1-Aminoalkylphosphonous Acids. Part 1. Isosteres of the Protein Amino Acids

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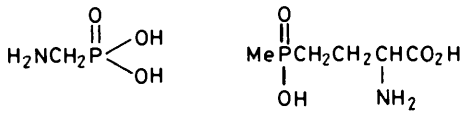
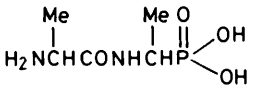
The synthesis of 1-aminoalkylphosphonous acids, isosteres of the protein amino acids, by addition of hypophosphorous acid to diphenylmethylimines is described. These analogues of glycine, alanine, valine, leucine, isoleucine, phenylalanine, tyrosine, tryptophan, serine, threonine, methionine, cysteine, cystine, glutamic acid, lysine, ornithine, arginine, and proline have been prepared and the analogues of alanine, valine, leucine, phenylalanine, and methionine resolved. Tha alanine, valine and methionine analogues have interesting antimicrobial activity and the alanine analogue has plant growth inhibiting properties. Oxidation of the appropriate 1-aminoalkylphosphonous acids gave the 1-aminoalkylphosphonic acid analogues of (±)-alanine, (−)-alanine, (±)-valine, (−)-valine, (±)-serine, (±)-threonine, (±)-lysine, (−)-leucine, and (±)-ornithine.

The study of phosphorus analogues of the natural α-amino acids, begun in the 1940's by Chavane,[1] has accelerated in the past 10 years, not least due to the finding of molecules with useful biological activity. For example, the glycine analogue (**1**) is a plant growth regulant,[2] the naturally occurring glutamic acid analogue (**2**) is a herbicide[3] and the dipeptide analogue (**3**) is an antibacterial agent which inhibits bacterial cell wall biosynthesis.[4]



(**1**)

(**2**)



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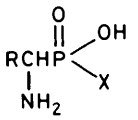

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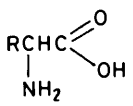

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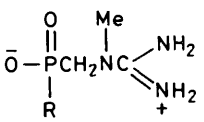

R = H, OH, OMe

(**6**)

Scheme 1.

The family of 1-aminoalkylphosphonic acids (**4**; X = OH) has been most studied and to date analogues of all but two of the common protein amino acids, threonine and histidine, have been described. Thus phosphonic analogues (first synthesis given) of glycine,[1] alanine,[5] valine,[6] leucine,[7] isoleucine,[8] phenylalanine,[5] proline,[9] serine,[10] tyrosine,[11] cystine,[12] cysteine,[13] methionine,[14] tryptophan,[15] lysine,[16] arginine,[17] aspartic acid (α-PO_3H_2,[18] β-PO_3H_2,[19] and α,β-di PO_3H_2[20]) and glutamic acid (α-PO_3H_2,[21] γ-PO_3H_2[22] and α,γ-di PO_3H_2[20]) are known. Recently the first naturally occurring 1-aminoalkylphosphonic acid, the tyrosine analogue, was isolated in the form of two tripeptides from *Actinomyces* K26 and *Actinomadura spiculosospora*.[23]

The isolation of phosphinothrycin (**2**)[24] and discovery of its herbicidal properties[3] led to an increased activity in the study of methylphosphinic acid analogues[25] and those of glycine,[26] alanine,[27] valine,[27] leucine,[28] proline,[29] aspartic,[18] and glutamic acid[24] have been reported.

A simple comparison of the possible 1-aminoalkylphosphorus acid types (**4**) with their carboxylic analogues (**5**) suggested that the closest parallel in properties would be obtained when the phosphorus acid was monobasic and the 'extra' ligand X was as small as possible and led us to consider the 1-aminoalkylphosphonous acids (**4**; X = H) as a potentially interesting family of amino acid isosteres, which could act as false substrates and so interfere with biological mechanisms. We were encouraged by the results of Rowley, Greenleaf and Kenyon[30] who had shown that of the three phosphorous analogues of creatine (**6**) the phosphonous acid (**6**; R = H) was by far the best substrate for the enzyme creatine kinase.

At the outset of our work only one 1-aminoalkylphosphonous acid, the glycine analogue, was described in the literature, prepared by the ammonolysis of chloromethylphosphonous acid.[31] Subsequently, Russian authors[32] have described in a brief note the synthesis of the 1-aminoalkylphosphonous acid analogues of alanine, valine, methionine, and glutamic acid by the addition of hypophosphorous acid to the corresponding oximes, the intermediate hydroxyamino acids presumably being reduced by excess of hypophosphorous acid. Very recently Japanese workers reported the isolation of two aminoalkylphosphonous acids from *Streptomyces* species.[33]

Results and Discussion

Synthesis.—Many methods for the synthesis of 1-aminoalkylphosphonic acids involve addition of phosphorous acid or its esters to imines[34] followed by removal of a labile group from nitrogen, *e.g.* benzyl removed by hydrogenolysis. Early work by Schmidt[35] had demonstrated the addition of hypophosphorous acid to imines to give *N*-substituted 1-aminoalkylphosphonous acids. Addition of hypophosphorous acid to benzylimines readily gave the 1-benzylaminoalkylphos-

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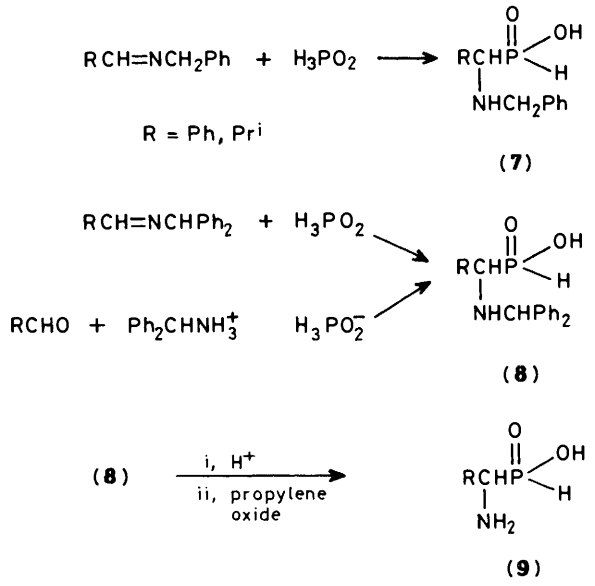
phonous acids (**7**), but all attempts to hydrogenolyse (**7**) failed because of catalyst poisoning by the phosphonous acid, and under more drastic conditions with higher catalyst loadings carbon–phosphorus bond cleavage occurred.



Scheme 2.

Needing instead an acid-labile protecting group we turned to diphenylmethylimines. Addition of 100% hypophosphorous acid to diphenylmethylimines in ethanol (method A) gave the diphenylmethylaminoalkylphosphonous acids (**8**). Alternatively, reaction of the diphenylmethylamine salt of hypophosphorous acid with aldehydes in refluxing ethanol (method B) or preferably dioxane (method C) gave the same product.

Requirements for larger quantities of the alanine analogue (**9b**) led us to investigate the reaction of diphenylmethylamine hypophosphite with acetaldehyde in more detail and we found a maximum yield of the intermediate (**8b**) was formed in aqueous solution in the presence of 1 mol equivalent of hydrochloric acid (method D). Similarly, maximum yields of the intermediates (**8l**) and (**8i**) were obtained in ethanol with 0.6 mol equivalents of hydrochloric acid (method E). By analogy with the work of Redmore[36] on imines and orthophosphorous acid, the role of acid could be to suppress a competing reduction of the imine by hypophosphite anion. The results are summarised in Table 1.

