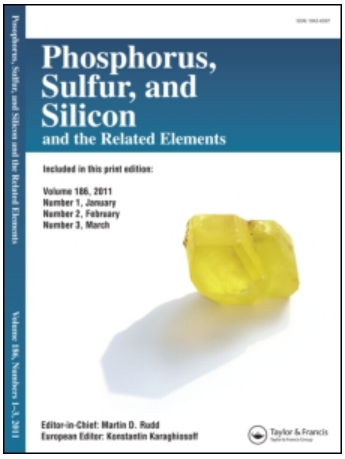

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ORGANIC PHOSPHORUS COMPOUNDS 91.[1] SYNTHESIS AND PROPERTIES OF 1-AMINO-2-ARYLETHYLPHOSPHONIC AND-PHOSPHINIC ACIDS AS WELL AS -PHOSPHINE OXIDES

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ORGANIC PHOSPHORUS COMPOUNDS 91.[1] SYNTHESIS AND PROPERTIES OF 1-AMINO-2-ARYLETHYLPHOSPHONIC AND -PHOSPHINIC ACIDS AS WELL AS -PHOSPHINE OXIDES*

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Dedicated to my friend Prof. Dr. A. Schmidpeter on the occasion of his 60th birthday

(*Received November* 20, 1989)

Key words: 1-Amino-2-arylethylphosphonic and -phosphinic acids and -phosphine oxides; preparation; structure; biological activity.

The preparation, physical and spectroscopic properties of 1-amino-2-arylethylphosphonic, and -phosphinic acids as well as -phosphine oxides, the phosphorus analogues of phenylalanine are described, and the reactions of 1-amino-2-(4-fluorophenyl) ethylphosphonates with acetals, isocyanides, esters, acid anhydrides, activated aromatic nitro- and halogen compounds, and with *N*-protected alanine are reported.

It is shown that several of the 1-amino-2-arylethylphosphonic acids are strong inhibitors of PAL and anthocyanin synthesis and also are quite active botryticides. Among the active compounds were 1-amino-2-(4-fluorophenyl)ethylphosphonic acid, **3f**, and the methyl-substituted compounds **3k**, **3l**, and **3m**. The fluoroderivative **3f** was also effective as a seed-dressing agent in barley showing a 100% protection against the fungus Fusarium nivale at 600 ppm.

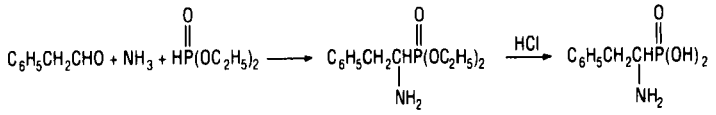
INTRODUCTION

The study of phosphorus analogues of the natural α-amino acids has accelerated in the past ten years, not least due to the finding of molecules with useful biological activity. In a recent review article we have summarized our knowledge in this area.[2] Furthermore they find increasing use as a tool in investigating the metabolism of natural amino acids.[3] 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 (see References 4,4a).

The phosphonic acid analog of phenylalanine was first synthesized by

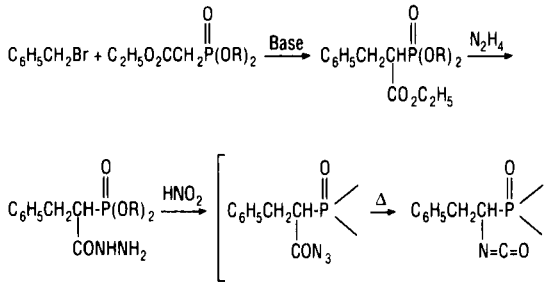
* Expanded version of a lecture given at the First National Phosphorus Congress, Chinese Chemical Society, Beijing, May 30 to June 2, 1988; and at the XI. ICPC, Tallinn, USSR, July 3–7, 1989.

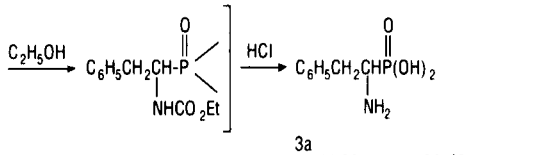
Kosolapoff *et al.*[5] in 1953 by causing 2-phenyl-acetaldehyde and ammonia to react with diethylphosphite followed by hydrolysis with hydrochloric acid



3a
(yield 25%; m.p. 225.7°C)

However, the properties of this compound do not agree with those of a sample which was obtained through the Curtius degradation of substituted diethyl phosphonoacetylhydrazides by Isbell and Chambers.[6]

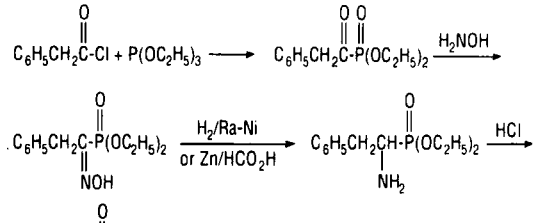




3a
(yield 56%; m.p. 281°C (dec.))

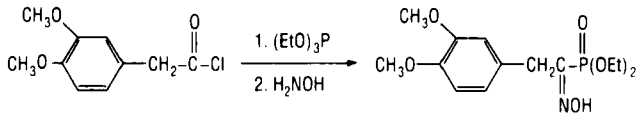
Furthermore, the method of Kosolapoff *et al.*[5] failed in the preparation of 1-amino-2-(3,4-dihydroxyphenyl)ethylphosphonic acid[7] (Stringer *et al.*, 1974) (phosphonic acid analog of DOPA), **3p**.

