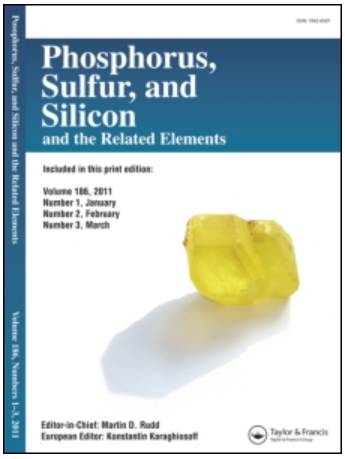

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ORGANIC PHOSPHORUS COMPOUNDS 105[1] SYNTHESIS AND PROPERTIES OF 2-AMINO-2-ARYLETHYLPHOSPHONIC ACIDS AND DERIVATIVES

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ORGANIC PHOSPHORUS COMPOUNDS 105[1] SYNTHESIS AND PROPERTIES OF 2-AMINO-2-ARYLETHYLPHOSPHONIC ACIDS AND DERIVATIVES*

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Dedicated in friendship to Professor T. A. Mastryukova
on the occasion of her 70th birthday

(Received August 8, 1995)

2-Amino-2-arylethylphosphonic acids, **6a** to **6q** have been prepared from the corresponding 2-acetoxyimino- or 2-methoxyimino-2-aryl-ethylphosphonates, **3** or **4**, by hydrogenation using Raney-Ni as a catalyst, followed by hydrolysis with HCl. **3** and **4** were obtained from the corresponding aryl-bromomethyl-ketoxime-O-acetates, **1**, or aryl-bromomethyl-O-methylketoximes, **2**, by an Arbuzov reaction with triethylphosphite. Several of the 2-amino-2-arylethylphosphonic acids **6** show activity against Botrytis cinerea and Cercospora. Among the more active compounds were **6a**, **6b**, **6g** and **6k**, whereby **6b** and **6k** gave full protection against Botrytis cinerea (on apple) down to 60 ppm. The same compounds show also a weak inhibition of anthocyanin synthesis in vivo.

Key words: 2-Amino-2-arylethylphosphonic acids, 2-amino-2-arylethylphosphonates, 2-acetoxyimino-2-arylethylphosphonates, 2-methoxyimino-2-arylethylphosphonates, reduction of oximes, biological activity.

INTRODUCTION

A few years ago we reported on the synthesis and properties of 1-amino-2-arylethylphosphonic acids.[2] It was shown that several compounds of this type are strong inhibitors of PAL and anthocyanin synthesis and are also quite active botryticides. It seemed of interest to prepare the 2-amino-2-arylethylphosphonic acids and compare their biological activity with that of the 1-amino-2-arylethylphosphonic acids.

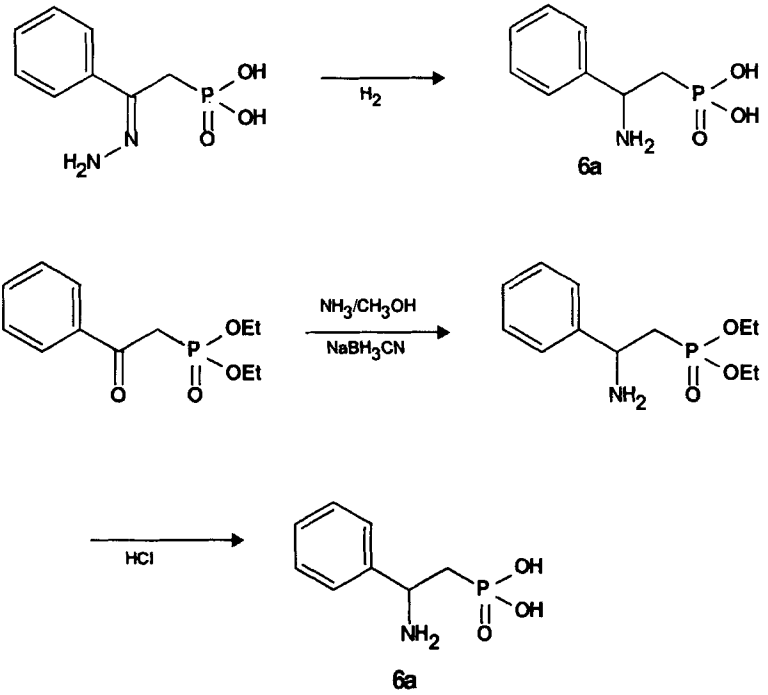
In the literature are already described some of these compounds. Thus Mastalerz *et al.*[3] obtained the unsubstituted 2-amino-2-phenylethylphosphonic acid, **6a**, by reduction of the hydrazon, and Varlet *et al.*[4] synthesized several compounds of this type by reductive amination of the corresponding keto-compounds (Scheme I).

