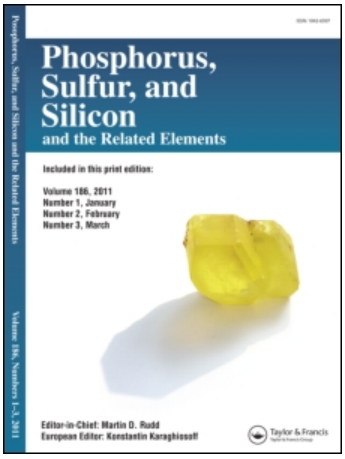

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Synthesis, Physical and Biological Properties of the Phosphorus Analogues Of Phenylalanine and Related Compounds

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Review

SYNTHESIS, PHYSICAL AND BIOLOGICAL PROPERTIES OF THE PHOSPHORUS ANALOGUES OF PHENYLALANINE AND RELATED COMPOUNDS

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(Received February 17, 1994)

Dedicated in friendship to Professor Dr. Reinhard Schmutzler
on the occasion of his 60th birthday.

INTRODUCTION

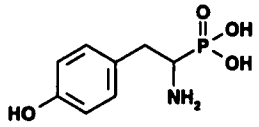
The study of phosphorus analogues of the natural α-amino acids has accelerated in the past fifteen years, not least due to the finding of molecules with useful biological activity. Our knowledge in this area has been summarized in several recent review articles.[1–5] Furthermore aminophosphonic acids find increasing use as a tool in investigating the metabolism of natural amino acids.[6] The family of 1-aminoalkylphosphonic acids has been most studied and to date analogues of all the common protein amino acids have been described in the literature.

In this article we shall summarize our knowledge on the phosphorus analogues of phenylalanine and related compounds.

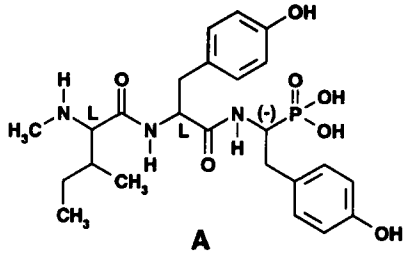
OCCURRENCE IN NATURE

The only naturally occurring 1-aminoalkylphosphonic acid is (−)-1-amino-2-(4-hydroxyphenyl)ethylphosphonic acid **17**† (Table I).[7] The absolute configuration of (−)**17** has been shown to be R.[8] Thus natural TyrP, **17**, belongs to the L-series of amino acids. TyrP, **17**, has been isolated in the form of hypotensive active tripeptides, N-(N-acetyl-L-isoleucyl-L-tyrosyl-(−)-1-amino-2-(4-hydroxyphenyl)ethylphosphonic acid **A** from the cultures of actinomycetes K-26 and N-(N-methyl-L-valyl-L-phenylalanyl-(−)-1-amino-2-(4-hydroxyphenyl)ethylphosphonic acid **B** from the cultures of actinomycetes K-4.

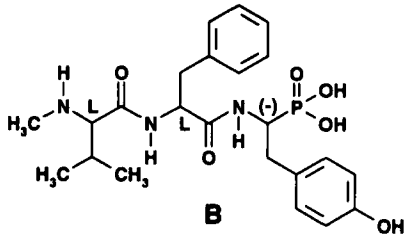
†These are the numbers under which the compounds are listed in Tables I to IV.



R (-) 17



A

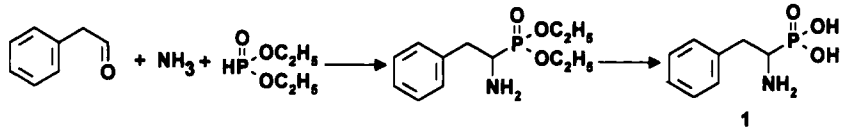


B

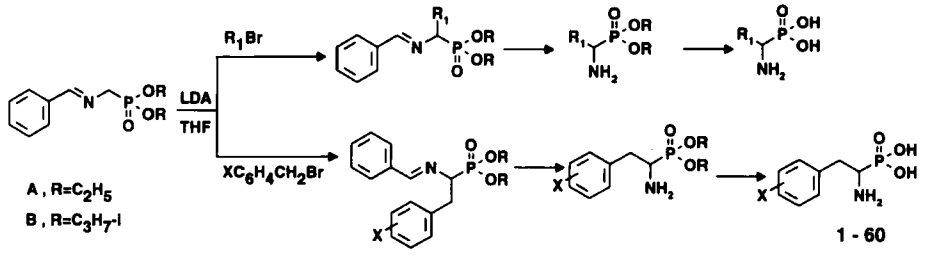
SYNTHESIS OF 1-AMINO-2-ARYLETHYLPHOSPHONIC ACIDS

The phosphonic acid analogue of phenylalanine, **1**, was first synthesized in 1953 by Kosolapoff *et al.*[9] by causing 2-phenylacetaldehyde and ammonia to react with diethylphosphite followed by hydrolysis with HCl (Scheme 1).

Since then many other methods have been developed which have been reviewed recently by us.[10] For the preparation of differently substituted 1-amino-2-aryl-



Scheme 1



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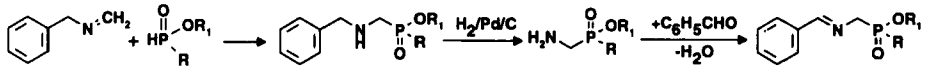
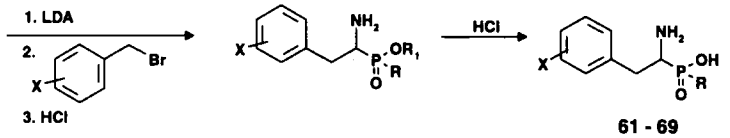




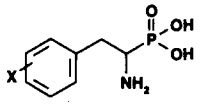
Scheme 2

ethylphosphonic acid derivatives (see Table I) the procedure of Ratcliffe *et al.*[11] is well suited. This involves alkylation of a Schiff base followed by hydrogenation and hydrolysis[10] (Scheme 2). Furthermore we observed that this procedure can be extended to the preparation of the corresponding phosphinic acid and phosphine oxide derivatives. In addition this method has the advantage that a large number of heteroaryl-,[12] aryl- and alkyl substituted 1-aminophosphonic- and phosphinic acid derivatives can be prepared from the same starting material.