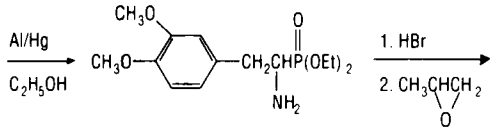
Berlin *et al.*[8] prepared several phosphonic acid analogs of substituted glycine from acylphosphonates which were converted to oximes and then reduced with B_2H_6 to the aminophosphonic acids. This procedure was successfully applied to the preparation of **3a** but reduction of the oxime was done with H_2 in the presence of Raney-Ni as a catalyst by Asano *et al.* in 1973.[9]



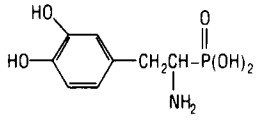
3a
yield 26.7%; m.p. 276-7°C
with Zn: 68%

Higher yields were obtained when the reduction was carried out with zinc in formic acid as found by Mastalerz *et al.* in 1981.[10] The phosphonic acid analog of DOPA was prepared by the same procedure but the reduction of the oxime had to be carried out with aluminum amalgam in C_2H_5OH[7] because reduction with B_2H_6[8] or catalytic reduction using Pd/C or Raney-Ni as a catalyst[9] gave only trace





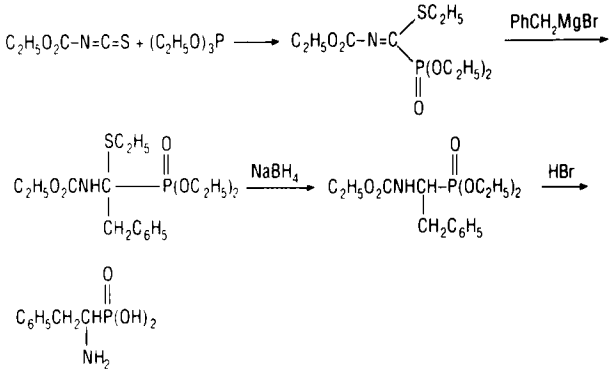
2p



3p

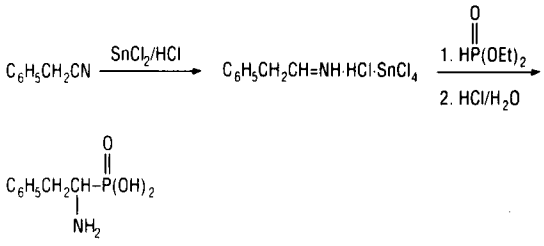
amounts of this particular compound. Hydrolysis of the aminophosphonate with hydrobromic acid proceeded with fission both of ester and ether groups. Attempts by Merijanian[11] to prepare the bis-methyl ether of the P-analog of DOPA by a modification of Chambers and Isbell's procedure[5] were not successful.

Interaction of O,O-diethyl-1-(*N*-ethoxycarbonylimino]-1-thioethyl methylphosphonate with benzylmagnesium bromide followed by reduction with $NaBH_4$ and



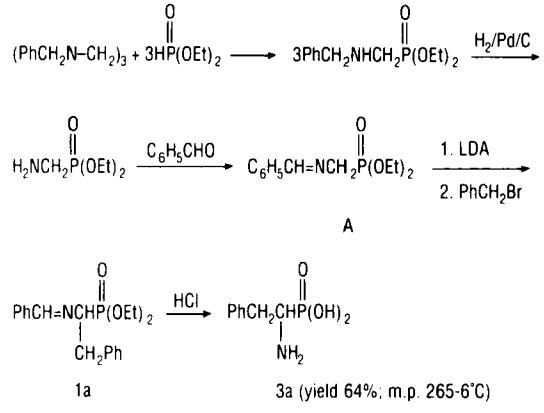
3a (yield 41%; m.p. 268-71°C)

hydrolysis with HBr gave **3a** in 41% yield[12] (Stec, 1976). Another procedure for the preparation of **3a** involves the addition of diethylphosphite to the aldimine salt, prepared by reduction of a nitrile with tin(II) chloride,[13] (Gancarz 1977).



3a (yield 67-71%; m.p. 274-6°C)

The simplest method for the preparation of **3a** is based on the findings of Ratcliffe and Christensen,[14] according to which the Schiff' base of aminomethylphosphonate with benzaldehyde (**A**) is, after metallation, readily alkylated.[14,15]

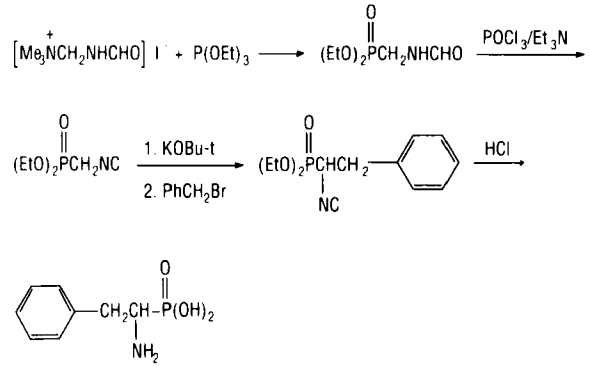


1a

3a (yield 64%; m.p. 265-6°C)

Finally, it was recently reported by Schöllkopf *et al.*[16] that O,O-diethylisocyanomethylphosphonate can be alkylated in the presence of a base and then hydrolyzed with HCl to give aminoalkylphosphonic acids.

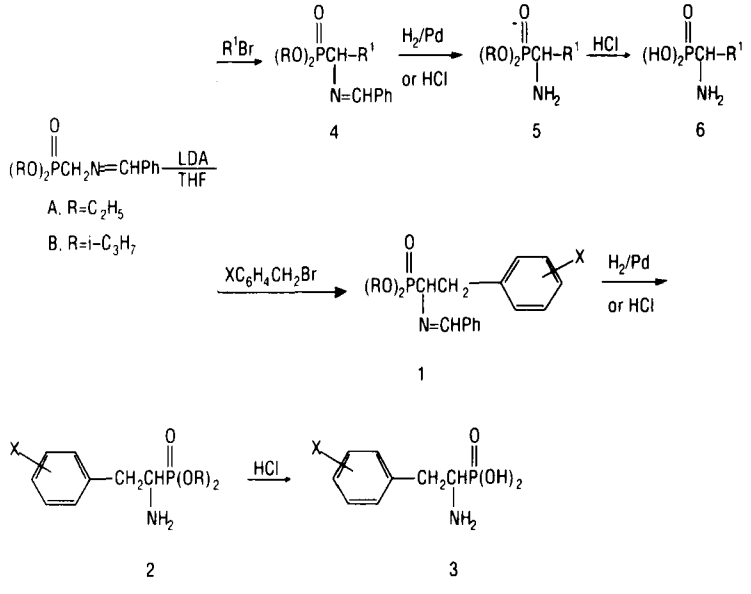
A variation of this procedure has recently been used[16a] to prepare optically active 1-aminoalkylphosphonic acids using a chiral ferrocenylphosphine–gold(I) catalyst in the interaction of aldehydes with isocyanomethylphosphonates.