Both methods need β-ketophosphonates as starting materials which are not so readily available. In the following we describe a new preparative procedure and also report on the biological activity of this type of compounds.

RESULTS AND DISCUSSION

To avoid the use of β-ketophosphonates we started with oxime acetates **1** (Table I) or oxime ethers **2** (Table II) of aryl-bromo-methylketones which can be easily pre-

*Expanded version of a lecture given at the 13th ICPC in Jerusalem, Israel, July 16–20, 1995.



SCHEME I

pared. Treatment of these with triethylphosphite yields the 2-aryl-2-acetoxyiminoethylphosphonates **3**[5] (Table III) and 2-aryl-2-methoxyiminoethylphosphonates **4** (Table IV) in high yields (Scheme II).

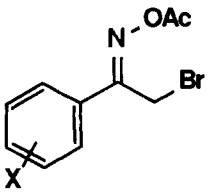
Reduction of **3** with hydrogen in ethanol at 80°C and 3 bars and of **4** at 100°C and 80 bars in the presence of Raney-Ni as catalyst produced **5** (Table V) in reasonable to good yields. It was observed that in general the reduction of **4** gave higher yields of **5** than that of **3**, e.g., reduction of **4k** (X = CH_3) yielded **5k** in 79.6% yield, whereas reduction of **3k** (X = CH_3) gave **5k** in only 51.5% yield. **4n** (3, 4-Cl_2) and **4o** (X = 2, 4-Cl_2) were reduced to **5n** and **5o**, respectively, with zinc in formic acid,[6] in order to avoid dehalogenation.

Hydrolysis of 2-amino-2-arylethylphosphonates **5** with 20% HCl under reflux afforded 2-amino-2-arylethylphosphonic acids, **6**, (Scheme, Table VI) in good yields. Since the difluormethoxysubstituent in **5l** was cleaved with HCl, **5l** was converted to **6l** by dealkylation with trimethylbromosilane followed by hydrolysis with methanol.

BIOLOGICAL ACTIVITY

Like 1-amino-2-arylethylphosphonic acids[2] several of the 2-amino-2-arylethylphosphonic acids **6**, described in this paper, also show activity against Botrytis cinerea (on apple) and cercospora (on peanuts). Among the more active compounds were **6a**, **6b**, **6g** and **6k**, whereby some of the compounds (**6b** and **6k**) gave full protection

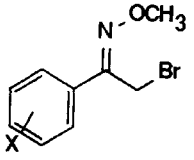
TABLE I

Physical properties of 

1

				^{1}H - NMR in $CDCl_3$				
	X	yield in %	b.p.°C/mbar (m.p.)	$OCCH_3$	$BrCH_2$	X	Ar	
a	H	81.2	solid	2.3	4.4		7.3 - 7.9	
b	4-F	85.1	115/0.08	2.2;2.3	4.4;4.45		7.0 - 8.0	syn - anti
d	4-Br	76.9	(96 - 97)	2.3	4.4;4.6		7.4 - 7.8	syn - anti
g	4-CH_3O	74.6	118/0.08	2.1;2.3	4.4	3.9	6.95(d);7.85(d)	syn - anti
k	4-CH_3	62	(82 - 83)	2.27	4.4;4.6	2.4	7.25(d);7.75(d)	syn - anti

