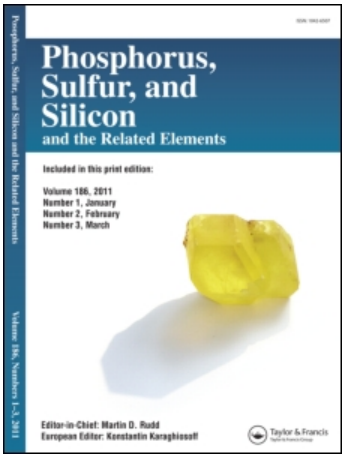

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ORGANIC PHOSPHORUS COMPOUNDS 97.[1] SYNTHESIS AND PROPERTIES OF 1-AMINO-2-ARYL- AND 2-PYRIDYL-ETHYLPHOSPHONIC ACIDS AND DERIVATIVES

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ORGANIC PHOSPHORUS COMPOUNDS 97.[1] SYNTHESIS AND PROPERTIES OF 1-AMINO-2-ARYL- AND 2-PYRIDYL-ETHYLPHOSPHONIC ACIDS AND DERIVATIVES

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1-Amino-2-(o, m, and p-pyridyl)-ethylphosphonic acids, **5α**, **5β** and **5γ**, have been prepared by alkylation of benzylideneaminomethylphosphonate, followed by hydrogenation and hydrolysis, whereas 1-amino-2-(o, m, and p-methoxyphenyl)-ethyl phosphonic acids, **5i**, **5k**, and **5l** and some other derivatives were obtained from the oximes by hydrogenation and hydrolysis.

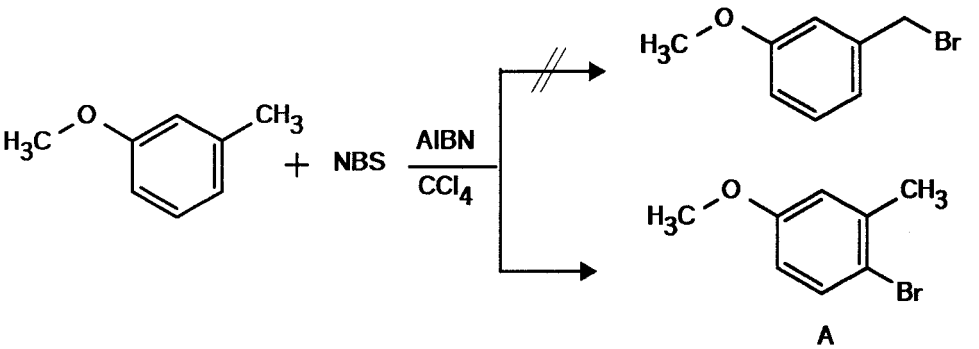
1-Amino-2-pyridylethylphosphonic acids, **5α**, **5β**, and **5γ**, and 1-amino-2-(alkoxy-substituted phenyl)-ethylphosphonic acids, **5l**, **5m**, and **5n** and others such as **5u** show activity against Botrytis cinerea (on apple) and Cercospora (on peanuts). **5q** is an inhibitor of anthocyanin synthesis in vivo. **3t** exhibits activity against Piricularia (on rice) and **3w** is active against Phytophthora (on tomato) and Plasmopora (on grapes).

Key words: 1-Amino-2-pyridylethylphosphonic acids; 1-amino-2-(alkoxy-substituted phenyl)-ethylphosphonic acids; 1-amino-2-(4-phenoxyphenyl)-ethylphosphonic acids; hydrogenation of oximes; biological activity.

INTRODUCTION

Recently we reported on the preparation and properties of 1-amino-2-arylethyl-phosphonic acids.[2] We also described the resolution of 1-amino-2-(4-fluorophenyl)-ethylphosphonic acid into its optical isomers.[1]

However, attempts to prepare 1-amino-2-(3-methoxyphenyl)-ethylphosphonic acid, **5k**, by the alkylation procedure[2] were not successful, because 3-methoxybenzyl bromide was not available. When it was attempted to prepare this compound by radical bromination of 3-methoxytoluene with NBS in CCl_4 in the presence of AIBN according to the literature,[3] only ring bromination was observed and 3-methyl-4-bromoanisol, **A**, was isolated in 75% yield.