3a (yield 71%; m.p. 270-1°C (dec.))

RESULTS AND DISCUSSION

For the preparation of differently substituted 1-amino-2-aryl-ethylphosphonic acid derivatives the procedure of Ratcliffe *et al.*[14] is well suited. 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 aryl- and alkyl substituted 1-aminophosphonic- and -phosphinic acids and derivatives can be prepared from the same starting materials (Tables I to XI).



And:

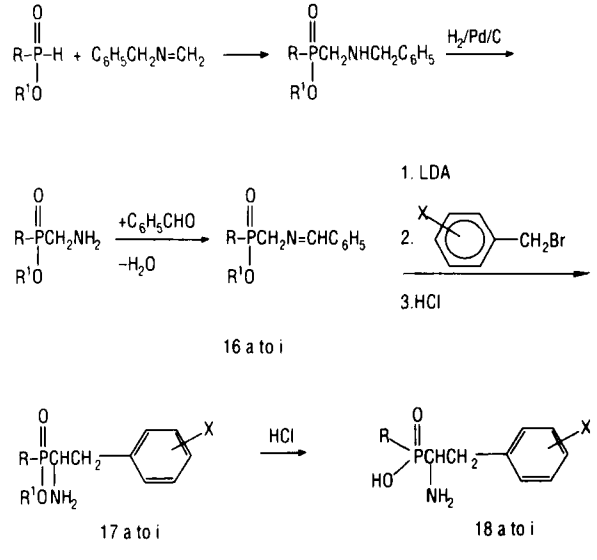
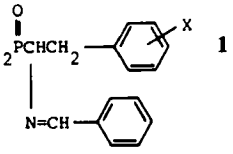
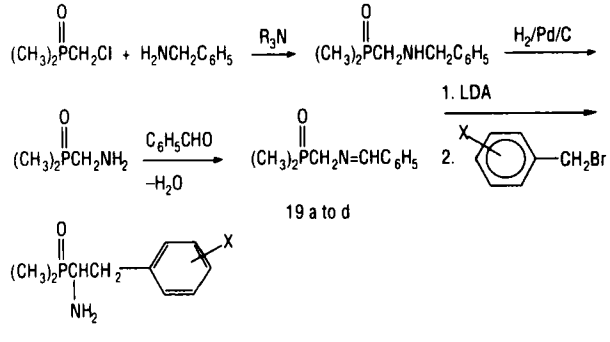


TABLE I

Physical properties of  1

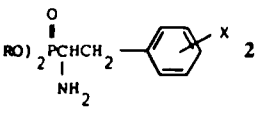
1	R	X	yield in %	b.p. °C/torr	^{1}H-NMR in $CDCl_3$ PCHCH$_2$	aryl	N=CH	X	^{31}P-chem. shift in ppm
a	C_2H_5	H	88.6	oil	3.1–4.0(m)	7.1–7.8	7.73 and 7.83		28.09
a*	i-C_3H_7	H	100.0	oil	3.13–4.0	7.1–7.8	7.7; 7.83		
b	C_2H_5	4-Cl	91.6	oil	3.0–4.0	7.0–7.7	7.88 and 7.95		
c	C_2H_5	3-Cl	72.4	oil	3.0–4.0	7.0–7.9	7.9; 7.97		
d	C_2H_5	4-Br	88.9	oil	3.1–4.0	6.9–7.8	7.85; 7.92		27.54
e	C_2H_5	4-I	51.5	160°/0.04					
f	i-C_3H_7	4-F	91.4	160°/0.08	3.1–4.0	6.7–7.7	7.83; 7.9		21.40
g	i-C_3H_7	3-F	70.3	160°/0.04	3.1–4.0	6.7–7.8	7.83; 7.92		
h	i-C_3H_7	2-F	51.3	150°/0.5	3.1–4.1	6.7–7.7	7.9; 7.97		
i	C_2H_5	2,4-Cl_2	90.3	oil	3.0–3.7	6.8–7.8	7.9 and 8.0		
j	C_2H_5	3,4-Cl_2	93.9	oil	3.05–3.9	6.9–7.9	7.97; 8.05		
k	C_2H_5	4-CH_3	80.4	oil	3.0–3.9	7.0–7.8	7.8; 7.88		
l	C_2H_5	3-CH_3	90.7	oil	3.0–4.0	6.9–7.7	7.8; 7.87	2.3	
m	C_2H_5	2-CH_3	89.3	oil	3.0–3.9	7.0–7.7	7.73; 7.82	2.3	
n	C_2H_5	3-CF_3	90.2	oil	3.1–4.0	7.0–7.8	7.87; 7.93		
o	i-C_3H_7	4-$(CH_3)_3C$	82.4	175°/0.08	3.1–4.0	6.9–7.75	7.83; 7.9	1.25	
p	i-C_3H_7	3,4-$(C_6H_5CH_2O)_2$	31.7	wax (Harz)	3.0–4.1	6.7–7.6	7.73; 7.8	4.9–5.05 (CH_2O)	
q	C_2H_5	4-CH_3O	30.9	160°/0.05	3.1–3.9	6.6–7.8	7.85; 7.92	3.73	
r	C_2H_5	2-CH_3O	50.6	155°/0.07	2.9–3.9	6.7–7.8	7.83; 7.9	3.8	
s	C_2H_5	2-$(CH_3)_3Si$	76.0	oil	3.3–4.0	7–7.8	7.8; 7.88	0.4	
t	C_2H_5	3-$(CH_3)_3Si$	42.0	155°/0.07	3.1–3.95	7.1–7.7	7.75; 7.82	0.1	
u	C_2H_5	4-$(CH_3)_3Si$	50.6	150°/0.03	3.17–3.9	7.1–7.8	7.87; 7.96	0.2	
v	i-C_3H_7	4-CN	72.8	oil	3.0–4.0	7.2–7.8	7.9; 7.97		20.65
w	C_2H_5	3,4-F_2	72.4	150°/0.08	3.0–3.7	6.8–7.8	7.93; 8.0		
x	C_2H_5	2,4-F_2	54.8	145°/0.08	2.9–3.8	6.55–7.8	7.9; 7.97		
y	i-C_3H_7	2,3-Cl_2	50.4	m.p. 99–101°	3.0–4.1	6.8–7.77	7.87; 7.95		
z	i-C_3H_7	3-I	61.9	160°/0.02	3.0–4.0	6.8–7.77	7.9; 7.98		
α	i-C_3H_7	4-CO_2CH_3	31.0	oil	3.12–4.0	7.1–7.8	7.8; 7.93		
β	C_2H_5	4-$CH_2CHPO_3(C_2H_5)_2$ N=CHC_6H_5	82.6	wax	3.0–3.8	7–7.7	7.73; 7.8		
γ	C_2H_5	2,6-F_2	60.7	153°/0.1	3.0–4.0	6.7–7.77	7.97; 8.05		
δ	C_2H_5	4-C_6H_5	22.5	oil	3.0–3.7	7.1–7.8	7.87; 7.95		
ε	C_2H_5	3,4-$(CH)_4$	43.6	190°/0.1	3.0–3.7	7.1–7.8	7.83; 7.9		