TABLE II

Physical properties of 

2

				^{1}H - NMR (in $CDCl_3$)			
	X	yield in %	b.p.°C/mbar (m.p.°C)	OCH_3	$BrCH_2$	X	Ar
a	H	88.2	59-62/0.05	3.97	4.23		7.1 - 7.7
c	4-Cl	81.9	(55 - 57)	4.1	4.33		7.3 - 7.8
d	4-Br	84	(48 - 51)	4.07	4.27		7.55
e	3-F	76.9	68-72/0.2	4	4.2		6.75 - 7.4
f	2-F	89.8	125/0.1	4.05	4.43;4.6		6.9 - 7.75
g	4-CH_3O	91.2	108-111/0.01	4.07	4.3	3.8	6.9(d);7.7(d)
h	2-CH_3O	86.4	83-87/0.02	4.3	3.95	3.7	6.7 - 7.4
k	4-CH_3	87.9	83/0.015	3.93	4.2	2.3	7.2(d);7.47(d)
l	4-CHF_2O	58	oil	4.05	4.5	6.53(J72)	7.15(d);7.73(d)
m	4-CF_3	85.5	71-76/0.1	4.05	4.3		7.7(d);7.8(d)
n	3,4-Cl_2	83.5	104-108/0.03	4.1	4.3		7.3 - 7.8
o	2,4-Cl_2	78.1	86-91/0.02	4.07	4.37		7.2 - 7.7
p	2-F-4-(4'-BrC_6H_4O)-		oil				
r	3-CH_3O	73.9	100-110/0.08	4.1	4.3;4.5	3.8	6.8 - 7.5
s	3-(4-BrC_6H_4O)-		oil				

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).

EXPERIMENTAL

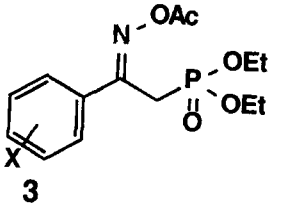
General see lit.[1] All the reactions were run under an atmosphere of argon.

Preparation of 4-methylphenyl-bromomethyl-ketoxime, **A**

To a suspension of 103.3 g (0.485 mol) of 4-methylphenyl-acetyl-bromide in 270 ml of methanol is added with stirring a solution of 79.6 g of hydroxylamine sulfate in 270 ml of water. A milky suspension forms. After 2 days standing 350 ml of $CHCl_3$ are added and the organic phase separated and washed twice with 180 ml of water each. During the washing part of the product cystallized. Therefore ethyl-acetate is added, the solution dried with sodium sulfate, filtered and the solvent evaporated. The residue of crude **A**, (103.9 g, 93.9%) is recrystallized from chloroform to give white crystals of **A**, m.p. 121–123°C.

^{1}H-NMR ($CDCl_3$) δ: 2.33 (s, CH_3); 4.4 (s, CH_2Br); 7.35 (m, aryl); 11.6 (s, OH).