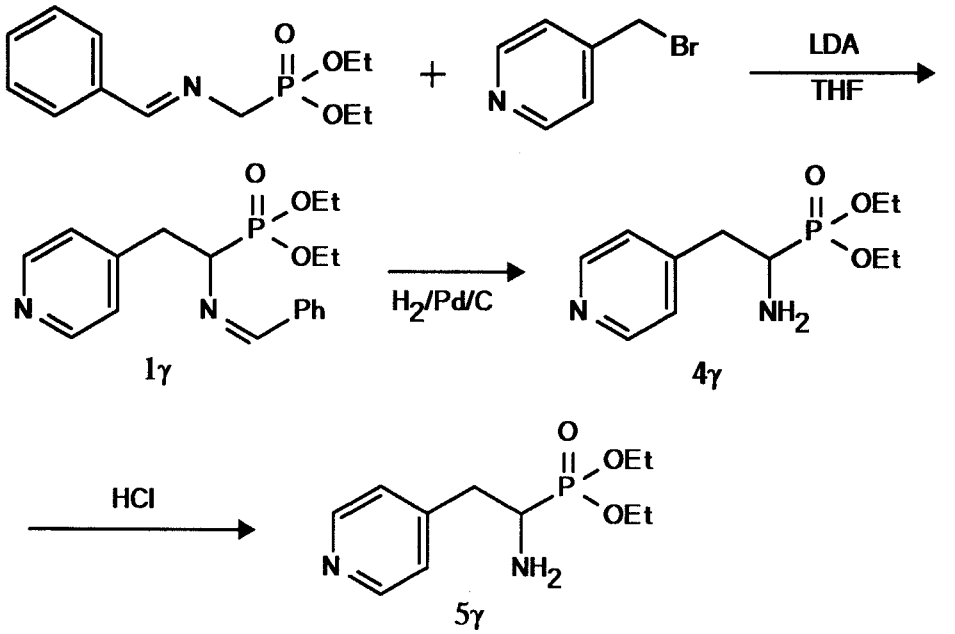


A

On the other hand this compound was described in the literature.[4] It was prepared by treating 3-methoxybenzyl alcohol with HBr. However it is rather unstable. Therefore we have investigated other methods to prepare **5k** and several other derivatives.

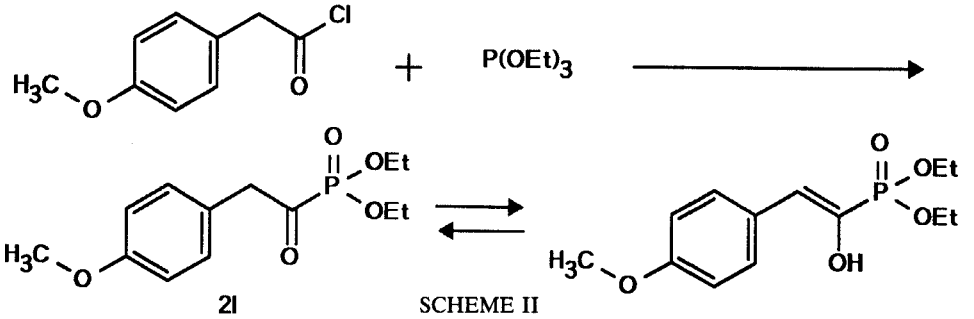
RESULTS AND DISCUSSION

The 1-amino-2-pyridylethylphosphonic acids and some others (Tables I, IV and V) were prepared by the alkylation procedure described previously by us,[2] e.g., (Scheme I):

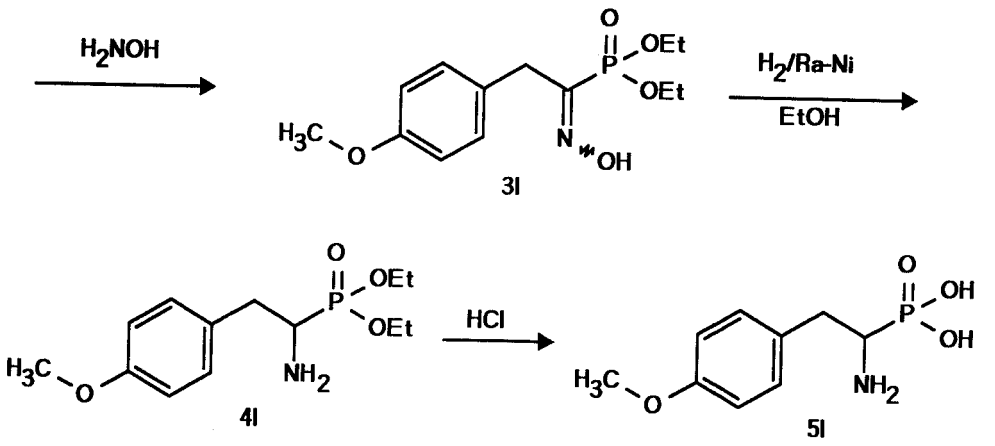


SCHEME I

Several other 1-amino-2-arylethylphosphonic acids including the methoxy- and phenoxy-substituted ones were prepared from the acylphosphonates (Table II) which were converted to oximes (Table III) and then reduced to aminophosphonates (Table IV) with H_2 in the presence of Raney-Ni as a catalyst. These on hydrolysis with HCl gave the aminophosphonic acids (Table V) (Scheme II), e.g.:



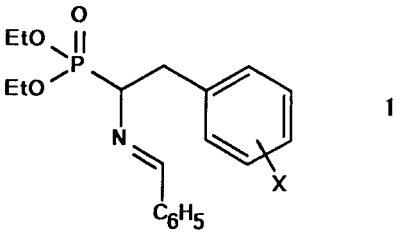
SCHEME II



SCHEME II *(continued)*

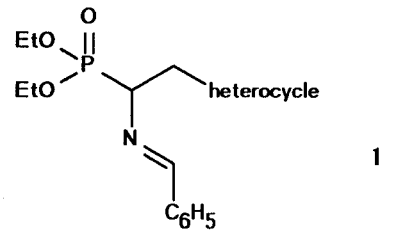
TABLE I

Physical properties of 1-benzylideneamino-2-arylethylphosphonates



1

No.	X	yield in %	m.p. °C	^{1}H-NMR in $CDCl_3$ PCH_2CH	N=CH
e	2,3,4,5,6-F_5	84.8	resin	2.9–3.7	8.0 and 8.07
f	4-CF_3	84.4	resin	3.0–3.6	7.83; 7.93
q	2-NO_2	6.8	oil	3.3–3.7	7.9; 7.97
r	2-CH_3-3-F	89.1	oil	2.8–3.6	7.9; 8.0

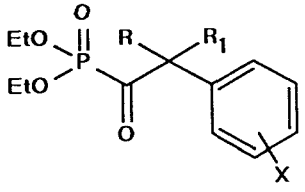


1

	Heterocycle				
α	pyridyl(2)	84.8	resin	2.9–3.7	8.0; 8.07
β	pyridyl(3)	73.1	resin	2.8–3.6	7.93; 8.0
γ	pyridyl(4)	71.6	resin	3.0–3.5	8.3; 8.4

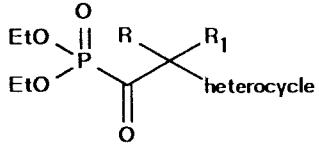
TABLE II

Physical properties of arylacetylphosphonates



2

No.	R	R^1	X	yield in %	b.p. °C/torr (m.p. °C)	^{1}H-NMR in $CDCl_3$ R	R^1	X	Aryl	Structure
c	H	CH_3	H	97.9	115/0.06	4.5	1.5		7.35	keto
g	$-CH_2-CH_2-$	H	4-CH_3	95.2	115/0.6	1.27	1.9	2.38	7.0–7.4	keto
h	H	H	4-C_2H_5	97.8	145–150/0.01	6.0(J12)		2.4(CH_2Ar)	6.9–7.7	~60% enol
i	H	H	2-CH_3O	85.8	164/0.04	4.1		3.8	6.8–7.5	little enol
k	H	H	3-CH_3O	79.8	165/0.04	6.2(J12)		3.8	6.7–7.5	mainly enol
l	H	H	4-CH_3O	90.7	160/0.1	5.95(J11)		3.8	6.8–8.2	mainly enol
m	H	H	4-C_2H_5O	76.8	solid	6.03(J12)		4.0(OCH_2)	6.87–7.7	100% enol
n	H	H	4-n-C_4H_9O	67.6	solid	6.1(J12)		4.1(OCH_2)	6.87–7.8	100% enol
s	H	H	2,3-OCF_2O-	97.1	oil	6.1(J12)			6.77–7.1	~30% enol
t	C_3H_5-cycl.	H	4-Cl	76.7	170/0.06	0.1–0.9(m)	3.6(J10)		7.35	keto
u	C_3H_7-i	H	4-Cl	86.9	165/0.06	2.4(m)CH 0.7; 1.05(Me)	3.9(m)		7.35	keto
v	H	H	4-phenoxy	97.7	yellow oil	6.2(J12)			6.8–7.6	100% enol
w	H	H	4-(4′-chlorophenoxy)	95.2	yellow oil	6.1(J12)			6.6–7.6	100% enol
x	H	H	4-(4′-fluorophenoxy)	99.5	yellow oil	6.15(J13)			6.8–7.6	100% enol

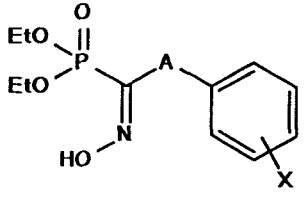


2

	Heterocycle						
α	pyridyl(2)	96.2	(52–54)	6.4(J10)		7.1–8.6	100% enol
δ	2-CH_3-pyridyl(6)	57.9	oil	6.35(J10)	2.55	6.9–7.8	100% enol
ε	2-phenoxypyridyl(6)	51.3	yellow oil	6.3(J11)		6.7–7.85	100% enol