2-Aryl-1-aminoethyl-dimethylphosphine oxide derivatives were prepared as follows



20 a to d

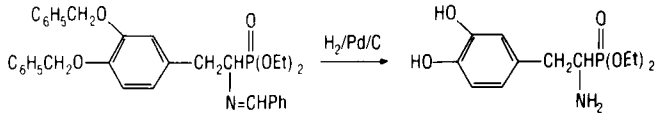
TABLE II

Physical properties of  2

2	R	X	yield in %	b.p. °C/torr	^{1}H-NMR in $CDCl_3$ NH_2	$PCHCH_2$	aryl	X	^{31}P-chem. shift in ppm
a*	C_2H_5	H	42.1[a]	170°/0.5	1.3	2.4–3.5	7.3		
a	i-C_3H_7	H	31.4[a]	oil	1.3	2.5–3.5	7.3		
b	C_2H_5	4-Cl	36.3[a]	n_D^{20} 1.5140	1.43	2.5–3.5	7.23		
c	C_2H_5	3-Cl	35.5[a]	oil	1.3	2.4–3.5	7.2		
d	C_2H_5	4-Br	61.3[a]	125°/0.04	1.25	2.3–3.5	7–7.5		27.54
e	C_2H_5	4-I	48.3[a]	yellow oil	1.3	2.3–3.4	7; 7.67		
f*	C_2H_5	4-F	50.4[a]	150–60°/0.06	1.4	2.5–3.5	6.9–7.4		
f	i-C_3H_7	4-F	83.1[b]	170°/0.06	1.30	2.4–3.4	6.8–7.35		26.0
g	i-C_3H_7	3-F	79.4[b]	150°/0.04	1.3	2.3–3.2	6.5–7.3		
h	i-C_3H_7	2-F	62.6[b]	150°/0.06	1.4	2.6–3.5	6.8–7.5		
i	C_2H_5	2,4-Cl_2	24.1[a]	m.p. (59–62°C)	1.33	2.6–3.6	7.2–7.4		
j	C_2H_5	3,4-Cl_2	30.0[a]	n_D^{20} 1.5272	2.73	2.5–3.4	7–7.6		
k	C_2H_5	4-CH_3	47.7[a]	oil	1.4	2.5–3.5	7.15	2.32	28.09
l	C_2H_5	3-CH_3	28.0[a]	n_D^{20} 1.5060	1.37	2.5–3.5	6.9–7.4	2.33	
m	C_2H_5	2-CH_3	51.2[a]	oil	1.33	2.5–3.5	7.2	2.33	28.19
n	C_2H_5	3-CF_3	27.3[a]	n_D^{20} 1.4659	1.4	2.6–3.5	7.5(br)		
o	i-C_3H_7	4-$(CH_3)_3C$	72.4[b]	140°/0.01	1.3	2.3–3.4	7.25	1.3	
p	i-C_3H_7	3,4-$(HO)_2$	53.5[b]	resin	4.4	2.3–3.3	6.4–6.8	4.4	
q	C_2H_5	4-CH_3O	23.0[b]	165°/0.15	1.3	2.4–3.4	6.9; 7.2	3.8	
r	C_2H_5	2-CH_3O	39.6[b]	125°/0.08	1.45	2.3–3.6	6.7–7.4	3.8	
s	C_2H_5	2-$(CH_3)_3Si$	53.2[b]	110°/0.07	1.31	2.5–3.5	7.3	0.36	
t	C_2H_5	3-$(CH_3)_3Si$	27.7[b]	150°/0.1	1.33	2.5–3.5	7.3	0.25	
u	C_2H_5	4-$(CH_3)_3Si$	60.4[b]	120°/0.08	1.3	2.5–3.5	7.3; 7.6	0.25	
v	i-C_3H_7	4-CN	26.4[a]	oil	1.35	2.6–3.5	7.4; 7.6		
w	C_2H_5	3,4-F_2	71.9[b]	115°/0.08	1.4	2.5–3.5	6.8–7.5		
x	C_2H_5	2,4-F_2	77.0[b]	110°/0.06	1.43	2.4–3.5	6.6–7.5		
y	i-C_3H_7	2,3-Cl_2	90.4[b]	160°/0.06	2.37	2.5–3.5	7.2		
α	i-C_3H_7	4-CO_2CH_3		160°/0.06	2.8	2.4–3.3	7.2; 7.9		
γ	C_2H_5	2,6-F_2	54.5[b]	105°/0.09	1.5	2.7–3.5	6.6–7.5		
δ	C_2H_5	4-C_6H_5	62.2[b]	oil	1.7	2.3–3.7	7.1–7.7		
ε	C_2H_5	3,4-$(CH)_4$	59.4[b]	140°/0.1	1.5	2.6–3.4	6.9–8		

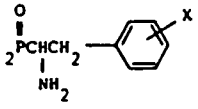
[a] Cleavage of the Schiff' base done with HCl.
[b] Cleavage of the Schiff' base done catalytically with H_2.