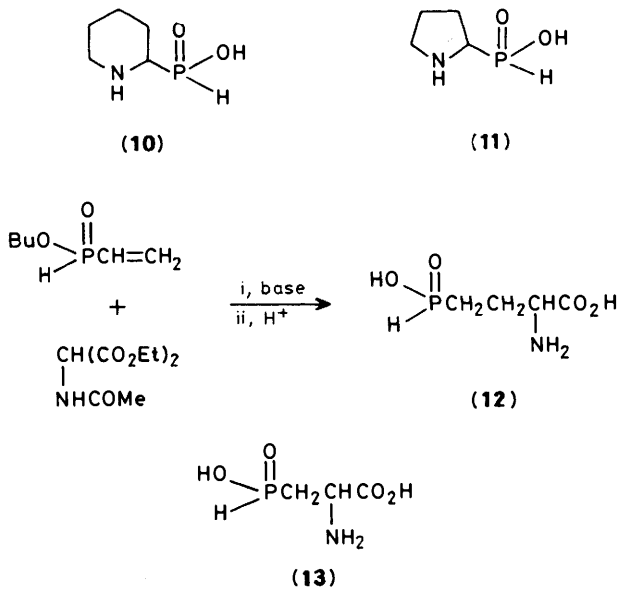
Cleavage of the diphenylmethyl group was achieved under a variety of conditions, *e.g.* 49% HBr, 100 °C, 45—120 min (method F); 18% HCl, reflux, 120—240 min (method G); trifluoroacetic acid–anisole, reflux, 60 min (method H). Esters and ethers were cleaved concurrently during treatment with HBr, *e.g.* products (**9g**), (**9i**), (**9j**), (**9l**) and (**9m**). HBr cleavage of alcohols (**8p**) and (**8q**) led to clean replacement of the OH group by Br to give (**9p**) and (**9r**). For (**8n**) and (**8o**) the phthalimido group was cleaved with hydrazine prior to acid hydrolysis. The free 1-aminoalkylphosphonous acids were obtained by treatment of their hydrobromides or hydrochlorides with propylene oxide in ethanol, or by refluxing their trifluoroacetates in ethanol. The 1-aminoalkylphosphonous acids obtained are summarised in Table 2.

Attempts to convert the bromo acid (**9r**) with ammonia into the lysine analogue (**9n**) resulted in a clean cyclisation to give the pipecolic acid analogue (**10**), and on treatment with base in a two-phase system (**9p**) was converted in 74% yield into the proline analogue (**11**). Reaction of the ornithine analogue (**9o**) with *S*-ethylisothiourea hydrobromide at pH 10 and room temperature gave the arginine analogue (**9t**).

Table 1. Synthesis of 1-diphenylmethylaminophosphonous acids (**8**).

Compd.	R	Method (Yield %)	M.p. (°C)
(**8a**)	H	C[a](10)	242—243
(**8b**)	Me	A(0), B(0), C(44), D(91)	235
(**8c**)	Me_2CH	B(66)	186
(**8d**)	Me_2CHCH_2	A(51), B(88)	215—218
(**8e**)	$MeCH_2CHMe$	A(69)	175
(**8f**)	$PhCH_2$	C(26)	211
(**8g**)	*p*-$MeO\text{-}C_6H_4CH_2$	C(26)	199—202
(**8h**)	Indol-3-ylmethyl	C[b](22)	222—224
(**8i**)	$PhCH_2OCH_2$	C(10), E(48)	212—214
(**8j**)	$MeCH(OCH_2Ph)$	C(10), E(40)	164—166
(**8k**)	$MeSCH_2CH_2$	C(21)	207—208
(**8l**)	$PhCH_2SCH_2$	E(42)	217—219
(**8m**)	$MeOOCCH_2CH_2$	C(50)	162—164
(**8n**)	$PhthalylNCH_2CH_2CH_2CH_2$	C(35)	134—135
(**8o**)	$PhthalylNCH_2CH_2CH_2$	C(45)	120
(**8p**)	$HOCH_2CH_2CH_2$	C(42)	155
(**8q**)	$HOCH_2CH_2CH_2CH_2$	C(42)	188—190

[a] The imine trimer 1,3,5-tris(diphenylmethyl)hexahydro-*s*-triazine was treated with hypophosphorous acid under the conditions of method C. It was prepared from formalin and diphenylmethylamine at 85 °C using a catalytic amount of potassium hydroxide. The solid which formed on admixture was crystallised from toluene, and had m.p. 252 °C. [b] Indol-3-ylpyruvic acid (*Chem. Abstr.*, 1960, 13146c) was used in place of the aldehyde, decarboxylation presumably occurring at the imine stage.



Scheme 3.

The isomeric glutamic acid analogue (**12**) was prepared by Michael addition of diethyl acetamidomalonate to butyl vinylphosphonite followed by hydrolysis. The phosphonous acid (**12**) has recently been isolated along with the aspartic acid analogue (**13**) from *Streptomyces hygroscopicus*[33] and has been shown to be an intermediate in the biosynthesis of phosphinothrycin (**2**).

Table 2. Synthesis of 1-aminoalkylphosphonous acids (**9**).

Compd.	R′	Analogue of	Method (Yield %)	M.p. (°C) (decomp.)
(**9a**)	H	Glycine	F(60)	254—236
(**9b**)	Me	Alanine	G(75)	223—224[d]
(**9c**)	Me_2CH	Valine	F(90)	201—202[d]
(**9d**)	Me_2CHCH_2	Leucine	F(95)	222—223
(**9e**)	$MeCH_2CHMe$	Isoleucine	F(92)	203
(**9f**)	$PhCH_2$	Phenylalanine	F(84)	227—228
(**9g**)	p-$HOC_6H_4CH_2$	Tyrosine	F(50)	235
(**9h**)	Indoyl-3-ylmethyl	Tryptophan	H(25)	253—254
(**9i**)	$HOCH_2$	Serine	G(92)	210
(**9j**)	MeCH(OH)	Threonine	G(61)	218—220
(**9k**)	$MeSCH_2CH_2$	Methionine	F(61)	231[d]
(**9l**)	$HSCH_2$	Cysteine	G(73)	203—204
(**9m**)	$HOOCCH_2CH_2$	Glutamic acid	F(58)[a]	154[d]
(**9n**)	$H_2NCH_2CH_2CH_2CH_2$	Lysine	I(50)	217
(**9o**)	$H_2NCH_2CH_2CH_2$	Ornithine	I(50)	170
(**9p**)	$BrCH_2CH_2CH_2$		F(61)	128—130
(**9q**)	$HOCH_2CH_2CH_2CH_2$		H(60)	216—217
(**9r**)	$BrCH_2CH_2CH_2CH_2$		F(66)[b]	171—174
(**9s**)	$H_2NCH(PO_2H_2)CH_2SSCH_2$	Cystine	(100)[c]	218—220
(**9t**)	$NH(NH_2)=NH(CH_2)_3$	Arginine	(26)[e]	119

[a] After reaction with HBr and evaporation of the aqueous phase the oily residue was stirred with neat propylene oxide until free of bromide ions. Cold ethanol was then added and the mixture stirred a further hour before filtration. [b] From (**8q**). [c] Evaporation of an ammoniacal solution of (**9l**) in air gave (**9s**). [d] Literature metlting points[32] are (**9b**) 208—213 °C, (**9c**) 205—210 °C, (**9k**) 201—204 °C, (**9m**) 165—168 °C. [e] From (**9o**), see Experimental section.