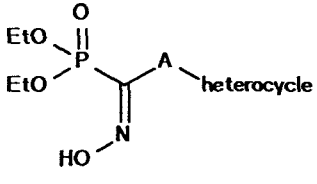
TABLE III

Physical properties of 1-oximido-2-arylethylphosphonates



3

No.	A	X	yield in %	b.p. °C/torr (m.p. °C)	^{1}H-NMR in $CDCl_3$ CH_2	other	aryl	OH
c	CH(Me)	H	92.4	yellow oil	1.45(Me)	4.0(CH)	7.25	11
g	C_3H_5-cycl.	4-CH_3	75.9	(84–86)	1.3(CH_2CH_2)	2.2(Me)	6.9–7.4	11.3
h	CH_2	4-C_2H_5	49.3	oil	4	2.6(CH_2Me)	7.0–7.4	11.3
i	CH_2	2-CH_3O	95.1	solid	4	3.75(OCH_3)	6.6–7.3	11.3
k	CH_2	3-CH_3O	93.8	oil	4	3.8(OCH_3)	6.6–7.4	11.4
l	CH_2	4-CH_3O	89.9	oil	4.05	3.75(OCH_3)	6.55–7.3	11.3
m	CH_2	4-C_2H_5O	93.3	resin	3.9	3.8(OCH_2)	6.7–7.4	11.3
n	CH_2	4-n-C_4H_9O	54.8	oil	4	4.0(OCH_2)	6.77–7.3	10.75
s	CH_2	2,3-OCF_2O-	79.5	oil	4.1		6.8–7.2	11.6
t	CH(C_3H_5-cycl.)	4-Cl	77.3	133–135	3.2(m)	0.1–0.8(m)	7.35	11.2
u	CH(C_3H_7-i)	4-Cl	99.8	yellow oil	3.2(m)	2.3(CH) 0.65; 1.05(Me)	7.35	12.1
v	CH_2	4-phenoxy	66.2	yellow oil	3.9		6.7–7.6	11.4
w	CH_2	4-(4′-chlorophenoxy)	77.4	yellow oil	4.05		6.7–7.5	11
x	CH_2	4-(4′-fluorophenoxy)	58.9	yellow oil	3.9		6.8–7.3	10.6

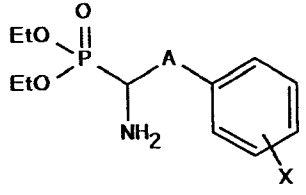


3

	Heterocycle						
α	pyridyl(2)	66.9	resin	4.1(J13)		7.0–8.5	12.2
δ	2-CH_3-pyridyl(6)	30.3	oil	4.1	2.0(Me)	6.9–7.6	11
ε	2-phenoxypyridyl(6)	88.75	yellow oil	4.05		6.5–7.7	11.4

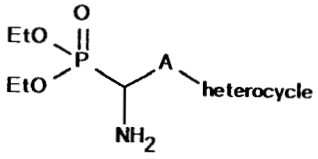
TABLE IV

Physical properties of 1-amino-2-arylethylphosphonates



4

No.	A	X	Method*	yield	b.p. °C/torr (m.p.)	^{1}H-NMR in $CDCl_3$ CH_2CHP	NH_2	subst.	aryl
c	CH(Me)	H	a	82.9	125/0.1	3.1–3.3	1.9	1.5(Me)	7.3
d	CH_2	[a]	b	69.6	100/0.08	3.1	1.6	0.7–2.0(C_6H_{11})	
e	CH_2	2,3,4,5,6-F_5	c	27.7	(102–104)	2.7–3.4	1.4		
f	CH_2	4-CF_3	d	33.1	106/0.1	2.5–3.5	1.4		7.2–7.7
g	C_3H_5-cycl.	4-CH_3	a	57.9	190–200/0.05	2.6(J17)	1.63	2.3(Me)	6.9–7.5
h	CH_2	4-C_2H_5	a	90	170/0.01	2.5–3.5	1.4	2.5(CH_2)	7.2
i	CH_2	2-CH_3O	a	75.3	125/0.08	2.4–3.3	1.45	3.8(OMe)	6.8–7.4
k	CH_2	3-CH_3O	a	78.4	140/0.04	2.5–3.5	1.6	3.8(OMe)	6.7–7.4
l	CH_2	4-CH_3O	a	84	145/0.1	2.3–3.6	1.38	3.8(OMe)	6.7–7.3
m	CH_2	4-C_2H_5O	a	90	170/0.01	2.5–3.5	1.47	3.9(OCH_2)	6.75–7.3
n	CH_2	4-n-C_4H_9O	a	98.8	oil	2.3–3.5	1.4	4.0(OCH_2)	6.7–7.3
q	CH_2	2-NO_2	c	36.8	oil	2.9–3.7	1.4		7.3–8.1
r	CH_2	2-CH_3-3-F	d	64.2	140/0.08	2.5–3.5	1.5	2.25(Me)	6.9–7.3
s	CH_2	2,3-OCF_2O-	a	56.5	110/0.06	2.5–3.7	1.6		7
t	CH(C_3H_5-cycl.)	4-Cl	a	65.3	150/0.7	3.35(4d,J_{PH}15) 2.28(m)	1.7		7.2–7.4
u	CH(C_3H_7-i)	4-Cl	a	22.8	125/0.4	2.0–3.8(m)	1.55		7.2–7.4
v	CH_2	4-phenoxy	a	83.3	yellow oil	2.3–3.5(m)	1.35		6.7–7.5
w	CH_2	4-(4′-chlorophenoxy)	a	69.5	yellow oil	2.65(m)(CH) 3.2(m)(CH_2)	1.35		6.8–7.3
x	CH_2	4-(4′-fluorophenoxy)	a	89.9	yellow oil	2.3–3.5(m)	1.65		6.5–7.3