1-Amino-2-arylethyl-dimethylphosphine oxide derivatives were prepared as shown in Scheme 3.

TABLE I

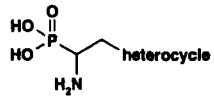
Physical properties of



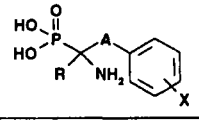
	X	yield in %	m.p. °C(dec.)	^{31}P-chem.shift in ppm	pH	Ref.
1	H	89.5	278-82	20.37	(11)	10
2	4-Cl	82.8	280-82	20.19	(11)	10
3	3-Cl	79.3	268-72			10
4	4-Br	84.5	284-86			10
5	4-I	61.2	255-59			10
6	4-F	89.2	266-70	20.28		10
7	3-F	71.2	278-80	20.09	(11)	10
8	2-F	77.7	275-6	20.28	(11)	10
9	2,4-Cl_2	90.1	279-80	20.19	(11)	10
10	3,4-Cl_2	66.7	274-78	19.91	(11)	10
11	4-CH_3	58.6	276-79	20.37	(11)	10
12	3-CH_3	84.9	270-73			10
13	2-CH_3	77.4	244-45	18.79	(11)	10
14	3-CF_3	89.1	258-62	20-09	(11)	10
15	4-$(CH_3)_3C$	80.9	264-68			10
16	3,4-$(OH)_2$	81.5	196[a]			10
17	4-OH	60.9	258-60			10
18	3,4-F_2	66.1	267-69	14.86	(10.5)	10
19	2,4-F_2	84.4	271-74			10
20	2,6-F_2	46.8	258-61			10
21	4-C_6H_5	67.8	273			10
22	3,4-$(CH)_4$	71.7	267-71			10
23	4-F	84.5(+)	259-63			12
24	4-F	77.6(-)	261-63			12
25	b	75.3	265-68			12
26	2,3,4,5,6-F_5	85.8	283-89			12
27	4-CF_3	66.8	>320			12
28	4-C_2H_5	84.3	277-80			12
29	2-CH_3O	82.1	264-65			12
30	3-CH_3O	51.8	~270			12

TABLE I (*Continued*)

	X	yield in %	m.p. °C(dec.)	^{31}P-chem.shift in ppm	pH	Ref.
31	4-CH_3O	79.7	280-82			12
32	4-C_2H_5O	73.5	267-71			12
33	4-n-C_4H_9O	54.8	236-40			12
34	2-OH	90.6	>300			12
35	3-OH	73.7	270			12
36	2-NO_2	91.8	243-46			12
37	2-CH_3-3-F	82.3	280			12
38	2,3-OCF_2O	52.9	238-39			12
39	4-NO_2					46
40	4-NH_2					46
41	3,4-$(CH_3O)_2$	77.0	259-60			38,47
42	4-OH, 3-I					41,43
43	4-OH, 3,5-I_2					41,43
44	c					43
45	4-C_6H_5O	89.3	220-25			12
46	4-(4'-ClC_6H_4O)	77.3	243-45			12
47	4-(4'-FC_6H_4O)	65.3	235-37			12
48	4-$C_6H_5CH_2O$	61.0	230-31(R)			14
49	4-$C_6H_5CH_2O$	60.0	222-24(S)			14



	Heterocycle	yield in %	m.p. °C(dec.)	Ref.
50	pyridyl(2)	71.4	solid	12
51	pyridyl(3)	81.7	solid	12
52	pyridyl(4)	91.6	solid	12
53	2-CH_3-pyridyl(6)	78.9	203-04	12
54	2-phenoxypyridyl(6)	77.4	>105	12

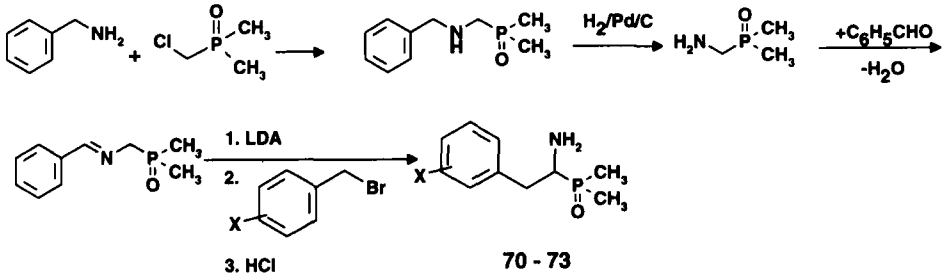


	A	R	X	yield in %	m.p. °C(dec.)	Ref.
55	CHMe	H	H	59.5	249	12
56	C_3H_4-cyclo	H	4-CH_3	66.4	246-47	12
57	CH(C_3H_5-cyclo)	H	4-Cl	15.5	253-55	12
58	CH(C_3H_7-i)	H	4-Cl	35.0	262-64	12
59	CH_2	CH_3	4-F	73.0	231-34	10
60	CH_2	CH_3	H	64.0	245-47	10

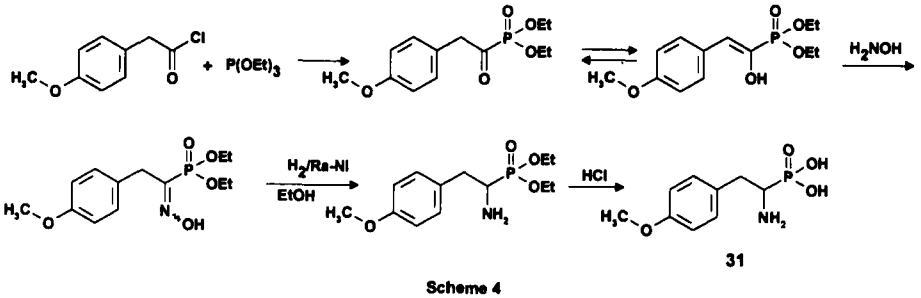
a. m.p. 255°C(dec.[30]); m.p. 265-66°C (dec.[47]).