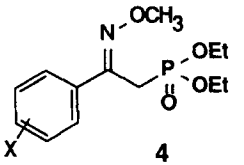
TABLE III

Physical properties of 

3

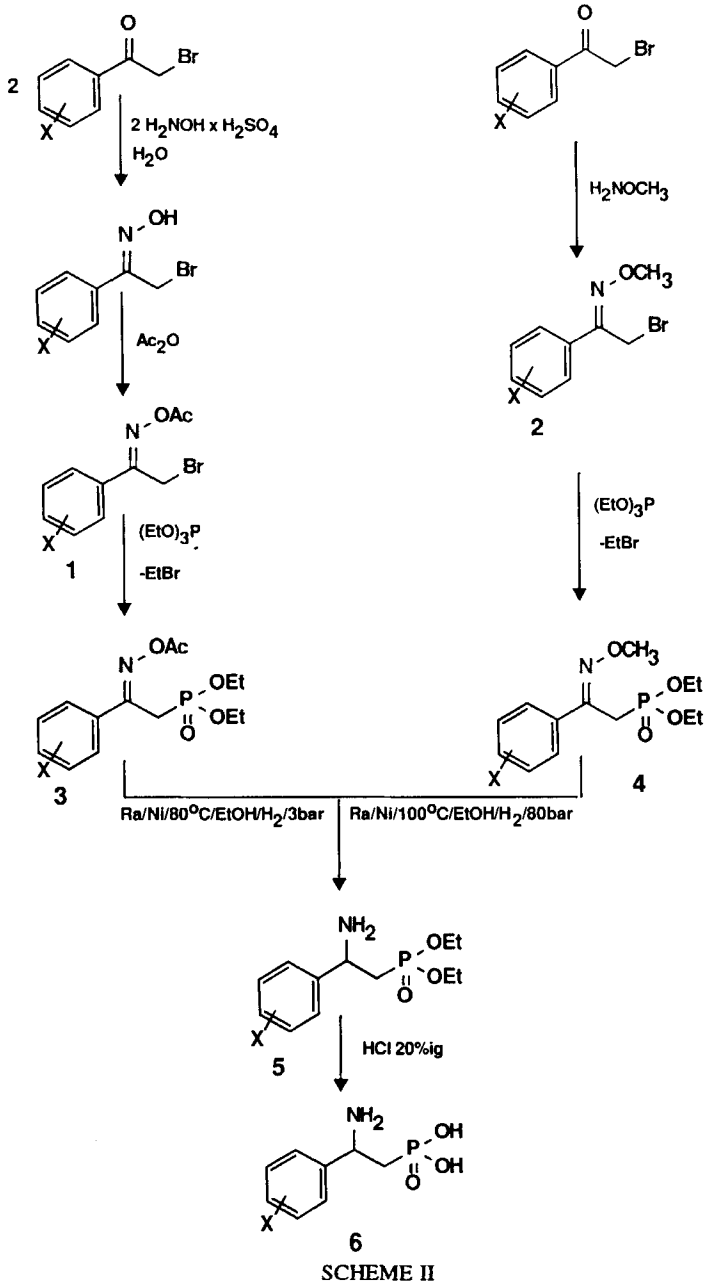
				^{1}H - NMR in $CDCl_3$				
	X	yield in %	b.p.°C/mbar	$COCH_3$	CH_2P	X	Ar	
a	H	84.9	140/0.08	2.33	3.6(J24)		7.3 - 8.0	
b	4-F	84.5	145/0.05	2.3	3.5(J24)		6.95 - 8.1	
d	4-Br	71.9	150/0.09	2.3	3.55(J24)		7.4 - 8.0	
g	4-CH_3O	77.5	175/0.1	2.3;2.1	3.5(J24 3.3(J22)	3.7	6.95(d);7.9(d)	syn - anti (8 : 1)
k	4-CH_3	90	(m.p. 83-84°C)	2.3	3.47(J24)	2.4	7.2(d);7.8(d)	

TABLE IV

Physical properties of 

4

				^{1}H - NMR in $CDCl_3$				^{31}P-NMR (95% H_3PO_4 Ref.)
	X	yield in %	b.p.°C/mbar	CH_2P	OCH_3	X	Ar	
a	H	95.9	129-133/0.05	3.4(J23)	3.9		7.1 - 7.7	
c	4-Cl	92.6	142-146/0.04	3.37(J23)	3.97		7.2(d);7.6(d)	22.35
d	4-Br	97.7	215-220/0.08	3.43(J23)	4.07		7.4 - 7.6	22.53
e	3-F	87.9	116-117/0.02	3.3(J23)	3.9		6.7 - 7.5	
f	2-F	79.2	122-125/0.03	3.53(J24)	4.03		6.9 - 7.7	22.51
g	4-CH_3O	92.3	155-158/0.01	3.4(J23)	4.03	3.8	6.9(d);7.73(d)	22.7
h	2-CH_3O	89.4	140-144/0.03	3.5(J24)	3.9	3.7	6.6 - 7.3	
k	4-CH_3	88.5	139-147/0.03	3.4(J22)	3.9	2.3	7.03(d);7.5(d)	
l	4-CHF_2O	67	liquid	3.13(J22)anti 3.43(J24) syn	3.85 anti 4.03 syn	6.55(J72)	7.1(d);7.55(d) 7.15(d);7.8(d)	23.7;22.23; 10 : 11
m	4-CF_3	90.6	170/0.1	3.45(J24)	4.05		7.6(d);7.9(d)	21.89
n	3,4-Cl_2	91.5	185/0.07	3.4(J24)	4.07		7.3 - 8.0	21.85;23.34 ; 8 : 1
o	2,4-Cl_2	92.7	170/0.04	3.17(J23)	4.07		7.3 - 7.6	22.11;23.35 ; 20 : 1
p	2-F-4-(4'-BrC_6H_4O)-	77.8	n_D^{20} 1.5521	3.5(J23)	4.05		6.6 - 7.5	22.47
q	2-Cl-4-(4'-ClC_6H_4O)-	98	n_D^{20} 1.5421	3.5(J23)	3.97		6.7 - 7.5	
r	3-CH_3O	99	190/0.03	3.4(J23)	4.03	3.8	6.7 - 7.4	22.57:23.95; 20 : 1