The catalytic debenzylation of the Schiff's bases was sometimes accompanied by undesired side reactions. Thus when it was attempted to catalytically debenzylate the 4-bromophenyl- or the 2,3-dichlorophenyl derivative with H_2 in the presence of Pd/C as catalyst aminophosphonates were obtained which contained no or only little halogen in the aromatic ring. In these cases the cleavage of the Schiff's bases was accomplished with hydrochloric acid. Catalytic debenzylation of 1-benzylidenamino-2-(3,4-dibenzyloxyphenyl)ethylphosphonate cleaved all three benzyl groups in one step.



1p 2p

TABLE III

Physical properties of  3

3	X	yield in %	m.p. °C(dec.)	^{1}H-NMR in D_2O/NaOD				^{31}P-chem. shift in ppm	pH
				$PCHCH_2$	NH_2/OH	aryl	X		
a	H	89.5	278–82	2.5–3.5	5.3	7.43		20.37	(11)
b	4-Cl	82.8	280–2					20.19	(11)
c	3-Cl	79.3	268–72	2.5–3.5	5.1	7.4			
d	4-Br	84.5	284–6	2.4–3.4	4.8	7.4			
e	4-I	61.2	255–9	2.2–3.2	4.8	6.87; 7.45			
f	4-F	89.2	266–70	2.45–3.4	4.85	7–7.5		20.28	(11)
g	3-F	71.2	278–80	2.3–3.3	4.65	6.7–7.4		20.09	(11)
h	2-F	77.7	275–6					20.28	(11)
i	2,4-Cl_2	90.1	279–80					20.19	(11)
j	3,4-Cl_2	66.7	274–8					19.91	(11)
k	4-CH_3	58.6	276–9	2.5–3.5	5.0	7.35	2.43	20.37	(11)
l	3-CH_3	84.9	270–3	2.2–3.2	4.9	7.0	2.1		
m	2-CH_3	77.4	244–5	2.5–3.5	5.0	7.25	2.4	18.79	(11)
n	3-CF_3	89.1	258–62					20.09	(11)
o	4-$(CH_3)_3C$	80.9	264–8	2.1–3.1	4.7	7.0	0.9		
p	3,4-$(OH)_2$	81.5	196	1.87–3.0	4.65	6–6.4			
q	4-OH	60.9	258–60	1.8–2.8	4.55	6.17; 6.63			
w	3,4-F_2	66.1	267–69					14.86	(10.5)
x	2,4-F_2	84.4	271–274	2.2–3.0	4.65	6.4–7.2			
y	2,6-F_2	46.8	258–261	2.4–3	4.8	6.5–7.2			
δ	4-C_6H_5	67.8	273	2.5–3.7	5.35	6.9–7.5			
ε	3,4-$(CH)_4$	71.7	267–261	2.4–3.3(m)	4.93	6.7–7.6			

In general however, hydrogenolytic cleavage of the Schiff' bases gave higher yields of the corresponding aminophosphonates than cleavage with HCl. Furthermore the work-up procedure was also simpler. Hydrolysis of the aminophosphonate esters was normally done with 20% HCl under reflux. Under these conditions 1-amino-2-(2-trimethylsilylphenyl)ethylphosphonate lost the trimethylsilylgroup and gave 1-amino-2-phenyl-ethylphosphonic acid **3a**

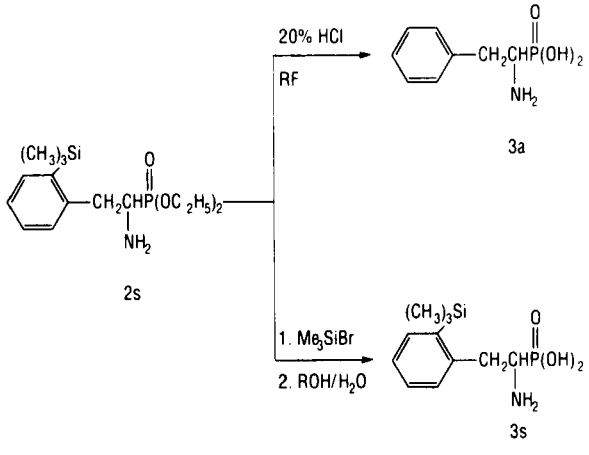


TABLE IV

Physical properties of $(i\text{-}C_3H_7O)_2P(O)-C(R^1)(N{=}CH{-}C_6H_5)-R$ **4**

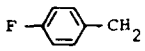
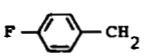
R^1	R	yield in %	b.p. °C/torr	^{1}H-NMR in $CDCl_3$			^{30}P-chem. sh in ppm
				R^1	R	N=CH	
CH_3	H	88.1	108°/0.08	1.67(*J*7)	3.8 (m)	8.25; 8.33	
CH_3		56.7	165°/0.1	1.35	CH_2: 3.33 (m)	7.95; 8.03	24.56
$CH_2{=}CHCH_2$	H	90.4	oil	CH 2.9(m) $CH_2{=}CH$ 5.6(m)	3.7 (m)	8.21; 8.28	
$CH{\equiv}CCH_2$	H	95.0	oil				

TABLE V

Physical properties of $(i\text{-}C_3H_7O)_2P(O)C(R^1)(R)NH_2$ 5

5	R^1	R	yield in %	b.p. °C/torr	^{1}H-NMR in $CDCl_3$		
					R^1	R	NH_2
b	CH_3		77.2	150°/0.06	1.07(*J* 16 Hz)	CH_2: 2.8(*J* 9.8 Hz)	1.8(s)
c	$CH_2{=}CHCH_2$	H	38.6[a]	colorless liquid	CH_2 2–2.7(m) $CH_2{=}CH$ 5–6.3(m)	3.02(2t)	1.5(s)
d	$CH{\equiv}CCH_2$	H	32.5[a]	colorless liquid	$HC{\equiv}CCH_2$ 2–2.8	3.0(2t)	1.7(s)

[a] Cleavage of the Schiff' base done with HCl.