b. C_6H_4X = cyclo-C_6H_{11}

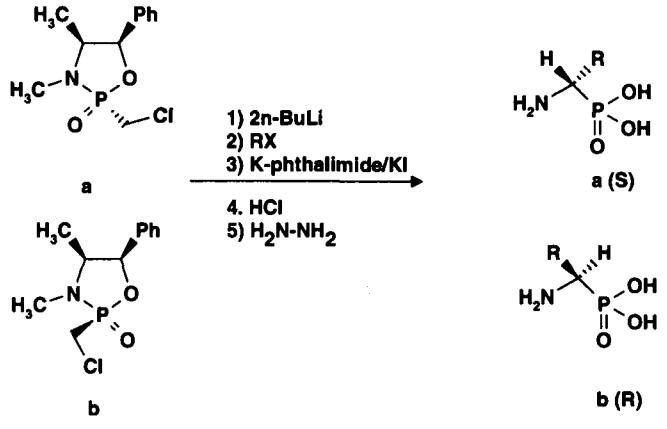
c. 4-(4-HO-3,5-$I_2C_6H_2O$)-3,5-I_2



Scheme 3



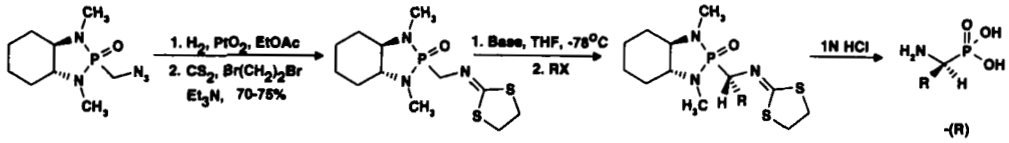
Scheme 4



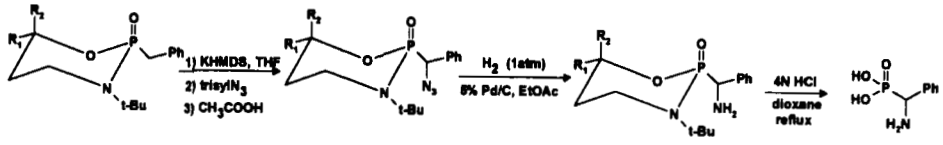
Scheme 5

Sometimes the alkylation procedure according to Scheme 2 is not applicable because of lack of starting materials or other reasons.[12] In this case the procedure shown in Scheme 4 is used advantageously.[12] This involves preparation of acylphosphonates, conversion to oximes, reduction to amino-compounds and hydrolysis.

Strategies for the synthesis of optically active 1-aminoalkylphosphonic acids are numerous and have been reviewed recently.[4] During the past three years new procedures for the preparation of these compounds were reported, i.e. alkylation of chiral aminomethyl-[13] or halomethyl-1,3,2-oxazaphospholanes[14] (Scheme 5) or bicyclic phosphonamides[15] (Scheme 6), and asymmetric electrophilic amination of chiral phosphorus stabilized anions[16,17] (Scheme 7).



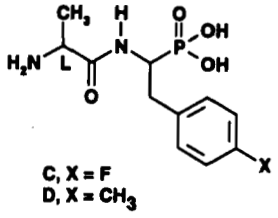
Scheme 6

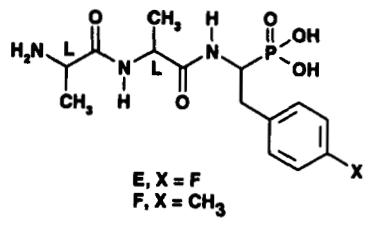


Scheme 7

Because of the easy availability of 1-amino-2-(4-fluorophenyl)ethylphosphonate we have used the resolution of the racemic mixture with L(−) and R(+) dibenzoyltartrate to obtain the optically active compounds **23** and **24**,[18] similar to that used for the resolution of 1-amino-2-phenylethylphosphonic acid.[18a] Peptides containing P-terminal aminophosphonic acids can easily be prepared by coupling N-blocked amino acids or small peptides with free aminoalkane-phosphonic acids or their esters followed by removal of the blocking groups.[19] Of the more than fifty coupling procedures known in peptide chemistry only a few of them have been used for phosphonopeptide synthesis.[19]

We have chosen aminophosphonate esters, N-benzyloxycarbonyl protected aminoacids and dicyclohexylcarbodiimide (DCC as a condensing agent) for the synthesis of the dipeptides **C** and **D**, and the tripeptides **E** and **F**.[18]





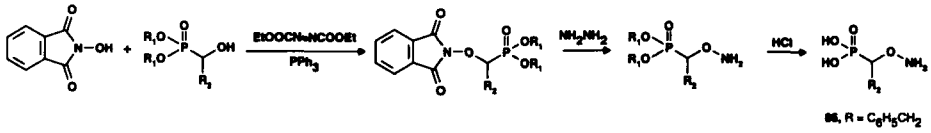
PREPARATION OF ANALOGUES AND HOMOLOGUES

1-Aminooxy-2-phenylethylphosphonic acid **85** has been prepared by a Mitsunobu type reaction[20] from 1-hydroxyalkylphosphonates and N-hydroxyphthalimide[21] in good yield (Scheme 8).

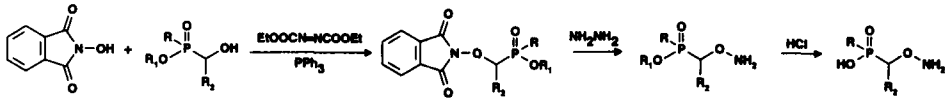
Furthermore this procedure is also useful for the synthesis of 1-aminooxyalkylphosphonous- and phosphinic acids as well as phosphine oxides[22] (Scheme 9).

A method for the synthesis of 1-hydroxy-1-aryl-2-aminoethylphosphonic acids is based on the hydrogenation of dialkyl-1-hydroxy-1-aryl-2-nitroethylphosphonates over Raney nickel in acidic medium followed by hydrolysis[23] (Scheme 10).