SCHEME II

1. 4-Methylphenyl-bromomethyl-ketoxime-o-acetate, **1k**

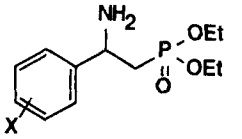
A mixture of 365 g of **A** and 750 ml of acetic acid anhydride is stirred for 1 h at 110°C; then the clear solution is evaporated and the residue recrystallized from diisopropyl ether to give 268 g (62%) of **1k**, m.p. 82–83°C.

^{1}H-NMR ($CDCl_3$) δ: 2.27 (s, $OCCH_3$); 2.4 (s, $ArCH_3$); 4.4 and 4.6 (s, CH_2Br, syn/anti); 7.25 (d) and 7.75 (d) (C_6H_4).

The compounds listed in Table I have been prepared similarly.

TABLE V

Physical properties of



5

				^{1}H - NMR in $CDCl_3$					^{31}P - NMR (85% H_3PO_4 Ref.)
	X	yield[1] in %	b.p.°C/mbar	NH_2	PCH_2	CH	X	Ar	
a	H	52.1	120/0.04	1.83	2.1(2d;J20,J7)	4.4 (2t)		7.3	
b	4-F	44	155/0.03	2	2.05(2d;J18,J7)	4.1		6.8 - 7.4	
c	4-Cl	72	140/0.08	2	2.05(2d;J18,J7)	4.25 (m)		7.2	28.97
d	4-Br	53.6	155/0.12	2	2.1(2d;J18,J7)	4.2 (m)		7.0 - 7.5	28.91
e	3-F	46	155/0.12	1.9	2.1(2d;J18,J7)	4.4 (m)		6.8 - 7.4	
f	2-F	65.4	170/0.06	2.3	2.2(2d;J18,J7)	4.5 (2t)		6.8 - 7.6	
g	4-CH_3O	65.0[2]	120/0.03	1.9	2.07(2d;J17,J7)	4.3 (m)	3.8	6.9(d);7.3(d)	29.61
h	2-CH_3O	61.5	185/0.08	1.93	2.2 (m)	4.5 (m)	3.77	6.67 - 7.4	
k	4-CH_3	79.6[3]	120/0.06	1.93	2.1(2d;J18,J7)	4.4 (m)	2.33	7.13(d);7.25(d)	
l	4-CHF_2O	70.5	200/0.195	1.9	2.3 (m)	4.45 (m)	6.52(t;J70)	7.1;7.45(2d)	27.6
m	4-CF_3	63.5	105/0.08	1.95	2.15 (m)	4.5 (m)		7.5(d);7.6(d)	28.66
n	3,4-Cl_2	72.0[4]	140/0.08	1.95	2.05(2d;J18,J7)	4.4 (m)		7.25;7.4;7.5	28.52
o	2,4-Cl_2	42.0[4]	140/0.05[5]	2	2.15 (m)	4.8 (m)		7.2 - 7.7	
p	2-F-4-(4'-BrC_6H_4O)-	74	n_D^{20} 1.548	2.05	2.2 (m)	4.6 (m)		6.6 - 7.5	
q	2-Cl-4-(4'-BrC_6H_4O)-	84	n_D^{20} 1.5464	1.98	2.2 (m)	4.8 (m)		6.9 - 7.65	29.04

