 16–20 Hz for the ω-series. The remaining carbon atoms of the alkyl chain appear as singlets. In all cases, acidification generally gives rise to a small upfield shift of the ^{13}C nmr signal for the α-carbon atom of between 1 and 3 ppm, with a corresponding increase in the one-bond coupling constant of ca. 10 Hz for the α-aminophosphonic acids. (The solubility of the α-guanidinophosphonic acids in D_2O was too small for measurements to be made in the absence of acid). The increase in coupling ($^1J_{PC}$) for the α-carbon atom on acidification of the ω-amino- and ω-guanidinophosphonic acids becomes less as the chain length (and hence the distance of the amino or guanidino group from the phosphonate group) increases, falling from 8.0 and 4.7 Hz, respectively, for the C_1 compounds to 1.2 and 1.7 for the C_4 compounds, a result which is in accord with decreasing intramolecular interaction between the phosphonate and amino- or guanidino-groups as the chain length increases. In the ω-substituted series, small increases in shielding and in phosphorus-carbon coupling are seen for C_2 [$\Delta(\delta_C)$ = 0.6–2.0 ppm); $\Delta(J_{PC})$ 0–1.1 Hz] and for C_3 [$\Delta(\delta_C)$ = 0.2–0.9 ppm); $\Delta(J_{PC})$ 0.1–2.7 Hz], on acidification. Acidification has no significant effect on the chemical shifts of the carbon atoms adjacent to the amino or guanidino groups in longer chain compounds, as would be expected for zwitterionic structures. The guanidinium carbon atoms in both the α- and ω-guanidinoalkanephosphonic acids show characteristic signals at δ_C 160 ± 0.5 ppm in all cases. For the α-guanidino compounds (**3**, R = Me, Et, n-C_7H_{15}; **4**, n = 1), three-bond coupling $^3J_{PC}$ of ca. 4–5 Hz is observed.

The α-thioureido derivatives (**5** and **6**) are only soluble in organic solvents and are presumably not zwitterionic. ^{31}P and ^{13}C nmr data are given in Table V. For solutions in DMSO-d_6, the ^{13}C nmr chemical shifts for atoms of the carbon chain are not significantly different from those for corresponding carbon atoms of α-

TABLE IV

^{31}P and ^{13}C nmr data for ω-guanidinoalkanephosphonic acids $(HO)_2P(O)(CH_2)_nNHC(:NH)NH_2$

n	solvent	δ_P/ppm	δ_C/ppm (J_{PC}/Hz)			
			C(1)	C(2)	C(3)	
1	D_2O	14.2	42.6 (d, 145.2)	-	-	[a]
1	D_2O/D_2SO_4	19.0	41.2 (d, 149.9)	-	-	[b]
2	D_2O	20.6	30.4 (d, 131.6)	39.8 (s)	-	[c]
2	D_2O/D_2SO_4	28.8	29.1 (d, 136.3)	39.1 (s)	-	[d]
3	D_2O	24.7	27.7 (d, 134.3)	25.7 (d, 4.1)	44.6 (d, 17.0)	[e]
3	D_2O/D_2SO_4	38.6	25.6 (d, 137.0)	24.1 (d, 4.1)	44.2 (d, 19.7)	[f]
4	D_2O	25.7	30.1 (d, 133.3)	23.2 (d, 4.4)	31.9 (d, 16.2)	[g]
4	D_2O/D_2SO_4	35.2	27.9 (d, 135.0)	21.7 (d, 4.7)	31.3 (d, 16.3)	[h]
6	D_2O	27.1[i]	30.5 (d, 133.1)	25.7 (d, 4.3)	32.4 (d, 16.5)	[j]
8	D_2O/D_2SO_4	39.3	27.7 (d, 132.9)	23.9 (d, 5.4)	32.0 (d, 17.0)	[k]

[a] δ_C 160.6 [d, $NH\underline{C}(:NH)NH_2$, $^3J_{PCNC}$ 5.5 Hz]. [b] δ_C 160.2 [d, $NH\underline{C}(:NH)NH_2$, $^3J_{PCNC}$ 4.1 Hz]. [c] δ_C 159.6 [s, $NH\underline{C}(:NH)NH_2$]. [d] δ_C 160.2 [s, $NH\underline{C}(:NH)NH_2$]. [e] δ_C 159.8 [s, $NH\underline{C}(:NH)NH_2$]. [f] δ_C 159.6 [s, $NH\underline{C}(:NH)NH_2$]. [g] δ_C 159.9 [s, $NH\underline{C}(:NH)NH_2$]; also 43.7 (s, $\underline{C}H_2NH$). [h] δ_C 159.9 [s, $NH\underline{C}(:NH)NH_2$]; also 43.8 (s, $\underline{C}H_2NH$). [i] δ_P 33.2 (D_2O/D_2SO_4). [j] δ_C 159.8 [s, $NH\underline{C}(:NH)NH_2$]; also 28.1 (s), 30.5 (s), 00.0 (s, $\underline{C}H_2NH$). [k] δ_C 159.5 [s, $NH\underline{C}(:NH)NH_2$]; also 28.5 (s), 30.5 (s), 44.4 (s, $\underline{C}H_2NH$).