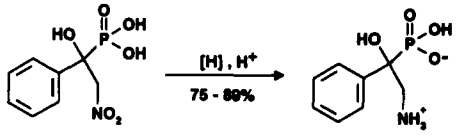
Another procedure also producing these compounds involves the addition of dimethylphosphite to acylamino ketones[24] (Scheme 11).



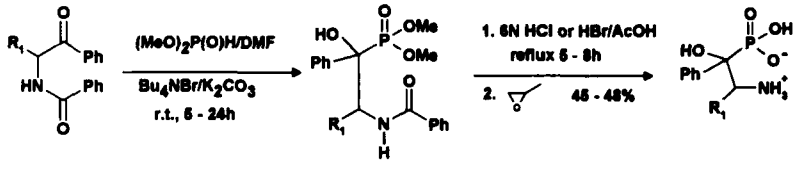
Scheme 8



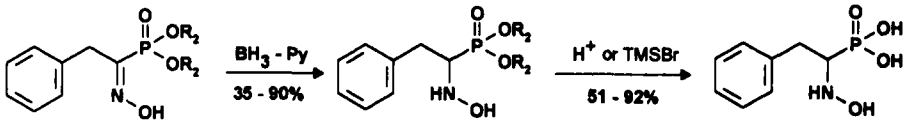
Scheme 9



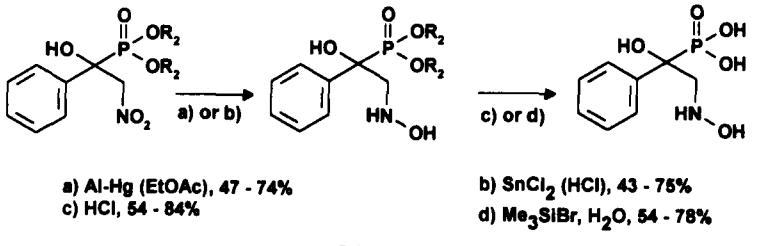
Scheme 10



Scheme 11



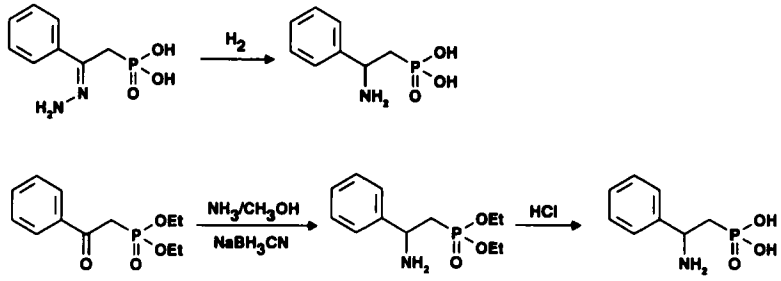
Scheme 12



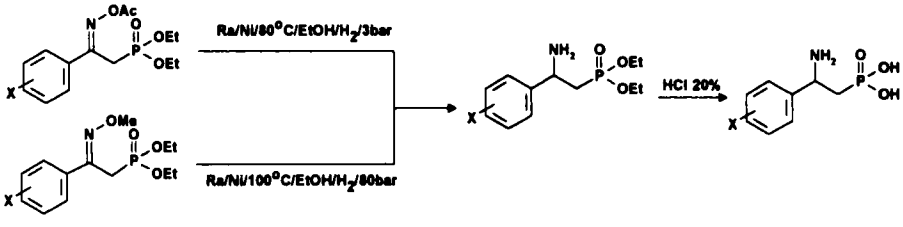
Scheme 13

Recently 1-hydroxyamino-2-phenylethylphosphonic acid and analogues have been synthesized by reduction of 1-hydroxyimino-2-arylethylphosphonates with the borane-pyridine complex followed by acidic hydrolysis[25] (Scheme 12).

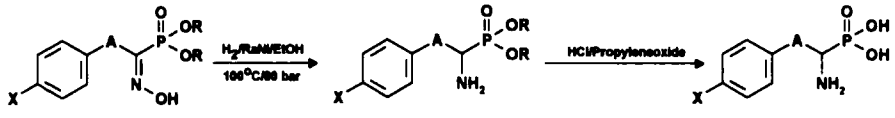
2-Hydroxyamino compounds are obtained when 1-aryl-1-hydroxy-2-nitroethylphosphonates are reduced either with aluminum amalgam in ethylacetate or with stannous chloride in hydrochloric acid solution[26] (Scheme 13).



Scheme 14

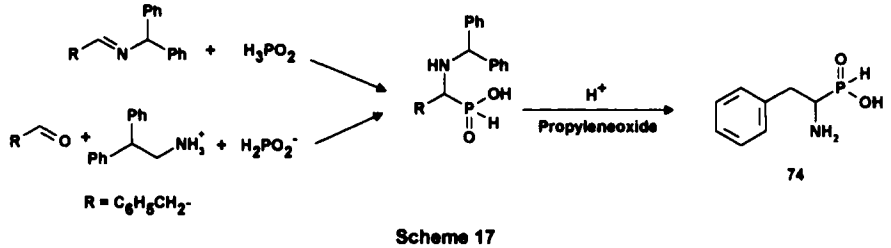


Scheme 15

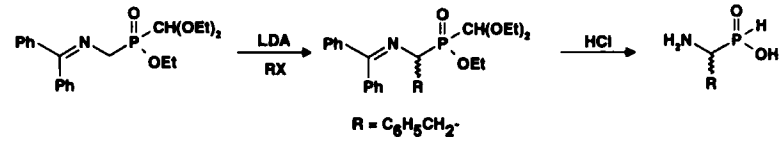


A	X	m.p. ^{0}C (dec.)
-$(CH_2)_2$-	F	271 -273
-$(CH_2)_2$-	CH_3	298 - 300
-$(CH_2)_2$-	H	256 - 257
-$(CH_2)_3$-	H	298 - 299

Scheme 16



Scheme 17



Scheme 18

2-Amino-2-arylethylphosphonic acids have been prepared by reduction of hydrazones,[27] by amination of 2-ketophosphonates[28] (Scheme 14) and from the corresponding 2-acetoxyimino- or 2-methoxyimino-2-arylethylphosphonates by hydrogenation using Raney nickel as a catalyst, then hydrolysis with HCl[29] (Scheme 15).