Physical Properties.—The 1-aminoalkylphosphonous acids are white, microcrystalline solids with melting points generally above 200 °C, the exceptions being (**9m**), (**9o**), (**9p**), and (**9r**) which can undergo thermal ring-closure reactions below 200 °C. All decompose at their melting point with a characteristic phosphine odour (disproportionation[37]). The acids are very soluble in water [(**9f**), (**9g**), (**9h**), and (**9s**) less so] and in dilute NaOH. In their behaviour on t.l.c. the 1-aminoalkylphosphonous acids closely follow the pattern of the 1-aminoalkylcarboxylic acids both in R_F values and colour response to ninhydrin. The R_F values for a typical solvent system are compared in Figure.

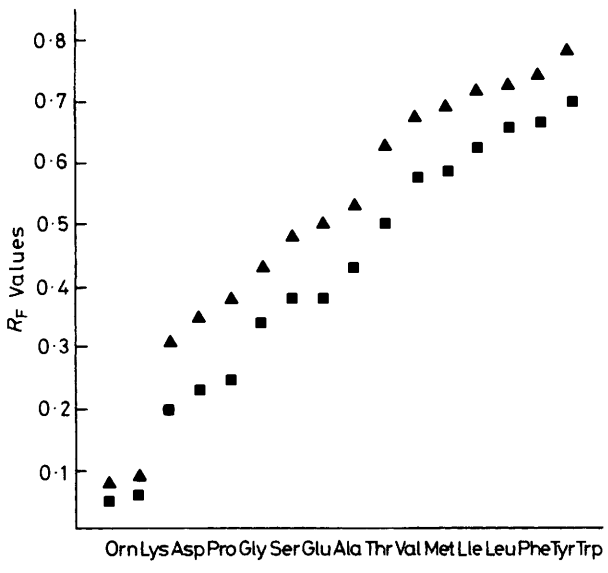


Figure. R_F values of 1-aminoalkyl acids ▲ and 1-aminoalkylphosphonous acids ■ on silica plates with acetic acid, water, acetone, isopropyl alcohol (2:5:7.5:5.5).

Table 3. Ionisation constants and isoelectric points of valine and its phosphonous and phosphonic analogues.

Acid	pK_1	pK_2	pK_3	pI
Valine	2.28	9.36	—	5.82
$Me_2CHCH(NH_2)PH(OH)O$	1.19	7.79	—	4.49
$Me_2CHCH(NH_2)P(OH)_2O$	1.23	5.68	10.46	3.46

Determination of the pK values of valine and its phosphonous and phosphonic analogues by potentiometric titration at 22 ± 1 °C (for method of calculation see ref. 38) gave the results shown in Table 3. The phosphonous acid is a slightly stronger acid which is expected from literature comparisons of phosphonous and phosphonic acids.[39] From its pK_2 value it is clear that the phosphonic acid is doubly ionised at physiological pH (7.4).

Spectra.—The main i.r. absorptions of the 1-aminoalkylphosphonous acids are given in Table 6. Characteristic frequencies are 2 300—2 400 (sharp, medium, P–H), 1 150—1 200br, s (P=O), and 1 000—1 100br, s cm^{-1} (P–O).

The ^{31}P and ^1H n.m.r. spectra are detailed in Table 4. The typical ^{31}P chemical shift lies between 14 and 22 p.p.m. with a P–H coupling constant of 530—546 Hz and can be assigned to the zwitterionic form $^+H_3NCHRPO_2H^-$. On addition of NaOD the free amine $NH_2CHRPO_2H^-$ is formed and the signal shifts 10—12 p.p.m. to lower field and the coupling constant decreases by *ca.* 40 Hz [*e.g.* (**9c**), δ 18.6 and J 540 in D_2O, δ 31.2 and J 501 in NaOD]. Similar downfield shifts were observed in the pH dependent ^{31}P chemical shifts of bis(amino methyl)phosphinic acid.[40] The diaminoalkylphosphonous acids (**9n**) and (**9o**) also have δ ≈ 30 and J_{PH} ≈ 500, indicating that the zwitterionic form is $^+NH_3(CH_2)_nCH(NH_2)PO_2H^-$. The structure of the ornithine analogue (**9t**) rests on its ^{31}P chemical shift (35.14 p.p.m.) and P–H coupling constant (504 Hz) which are very similar to those of its precursor (**9o**) (31.7 p.p.m. and 500 Hz). Further, in the ^{13}C n.m.r. spectrum (see

Table 4. N.m.r. data for 1-aminoalkylphosphonous acids (**9**), (**10**), and (**11**).

	^{31}P-N.m.r. (D_2O)		^{1}H N.m.r. (D_2O)				
Compd.	δ_P	J_{PH}	δ_{PH}	J_{PH-CH_α}	δ_{CH_α}	J_{P-CH_α}	Other
(**9a**)	14.2	546	7.25 (dt)	2	3.1 (dd)	11.5	
(**9b**)	22.2	538	7.1 (dd)	2	2.9—3.6 (m)	10.5	1.5 (3 H, dd, *J* 8, 17 Hz, CH_3)
(**9c**)	18.6[a]	540	7.1 (dd)	1.6	2.7—3.2 (m)	12	1.18, 1.2 (6 H, 2 d, *J* 6.8 Hz, CH_3), 1.8—2.7 (1 H, m, CH)
(**9d**)	21.6	532	7.0 (dd)	1.9	2.8—3.6 (m)		0.98, 1.0 (6 H, 2 d, *J* 6 Hz, CH_3), 1.2—2.2 (3 H, m, CH_2CH)
(**9e**)	18.5, 18.8[b]	534	7.15 (dm)				0.8—3.3 (10 H, br, $CH_3CH_2CHCH_3$)
(**9f**)	19.2[c]	543	7.0 (d)				2.3—3.4 (3 H, m, CH_2CH), 7.45 (5 H, s, PhH)
(**9g**)	31.8	507	6.9 (d)				2.0—3.3 (3 H, m, PCH_2CH), 6.9 (4 H, A_2B_2 aromatic)
(**9h**)	32.0[d]	507	7.1 (d)				2.9—3.8 (3 H, m, CH_2CH), 6.9—8.1 (5 H, m, ArH and NHCH=C)
(**9i**)	15.9	540	7.2 (dd)	1.5	3.1—3.6 (m)		3.6—4.4 (2 H, m, CH_2OH)
(**9j**)	14.8, 16.5[b]	543	7.07,7.15(2d)	2	2.8—3.5 (m)		1.35 (3 H, d, *J* 7 Hz, CH_3), 3.5—4.5 (1 H, m, CHOH)
(**9k**)	19.5	540	7.05 (dd)	1.8	3.0—3.6 (m)		1.6—2.3 (5 H, m, CH_3S and CH_2CH), 2.4—3.0 (2 H, m, CH_2S)
(**9l**)	18.1	541	7.05 (d)				2.7—3.5 (3 H, m, CH_2CH)
(**9m**)	18.8	537	7.0 (d)		3.2 (dd)	11	1.6—2.4 (2 H, m, CH_2CH), 2.7 (2 H, t, CH_2CO_2H)
(**9n**)	32.5	504	6.8 (d)				1.1—2.1 (6 H, br, $CHCH_2CH_2CH$), 2.3—3.4 (3 H, br, CH_2 NH_2 and CH)
(**9o**)	31.7	500	6.8 (d)				1.1—2.2 (4 H, br, CH_2CH_2CH), 2.3—3.3 (3 H, br, CH_2NH_2 and CH)
(**9p**)	19.2	536	7.05 (dd)	1.6			1.5—2.5 (4 H, br, CH_2CH_2CH), 2.7—3.8 (3 H, br, CH_2Br and CH)
(**9q**)	20.5	532	7.03 (dd)	1.8	3.0—3.6 (br)		1.5—2.5 (6 H, br, $CH_2CH_2CH_2CH$), 3.6 (2 H, t, CH_2OH)
(**9r**)	19.6	530	7.00 (dd)	1.8	3.3—3.6 (br)		1.5—2.3 (6 H, br, $CH_2CH_2CH_2CH$), 2.8—3.3 (2 H, br, CH_2Br
(**9s**)	29.3, 29.4[b]	516	6.7 (d)				2.1—3.2 (6 H, m, SCH_2CH
(**9t**)	35.14	504	6.85 (d)		2.3—2.7 (br)		1.3—2.2 (4 H, br), 3.0—3.5 (2 H, br)
(**10**)	19.0	533	6.85 (dd)	2			1.2—3.6 (9 H, br)
(**11**)	19.2	538	7.07 (dd)	2			1.6—2.5 (4 H, m, CH_2CH_2CH), 2.8—3.8 (3 H, m, CH_2NH and CH)