guanidino-octanephosphonic acid (**3**, R = *n*-C_7H_{15}) in D_2O/D_2SO_4, although the phosphorus-carbon coupling constants ($^1J_{PC}$ = ca. 151 and $^3J_{PC}$ = ca. 12 Hz) are a little smaller. The chemical shift for the carbon atom of the thioureido group (δ_C ca. 184 ppm) is, however, at a characteristically lower field than for the guanidino analogue whilst the coupling to phosphorus ($^3J_{PCNC}$ ca. 8 Hz) is greater.

Characterization by Fast-Atom Bombardment Mass Spectrometry

We have previously reported the use of fast-atom bombardment mass spectrometry (FAB ms) for the characterization of selected examples of amino- and guanidinophosphonic acids,[16,24,25] and we showed, using a glycerol matrix, that strong pseudomolecular ions MH^+ were obtained in all cases. Further data are now given in Tables VI–IX, some obtained by the use of a primary beam of xenon atoms

TABLE V

^{31}P and ^{13}C nmr data for α-thioureido-octanephosphonic acids (**5** and **6**)

Compound	solvent	δ_P/ppm	δ_C/ppm (J_{PC}/Hz)		
			C(1)	C(2)	C(3)
5	DMSO-d_6	(21.0)[a]	51.5 (d, 151.5)	30.4 (s)	25.2 (d, 11.0)[b]
6	DMSO-d_6	20.5	51.4 (d, 150.7)	30.6 (s)	25.4 (d, 12.5)[c]

[a] ^{31}P chemical shift determined in CD_3OD. [b] δ_C 183.8 [d, $NH\underline{C}(:S)NH_2$, $^3J_{PCNC}$ 8.8 Hz]. Also singlets at 31.2, 29.0, 22.0, 13.9. [c] δ_C 184.0 [d, $NH\underline{C}(:S)NH_2$, $^3J_{PCNC}$ 7.0 Hz]. Also singlets at 31.2, 29.0, 28.9, 22.1, 13.8.

and others (where indicated) by the LSIMS technique using Cs^+ ion bombardment. Similar results were obtained by both methods. Apart from the pseudomolecular ion, higher aggregates $[MH + G]^+$, $[2M + H]^+$, and $[MH + 2G]^+$ (where G = glycerol) were generally detected, sometimes with relatively high intensity. The principal fragment ions arise by the elimination of either HPO_3 or H_3PO_3, although intensities may vary considerably. In addition, there is some evidence for the elimination of ammonia (from the aminophosphonic acids) or of guanidine or cyanamide from the guanidino compounds. Fragment ions $[MH - 57]^+$ which are also sometimes detected in the spectra of the guanidino compounds, may possibly be formed by the elimination of a neutral fragment CH_3N_3 (e.g. 3-imino-1,2-diazacyclopropane) as discussed previously for the ω-guanidinoalkylaminoalkanephosphonic acids.[1] Our observations do not accord with an earlier report that poor spectra are obtained from polar amino compounds in a glycerol matrix and that aminomethanephosphonic acid (**2**, $n = 1$) gives no pseudomolecular ion unless derivatized.[26] We obtained a strong MH^+ ion as the base peak for the latter compound as shown (Table VII).

α-Thioureido-octanephosphonic acid (**5**) gave a pseudomolecular ion $[MH]^+$ at *m/z* 269 with a relative intensity of 43% but the corresponding ion for the bisphosphonic acid (**6**) was weak (relative intensity 6%). There is evidence for the loss of sulphur to give ions at $[MH - 32]^+$ [*m/z* 237 (46%) for **5** and *m/z* 429 (3%) for **6**] and the additional loss of H_3PO_3 from compound **5** to give an ion, *m/z* 155 (16%). For both compounds the base peak, *m/z* 128, is most reasonably assigned to $[CH_3(CH_2)_6\,CH{=}NH_2]^+$, formed by cleavage of the P—C and N—C(S) bonds with proton transfer.