TABLE VI

Physical properties of $(HO)_2P(O)-C(R^1)(R)-NH_2$ **6**

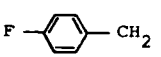
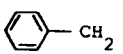
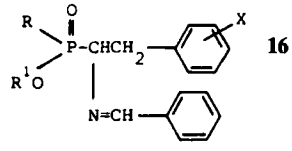
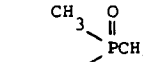
6	R^1	R	yield in %	m.p. (dec.)	solvent	^{1}H-NMR		
						R^1	R	NH_2/OH
b	CH_3		73	231–234°C	D_2O/NaOD	0.83(*J* 13 Hz)	CH_2: 2.7(*J* 6 Hz)	4.83
c	$CH_2{=}CHCH_2$	H	60.1	220–2°C	D_2O			
d	$CH{\equiv}CCH_2$	H	52.7	225–32°C	D_2O		2.5–3.7 (m)	4.8
e	CH_3		64	245–7°C	D_2O/DCl	1.53(*J* 15 Hz)	CH_2: 3.25(*J* 9 Hz) C_6H_5: 7.4	7.2

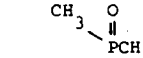
TABLE VII

Physical properties of  **16**

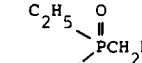
16	R	R^1	X	yield in %	b.p.	^{1}H-NMR in $CDCl_3$ R-P	PCHCH$_2$	aryl H	N=CH	X
a	CH_3[a]	i-C_3H_7	H	87.4	oil	1.47(*J*16)	3–4	7–7.6	7.73; 7.81	
b	C_2H_5[b]	i-C_3H_7	2-CH_3	96.3	oil	0.8–2.0	3–4	7–7.6	7.65; 7.7	2.3
c	C_2H_5	i-C_3H_7	3-CH_3	96.5	oil	0.9–2.0	3–4	6.9–7.8	7.77; 7.83	2.2
d	C_2H_5	i-C_3H_7	4-CH_3	94	oil	0.8–2.0	3–4	7–7.7	7.78; 7.87	2.23
e	CH_3	i-C_3H_7	4-F	98.8	oil	1.5(*J*14)	3–4	6.8–7.9	8.27; 8.33	
f	CH_3	i-C_3H_7	4-Br	44.1	oil	1.5(*J*13)	3–4	6.95–7.9	7.83; 7.9	
g	CH_3	i-C_3H_7	4-Cl	84.3	resin	1.5(*J*14)	2.9–3.9	7–7.8	7.8; 7.87	
h	CH_3	i-C_3H_7	3-CH_3	73.3	oil	1.5(*J*14)	2.8–4.1	6.9–7.9	8.28; 8.37	2.2
i	C_2H_5	i-C_3H_7	H	99.3	oil	0.8–2.0	3–4	7–7.7	7.73; 7.8	

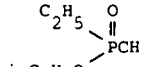
[a] Starting material

 , b.p. 64-68 °C/0.03 torr; ^{1}H-NMR in $CDCl_3$: $(CH_3)_2$ 1.3 (d), NH_2 1.37 (s); PCH_3 1.47 (d,J_{PCH}16 Hz) 11H; PCH_2 2.95 (d,J_{PCH}9 Hz, 2H); OCH 4.7 (m, 1H)

 , b.p. 93 °C/0.06 torr, n_D^{20} 1.5293; ^{1}H-NMR (in $CDCl_3$) $(CH_3)_2$ 1.32 (d); CH_3P 1.52 (d,J_{PCH}14 Hz); CH_2P 4.07 (d,J_{PCH}14 Hz); CHO 4.75 (m); C_6H_5 7.57 (m); CH=N 8.3 (d)

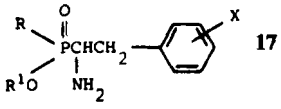
[b]

 , b.p. 80 °C/0.15 torr; ^{1}H-NMR (in $CDCl_3$: C_2H_5 0.9-1.3 (m), $(CH_3)_2$ 1.4 (d) + NH_2, (13H); CH_2P 3.0 (d,J_{PCH}9 Hz, 2H); CHO 4.7 (m, 1H)

 , b.p. 100 °C/0.06 torr; ^{1}H-NMR (in $CDCl_3$): $(CH_3)_2$ 1.3 (d), C_2H_5P 0.8-2.1 (m) 11H; CH_2P 4.07 (d,J_{PCH}14 Hz, 2H); OCH 4.75 (m, 1H); C_6H_5 7.5 (m, 5H); CH=N 8.3 (d, 1H).

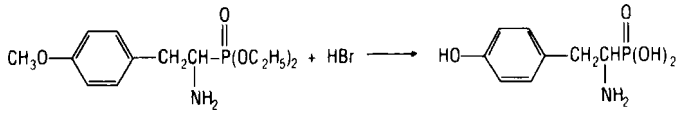
The 3- and 4-substituted trimethylsilylphenyl derivative were, however, stable towards HCl. Conversion of the diethyl ester to the bis-trimethylsilyl-ester with Me_3SiBr followed by hydrolysis with alcohol/H_2O allowed also the isolation of 1-amino-2-(2-trimethylsilylphenyl)ethylphosphonic acid. Treatment of 1-amino-2-(4-methoxyphenyl)ethylphosphonate (**2q**) with hydrobromic acid proceeded smoothly, with fission both of ester and ether groups.