Because most of the ω-arylalkylcarboxylic acids are commercially available the preparation of the homologous 1-amino-ω-arylalkylphosphonic acids was readily achieved by the steps shown in Scheme 16: acid chloride, acylphosphonate, oxime, reduction to amine and hydrolysis.

Finally 1-amino-2-phenylethylphosphinic acid **74** has been synthesized by addition of hypophosphorous acid to the imine derived from benzhydrylamine and 2-phenylacetaldehyde followed by cleavage of the diphenylmethyl group under acidic conditions[2] (Scheme 17). This compound has also been obtained by alkylation of aminomethylphosphinic acid protected at nitrogen as the imine derived from benzophenone and at phosphorus as the diethylacetal and ethyl ester followed by hydrolysis[2b] (Scheme 18).

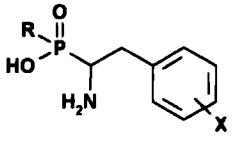
PHYSICAL AND SPECTROSCOPIC PROPERTIES OF 1-AMINO-2-ARYLETHYLPHOSPHONIC ACIDS AND ANALOGUES

The physical properties of the phosphonic-, phosphinic- and phosphine oxide analogues of phenylalanine are summarized in Tables I, II and III.

Like in other aminosubstituted phosphonic acid compounds[48] the ^{31}P-chemical shift of 1-amino-2-arylethylphosphonic acids is strongly dependent on the pH of

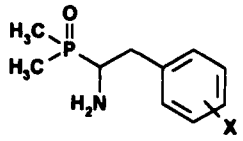
TABLE II

Physical properties of



	R	X	yield in %	m.p. °C(dec.)	^{31}P-chem.shift in ppm	Ref.
61	CH_3	H	76.3	261-62	43.35(pH11)	10
62	C_2H_5	2-CH_3	61.7	234-35	46.15(pH11)	10
63	C_2H_5	3-CH_3	79.3	229-32	42.7(pH8)	10
64	C_2H_5	4-CH_3	88.1	233-36	38.98(pH7)	10
65	CH_3	4-F	75.1	254-57	35.72(pH7)	10
66	CH_3	4-Br	83.3	254-57	43.17(pH11)	10
67	CH_3	4-Cl	100.0	242-45	41.40(pH8)	10
68	CH_3	3-CH_3	89.2	260-62	34.05(pH5)	10
69	C_2H_5	H	80.7	230-31	37.12(pH5)	10

TABLE III
Physical properties of

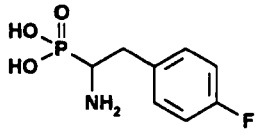


	X	yield in % (HCl-work up)	b.p. °C/torr	Ref.
70	H	21.5	160-170/0.04[a]	10
71	2-CH_3	26.3	160/0.04	10
72	3-CH_3	24.6	160/0.05	10
73	4-CH_3	27.4	150-55/0.07	10

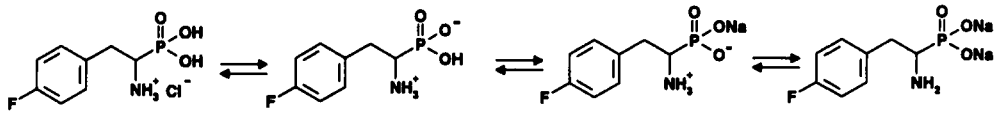
a. Hygroscopic solid

TABLE IV
Dependence of the ^{31}P-chemical shift of 1-amino-2-(4-fluorophenyl)ethylphosphonic acid on the pH in D_2O solution

Compound:



pH	1	4	7	10	11
^{31}P-chemical shift in ppm	14.12	11.16	10.97	16.83	20.28



Scheme 19

the solution (Table IV). Very likely all acids possess the betaine structure, and on neutralization with sodium hydroxide produce the disodium salts[10] (19).

The pK values of several 1-amino-2-arylethylphosphonic acids have been determined.[10,12] They lie in the range of pK_1 = <2.5; pK_2 = 5.42–5.94; pK_3 = 9.48–10.3.

The ^1H-NMR spectrum of 1-amino-2-(4-fluorophenyl)ethylphosphonic acid is shown in Figure 1.

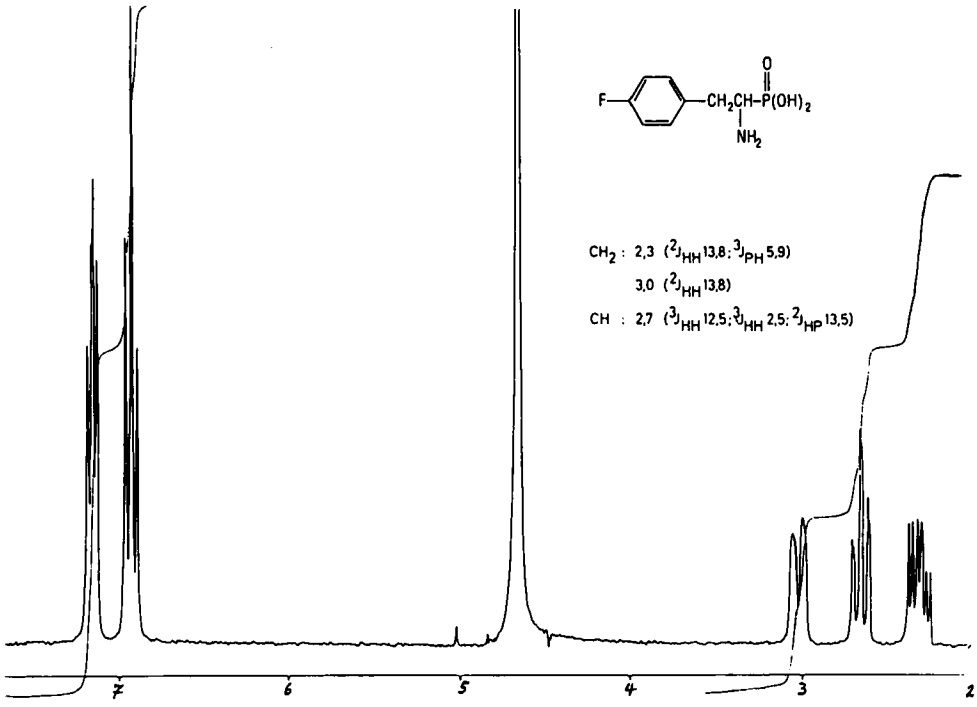


FIGURE 1 ^{1}H-NMR spectrum of 1-amino-2-(4-fluorophenyl)ethyl-phosphonic acid in D_2O at 250 MHz.