[a] In NaOD, δ 31.2, J_{PH} 501. [b] Diastereoisomeric mixtures. [c] In NaOD, δ 31.7, J_{PH} 513; in DCl δ 24.8, J_{PH} 574. [d] NaOD.

Experimental section) C-1 has almost identical chemical shifts and C–P coupling constants in both (**9o**) and (**9t**). In (**9t**) the guanidine C shows as a singlet at δ 159.58 p.p.m. If reaction had occurred at the 1-amino group a P–C–N–C coupling of *ca.* 4 Hz would be expected.[41]

In aminoalkylphosphonous acids with a second asymmetric centre the diastereoisomers are clearly seen as separate ^{31}P signals [(**9e**), (**9j**), and (**9s**)].

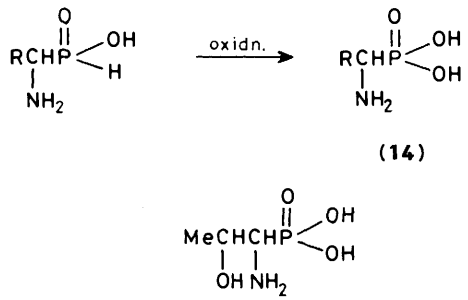
In the ^{1}H n.m.r. spectra the P–H proton appears as a large doublet (J_{PH} 500—550 Hz) centred on 6.7—7.3 p.p.m. and in some cases a H–P–C–H coupling of 1.5—2 Hz is visible. H_α Lies between 2.7 and 3.6 p.p.m. with a P–C–H coupling of 10.5—12 Hz. In (**9b**) the P–C–C–H coupling constant is 17 Hz.

Resolution.—The acids (**9b**), (**9c**), (**9d**), (**9f**), and (**9k**) were resolved by recrystallisation of the (+)- and (−)-α-methylbenzylamine salts of their *N*-benzyloxycarbonyl derivatives to constant melting point and specific rotation. The specific rotations of the resolved 1-aminoalkylphosphonous acids were:

(**9b**) (alanine analogue) $[\alpha]_D^{20}$ +7.0, −6.4 (2% in H_2O)
(**9c**) (valine analogue) $[\alpha]_D^{20}$ +3.5, −3.6 (1.5% in H_2O)
(**9d**) (leucine analogue) $[\alpha]_D^{22}$ −23 (1% in H_2O)
(**9f**) (phenylalanine analogue) $[\alpha]_D^{22}$ −62° (1% in H_2O)
(**9k**) (methionine analogue) $[\alpha]_D^{22}$ +30, −31 (1% in H_2O)

The optical purity of the antipodes of (**9c**) was found to be >99.5% (see Experimental section).

Oxidation to 1-Aminoalkylphosphonic Acids.—Oxidation of the 1-aminoalkylphosphonous acids with, *e.g.* mercuric chloride or bromine water, proved an efficient synthesis of the corresponding 1-aminoalkylphosphonic acids (**14**). The known phosphonic acid analogues of (±)-alanine, (−)-alanine, (±)-valine, (−)-valine, (−)-leucine, (±)-serine, (±)-ornithine, (±)-lysine were prepared in high purity and yield as well as the



(**14**)

(**15**)

Scheme 4.

phosphonic analogue of threonine (**15**), reported here for the first time. Since (−)-1-aminoethylphosphonic acid is known to have the absolute configuration *R*,[42] this allows the assignment of the *R*(-) configuration to 1-aminoethylphosphonous acid (**9b**).

Biological Properties.—Several 1-aminoalkylphosphonous acids showed moderate to good antimicrobial activity[43] against a wide microbial spectrum when tested *in vitro* in a minimal medium. The most active compounds were the analogues of alanine (**9b**), valine (**9c**), and methionine (**9k**) and in the first two examples the antimicrobial activity was due solely to the laevorotatory form. Preliminary mode of action studies[44] with (−)-(**9c**) showed that it was antagonised by L-valine and inhibited the protein synthesis of *E. coli* B, perhaps by inactivation of val-t-RNA-synthetase. The racemic valine and methionine analogues have been shown[45] to be effective and specific inhibitors of valyl- and methionyl-t-RNA-synthetases.

The alanine analogue (**9b**) showed interesting plant growth inhibiting properties.[46] Pea seedlings treated with (**9b**) showed a massive accumulation of alanine.[47]

Conclusions.—The synthesis described here offers a general approach to 1-aminoalkylphosphonous acids by which 18 analogues of protein 1-aminoalkyl acids have been prepared. The use of the diphenylmethylamino group in this synthesis has two major advantages. Firstly, its bulk makes for highly crystalline intermediate acids (**8**), an extremely important condition for clean amino acid synthesis, and secondly it can be cleaved under a variety of conditions which offers versatility in the handling of functionality.

The biological activities of the 1-aminoalkylphosphonous acids (partially reported here) have confirmed that appropriate amino acid isoteres are able to act as false substrates and interfere with biological mechanisms in a useful way. Because of their chemical reactivity the 1-aminoalkylphosphonous acids are key intermediates for further synthetic transformations, *e.g.* the oxidation to 1-aminoalkylphosphonic acids. Further chemistry of the 1-aminoalkylphosphonous acids will be reported later.

Experimental

General.—Melting points were determined on a Büchi melting-point apparatus and are uncorrected. ^{1}H N.m.r. spectra were obtained on a Varian EM 360 A spectrometer operating at 60 MHz using 3-(trimethylsilyl)propionic acid sodium salt as internal reference. ^{31}P N.m.r. spectra were obtained on a Jeol FX60 spectrometer operating at 24.15 MHz with phosphoric acid as external reference. ^{13}C N.m.r. spectra were obtained on a Jeol FX90 spectrometer operating at 90 MHz with tetramethylsilane as external reference. Chemical shifts are reported in p.p.m., with positive values being downfield from standard. Coupling constants are reported in Hz. I.r. spectra were measured on a Perkin-Elmer 457 grating spectrophotometer. Optical rotations were measured on a Bellingham and Stanless PIO polarimeter.