[1] By reduction of 4, unless otherwise stated

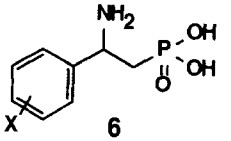
[2] Reduction of acetate 3 gave only 33.1% yield

[3] Reduction of acetate 3 gave 51.5% yield

[4] with Zn/HCOOH reduced

[5] contained NHCHO group

TABLE VI

Physical properties of 

6

				^{1}H - NMR in D_2O/NaOD					^{31}P-NMR (85% H_3PO_4 Ref)
	X	yield[1] in %	m.p.°C(dec)	CH_2P	CH	X	OH,NH_2	Ar	
a	H	92.3	298-302	1.9(2d;J16,J7)	4.13(m)		5	7.13-7.23	
b	4-F	61.6	294-296	2.1(2d;J16,J7)	4.6(m)		5.35	7.2-7.9	
c	4-Cl	74.7	>300	1.9(2d;J16,J7)	4.15(2t)		4.95	7.2	
d	4-Br	78.6	299-300	1.85(2d;J16,J7)	4.25(2t)		5.05	7.3(d);7.5(d)	
e	3-F	61.6	>300	1.8(m)	4.25(2t)		5.05	7.0-7.4(m)	
f	2-F	47.4	>300	1.9(m)	4.1(m)		4.9	7.0-7.7	
g	4-CH_3O	57.6	259	1.8(2d;J16,J7)	4.2(m)	3.85	5	7.0(d);7.4(d)	19.7
h	2-CH_3O	66.3	225-226	1.8(m)	4.25(2t)	3.85	4.9	7.0-7.3	
i	4-OH	64.4	214-218	1.8(m)	4.15(m)		5	6.6(d);7.2(d)	20.22
k	4-CH_3	94.4	296-297	1.8(2d;J16,J7)	4.25(2t)	2.35	5.05	7.25(d);7.35(d)	
l	4-CHF_2O	68.1[2]	262	1.8(m)	4.25(m)	6.8(t;J70)	4.95	7.15;7.45(2d;J10)	19.62
m	4-CF_3	84.2	>300	1.8(m)	4.35(m)		4.9	7.6(d);7.7(d)	
n	3,4-Cl_2	90.7	>300	1.8(m)	4.2(m)		5	7.3;7.55;7.6	
o	2,4-Cl_2	81.5	297-300	1.8(m)	4.6(2t)		5	7.1-7.3	
p	2-F-4-(4'-BrC_6H_4O)-	78	293-296	1.7(m)	4.4(m)		5	6.4-7.4	
q	2-Cl-4-(-4'ClC_6H_4O)-	75.5	288-290	1.8(m)	4.6(m)		4.95	6.7-7.6	

[1] From esters 5 and 20% HCl; [2] from ester 5l by dealkylation with Me_3SiBr and hydrolysis with CH_3OH

2. 2-Fluorophenyl-bromomethyl-o-methylketoxime, **2f**

To a solution of 21.7 g (0.1 mol) of 2-fluorophenyl-acetylbromide in 50 ml of methanol is added with stirring a solution of 10.02 g of O-methylhydroxylamine hydrochloride in 50 ml of water. An emulsion is formed. After 2 days standing 200 ml of $CHCl_3$ are added, the organic phase separated and washed twice with 100 ml of water each, dried with sodium sulfate, filtered and the solvent distilled to give 22.1 g (89.8%) of **2f**, b.p. 125°C/0.1 mbar. ^{1}H-NMR ($CDCl_3$) δ: 4.07 (s, OCH_3); 4.43 and 4.6 (s, CH_2Br, syn/anti); 6.9–7.75 (m, C_6H_4).