Fungicidal Activity

Aminophosphonic acids and related compounds have attracted widespread interest on account of their potential as biologically active compounds.[27–31] In the agrochemical field, particular interest has centered on their activity as plant growth

TABLE VI

Principal ions in the FAB mass spectra of α-aminoalkanephosphonic acids (**1**)[a]

R	$[MH + 2G]^+$	$[2M + H]^+$	$[MH + G]^+$	$[MH]^+$	$[MH - HPO_3]^+$	$[MH - H_3PO_3]^+$	
Me	310/14	251/7	218/89	126/100	46/5	44/63	[b]
Et	324/8	279/16	232/36	140/75	60/12.5	58/100	
Pr^n	-	307/11	-	154/100	-	-	[c]
Bu^n	-	335/40	260/27	168/100	-	-	[c]
n-C_7H_{15}	-	419/12	302/1	210/20	130/35	128/100	[d]

[a] G = glycerol. [b] Also *m/z* 109/1 ($[MH - NH_3]^+$) [c] Using Cs^+ ion source. [d] Also *m/z* 193/1 ($[MH - NH_3]^+$).

TABLE VII

Principal ions in the FAB mass spectra of ω-aminoalkanephosphonic acids (**2**)[a]

n	$[MH + 2G]^+$	$[2M + H]^+$	$[MH + G]^+$	$[MH]^+$	$[MH - HPO_3]^+$	$[MH - H_3PO_3]^+$	
1	296/8	223/2	204/48	112/100	32/3	30/27	[b]
2	310/8	251/5	218/35	126/100	-	-	
3	324/7	279/4	232/23	140/100	-	-	[c]
4	338/2	307/14	246/13	154/100	74/3	72/2	[d]
6	366/2	363/8	274/9	182/100	102/54	100/15	[e]
8	-	419/2	302/7	210/100	130/11	128/3	
11	-	-	-	252/100	172/5	170/9	

[a] G ◻ glycerol. [b] Also *m/z* 95/18 ($[MH - NH_3]^+$). [c] Also *m/z* 123/12 ($[MH - NH_3]^+$). [d] Also *m/z* 137/16 ($[MH - NH_3]^+$). [e] Also *m/z* 165/3 ($[MH - NH_3]^+$).

regulators (e.g. aminomethanephosphonic acid)[32] or herbicides[33] such as glyphosate (*N*-phosphonomethylglycine),[34] glufosinate (phosphinothricin),[35] and bilanafos (phosphinothricyl-*L*-alanyl-*L*-alanine).[36] Whilst the latter compound (an aminophosphinic derivative)[37] also shows fungicidal activity against *Botrytis cinerea*[38] and against *Piricularia oryzae* and *Rhizoctonia solani* on rice,[39] and diethyl 2-aminoethylphosphonate has been shown to be active against a range of fungi and other microbial organisms,[40] it is only more recently that the possible application of free aminophosphonic acids as agricultural fungicides has been investigated. We first showed the potential of simple unsubstituted α-aminoalkanephosphonic acids as

TABLE VIII

Principal ions in the FAB mass spectra of α-guanidinoalkanephosphonic acids (**3**)[a]

R	$[MH + 2G]^+$	$[2M + H]^+$	$[MH + G]^+$	$[MH]^+$	$[MH - HPO_3]^+$	$[MH - H_3PO_3]^+$	
Me	-	-	260/13	168/100	88/3	86/8	[b]
Et	-	-	274/1	182/100	102/5	100/30	[c]
n-C_7H_{15}	-	503/8	344/3	252/100	172/37	170/33	

[a] G ◻ glycerol. [b] Also *m/z* 126/1 ($[MH - CNNH_2]^+$), 107/1 ($[MH - NHC(NH_2)_2]^+$). [c] Also *m/z* 125/2 ($[MH - CH_3N_3]^+$). [d] 193/1 ($[MH - NHC(NH_2)_2]^+$).

TABLE IX

Principal ions in the FAB mass spectra of ω-guanidinoalkanephosphonic acids (**4**)[a]

n	$[MH + 2G]^+$	$[2M + H]^+$	$[MH + G]^+$	$[MH]^+$	$[MH - HPO_3]^+$	$[MH - H_3PO_3]^+$	
1	338/3	307/6	246/13	154/100	-	72/6	[b]
2	352/2	335/19	260/8	168/100	-	-	[c]
3		363/3	274/4	182/100	102/3	100/6	[d]
4	-	391/3	288/7	196/100	116/6	114/5	[e]
6	408/1	447/3	316/3	224/100	144/17	142/16	[f]
8	-	-	342/1	252/100	172/25	170/35	[g]