TOXICOLOGY

The P-DOPA analogue **17** was well tolerated when given subcutaneous to mice in a single dose.[30] A lethal dose was not established, but the compound caused no deaths, or apparent tissue damage, up to 2000 mg/kg. Repeated administration of **17** (80 mg/kg/day × 10) in a chemotherapy experiment caused no apparent ill effects.[30] The para-fluorophenyl-, **6**, and the para-methyl-phenyl-, **11**, derivatives were well tolerated when given orally to rat. A lethal dose was not established, but the compounds caused no death up to 2000 mg/kg.[10,49]

BIOCHEMISTRY AND BIOLOGICAL ACTIVITY

The P-DOPA analogue **17** was compared with DOPA as a substrate for mushroom tyrosinase. The rates of melanin formation were of the same order.[30] Two hours after injection of tritium labelled **17** the melanoma tissue contained about 4% of the total radioactivity administered to mice. As the tumor at that time represented about 15% of the weight of the animal, it may be concluded that the greater part of the tritium had been excreted within 2 h. This is confirmed by the high tritium content of the kidneys at 2 h.

Racemic 1-amino-2-phenylethylphosphonic acid **1** is a specific competitive inhibitor of phenylalanyl-tRNA synthase, but the phosphonic acid analogs of valine, leucine, isoleucine, and tyrosine had no effect on the activity of phenylalanine-tRNA synthase (prepared from Aesculus hippocastanum) when tested at a concentration of 2 mM (with respect to the L-form) using 1 mM L-phenylalanine as substrate.[31] The calculated inhibitor constant (K_i) of **1** for phenylalanyl-tRNA synthase of Aesculus hippocastanum was 0.017 mM.[31]

In contrast, the leucyl-, tyrosyl- and valyl-tRNA synthase were not inhibited by the phosphorus analogues of leucine, tyrosine and valine.[31]

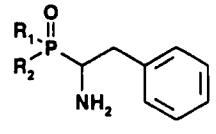
L-1-amino-2-phenylethylphosphonic acid **1** has been found to interact with rabbit muscle pyruvate kinase, in a mode depending on the pH and substrate concentration, exhibiting activatory and inhibitory effects at low (1–5 mM) and at high (above 5 mM) ligand concentrations, respectively.[32] Other biochemical interactions of **1** include transamination with ketoglutarate in mouse tissues[33] and inhibition of one of the key enzymes of plant metabolism, the phenylalanine ammonia lyase (PAL).[34,35] In fact **1** is the most active compound in the buckwheat-PAL inhibition test[35] (see Table VI) of a series of 1-amino-2-arylethylphosphonic acids.[10] Furthermore the data in Table V show clearly that the PAL-inhibition is associated with the phosphonic group, since the corresponding phosphonous and phosphinic acid derivatives are much less active. The phosphine oxide 1-amino-2-phenylethyl-dimethylphosphine oxide **70** shows no inhibition of PAL.

A quantitative structure activity study of the PAL inhibition shows (Table VI) that the 4-fluorophenyl compound has about the same activity as the unsubstituted compound **1**, whereas other substituents cause a marked decrease in the activity. Also the introduction of a second substituent in the phenyl ring or a substituent on the carbon atom which also bears the NH_2-group causes a lowering of the activity.

The effect of the same substituent in different positions in the aryl ring is shown in Table VII. The fluoro and methyl-substituents follow the same pattern: the ortho

TABLE V

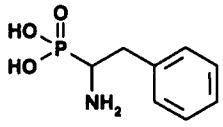
Inhibitions constants for buckwheat PAL and anthocyanin synthesis of phosphonic-, phosphonous-, phosphinic- and phosphine oxid analogues of phenylalanine



R_1	R_2	Inhibition const. for buckwheat PAL (μM)K_i	Inhibition of anthocyanin synth. in vivo by 1 mM in %
OH	OH	2.6	83
OH	H	110	~0
OH	CH_3	850	0
CH_3	CH_3	∞	0

TABLE VI

Inhibition constants for buckwheat PAL and anthocyanin synthesis of variously substituted phosphonic acid analogues of phenylalanine



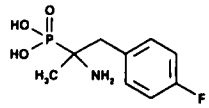
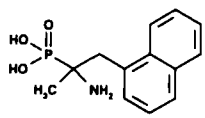
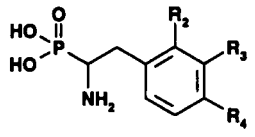
X (racemates)	Inhibition constants for buckwheat PAL (μM)	Inhibition of anthocyanin synthesis in vivo by 1 mM (in%)
H	2.6	83
2-F	1.6	65
3-F	2.7	73
4-F	3.5	87
4-Cl	120	0
4-Br	~1100	0
4-I	~2200	0
2-CH_3	12.3	72
3-CH_3	21	54
4-CH_3	780	0
3-CF_3	200	
4-$(CH_3)_3C$	~2000	4
4-OH	410	0
3,4-Cl_2	170	
2,4-Cl_2	380	
2,4-F_2	6.1	63
2,6-F_2	55	25
3,4-$(OH)_2$	260	
	180	4
	82	0

TABLE VII

Dependence of the inhibition constants for buckwheat PAL and anthocyanin synthesis from the position of the substituent in the phenyl ring



R_2	R_3	R_4	Inhibition const. PAL (μM) K_i	Inhibition of anthocyanin synth. by 1mM (in %)
F	H	H	1.6	65
H	F	H	2.7	73
H	H	F	3.5	87
CH_3	H	H	12.3	72
H	CH_3	H	21.0	54
H	H	CH_3	780	0

substituted derivative is most active followed by meta then para. Inhibition of anthocyanin synthesis is sometimes reversed (e.g. with fluoro).