4

	Heterocycle						
α	pyridyl(2)	d	52.7	150–160/0.02	2.6–3.9	1.73	7.0–8.5[b]
β	pyridyl(3)	c	28.8	135/0.08	2.5–3.5	1.4	7.2–8.7
γ	pyridyl(4)	d	25.3	140/0.1	2.5–3.6	1.6	7.3–8.6
δ	2-CH_3-pyridyl(6)	a	48.4	oil	2.6–3.7	1.6	6.7–7.4
ε	2-phenoxypyridyl(6)	a	82.3	yellow oil	2.35–3.7(m)	1.65	6.6–7.7

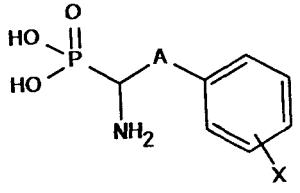
* a) From oxime and H_2/RaNi/EtOH/100°C/80 bar; b)hydrogenation of phenyl-compound with H_2/Rh/Al_2O_3/t-BuOH/50°/150 bar; c) from Schiff base and 1N HCl[2]; d) from Schiff base and H_2/Pd/C/20–25°C in EtOH/normal pressure.[2]

[a] C_6H_4X = cyclo-C_6H_{11}.

[b] ^{31}P 28.16 ppm.

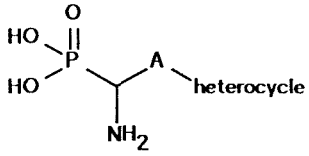
TABLE V

Physical properties of 1-amino-2-arylethylphosphonic acids



5

No.	A	X	yield in %	m.p. °C (dec.)	PCHCH$_n$	^{1}H-NMR in D_2O/NaOD NH_2/OH	aryl
a	CH_2	4-F	84.5(+)	259–263[a]	2.3–3.1	4.65	6.6–7.1
b	CH_2	4-F	77.6(−)	261–263[b]	2.5–3.4	4.85	6.8–7.4
c	CHMe	H	59.5	249	2.9–3.3 1.3(CMe)	4.8	7.3
d	CH_2	[i]	75.3	265–268	2.4(CHP)	4.85	
e	CH_2	2,3,4,5,6-F_5	85.8	283–289	2.5–3.4	4.85	
f	CH_2	4-CF_3	66.8	>320	2.0–3.0	4.6	6.9–7.4
g	C_3H_5-cycl.	4-CH_3	66.4	246–247	2.4(CHP) 0.4–1.2(CH_2CH_2)	4.9	6.9–7.6
h	CH_2	4-C_2H_5	84.3	277–280	2.1–3.3	4.9	6.9–7.3
i	CH_2	2-CH_3O	82.1	264–265	2.5–3.3	4.95	6.8–7.5
k	CH_2	3-CH_3O[c]	51.8	~270	2.2–3.3	4.85	6.7–7.3
l	CH_2	4-CH_3O	79.7	280–282	2.3–3.3	5.3	6.7–7.4
m	CH_2	4-C_2H_5O	73.5	267–271	2.3–3.3	4.95	6.7–7.4
n	CH_2	4-n-C_4H_9O	54.8	236–240	2.4–3.5	4.9	6.9–7.6
o	CH_2	2-OH	90.6	>300	2.2–3.2	4.7	6.3–7.2
p	CH_2	3-OH[d]	73.7	270	2.0–3.2	4.6	6.1–7.0
q	CH_2	2-NO_2	91.8	243–246	2.9–3.7	5.2	7.4–8.2
r	CH_2	2-CH_3-3-F	82.3	280	2.2–3.3	4.95	6.9–7.2
s	CH_2	2,3-OCF_2O	52.9	238–239	2.5–3.3	4.95	7.03
t	CH(C_3H_5-cycl.)	4-Cl	15.5	253–255	2.1; 2.7(m)	4.9	7.0–7.3[e]
u	CH(C_3H_7-i)	4-Cl	35	262–264	2.1(m); 3.1(2d,J10)	5	7.2–7.4
v	CH_2	4-phenoxy	89.3	220–225[f]	2.8–4.0(m)[g]	8.15	6.6–7.5
w	CH_2	4-(4′-chlorophenoxy)	77.3	243–245	3.2; 3.6(m)[g]	6.75/8.3	6.8–7.4
x	CH_2	4-(4′-fluorophenoxy)	65.3	235–237	not soluble enough[h]		