Materials.—100% Hypophosphorous acid was prepared according to the method of Fitch[48] starting from a 49—53% aqueous solution ex. B. D. H. Diphenylmethylamine was 96% ex. Aldrich. Diphenylmethylamine hypophosphite (m.p. 179—80 °C) was prepared by mixing equimolar amounts of diphenylmethylamine and hypophosphorous acid (100%) in ethanol <50 °C. The following aldehydes were prepared by Rosenmund reduction of the appropriate acid chlorides: *p*-methoxyphenylethanal, b.p. 80—86 °C/1 mmHg; 3-methoxycarbonylpropanal, b.p. 75—77 °C/16 mmHg; 4-phthalimidobutanal, oil [δ($CDCl_3$) 1.8—2.3 (2 H, m), 2.4—2.9 (2 H, m), 3.5—3.9 (2 H, t), 7.8 (4 H, s, br), and 9.9 (1 H, s)]; 5-phthalimidopentanal, waxy solid [δ($CDCl_3$) 1.5—2.0 (4 H, m), 2.2—2.8 (2 H, m), 3.4—4.0 (2 H, m), 7.8 (4 H, s, br), and 9.9 (1 H, s)].

Benzylthioethanal, b.p. 130 °C/0.01 mmHg [δ($CDCl_3$) 2.9 (2 H, s), 3.6 (2 H, s), 7.3 (5 H, s), 9.3 (1 H, s)] and 2-benzyloxypropanal, b.p. 108 °C/12 mmHg [δ($CDCl_3$) 1.15 (3 H, d), 3.4—4.0 (1 H, br), 4.6 (2 H, s), 7.2 (5 H, s), and 9.65 (1 H, s)] were prepared by sodium borohydride reduction[49] of the appropriate acid chlorides.

Benzyloxyethanal, b.p. 125 °C/18 mmHg [δ($CDCl_3$) 4.0 (2 H, s), 4.6 (2 H, s), 7.4 (5 H, s), and 9.7 (1 H, s)] was prepared by sodium bismuthate oxidation of monobenzylglycerol.[50]

4-Hydroxybutanal was prepared by treatment of dihydrofuran with 0.2M-HCl at room temperature for 30 min followed by evaporation. The aldehyde was used crude.

Synthesis of 1-*diphenylmethylaminophosphonous Acids* (**8**).—*Method A.* An equimolar mixture of the aldehyde and diphenylmethylamine was refluxed in toluene (80 ml for 0.1 mol) for several hours with azeotropic removal of water. After cooling, the solution was filtered and evaporated to give the crude imine. Hypophosphorous acid (100%, 1 mol equivalent) in ethanol (50 ml for 0.1 mol) was added to the imine in ethanol (150 ml for 0.1 mol) and the mixture refluxed for 1 h and then cooled. The precipitate of the diphenylmethylaminophosphonous acid was filtered off, washed with ethanol and then ether, and dried.

Method B. Equimolar amounts of diphenylmethylamine hypophosphite and aldehyde were dissolved in absolute ethanol (25 ml for 0.1 mol) and the mixture was heated at reflux for 3 h. On cooling of the solution a precipitate of the diphenylmethylaminophosphonous acid formed and this was filtered off, washed with ethanol and then ether, and dried.

Method C. The aldehyde, dissolved in an equal volume of dry dioxane, was added to a suspension of an equimolar amount of diphenylmethylaminohypophosphite in dry dioxane (10—20 ml for 1 g) at 100 °C under nitrogen at such a rate that the temperature at reflux remained at *ca.* 100 °C. This could be achieved only if the water which formed was removed azeotropically with dioxane. When two thirds of the dioxane had been removed the reaction mixture was cooled and diluted with an equal volume of absolute ethanol. The diphenylmethylaminophosphonous acid which crystallised slowly was filtered off, washed with ethanol and then ether, and dried.

Method D. Acetaldehyde (44 g, 1 mol) in water (250 ml) was added dropwise to a refluxing solution of diphenylmethylamine hydrochloride (219.5 g, 1 mol) and 50% aqueous hypophosphorous acid (132 g, 1 mol) in water (500 ml). Precipitation commenced when about two thirds of the aldehyde had been added. Heating was continued for 2 h, after which the solution was cooled and the solid filtered off, washed with acetone, and dried to give (**8b**) (249 g, 91%).

Method E. Benzyloxyacetaldehyde (15 g, 0.1 mol) dissolved in ethanol (30 ml) was added during 90 min to a solution of diphenylmethylamine hydrochloride (14.6 g, 0.066 mol), diphenylmethylamine hypophosphite (8.3 g, 0.033 mol), and hypophosphorous acid (100%; 4.4 g, 0.066 mol) in absolute ethanol (200 ml) at reflux. Solid separated towards the end of the addition and reflux was maintained for a further 2 h. The mixture was then cooled, and the solid filtered off, washed with ethanol and then ether, and dried to give (**8i**) (18.6 g, 48%).

Synthesis of Aminoalkylphosphonous Acids (**9**)—(**12**).—*Method F.* The diphenylmethylaminophosphonous acid was heated together with an excess of 48% hydrobromic acid (5 times by weight) at 100 °C for 1—2 h until two distinct phases had separated. The mixture was evaporated to dryness under reduced pressure and the residue taken up in water. The aqueous solution was washed several times with ether to remove diphenylmethyl bromide and then evaporated to dryness. The oily residue of 1-aminoalkylphosphonous acid hydrobromide was dissolved in ethanol (10 ml/g) and propylene oxide added dropwise until precipitation started. The mixture was allowed to stand until complete precipitation and the solid was then filtered off, washed with ethanol and then ether, and dried.

Method G. This method is identical to method F except that 18% HCl is used instead of 48% HBr.

Method H. The diphenylmethylaminophosphonous acid was heated together with an excess of trifluoroacetic acid (10 times by weight) and one equivalent of anisole at reflux for 1 h. The mixture was then cooled, evaporated to dryness, and the residue taken up in water and washed several times with ether. The aqueous phase was then evaporated to dryness and the residue heated with absolute ethanol and again evaporated to dryness. This procedure was repeated until a filterable precipitate was obtained. The filter cake was washed with absolute ethanol and then ether, and dried.

Synthesis of (**9o**). A solution of (**8o**) (12.8 g, 0.028 mol) and hydrazine hydrate (1.5 g) in ethanol (50 ml) was heated at reflux

Table 5. Analytical data for the 1-diphenylmethylaminophosphonous acids (**8**).