[a] G ◻ glycerol. [b] Also *m/z* 137/11 ($[MH - NH_3]^+$). [c] Also *m/z* 151/5 ($[MH - NH_3]^+$); 109/3 ($[MH - NHC(NH_2)_2]^+$). [d] Also *m/z* 140/2 ($[MH - CNNH_2]^+$); 125/3 ($[MH - CH_3N_3]^+$); 123/2 ($[MH - NHC(NH_2)_2]^+$). [e] Also *m/z* 154/2 ($[MH - CNNH_2]^+$); *m/z* 139/7 ($[MH - CH_3N_3]^+$); *m/z* 137/9 ($[MH - NHC(NH_2)_2]^+$). [f] Also *m/z* 207/4($[MH - NH_3]^+$); 182/4 ($[MH - CNNH_2]^+$); 167/17 ($[MH - CH_3N_3]^+$); 165/8 ($[MH - NHC(NH_2)_2]^+$). [g] *m/z* 210/7 ($[MH - CNNH_2]^+$).

agricultural fungicides, particularly as seed-dressing agents for the control of *Drechslera* spp. and other pathogens of cereal crops.[4] When tested in vitro at 500 ppm, the α-aminoalkanephosphonic acids (**1**, R = Me, Et, Pr^n, Bu^n, n-C_7H_{15}) all gave between 75 and 100% control of *Drechslera sativa* or *Drechslera teres*. When used as a seed dressing agent in field trials (2 cm^3 of 20% solution per kg of seed), α-aminopropanephosphonic acid (**1**, R = Et) gave 99–100% control of *Drechslera teres* and *Drechslera avenae*, 96–99% control of *Drechslera graminea*, 95–96%

control of *Ustilago avenae*, and about 70–80% control of *Septoria nodorum*, *Ustilago hordei*, and *Tilletia caries*. A comparison of the effectiveness of various aminophosphonic acids as seed dressing agents against *Drechslera teres* was obtained by the so-called "osmos" test in which infected seeds are treated with a solution of the test compound and are then incubated on filter papers moistened with buffered sugar solution as described.[4(a)] Results of this test (Tables X and XI), show that the α-amino compounds are significantly more active than the ω-amino types, but that maximum activity occurs at a chain length of three carbon atoms in both cases. Branched-chain compounds are considerably less active than the straight chain isomers (Table XII). The mode of action of the aminophosphonic acids is as yet unknown but it is of interest to note that the (*R*)- and (*S*)-isomers of α-aminopropanephosphonic acid (**1**, R = Et) have similar levels of activity.

A number of 1-amino-2-arylethylphosphonic acids have recently been shown to be active against *Botrytis* spp. and other fungal organisms,[41,42] with the *p*-fluoro-substituted derivative giving 100% control of *Fusarium nivale* when used as a seed dressing at 600 ppm.[41] Fungicidal activity has also been reported for some 1-aminobenzylphosphonic esters and for 1-amino-*p*-fluoro-benzylphosphonous acid.[43]

TABLE X

Fungicidal activity of α-aminophosphonic acids (**1**)[a]

R =	H	Me	Et	Pr^n	Bu^n	Pe^n	$n\text{-}C_7H_{15}$
activity (%)	21	52	91	87	82	67	12

[a] Tested as seed dressing agent at 0.4 g/kg of seed against *Drechslera teres*.

TABLE XI

Fungicidal activity of ω-aminophosphonic acids (**2**)[a]

n =	1	2	3	4
activity (%)	21	54	64	32

[a] Tested as seed dressing agent at 0.4 g/kg of seed against *Drechslera teres*.

TABLE XII

Fungicidal activity of branched-chain α-aminophosphonic acids $(HO)_2P(O)CR^1R^2NH_2$[a]

R^1 =	H	Me	Me	Et	$-(CH_2)_5-$
R^2 =	Pr^i	Me	Pr^i	Et	
activity (%)	65	23	6	21	24

[a] Compounds supplied by KenoGard AB and tested as seed dressing agents at 0.4 g/kg of seed against *Drechslera teres*.

The guanidinophosphonic acids of both the α- (**3**) and ω-substituted series (**4**) showed only low activity (<25% inhibition) when tested in vitro at 300 or 500 ppm against *Piricularia oryzae*, *Rhizoctonia solani*, *Botrytis cinerea*, and *Septoria nodorum*. α-Thioureido-octanephosphonic acid (**5**) and thioureylene-*N*,*N*′-bis-(1-octanephosphonic acid) (**6**) were more active, each giving 51–75% inhibition of *Piricularia oryzae* and *Botrytis cinerea*, and 76–99% inhibition of *Septoria nodorum*, at 500 ppm in vitro. The bisphosphonic derivative (**6**) also gave 76–99% control of *Rhizoctonia solani* under these conditions.