5

	Heterocycle					
α	pyridyl(2)[k]	71.4	solid	2.9–3.7	4.7	7.2–8.5
β	pyridyl(3)	81.7	solid	3–4	4.9	8–9
γ	pyridyl(4)	91.6	solid	3–4	4.8	8.0–8.4
δ	2-CH_3-pyridyl(6)	78.9	203–204	3.3–3.5	4.8	7.4–8.05
ε	2-phenoxypyridyl(6)	77.4	>105	not soluble enough		

[a] $[\alpha]Na_D^{20} + 37.5 \pm 0.4°$ (c = 2.63 in 1N NaOH)[1].
[b] $[\alpha]Na_D^{20} -36.9 \pm 0.5°$ (c = 2.081 in 1N NaOH)[1].
[c] From phosphonate and HCl.
[d] From phosphonate and HBr.
[e] ^{31}P-NMR (85% H_3PO_4 ref.) 20.02 ppm ($NaOD/D_2O$, pH = 11).
[f] HBr-salt.
[g] ^{1}H-NMR (in $CDCl_3$/DMSO-d_6).
[h] $C_{14}H_{15}FNO_4P \cdot H_2O$(329) calc.: C 51.0, H 5.16, F 5.77, N 4.25, P 9.4, H_2O 5.4%
found: C 52.0, H 5.2, F 6.0, N 4.2, P 9.1, H_2O 5.4%
[i] C_6H_4X = cyclo-C_6H_{11}.
[k] isolated as ketimine with acetone.
[l] $C_{13}H_{15}N_2O_4P \cdot 1.9HBr \cdot H_2O$ (466) calc.: C 33.4, H 4.07, Br 32.6, N 6.0, P 6.6, H_2O 3.8%
found: C 34.6, H 4.10, Br 32.4, N 5.9, P 6.2, H_2O 3.4%

The interaction of arylacetyl chlorides and triethylphosphite gives high yields of arylacetyl phosphonates (Table II). These are in equilibrium with the enol-structure as indicated in Scheme II and reported previously.[5]

The keto- as well as the enol-phosphonates, **2**, give, on treatment with hydroxylamine hydrochloride in pyridine solution, high yields of the corresponding oximes, **3**, (Table III). Hydrogenation of the oximes with Raney-Ni proceeds only then satisfactorily when it is carried out in ethanol. Use of THF or dioxane as solvents led to no isolable products. Asano et al., who also prepared aminophosphonic acids, albeit in low yields, by hydrogenation of oximes in the presence of Raney-Ni[6] did not indicate the solvent used.

Hydrolysis of the aminophosphonates **4** with 20% HCl under reflux produced the aminophosphonic acids **5** in good yields. Hydrolysis of **4k** with HBr cleaved the ester and ether linkages simultaneously and gave **5p**.

The ^{31}P-chemical shift of 20 ppm at pH 11 for **5t** is in the range of other 1-amino-2-arylethylphosphonic acids.[2] The ^{1}H-NMR spectrum of **5** is given in Fig. 1, and the pK-values of several aminophosphonic acids **5** are summarized in Table VI.

BIOLOGICAL ACTIVITY

As previously observed for other compounds of this type[2] several of the aminophosphonic acids **5** described in this paper also show activity against Botrytis cinerea (on apple) and Cercospora (on peanuts). Among the more active compounds were **5l**, **5m**, **5n**, **5r**, **5α**, **5β**, and **5γ**, whereby some of the compounds (**5l**, **5α**, **5β**, and **5γ**) gave full protection against Botrytis cinerea down to 200 ppm. In addition **5q** gave a 69% inhibition of anthocyanin synthesis in vivo by 1 mM.[7] **3t** exhibits activity against Piricularia (on rice) and **3w** is active against Phytophthora (on tomato) and Plasmopora (on grapes).

EXPERIMENTAL

Phosphorus NMR-spectra were recorded using a Bruker WP 80 spectrometer at 32.28 MHz (ref. 85% H_3PO_4), and ^{1}H-NMR-spectra were recorded with a Varian EM 360 spectrometer at 60 MHz or a Bruker WM 250/250 MHz spectrometer (ref. $(CH_3)_4Si$). The chemical shifts are reported in ppm, with negative values being upfield of the standard, and positive downfield. All reactions were run under an atmosphere of argon.

1. 3-Methyl-4-bromoanisol, **A**. A suspension of 98 g (0.55 mol) of NBS and 63.1 ml (0.5 mol) of 3-methylanisol in 200 ml of carbontetrachloride is heated under stirring to 80°C and 1 g of AIBN added. An exothermic reaction ensues and the temperature increases to 83°C. Stirring and heating is continued for one hour then the mixture is filtered and the filtrate evaporated. The residue is distilled to give 75.6 g (72.2%) of **A**, b.p. 61°C/0.08 torr.
^{1}H-NMR (in $CDCl_3$)δ: 2.33 (s, CH_3, 3H); 3.73 (s, OCH_3, 3H); 6.6 (2d, J9 and J2, C6, 1H); 6.8 (d, J2, C2, 1H); 7.3 (d, J9, C5, 1H).