TABLE VIII

Physical properties of  **17**

17	R	R^1	X	Yield in % (HCl-work up)	b.p.	^{1}H-NMR in $CDCl_3$ R–P	PCHCH$_2$	aryl	X	^{31}P-chem. shift in ppm
a	CH_3	i-C_3H_7	H	42.2	n_D^{20} 1.5103	1.35 (*J* 14)	2.3–3.3	7.23		
b	C_2H_5	i-C_3H_7	2-CH_3	35.5	oil	0.8–2.0	2.5–3.5	7.17	2.3	56.75[a] 56.47
c	C_2H_5	i-C_3H_7	3-CH_3	35.5	oil	0.8–2.0	2.5–3.5	6.9–7.3	2.33	56.66[a] 56.38
d	C_2H_5	i-C_3H_7	4-CH_3	31.2	oil	0.8–2.0	2.3–3.4	7.13	2.33	56.66[a] 56.38
e	CH_3	i-C_3H_7	4-F	22.8	n_D^{20} 1.4970	1.52(*J*13)	2.3–3.4	6.9–7.4		
f	CH_3	i-C_3H_7	4-Br	16.5	oil	1.4(*J*13)	2.2–3.3	6.9–7.5		
g	CH_3	i-C_3H_7	4-Cl	24.2	oil	1.4(*J*13)	2.2–3.4	7.1–7.5		
h	CH_3	i-C_3H_7	3-CH_3	31.2	oil	1.4(*J*13)	2.3–3.3	6.8–7.3	2.33	
i	C_2H_5	i-C_3H_7	H	58.4	oil	0.7–2	2.3–3.4	7.2		

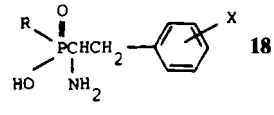
[a] Enantiomers.



2q 3q

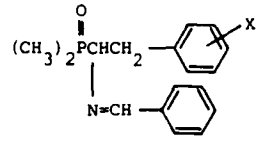
α-Methylsubstituted derivatives were obtained either by double alkylation of *N*-benzylidenaminomethylphosphonates, e.g.

TABLE IX

Physical properties of  **18**

18	R	X	yield in %	m.p. (dec.)	^{1}H-NMR Solvent	R–P	PCHCH$_2$	OH/NH$_2$	aryl	R	^{31}P-chem. shift in ppm
a	CH_3	H	76.3	261–2°C	D_2O	1.37(*J*14)	2.7–3.7	4.8	7.45		43.35 (pH11)
b	C_2H_5	2-CH_3	61.7	234–5°C	D_2O	0.8–2.0	2.8–3.6	4.7	7.23	2.3	46.15 (pH11)
c	C_2H_5	3-CH_3	79.3	229–32°C	D_2O/NaOD	0.8–2.0	2.3–3.3	4.8	7.1	2.3	42.7 (pH8)
d	C_2H_5	4-CH_3	88.1	233–36°C	D_2O/NaOD	0.7–2.0	2.4–3.4	4.8	7.2	2.3	38.98 (pH7)
e	CH_3	4-F	75.1	254–7°C	D_2O	1.4(*J*14)	2.7–3.7	4.8	7–7.5		35.72 (pH7)
f	CH_3	4-Br	83.3	254–7°C	D_2O/NaOD	0.95(*J*13)	1.8–3.0	4.75	6.6–7.3		43.17 (pH11)
g	CH_3	4-Cl	100.0	242–5°C							41.40 (pH8)
h	CH_3	3-CH_3	89.2	260–2°C							34.05 (pH5)
i	C_2H_5	H	80.7	230–1°C	D_2O/NaOD	0.6–2.0	2.1–3.3	4.8	7.2		37.12 (pH5)

TABLE X

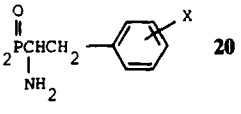
Physical properties of  **19**

				^{1}H-NMR in $CDCl_3$				
19	X	yield	b.p.	P-CH_3	$PCHCH_2$	aryl	X	N=CH
a	H[a]	87.3	oil	1.37(J13) 1.63(J13)	2.7–4.0	7–7.6		7.7; 7.77
b	2-CH_3	98.3	resin	1.4 (J13) 1.65(J13)	2.8–3.9	7.05–7.5	2.3	7.6; 7.67
c	3-CH_3	96.2	resin	1.37(J13) 1.6 (J13)	2.6–3.9	6.8–7.6	2.2	7.73; 7.8
d	4-CH_3	86.9	resin					

[a] Starting material $(CH_3)_2PCH_2NH_2$, b.p. 87–89°C/0.02 torr, crystallizes on standing; ^{1}H-NMR in $CDCl_3$: CH_3P 1.47 (d, J_{PCH} 12.8 Hz), NH_2 1.5 (s) 8H; CH_2P 2.97 (d, J_{PCH} 7 Hz, 2H).

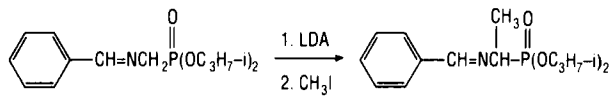
$(CH_3)_2PCH_2N{=}CHC_6H_5$, b.p. 133–138°C/0.06 torr, crystallizes on standing: ^{1}H-NMR in $CDCl_3$: CH_3P 1.5 (d, J 13 Hz, 3H); CH_2P 4.03 (d, J 13 Hz, 2H); C_6H_5 7.5 (m, 5H) CH=N 8.25 (d, 1H).

TABLE XI

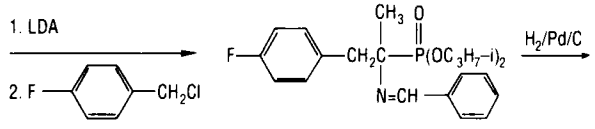
Physical properties of  **20**

				^{1}H-NMR in $CDCl_3$				
20	X	Yield in % (HCl-work up)	b.p. °C/torr	P-CH_3	NH_2	$PCHCH_2$	aryl	X
a	H	21.5	160–170°/0.04[a]	1.47(J12)	1.23	2.4–3.4	7.27	
b	2-CH_3	26.3	160°/0.04	1.53(J12)	1.3	2.4–3.4	7.2	2.33
c	3-CH_3	24.6	160°/0.05	1.5 (J12)	1.3	2.4–3.5	6.9–7.4	2.33
d	4-CH_3	27.4	150–5°/0.07	1.55(J12)	1.3	2.4–3.4	7.1–7.2	2.33

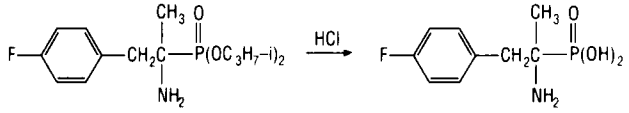
[a] Hygroscopic solid.