EXPERIMENTAL

Starting Materials

Starting materials were obtained commercially, except for the longer-chain *N*-(ω-halogenoalkyl)phthalimides which were prepared by the interaction of 6-chlorohexan-1-ol, 8-chloro-octan-1-ol, or 11-bromoundecan-1-ol with phthalimide in dimethylformamide at 100–130°C, isolation of the so-formed *N*-(ω-hydroxyalkyl)phthalimide, and replacement of hydroxyl by halogen using thionyl chloride to give 6-chlorohexylphthalimide, or bromomethylenedimethylammonium bromide[44] in acetonitrile to give 8-bromoctyl- or 11-bromoundecyl-phthalimide.[45]

Spectroscopy

^{1}H nmr spectra were recorded on a Perkin-Elmer R12B instrument (60 MHz), whilst ^{13}C and ^{31}P nmr spectra were obtained using a Bruker WP-80 instrument operating at 20.12 and 32.395 MHz respectively. Measurements were made in D_2O or in D_2O/D_2SO_4 (excess acid, pH ca. 1). Chemical shifts (downfield positive are relative to sodium 3-trimethylsilylpropionate (for ^{1}H and ^{13}C spectra) and to 85% phosphoric acid for ^{31}P spectra. Fast-atom bombardment mass spectra were obtained using a glycerol matrix on (a) a VG Micromass ZAB-1F instrument, with a primary beam of xenon atoms operating at 8 kV, and (b) a Kratos Profile mass spectrometer equipped with LSIMS ionization, using a Cs^+ ion source and operating at 10 kV.

Preparations of α-Aminoalkanephosphonic Acids

Preparations were carried out as described,[8] by heating a mixture of the appropriate aldehyde with triphenyl phosphite and either ethyl carbamate (Method A) or benzyl carbamate (Method B) in glacial acetic acid, followed by hydrolysis with concentrated hydrochloric acid and liberation of the free aminophosphonic acid by treatment with propylene oxide.[46] Products were recrystallised from aqueous ethanol and dried in vacuo at 60–70°C to give the following.

α-Aminoethanephosphonic acid (**1**, R = Me) (3.4 g, 44.5% by method A), m.p. 273–275°C (lit.[8] m.p. 272–274°C) (Found: C, 19.3; H, 6.4; N, 11.2. Calc. for $C_2H_8NO_3P$: C, 19.2; H, 6.4; N, 11.2%), δ_H (D_2O) 1.27 (dd, 3H, CH_3, $^3J_{HH}$ 7.8, $^3J_{PH}$ 16.2 Hz), 2.9–3.65 (m, 1H, PCH).

α-Aminopropanephosphonic acid (**1**, R = Et) (4.2 g, 31.5% by method A), m.p. 263–265°C (lit.[8] m.p. 264–266°C) (Found: C, 26.1; H, 7.3; N, 9.9. Calc. for $C_3H_{10}NO_3P$: C, 25.9; H, 7.2; N, 10.1%), δ_H (D_2O) 1.12 (t, 3H, CH_3, $^3J_{HH}$ 7.5 Hz), 1.33–2.25 (m, 2H, CH_2), 2.7–3.3 (m, 1H, PCH).

α-Aminobutanephosphonic acid (**1**, R = Pr^n) (1.1 g, 19% by method A), m.p. 258–260°C (lit.[47] m.p. 263–265°C) (Found: C, 32.7; H, 8.0; N, 9.4. Calc. for $C_4H_{12}NO_3P$: C, 31.4; H, 7.9; N, 9.2%), δ_H (D_2O) 0.96 (t, 3H, CH_3, $^3J_{HH}$ 6.6 Hz), 1.25–2.0 [m, 4H, $(CH_2)_2$], 3.25–3.62 (m, 1H, PCH).

α-Aminopentanephosphonic acid (**1**, R = Bu^n) (1.2 g, 20% by method A), m.p. 268–270°C (lit.[8] m.p. 267–269°C) (Found: C, 36.0; H, 8.2; N, 8.4. Calc. for $C_5H_{14}NO_3P$: C, 35.9; H, 8.4; N, 8.4%), δ_H (D_2O) 0.90 (t, 3H, CH_3, $^3J_{HH}$ 6.4 Hz), 1.25–2.25 [m, 6H, $(CH_2)_3$], 3.1–3.4 (m, 1H, PCH).

α-Aminohexanephosphonic acid (**1**, R = *n*-C_5H_{11}) (2.7 g, 41% by method B), m.p. 260–261°C (lit.[48] 274–277°C) (Found: C, 38.4; H, 8.8; N, 8.7. Calc. for $C_6H_{16}NO_3P$: C, 39.9; H, 8.8; N, 7.7%), δ_H (D_2O/D_2SO_4) 0.88 (3H, t, CH_3, $^3J_{HH}$ 7.0 Hz), 1.37 (6H, br m, CH_2 groups), 1.63–2.20 (2H, br m, $C\underline{H}_2CHP$), 3.42–3.80 (1H, m, PCH).