C_8H_9BrO (201.06): calc.: C 47.79 H 4.51 Br 39.74%
found: C 47.8 H 4.6 Br 39.8%

2. O,O-Diethyl-4-methoxyphenylacetylphosphonate, **2l**. A solution of 73.2 ml (0.42 mol) of triethylphosphite in 100 ml of diethyl ether is treated dropwise with 70.4 g (0.382 mol) of 4-methoxy-phenylacetyl chloride. An exothermic reaction ensues. After evaporation of the solvent, thin layer distillation of the residue gives 98.8 g (90.7%) of **2l**, b.p. 160°C/0.1 torr, a yellow oil.

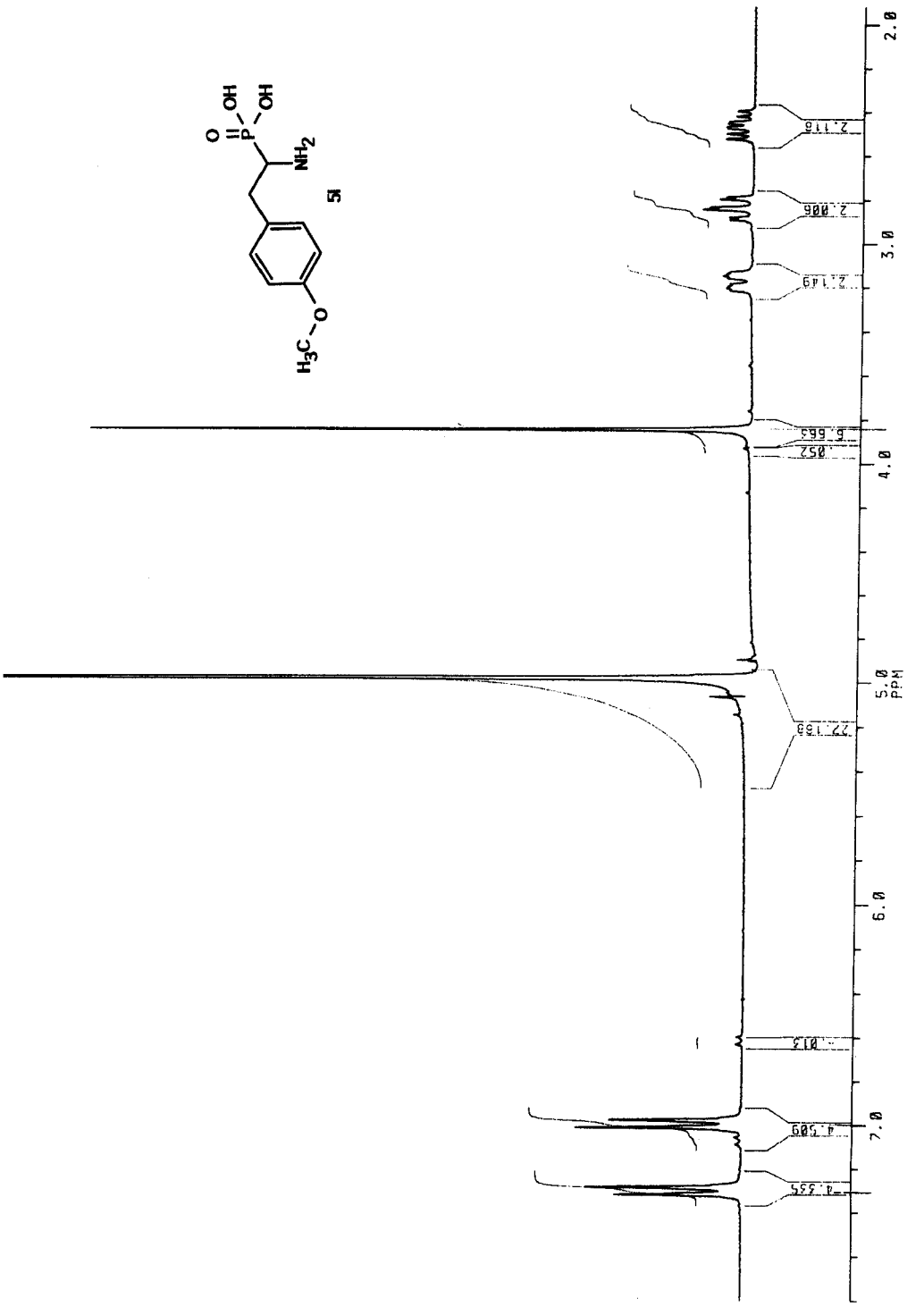


FIGURE 1 ^{1}H-NMR spectrum of **5l** at 250 MHz (in D_2O/NaOD).