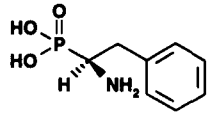
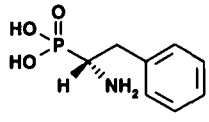
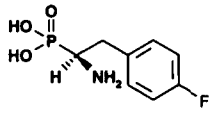
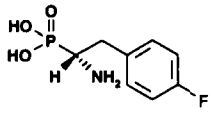
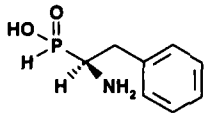
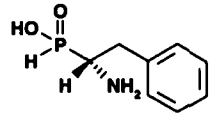
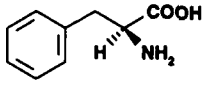
When comparing the activity of the optically active compounds in the phosphonic and phosphonous acid series it is seen that the R-(−) compounds (corresponding to L-amino acids) are about 5–8 times as active as the S-(+) compounds (Table VIII).

A comparison of the activity of racemic 1-amino-2-(4-fluorophenyl)ethylphosphonic acid **6** and 4-fluorophenylalanine shows that **6** is a better inhibitor (by two orders of magnitude) of anthocyanin synthesis than 4-fluoroalanine. This indicates that the inhibition is mainly due to the introduction of the phosphonic acid group.[34]

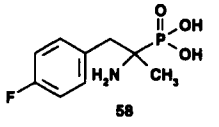
1-Amino-2-(4-hydroxyphenyl)ethylphosphonic acid **17** shows inhibitory properties in the tyrosyl-tRNA synthetase catalyzed ATP-PP_i exchange reaction. It is competitive with respect to tyrosine but binds 5-fold less effectively than tyrosine.[36] Neuzil *et al.*[37] observed that **17** is oxidized by mushroom tyrosinase at a lower rate than that observed with tyrosine. The oxidation process looks similar in both cases: the analogues of DOPA, of DOPA-quinone, of DOPA-chrome as well as melanins are formed during the course of the reaction.[6,37] The same authors reported[6] that **17** is one of the best competitive inhibitors of the tyrosine aminotransferase of rat liver and of tyrosine decarboxylase extracted from Streptococcus faecalis. Three aminophosphonates i.e. **75**, **76**, and **77** were active acaricides against Tetranychus cin. tol., particularly against larvae and eggs. Several of the compounds and in particular **58**, **70**, **78**, **79**, **80**, and **81** exhibited plant growth regulatory properties and **82** and **83** showed herbicidal activity[10,12].

TABLE VIII

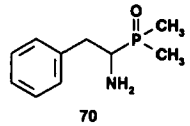
Inhibition constants for buckwheat PAL and anthocyanin synthesis of optically active compounds

Structure		Inhibition constans for buckwheat PAL K_I(μ M)	Inhibition of anthocyanin synthesis in vivo by 1mM (in %)
	(R)-(-)	1.5	88
	(S)-(+)	11.6	53
	(-)	2.8	
	(+)	13.5	
	(R)-(-)	35	0
	(S)-(+)	205	0
	(L)	K_m=45(μM)	

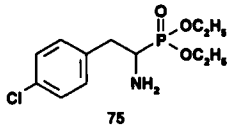
It was also reported that the phosphonic acid analogues of phenylalanine **1**, tyrosine **17**, and 3,4-dihydroxyphenylalanine **16** exhibited interesting plant growth regulatory properties when tested on Cucumis sativus L. Depending on the chemical structure, they slightly inhibited or strongly promoted the growth of C. sativus roots, while their influence on hypocotyls was negligible. Phosphono-peptides based on these acids showed less significant plant growth regulating activity.[38] A phenoxy-substituted phosphine oxide **84** showed a 75% herbicidal activity against 4 weeds



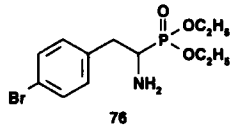
58



70



75



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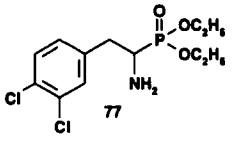

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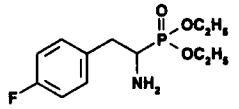

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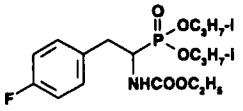

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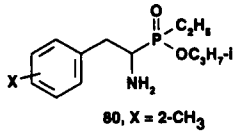
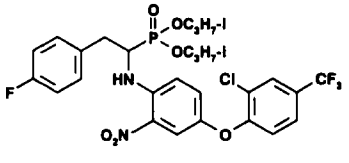
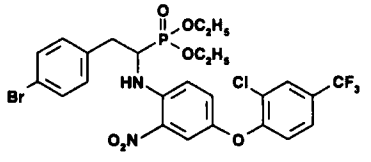


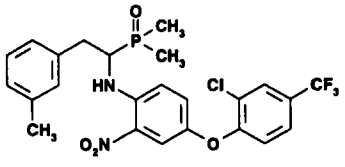
80, X = 2-CH_3
81, X = 4-CH_3



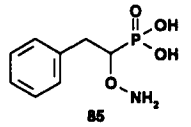
82



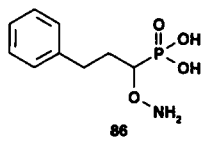
83



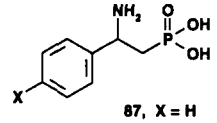
84



85



86



87, X = H
88, X = 4-F
90, X = 4-CH_3
91, X = 4-CH_3O

in the preemergent test while the postemergent herbicidal activity was less pronounced.[39]