α-Amino-octanephosphonic acid (**1**, R = *n*-C_7H_{15}) (0.5 g, 5.2% by method A), m.p. 269–270°C (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%), δ_H (D_2O/D_2SO_4) 0.85 (3H, t, CH_3, $^3J_{HH}$ 5.6 Hz), 1.30 (10H, br m, CH_2 groups), 1.62–2.12 (2H, br m, $C\underline{H}_2CH$), 3.20–3.53 (1H, m, PCH).

Preparations of ω-Aminoalkanephosphonic Acids

Preparations were carried out by a described procedure[10–12] by the interaction of triethyl phosphite and the corresponding *N*-(ω-bromoalkyl)phthalimide, followed by hydrolysis with concentrated hydrochloric acid. Products were isolated and recrystallized as described for the α-amino acids, to give the following.

Aminomethanephosphonic acid (**2**, n = 1) (6.1 g, 67.6%), m.p. 328°C (lit.[49] 325–330°C) (Found: C, 10.1; H, 5.1; N, 12.6. Calc. for CH_6NO_3P: C, 10.8; H, 5.4; N, 12.6%), δ_H (D_2O) 3.1 (d, $^2J_{PH}$ 12.2 Hz).

2-Aminoethanephosphonic acid (**2**, n = 2) (6.7 g, 55.1%), m.p. 272–273°C (lit.[50] 274–276°C) (Found: C, 19.3; H, 6.4; N, 11.2. Calc. for $C_2H_8NO_3P$: C, 19.2; H, 6.4; N, 11.2%), δ_H (D_2O) 1.95 (dt, 2H, PCH_2, $^2J_{PH}$ 17.8, $^3J_{HH}$ 8.0 Hz), 3.0–3.3 (m, 2H, $C\underline{H}_2NH_2$).

3-Aminopropanephosphonic acid (**2**, n = 3) (6.6 g, 49.5%), m.p. 278°C (lit.[51] 274°C) (Found: C, 25.9; H, 7.0; N, 10.5. Calc. for $C_3H_{10}NO_3P$: C, 25.9; H, 7.2; N, 10.1%), δ_H (D_2O) 1.5–2.0 (br m, 4H, PCH_2CH_2), 3.08 (2H, t, $C\underline{H}_2NH_2$, $^3J_{HCCH}$ 6.3 Hz).

4-Aminobutanephosphonic acid (**2**, n = 4) (3.7 g, 68.2%), m.p. 275°C (lit.[11] 133–134°C) (Found: C, 30.1; H, 7.8; N, 9.0. Calc. for $C_4H_{12}NO_3P$: C, 31.4; H, 7.8; N, 9.1%), δ_H (D_2O) 1.66 [br m, 6H, $P(CH_2)_3$], 3.0 (br t, 2H, $C\underline{H}_2NH_2$).

6-Aminohexanephosphonic acid (**2**, n = 6) (2.6 g, 27.1%), m.p. 274°C (Found: C, 39.4; H, 8.6; N, 7.9. $C_6H_{16}NO_3P$ requires: C, 39.8; H, 8.8; N, 7.7%), δ_H (D_2O) 1.2–2.1 [10H, br m, $(C\underline{H}_2)_5P$], 2.95 (2H, t, $C\underline{H}_2NH$, $^3J_{HH}$ 6.0 Hz).

8-Amino-octanephosphonic acid (**2**, n = 8) (2.8 g, 56.6%), m.p. 254–255°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%), δ_H (D_2O/D_2SO_4) 1.03–2.23 [14H, br m, $(CH_2)_7P$], 3.06 (2H, t, $C\underline{H}_2NH_2$, $^3J_{HH}$ 7.1 Hz).

11-Aminoundecanephosphonic acid (**2**, n = 11) (4.4 g, 60.7%), m.p. 256°C, δ_H (D_2O/D_2SO_4) 1.08–2.22 [20H, br m, $(CH_2)_{10}P$], 3.05 (2H, t, $C\underline{H}_2NH_2$, $^3J_{HH}$ 6.6).

Preparations of α-Guanidinoalkanephosphonic Acids

α-Guanidinoethanephosphonic acid (**3**, R = Me). By a described procedure,[13] thiourea (15.2 g, 200 mmol), triphenyl phosphite (62.0 g, 200 mmol), ethanal (8.8 g, 200 mmol), iodomethane (12.5 cm^3), and methanolic ammonia gave a product which, after acidification with glacial acetic acid, evaporation, and storage at 4°C, yielded white crystals which were filtered off, washed with methanol, and dried in vacuo (60°C) to give α-guanidinoethanephosphonic acid (5.7 g, 17%), m.p. 285–286°C (lit.[13] m.p. 286–287°C) (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%), δ_H (D_2O/D_2SO_4) 1.49 (3H, dd, CH_3, $^3J_{PH}$ 17.1, $^3J_{HH}$ 7.3 Hz), 4.01 (1H, dq, α-CH, $^3J_{HH}$ 7.1 Hz).