TABLE VI
pK values of 1-amino-2-arylethylphosphonic acids

No.	pK_1	pK_2	pK_3	pK_4
5c	<2.5	5.94	10.08	
5d	<2.5	5.85	10.42	
5g	<2.5	6.34	10.28	
5h	<2	5.59	9.97	
5i	<2.5	5.73	10.3	
5k	<2.5	5.57	9.81	
5l	<2.5	5.7	9.9	
5m	<2.5	5.63	9.9	
5n	<2.5	7.87	>11.0	
5o	<2.5	5.68	9.22	11.7
5p	<2.5	5.66	9.45	10.6
5r	<2.5	5.65	9.8	
5s	<2.5	5.42	9.48	

^{1}H-NMR (in $CDCl_3$)δ: 1.33 (2t, CH_3, 6H); 3.7 (s, OCH_3, 3H); 4.1 (m, OCH_2 + CH_2CO, 4.3H); 5.95 (d, J11, CH=C, 0.7H); 6.6–8.0 (m, C_6H_4 + OH, 4.7H).
The spectrum indicates that about 70% of **2l** are present in the enol form. The compounds listed in Table II have been prepared similarly.

3. O,O-Diethyl-1-oximato-2-(4-methoxyphenyl)-ethylphosphonate, **3l**. To a suspension of 18.1 g (0.26 mol) of hydroxylammonium chloride in 24 ml of pyridine and 60 ml of ethanol is added slowly 53.7 g (0.2 mol) of **2l**, dissolved in 20 ml of ethanol. After standing for 12 h the clear solution is evaporated and the oily residue treated with 200 ml of HCl (0.5%), then the mixture is extracted 5 times with 150 ml of CH_2Cl_2 each, the organic phase washed with $NaHCO_3$ (5%) and water, and then dried over Na_2SO_4. Filtration and evaporation yields 54.2 g (89.9%) of **3l**, a yellow oil.
^{1}H-NMR (in $CDCl_3$)δ: 1.2 (t, CH_3, 6H); 3.65 (s, OCH_3), 3.9 (m, OCH_2, CH_2) (9H); 6.5–7.3 (m, C_6H_4, 4H); 10.93 (br.s, NOH, 1H).

$C_{13}H_{20}NO_5P$ (301.28): calc.: C 51.83 H 6.69 N 4.65 P 10.28%
found: C 51.5 H 6.7 N 4.2 P 10.6%

The compounds listed in Table III have been prepared similarly.

4. O,O-Diethyl-1-amino-2-(4-methoxyphenyl)-ethylphosphonate, **4l**. To a solution of 45.2 g (0.15 mol) of **3l** in 450 ml of ethanol is added 9 g of Raney-Ni and the mixture hydrogenated at 100°C and 80 bar. After 6 h another 9 g of Raney-Ni are added and hydrogenation continued for 6 h. The mixture is filtered and the filtrate evaporated. Thin layer distillation of the residue yields 36.2 g (84%) of **4l**, b.p. 140°C/0.04 torr, a clear oil.
^{1}H-NMR (in $CDCl_3$)δ: 1.38 (m, CH_3, NH_2, 8H); 2.3–3.6 (m, CH_2CHP, 3H); 3.8 (s, OCH_3, 3H); 4.2 (qui, OCH_2, 4H); 7.05 (2d, C_6H_4, 4H).
The compounds listed in Table IV have been prepared similarly.

5. 1-Amino-2-(4-methoxyphenyl)-ethylphosphonic acid, **5l**. A mixture of 8.6 g of **4l** and 60 ml of 20% HCl is refluxed for 3.5 h. Then the clear solution is evaporated and the residue recrystallized from methanol/propylene oxide to give 5.5 g (79.7%) of **5l**, m.p. 280–282°C (dec.).
^{1}H-NMR (in D_2O/NaOD)δ: 2.45 ($^2J_{HH}$13.8; $^3J_{HP}$5.5) and 3.15 ($^2J_{HH}$13.8)(CH_2); 2.85 (2t, $^3J_{HH}$12.5; $^2J_{HP}$13.6; $^3J_{HH}$2.5, CHP); 3.84 (s, OCH_3); 5.0 (s, OH, NH); 7.0(d) and 7.3(d)(C_6H_4).

$C_9H_{14}NO_4P$ (231.19): calc.: C 46.76 H 6.11 N 6.06 P 13.40%
found: C 46.0 H 6.2 N 5.9 P 13.3%

Equiv. weight found 240; pK_1 = <2.5; pK_2 = 5.70; pK_3 = 9.90.
The compounds listed in Table V have been prepared similarly.
The pK-values of several aminophosphonic acids **5** are summarized in Table VI.

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