More important is the observation that many of the 1-amino 2-aryl ethylphosphonic acids are quite active botryticides.[10,12] Among the active compounds were 1-amino-2-(4-fluorophenyl)ethylphosphonic acid **6**, the methyl-substituted compounds **11**, **12**, and **13**, and **31**, **32**, **33**, **37**, **50**, **51**, and **53** whereby some of the compounds (**6**, **31**, **50**, **51**, and **53**) gave full protection against Botrytis cinerea down to 200 ppm. In addition **36** gave a 69% inhibition of anthocyanin synthesis *in vivo* by 1 mM.[35] The fluoroderivative **6** was also effective as a seed-dressing agent in barley and rye showing a 100% protection against the fungus Fusarium nivale at 600 ppm.[10]

The fungicidal activity of the optically active fluoroderivatives **23** and **24** and of the di- (**C**, **D**) and tripeptides (**E**, **F**) thereof was not higher than that of the parent racemic compound **6**.[18] Some other activities of the phosphorus analogues of phenylalanine are summarized in Table IX.

BIOLOGICAL ACTIVITY OF ANALOGUES AND HOMOLOGUES

In contrast to 1-amino-2-phenylethylphosphonic acid **1**, 1-aminooxy-2-phenylethylphosphonic acid **85** exhibits only weak antifungal activity and is only a weak inhibitor of PAL, but the inhibition of anthocyanin synthesis in vivo by 1 mM of 1-aminooxy-3-phenylpropylphosphonic acid **86** is 68%.[21]

Like 1-amino-2-arylethylphosphonic acids several of the 2-amino-2-arylethylphosphonic acids also show activity against Botrytis cinerea (on apple) and cercospora (on peanuts). Among the more active compounds were **87**, **88**, **90** and **91**, whereby some of the compounds (**88** and **91**) gave full protection against Botrytis cinerea down to 60 ppm. In addition, the same compounds show a weak inhibition of anthocyanin synthesis in vivo (3.4% by 1 mM). The anthocyanin and PAL inhibition data of 2-amino-2-arylethylphosphonic acids and of the homologues such 1-amino-3-arylpropyl- and 1-amino-4-arylbutylphosphonic acid are summarized in Table X.

Remarkable is the high PAL inhibition of 1-amino-3-(4-fluorophenyl)-propylphosphonic acid **95** and the stimulation and not inhibition of the anthocyanin synthesis by several derivatives. The highest value is reached with 2-amino-2-(4-methylphenyl)ethylphosphonic acid **90**.

Of the homologues 1-amino-4-(4-methoxyphenyl)butylphosphonic acid **96** showed fungicidal activity. It gave full protection against botrytis on apple at 200 ppm.

TABLE IX

Various biological activities of phosphorus analogues of phenylalanine and derivatives

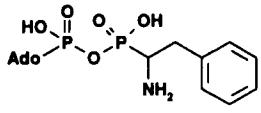
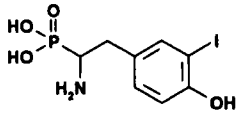
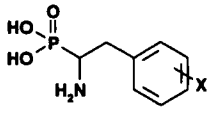
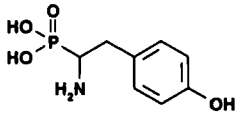
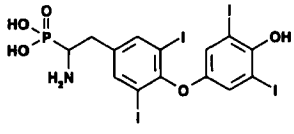
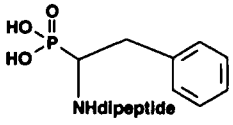
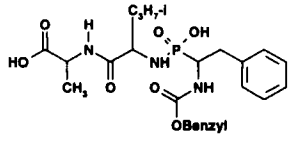
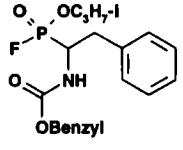
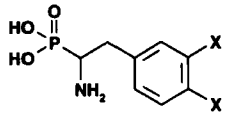
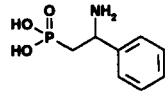
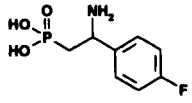
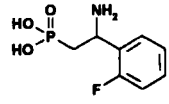
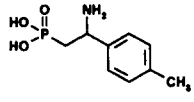
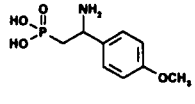
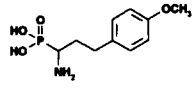
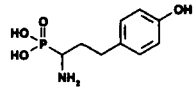
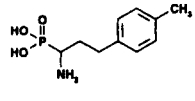
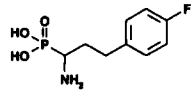
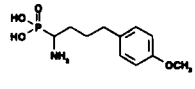
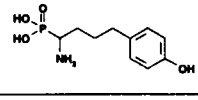
Compound	Activity	Reference
	is a substrate for phenyl-alanyl-*t* RNA synthetase from *E. coli* with $K_i/K_m \sim 10^{-4}$	40
	diodination by rat microsomal enzyme	41
	X=H, OH; growth inhibition of wild strains of S. typhimurum	42
	reduction of iodine uptake by chicken embryo thyroid gland	6
	growth stimulation of the toad of Rana dalmatina Bon.	43
	hypotensive activity; 600mg/kg (intravenous) not lethal to mice	7
	powerful inhibitor of thermolysin	44
	extremly effective and highly specific in the inactivation of chemotrypsin	45
	X=OH,CH_3O are substrates for mushroom tyrosinase with K_m values of 3.3 mM and 9.3 mM, respectively	47

TABLE X

Inhibition constants for buckwheat PAL and anthocyanin synthesis of phosphonic acid analogues and homologues of phenylalanine

	Compound	Anthocyan-Inh. [I] = 1mM (in %)	In Vitro PAL-Inh.[I]=1mM, [PHE]=3.2mM (in %)
87		n.d.	n.d.
88		17.8	0.0
89		16.2	2.2
90		121.8	3.4
91		n.d.	n.d.
92		105.0	10.0
93		103.3	13.8
94		1.0	0.0
95		80.2	75.9
96		109.4	10.3
97		105.8	10.3

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