Compd.	Found (%)				Molecular Formula	Required (%)				^{31}P n.m.r. (NaOH)	
	C	H	N	P		C	H	N	P	$\delta_{P\ (p.p.m.)}$	$J_{PH\ (Hz)}$
(**8a**)	62.0	6.15	5.05	11.65	$C_{14}H_{16}NO_2P$	64.35	6.15	5.35	11.85	23.9	514
(**8b**)	65.65	6.95	4.85	10.9	$C_{15}H_{18}NO_2P$	65.45	6.6	5.1	11.25	31.5	507
(**8c**)	67.25	7.55	4.45	10.2	$C_{17}H_{22}NO_2P$	67.3	7.3	4.6	10.2	21.6	600 (TFA)
(**8d**)	67.2	7.45	4.65	10.3	$C_{18}H_{24}NO_2P$	68.1	7.6	4.4	9.75	30.9	502
(**8e**)	66.68	7.35	4.35	9.45	$C_{18}H_{24}NO_2P$	68.1	7.6	4.4	9.75	29.3, 30.1	500
(**8f**)	70.75	6.3	3.8	8.9	$C_{21}H_{22}NO_2P$	71.8	6.3	4.0	8.8	26.1	490 (DMSO)
(**8g**)	68.95	6.6	3.8	7.6	$C_{22}H_{24}NO_3P$	69.3	6.35	3.65	8.1	22.8	600 (TFA)
(**8h**)	69.9	6.05	6.9	7.9	$C_{23}H_{23}N_2O_2P$	70.75	5.95	7.2	7.95	30.4	507
(**8i**)	68.95	6.45	3.45	8.0	$C_{22}H_{24}NO_3P$	69.3	6.3	3.65	8.15	26.0	512
(**8j**)					$C_{23}H_{26}NO_3P$	69.85	6.6	3.55	7.85	11.9	577 (HOAc)
(**8k**)	60.65	7.0	3.85	8.85	$C_{17}H_{22}NO_2PS$	60.9	6.6	4.2	9.25	28.7	494
(**8l**)	66.2	6.35	3.45	7.4	$C_{22}H_{24}NO_2PS$	66.5	6.05	3.55	7.8		
(**8m**)	62.2	6.65	4.1	8.8	$C_{19}H_{24}NO_4P$	62.25	6.4	4.05	8.9	27.9	517 (DMSO)
(**8n**)	67.3	5.95	6.0	6.8	$C_{26}H_{27}N_2O_4P$	67.5	5.9	6.05	6.7	29.9	500
(**8o**)	66.65	6.05	5.8	7.0	$C_{25}H_{25}N_2O_4P$	66.95	5.6	6.25	6.9	30.0	516
(**8p**)	62.9	7.2	4.05	9.7	$C_{17}H_{22}NO_3P$	63.95	6.9	4.4	9.7	29.7	520
(**8q**)	64.6	7.3	4.3	8.95	$C_{18}H_{24}NO_3P$	64.85	7.25	4.2	9.3	29.8	503

for 2 h. The reaction mixture was cooled and acidified (conc. HCl, to Congo Red). The phthalhydrazide was filtered off and the filtrate concentrated in stages removing more phthalohydrazide at each stage. When no more phthalohydrazide was present the mixture was evaporated to dryness and the residue dissolved in conc. HCl (20 ml) and heated to reflux for 4 h. The solution was then evaporated to dryness and the residue taken up in water and washed with ether. The aqueous phase was then evaporated to dryness and the residual white solid dissolved in water and passed down a column of Dowex 50W-X2 eluting with water to remove the HCl. The product was then eluted with aqueous ammonia (3%). Further purification was by column chromatography on silica gel eluting with ethanol–3% aqueous ammonia (2:1). The product-containing fractions were combined and the solvent evaporated under reduced pressure. The product solidified after repeated co-evaporation with absolute ethanol and was filtered off, washed with ethanol and then ether, and dried to give (**9o**) (1.8 g, 50%); $\delta_C(D_2O)$ 26.76 (d, J_{PC} 11, C-3), 28.91 (d, J_{PC} 2.2, C-2), 42.02 (s, C-4), 52.93 (d, J_{PC} 97.8, C-1).

In exactly the same way (**9n**) was prepared from (**8n**).

Synthesis of (**9t**). A solution of (**9o**) (2.8 g, 0.018 mol) and *S*-ethylisothiourea hydrobromide (3.3 g, 0.018 mol) in water (50 ml) was adjusted to pH 10 with ammonia and left at room temperature for 7 days. The solution was evaporated to give a glassy solid which was passed down an ion-exchange column (Dowex 50WX8) eluting first with water until free of Br^- ion and then with aqueous ammonia (5%). Evaporation of the ammonia solution gave a glassy solid. Crystallisation from ethanol (several days) gave (**9t**) as a monohydrate (1 g, 26%), m.p. 119 °C; $\delta_C(D_2O)$ 27.7 (d, J_{PC} 11, C-3), 29.11 (s, C-2), 43.74 (s, C-4), 53.02 (d, J_{PC} 97.8, C-1), 159.58 (s, N–C–N).

Synthesis of (**10**). A solution of (**9r**) (1.25 g, 0.0054 mol) and conc. ammonia (4 ml) in water (4 ml) was heated at reflux for 5 h. The mixture was evaporated to dryness and the residual oil dissolved in ethanol (10 ml) and 48% HBr (5 ml) and again evaporated to dryness. The residual oil was dissolved in ethanol (10 ml) containing just enough ether to precipitate ammonium bromide. The ammonium bromide was filtered off and the ethanol evaporated under reduced pressure. The residual oil was dissolved in methanol and propylene oxide was added until precipitation started. The mixture was left overnight and the solid filtered off, washed with ethanol and then ether, and dried to give (**10**) (0.4 g, 50%), m.p. 265—266 °C (decomp.) (aqueous acetone).

Synthesis of (**11**). A solution of (**9p**) (2.16 g, 0.01 mol) in water (20 ml) was mixed with *N*,*N*-dimethyldodecylamine (4.26 g, 0.02 mol) in methylene chloride (20 ml) and stirred vigorously. 40% Tetrabutylammonium hydroxide (2 drops) was added and stirring continued for 90 min. The aqueous layer was acidified (conc. HCl) and separated, washed well with methylene chloride and then ether, and finally evaporated to dryness. The residual oil was dissolved in ethanol and propylene oxide was added dropwise until precipitation occurred. The solvent was removed under reduced pressure and the partially solid oil redissolved in ethanol and re-treated with propylene oxide. On removal of solvent the semisolid residue was triturated with light petroleum (b.p. 40—60 °C) containing 10% ethanol and, after addition of a small amount of propylene oxide, allowed to stand overnight. The precipitate was filtered off, washed with ethanol and then light petroleum, and dried to give (**11**) (1.0 g, 74%), m.p. 218—221 °C (decomp.).

Synthesis of (**12**). (**With J. Mitchell**). Butyl vinylphosphonite[51] (18.9 g, 0.128 mol) and diethyl acetamidomalonate (18.3 g, 0.084 mol) were dissolved in dry acetonitrile (300 ml). A solution of sodium ethoxide (100 mg of sodium in 5 ml of ethanol made up to 55 ml with dry acetonitrile) was added dropwise over 1.5 h and the mixture then stirred at room temperature for 4 h and allowed to stand overnight. The solution was then neutralised with 4 drops of dilute HCl and evaporated to give an oil. This oil was purified by chromatography on silica gel using ether as eluant to remove impurities and then eluting the product with methanol. The methanol fractions were combined, evaporated, dissolved in ether and a small amount of solid was filtered off. The filtrate was then evaporated to give the oily Michael adduct (28.7 g, 77%) (^{31}P n.m.r., δ 38.4). The Michael adduct was heated to reflux with 18% HCl (300 ml) for 6 h, after which the mixture was cooled and evaporated to give a crystalline hydrochloride. The hydrochloride was heated to reflux with hexamethyldisilazane[40] (50 ml) until homogeneous and then one further hour; it was then distilled under reduced pressure b.p. 83—84 °C/0.01 mmHg. The silylated amino acid was dissolved in dry acetonitrile and hydrolysed by addition of 2% aqueous acetonitrile. The solid was filtered off, washed with acetonitrile, and then dissolved in water. The solution was filtered and then evaporated. The

Table 6. Analytical data for the 1-aminoalkylphosphonous acids (**9**), (**10**), (**11**), and (**12**).