α-Guanidinopropanephosphonic acid (**3**, R = Et). A similar preparation to the above, using propanal (1.6 g, 200 mmol) in place of ethanal, gave α-guanidinopropanephosphonic acid acetate as fine white crystals (6.0 g, 12.5%), m.p. 289°C (Found: C, 29.4; H, 6.5; N, 17.6; P, 12.8. $C_6H_{16}N_3O_5P$ requires: C, 29.9; H, 6.6; N, 17.4; P, 12.8%); the free product was obtained by addition of a few drops of acetone to a solution of the acetate (6.3 g) in the minimum of hot aqueous methanol (1:1) and allowing the mixture to stand at 4°C. After several days the crystals which separated were filtered off, washed with methanol, and dried in vacuo (60°C) to give fine white crystals of α-guanidinopropanephosphonic acid (4.1 g, 86.7%), m.p. 303°C (lit.[13] 296–298°C) (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%), δ_H (D_2O/D_2SO_4) 1.03 (3H, t, CH_3, $^3J_{HH}$ 7.3 Hz), 1.66 (1H, m, β-CH_A), 1.98 (1H, m, β-CH_B), 3.80 (1H, m, α-CH).

α-Guanidino-octanephosphonic acid (**3**, R = n-C_7H_{15}). In a further similar experiment, thiourea (15.2 g, 200 mmol), triphenyl phosphite (62.0 g, 200 mmol), octanal (25.6 g, 200 mmol), iodomethane (12.5 cm^3), and methanolic ammonia gave a product which, after acidification with glacial acetic acid, evaporation, and long storage at 4°C, gave a small crop of white crystals; the latter were filtered off, washed with methanol and dried in vacuo at 60°C to give α-guanidino-octanephosphonic acid (0.21 g, 0.4%), m.p. 314°C (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%), δ_H (D_2O/D_2SO_4) 0.84 (3H, br t, CH_3, $^3J_{HH}$ 4.9 Hz), 1.0–2.3 (12H, br m, $CH_3(C\underline{H}_2)_6$), 3.8 (m, α-CH).

Preparation of ω-Guanidinoalkanephosphonic Acids

Guanidinomethanephosphonic acid (**4**, n = 1). Aminomethanephosphonic acid (3.0 g, 27 mmol), *S*-methylisothiouronium chloride (6.8 g, 54.1 mmol), and potassium hydroxide (6.1 g, 108 mmol) were dissolved in water (14 cm^3) and heated at 60°C (4h) whilst methanethiol which was evolved was trapped

in aqueous potassium permanganate. The mixture was acidified (pH 2) by the addition of concentrated hydrochloric acid and volatile materials were removed on a rotary evaporator. The residue was dissolved in methanol (100 cm^3), potassium chloride (6.7 g, 83.1%) was filtered off, and propylene oxide was added to precipitate the crude product. Recrystallization from aqueous methanol gave white crystals which were washed with methanol and dried in vacuo at 70°C to give guanidinomethanephosphonic acid (2.9 g, 70.1%), 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%), δ_H (D_2O) 3.35 (d, α-CH_2, $^2J_{PH}$ 12.2 Hz).

Similar procedures gave the following:

2-Guanidinoethanephosphonic acid (**4**, n = 2) from 2-aminoethanephosphonic acid (4.0 g), as white crystals (2.6 g, 48.6%), m.p. 228–229°C (lit.[15] m.p. 228°C) (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%), δ_H (D_2O) 1.90 (2H, overlapping dt, α-CH_2, $^3J_{HH}$ 7.8 Hz, $^2J_{PH}$ 17.1 Hz), 3.2–3.7 (2H, m, $C\underline{H}_2NH$).

3-Guanidinopropanephosphonic acid (**4**, n = 3) from 3-aminopropanephosphonic acid (2.2 g), as white crystals (2.3 g, 80.3%), m.p. 278°C (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%), δ_H (D_2O) 1.54–1.94 (4H, m, $PC\underline{H}_2C\underline{H}_2$), 3.28 (2H, t, $C\underline{H}_2N$, $^3J_{HCCH}$ 6.6 Hz).

4-Guanidinobutanephosphonic acid (**4**, n = 4) from 4-aminobutanephosphonic acid (2.1 g) as white crystals (1.8 g, 67.3%), m.p. 265–266°C (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%), δ_H (D_2O/D_2SO_4) 1.34–2.20 [6H, m, $P(CH_2)_3$], 3.21 (2H, t, CH_2N, $^3J_{HCCH}$ 6.1 Hz).