The compounds listed in Table II have been prepared similarly.

3. O,O-Diethyl-2-(4-fluorophenyl)-2-acetoxyimino-ethylphosphonate, **3k**

To a melt of 270.1 g (1 mol) of **1k** is added at 110°C dropwise with stirring 191 g of triethylphosphite and the formed ethyl bromide distilled off. After completion the mixture is stirred for another hour at 110°C, the volatile parts distilled off on a rotavapor and the residue recrystallized from diisopropyl ether/petroleum ether (40/60). There is obtained 294.6 g (90%) of **3k**, a slightly beige solid, m.p. 83–84°C.

^{1}H-NMR ($CDCl_3$) δ: 1.20 (t, CH_3); 2.3 (s, $OCCH_3$); 2.4 (s, $ArCH_3$); 3.47 (d, J = 24, CH_2P); 4.03 (qui, OCH_2); 7.2 (d) and 7.8 (d) (C_6H_4).

$C_{13}H_{22}NO_5P$ (327.32) calc.: C 55.04 H 6.78 N 4.28 P 9.46%
found: C 54.8 H 6.8 N 4.4 P 9.4%

The compounds listed in Table III have been obtained similarly.

4. O,O-Diethyl-2-(2-fluorophenyl)-2-methoxyimino-ethylphosphonate, **4f**

To 12.3 g (0.05 mol) of **2f** is added at 80°C dropwise with stirring 9.57 ml of triethylphosphite and the formed ethyl bromide distilled off. After completion the mixture is stirred for another half hour at 120–130°C and then fractionated in the vacuum to give 12 g (70.2%) of **4f**, b.p. 122–125°C/0.03 mbar.

^{1}H-NMR ($CDCl_3$) δ: 1.17 (t, CH_3); 3.53 (d, J = 24, CH_2P); 4.0 (qui, OCH_2); 4.03 (s, OCH_3); 6.9–7.7 (m, C_6H_4).

The compounds listed in Table IV have been prepared similarly.

5. O,O-Diethyl-2-(4-methylphenyl)-2-aminoethylphosphonate, **5k**

To a solution of 89.8 g (0.03 mol) of **4k** in 1700 ml of ethanol is added 9 g Raney-Ni and the mixture hydrogenated at 100°C and 80 bar. After 10 h hydrogen uptake ceased. The catalyst is filtered off and from the filtrate the solvent removed on a rotavapor. Distillation of the residue gives 64.8 g (79.6%) of **5k**, b.p. 120°C/0.1 mbar.

^{1}H-NMR ($CDCl_3$) δ: 1.35 (t, CH_3); 1.95 (s, NH_2); 2.1 (m, CH_2P); 2.35 (s, $ArCH_3$); 4.1 (qui, OCH_2); 4.4 (m, CH); 7.15 (d) and 7.3 (d) (C_6H_4).

Reduction of **3k** is carried out at 80°C and 3 bar; the yield is 51.6%. The compounds listed in Table V have been prepared similarly.

6. 2-(4-Methylphenyl)-2-aminoethylphosphonic acid, **6k**

A mixture of 59.14 g (0.34 mol) of **5k** and 400 ml of 20% HCl is refluxed for 5h and then the solution evaporated on a rotavapor. The resinous residue is recrystallized from methanol/propylene oxide to give 44.3 g (94.4%) of **6k**, a white solid, m.p. 296–297°C (dec.).

^{1}H-NMR (D_2O/NaOD) δ: 1.7 (2d, J = 15, CH_2P); 2.35 (s, $ArCH_3$); 4.2 (m, CH); 5.1 (s, NH_2, OH); 7.25 (d) and 7.35 (d) (C_6H_4).

$C_9H_{14}NO_3P$ (215.19) calc.: C 50.24 H 6.56 N 6.51 P 14.39%
found: C 50.0 H 6.7 N 6.5 P 14.4%

Equiv. weight found: 216; $pK_1 < 2.5$; $pK_2 = 6.22$; $pK_3 = 10.39$.

The compounds listed in Table VI have been prepared similarly.

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