Compd.	Found (%) C	H	N	P	Molecular Formula	Required (%) C	H	N	P	I.r. $\gamma_{max.}$ (Nujol) (cm^{-1}) P–H	P=O	P–O⁻	Other
(**9a**)	12.9	6.2	14.1	32.45	CH_6NO_2P	12.65	6.35	14.75	32.6	2 340	1 180	1 040, 1 060	
(**9b**)	22.2	7.1	12.8	28.55	$C_2H_8NO_2P$	22.0	7.35	12.85	28.45	2 300	1 180	1 040	
(**9c**)	35.05	8.8	10.2	22.6	$C_4H_{12}NO_2P$	34.9	8.8	9.95	22.6	2 350	1 180	1 040	
(**9d**)	39.65	9.4	9.15	20.45	$C_5H_{14}NO_2P$	39.75	9.35	9.25	20.5	2 340	1 170	1 030	
(**9e**)	39.5	9.55	9.3	20.4	$C_5H_{14}NO_2P$	39.75	9.35	9.25	20.5	2 340	1 160	1 040	
(**9f**)	51.7	6.55	7.8	16.4	$C_8H_{12}NO_2P$	51.9	6.55	7.55	16.75	2 380	1 175	1 030	
(**9g**)	48.0	6.2	6.65	15.4	$C_8H_{12}NO_3P$	47.75	6.0	6.95	15.4	2 400	1 150	1 040	3 200 (OH)
(**9h**)	53.8	5.75	12.75	13.6	$C_{10}H_{13}N_2O_2P$	53.55	5.85	12.5	13.8	2 370	1 200	1 060	3 395 (NH)
(**9i**)	19.15	6.45	10.95	24.55	$C_2H_8NO_3P$	19.2	6.4	11.2	24.8	2 330	1 170	1 060	3 260 (OH)
(**9j**)	26.15	7.21	10.0	21.8	$C_3H_{10}NO_3P$	25.9	7.2	10.1	22.3	2 320	1 210, 1 170	1 040, 1 020	3 350 (OH)
(**9k**)	28.5	7.15	8.3	17.8	$C_4H_{12}NO_2PS$	28.4	7.15	8.3	18.3	2 350	1 180	1 035	
(**9l**)	17.25	5.55	9.45	—	$C_2H_8NO_2PS$	17.0	5.65	9.9	22.0	2 340	1 180	1 030	
(**9m**)	28.7	6.2	8.0	18.6	$C_4H_{10}NO_4P$	28.75	6.05	8.4	18.35	2 360	1 180	1 040	1 700 (C=O)
(**9n**)	36.15	8.95	16.35	18.3	$C_5H_{15}N_2O_2P$	36.15	9.1	16.85	18.65	2 260	1 150	1 010, 1 040	3 280, 3 360 (NH₂)
(**9o**)	31.6	8.75	18.1	19.9	$C_4H_{13}N_2O_2P$	31.6	8.6	18.4	20.35	2 280	1 160	1 040	3 280, 3 340 (NH₂)
(**9p**)	22.3	5.0	6.2	14.1	$C_4H_{11}BrNO_2P$	22.2	5.1	6.5	14.35	2 340	1 180	1 040	
(**9q**)	35.65	8.35	8.25	18.3	$C_5H_{14}NO_3P$	35.95	8.45	8.4	18.55	2 340	1 180	1 040	3 300 (OH)
(**9r**)	26.2	5.65	5.95	13.1	$C_5H_{13}BrNO_2P$	26.1	5.7	6.1	13.45	2 340	1 180	1 030	
(**9s**)	16.85	5.15	9.65	21.9	$C_4H_{14}N_2O_4P_2S_2$	17.15	5.0	10.0	22.15	2 320	1 175	1 030	
(**9t**)	28.4	8.3	26.35	14.8	$C_4H_{13}N_2O_2P{\cdot}H_2O$	28.3	8.0	26.4	14.6	2 300	1 150	1 050	1 600—1 700
(**10**)	40.15	7.95	9.65	20.1	$C_5H_{12}NO_2P$	40.25	8.1	9.4	20.75	2 300	1 180	1 050, 1 030, 1 010	
(**11**)	35.45	7.3	10.0	22.0	$C_4H_{10}NO_2P$	35.55	7.45	10.35	22.95	2 300	1 190	1 080, 1 070, 1 060	
(**12**)	28.6	6.05	8.05	18.35	$C_4H_{10}NO_2P$	28.25	6.05	8.4	18.55				

residual solid was triturated with ethanol, filtered, washed with ethanol, and dried to give 3-amino-3-carboxypropylphosphonous acid (7.0 g, 50%), m.p. 208—210 °C (decomp.) [lit.,[33] 221—222 °C (decomp.) (laevorotatory form)]; δ_P 29.4, J_{PH} 526; δ_H 1.4—2.5 (4 H, m, CH_2CH_2), 4.1 (1 H, t, CH_2), 7.0 (1 H, d, *J* 526, P–H).

Resolution of 1-*Aminoalkylphosphonous Acids* (**9b**), (**9c**), (**9d**), (**9f**) *and* (**9k**).—Compound (**9c**) (27.5 g, 0.2 mol) was dissolved in water (100 ml), the pH of the solution adjusted to 9.5 with 4M-NaOH and the mixture cooled to 0 °C. Benzyl chloroformate (34 g, 0.2 mol) was added over 1 h and the mixture stirred a further 6 h while the pH was maintained at 9.0—9.5 by periodic addition of 4M-NaOH. The mixture was then allowed to warm to room temperature and washed with ether. The aqueous solution was then slowly added to a mixture of water, concentrated HCl, and ice (120 ml, 80 ml, and 400 ml respectively). The solid product was collected by filtration, dried, and recrystallised from ethyl acetate–light petroleum to give (±)-1-benzyloxycarbonylamino-2-methylpropylphosphonous acid, m.p. 110—111 °C.

(+)-α-Methylbenzylamine (15 g, 0.125 mol) in ethanol (75 ml) was added to a refluxing solution of (±)-1-benzyloxycarbonylamino-2-methylpropylphosphonous acid (34 g, 0.125 mol) in ethanol (500 ml). 1-Benzyloxycarbonylamino-2-methylpropylphosphonous acid (+)-α-methylbenzylamine salt (22 g) with specific rotation $[\alpha]_D^{25}$ −9.5° and m.p. 163—168 °C crystallised out. This product was recrystallised from absolute ethanol (15 ml for 1 g) to constant m.p. and rotation, namely 169 °C and $[\alpha]_D^{25}$ −16.4° (DMF–H_2O, 9:1). (−)-1-Benzyloxycarbonylamino-2-methylpropylphosphonous acid α-methylbenzylamine salt, $[\alpha]_D^{25}$ −16.4°, was stirred with a slight excess of 45% HBr in acetic acid at 0 °C for 1 h. Propylene oxide was then added dropwise until precipitation started and finally ether was added to complete the precipitation. (−)-1-Amino-2-methylpropylphosphonous acid, m.p. 209 °C and specific rotation $[\alpha]_D^{25}$ −3.6° (1.5% in H_2O) was obtained.