6-Guanidinohexanephosphonic acid (**4**, n = 6) from 6-aminohexanephosphonic acid (1.0 g) as white crystals (0.7 g, 56.8%), m.p. 280–282°C (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%), δ_H (D_2O) 1.1–1.7 [10H, br m, $P(CH_2)_5$], 3.2 (2H, t, CH_2N, $^3J_{HCCH}$ 6.3 Hz).

8-Guanidino-octanephosphonic acid (**4**, n = 8) from 8-amino-octanephosphonic acid (2.0 g) as white crystals (1.8 g, 75.0%), 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%), δ_H (D_2O/D_2SO_4) 1.03–2.23 (14H, br m, $P(CH_2)_7$), 3.15 (2H, t, CH_2N, $^3J_{HCCH}$ 6.3 Hz).

Isolation of Thioureido Derivatives

1-Thioureido-octanephosphonic acid (**5**). Thiourea (15.2 g, 200 mmol), triphenyl phosphite (62.0 g, 200 mmol), glacial acetic acid (2 cm^3), and toluene (30 cm^3) were heated at 80°C; octanal (25.6 g, 200 mmol) was added (0.5 h), and the mixture was heated under reflux (0.25 h). Water (15 cm^3) and acetonitrile (20 cm^3) were added and the mixture was heated again under reflux (2 h). After the further addition of water (50 cm^3) the mixture was allowed to cool. The organic layer was then separated and the volatile components were removed under reduced pressure to leave a viscous oil (ca. 90 g). The combined products (ca. 540 g) of five similar experiments were dissolved in the minimum of diethyl ether and the precipitate which slowly formed was filtered off, washed with diethyl ether, and recrystallised from diethyl ether to yield 1-thioureido-octanephosphonic acid (10.2 g, 3.2%) as a waxy solid, m.p. 166–168°C (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%), δ_P (CD_3OD) 21.0; δ_H (DMSO-d_6) 0.86 (3H, t, CH_3, $^3J_{HH}$ 5.4 Hz), 1.0–2.1 [12H, br m, $(CH_2)_6$], 4.5 (1H, br m, α-CH), 7.1 (2H, br s, NH_2, exch. with D_2O), 7.6 (1H, d, NH, $^3J_{PCNH}$ 9.3 Hz, exch. with D_2O), 9.7 [2H, br s, $(HO)_2P$]; δ_C (DMSO-d_6) 13.9 (s, CH_3), 22.0 (s), 25.2 (d, $PCHCH_2\underline{C}H_2$, $^3J_{PC}$ 11.0 Hz), 29.0 (s), 30.4 (s), 31.2 (s), 51.5 (d, α-C, $^1J_{PC}$ 151.5 Hz), 183.8 (d, $NH\underline{C}(:S)NH_2$, $^3J_{PCNC}$ 8.8 Hz); FAB ms: *m/z* (%) 269 (MH^+, 43), 237 (46), 155 (16), 128 (100).

Thioureylene-N,N'-bis(1-octanephosphonic acid) (**6**). In a similar experiment to the above, the viscous oil (ca 90 g) was heated further under reduced pressure to remove phenol (40 g) and to leave a clear yellow oil. The products of five such experiments were combined and dissolved in acetone (500 cm^3). After several weeks at room temperature, the precipitate which formed was filtered off, washed with diethyl ether, recrystallised from water, washed with acetone, and dried in vacuo at 60°C to give thioureylene-N,N'-bis(1-octanephosphonic acid) (4.4 g, 0.8%) as a fine waxy solid, m.p. 263°C (Found: C, 44.1; H, 8.6; P, 12.6; S, 6.7. $C_{17}H_{38}N_2O_6P_2S$ requires: C, 44.3; H, 8.3; P, 13.5; S, 7.0%), δ_P (DMSO-d_6) 20.5; δ_H (DMSO-d_6) 0.85 (6H, br t, CH_3, $^3J_{HH}$ 4.5 Hz), 1.0–2.2 (24H, br m, $PCH(C\underline{H}_2)_6$), 4.6 (2H, br m, α-CH), 7.0 (4H, br m, $(\underline{H}O)_2P$, exchanged with D_2O), 8.0 (2H, d, PCHN$\underline{H}$, $^3J_{PCNH}$ 10 Hz, exchanged with D_2O); δ_C (DMSO-d_6) 13.8 (s, CH_3), 22.1 (s), 25.4 (d, $PCHCH_2\underline{C}H_2$, $^3J_{PC}$ 12.5 Hz), 28.9, 29.0, 30.6, 31.2 (singlets), 51.4 (d, α-CH_2 $^1J_{PC}$ 150.7 Hz), 184.0 (t, $NH\underline{C}(:S)NH$, $^3J_{PC}$ 7.0 Hz); FAB ms: *m/z* (%) 461 (MH^+, 6), 429 (3), 128 (100).

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