Repetition of the above procedure with (−)-α-methylbenzylamine gave (+)-1-benzyloxycarbonylamino-2-methylpropylphosphonous acid α-methylbenzylamine salt, m.p. 169 °C and specific rotation $[\alpha]_D^{25}$ +16.2° (DMF–H_2O, 9:1), and (+)-1-amino-2-methylpropylphosphonous acid, m.p. 209 °C and specific rotation $[\alpha]_D^{25}$ +3.5° (1.5% in H_2O).

The optical purity of (+)- and (−)-1-amino-2-methylpropylphosphonous acids was checked using an adaptation of the method of Manning and Moore.[52] Amino acid samples (20 μmol) were derivatised with *N*-carboxyanhydro-L-leucine and *ca.* 80 nmol was loaded onto the long column (60 × 0.9 cm) of the Beckman 120 C analyser. The eluting buffer was 0.3M-lithium citrate pH 2.8 and detection was by ninhydrin. The optical purity was found in both cases to be >99.5%.

Repetition of the above procedure with (**9b**) gave the following. (±)-1-Benzyloxycarbonylaminoethylphosphonous acid, m.p. 110 °C; salt with (+)-α-methylbenzylamine, m.p. 145—146 °C, $[\alpha]_D^{22}$ −12.8° (5% in EtOH); salt with (−)-α-methylbenzylamine, m.p. 146—147 °C, $[\alpha]_D^{22}$ +14.6° (5% in EtOH). (+)-1-Aminoethylphosphonous acid, m.p. 224—225 °C, $[\alpha]_D^{20}$ +7.0° (2% in H_2O). (−)-1-Aminoethylphosphonous acid, m.p. 223—224 °C, $[\alpha]_D^{20}$ −6.4° (2% in H_2O).

Repetition of the above procedure with (**9d**) gave the following. (±)-1-Benzyloxycarbonylamino-3-methylbutylphosphonous acid, m.p. 150—152 °C; salt with (+)-α-methylbenzylamine, m.p. 181—183 °C, $[\alpha]_D^{22}$ −32° (1% in *EtOH*). (−)-1-Amino-3-methylbutylphosphonous acid, m.p. 233 °C, $[\alpha]_D^{22}$ −23° (1% in H_2O).

Repetition of the above procedure with (**9f**) gave the following. (±)-1-Benzyloxycarbonylamino-2-phenylethylphos-

phonous acid, m.p. 137 °C; salt with (+)-α-methylbenzylamine, m.p. 190—193 °C, $[\alpha]_D^{24}$ −47.6° (1% in EtOH). (−)-1-Amino-2-phenylethylphosphonous acid, m.p. 224 °C, $[\alpha]_D^{25}$ −62.2° (1% in EtOH).

Repetition of the above procedure with (**9k**), but treating the resolved salt in two stages, firstly with dilute HCl to free the acid and then with 48% HBr in acetic acid (addition of anisole) at 0 °C gave the following. (±)-1-Benzyloxycarbonylamino-3-methylthiopropylphosphonous acid, m.p. 108—109 °C; salt with (+)-α-methylbenzylamine, m.p. 163—164 °C, $[\alpha]_D^{22}$ −25° (2% in EtOH); salt with (−)-α-methylbenzylamine, m.p. 163—164 °C, $[\alpha]_D^{22}$ +25° (2% in EtOH). (+)-1-Benzyloxycarbonylamino-3-methylthiopropylphosphonous acid, m.p. 126 °C, $[\alpha]_D^{22}$ +60° (1% in EtOH). (−)-1-Benzyloxycarbonylamino-3-methylthiopropylphosphonous acid, m.p. 128 °C, $[\alpha]_D^{22}$ −60° (1% in EtOH). (+)-1-Amino-3-methylthiopropylphosphonous acid, m.p. 230 °C, $[\alpha]_D^{22}$ +31° (1% in H_2O). (−)-1-Amino-3-methylthiopropylphosphonous acid, m.p. 232 °C, $[\alpha]_D^{22}$ −30° (1% in H_2O).

Oxidation of 1-Aminoalkylphosphonous Acids to 1-Aminoalkylphosphonic Acids.— With mercuric chloride. A 1-aminoalkylphosphonous acid (0.1 mol) and mercuric chloride (0.2 mol) were slowly heated to 90—95 °C in water (250 ml). When precipitation of the mercurous chloride was complete the reaction mixture was cooled, the mercurous chloride filtered off, and the filtrate treated with H_2S and then filtered through a filter aid (Hyflo). The filtrate was then evaporated to dryness, the residual oil dissolved in absolute ethanol (10 ml for 1 g), and propylene oxide added until precipitation of the 1-aminoalkylphosphonic acid was completed. The yield was quantitative.

Using this method the following 1-aminoalkylphosphonic acids were prepared. 1-Aminoethylphosphonic acid, m.p. 275—277 °C (lit.,[53] m.p. 275—276 °C). (−)-1-Aminoethylphosphonic acid, m.p. 286—288 °C (lit.,[54] m.p. 294—295 °C), $[\alpha]_D^{25}$ −2.6° (2% in H_2O), −16.6 °C (2% in 1M-NaOH) [lit.,[54] −16.9° (2% in 1M-NaOH)]. 1-Amino-2-methylpropylphosphonic acid, m.p. 279—281 °C (lit.,[55] 280—281 °C). (−)-1-Amino-2-methylpropylphosphonic acid, $[\alpha]_D^{24}$ −1° (2% in H_2O) [lit.,[56] −0.6° (H_2O)]. (−)-1-Amino-3-methylbutylphosphonic acid, m.p. 293—294 °C $[\alpha]_D^{24}$ −25.5° (1% in H_2O) (lit.,[56] $[\alpha]_D^{20}$ −24°). 1-Amino-2-hydroxyethylphosphonic acid, m.p. 214 °C (softens 180 °C) (lit.,[10] m.p. 80 °C]. *1-Amino-2-hydroxypropylphosphonic acid*, m.p. 212—215 °C (Found: C, 22.5; H, 6.5; N, 8.7; P, 19.55. $C_3H_{10}NO_4P$ requires C, 22.55; H, 6.45; N, 9.05; P, 20.0%); δ_P 10.4 (H_2O); δ_H 1.3 (3 H, br d, CH_3), 3—3.7 (1 H, br, CH–P), 3.8—4.5 (1 H, br, CHOH).

With bromine water. A 1-aminoalkylphosphonous acid (0.05 mol) and saturated bromine water (50 ml) was heated to 70 °C for 1 h. The mixture was then evaporated to dryness and the oily residue was successively treated with water and re-evaporated until a white solid was obtained. This solid was then dissolved in ethanol (20 ml) and propylene oxide was added until precipitation was completed. The yield was quantitative.

Using this method the following 1-aminoalkylphosphonic acids were prepared. 1-Aminoethylphosphonic acid, m.p. 275—277 °C. 1,4-Diaminobutylphosphonic acid, m.p. 295 °C [lit.,[16] m.p. 293 °C], δ_P 9.6. 1,5-Diaminopentylphosphonic acid, m.p. >300 °C (lit.,[16] 301—302 °C], δ_P 12.4.

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