4a

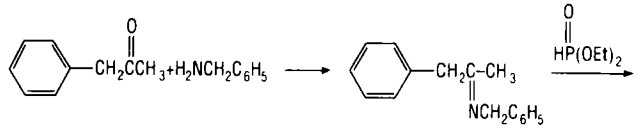


4b

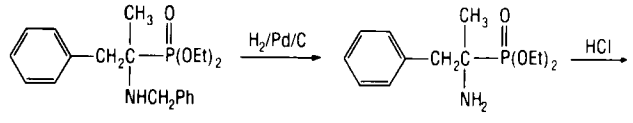


5b 6b

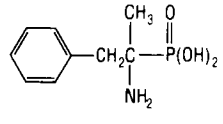
or by the interaction of the corresponding Schiff's base with secondary phosphites.



C



7 5e



6e

Reactions of 1-amino-2-aryl-ethylphosphonates

The 1-amino-2-aryl-ethylphosphonates give all the reactions typical for a primary amine. Thus the interaction of **2f** and dimethylformamid-dimethylacetal gives a formamidine **8**, with isocyanates a urea derivative **9** is obtained, and acylation with formate, oxalate or chloroacetic anhydride produces the acylated derivatives **10, 11**, and **12**. Arylation with trifluoro-methyl-dinitro-chlorobenzene proceeds well and gives **13** in 63% yield. A dipeptide **14** is obtained when **2f** is treated with Z-L-alanine in the presence of dicyclohexylcarbodiimide and **15** is formed when **2f** is caused to react with 3,4-dinitro-2'-chloro-4'-trifluoromethyl-diphenylether. Other 1-amino-2-aryl-ethyl-phosphonates react similarly (see exp. part.).

Toxicology

The P-DOPA analog **3p** was well tolerated when given subcutaneous to mice in a single dose (Stringer *et al.*, 1974)[7]. A lethal dose was not established, but the compound caused no deaths, or apparent tissue damage, up to 2,000 mg/kg. Repeated administration of **3p** (80 mg/kg/day × 10) in a chemotherapy experiment caused no apparent ill effects.[7] The para-fluorophenyl-derivative **3f** was well tolerated when given orally to rat. A lethal dose was not established, but the compound caused no death up to 2,000 mg/kg.

Biochemistry

The P-DOPA analog **3p** was compared with DOPA as a substrate for mushroom tyrosinase. The rates of melanim formation were of the same order.[7]

Two hours after injection of tritium labelled **3p**, 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[7].

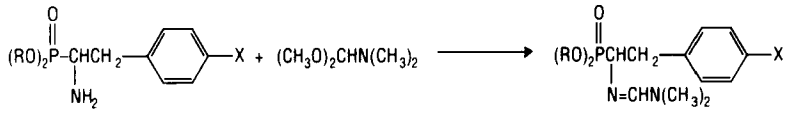
Racemic 1-amino-2-phenylethylphosphonic acid **3a** is a specific competitive inhibitor of phenylalanyl-tRNA synthase, but the phosphonic acid analogs of valine, leucine, isoleucine, and tyrosine had no effect on the activity of phenylalanine-*t*RNA synthase (prepared from Aesculus hippocastanum) when tested at a concentration of 2 mM (with respect to the L-form) using 1 mM L-phenylalanine as substrate.[18]

i) The apparent Michaelis constant (K_m) of the enzyme for phenylalanine increases indefinitely with the concentration of APEP, **3a**,

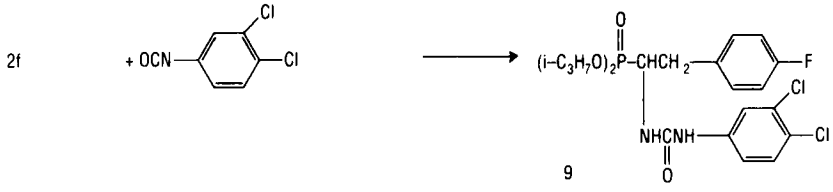
ii) The inhibition of phenylalanyl-*t*RNA synthetase increases indefinitely with concentration of APEP at specified concentrations of phenylalanine

iii) Enzyme activity 1/v is a linear function of the APEP concentration at specified concentration of phenyl-alanine.

These properties indicate that APEP is a true competitive inhibitor of the phenylalanyl-*t*RNA synthetase of Aesculus hippocastanum. The calculated inhibitor constant (K_i) was 0.017 mM.[18]

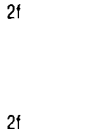


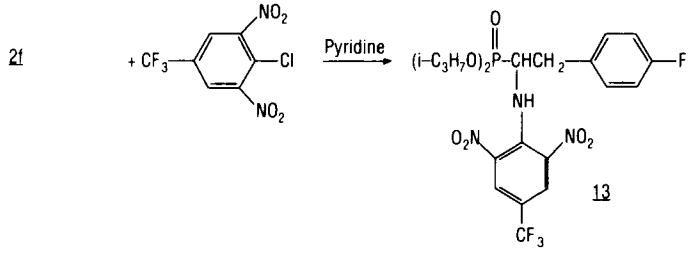
8a, R=i-C_3H_7; X=F
8b, R= C_2H_5; X=Br



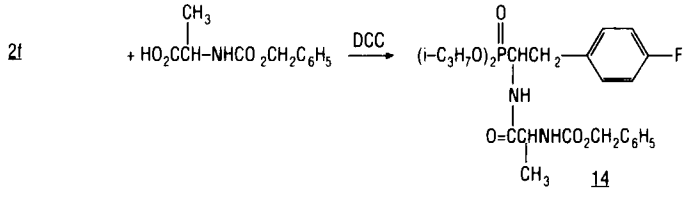
9

10, R=H
11, R=$CO_2C_2H_5$
12, R=$ClCH_2$

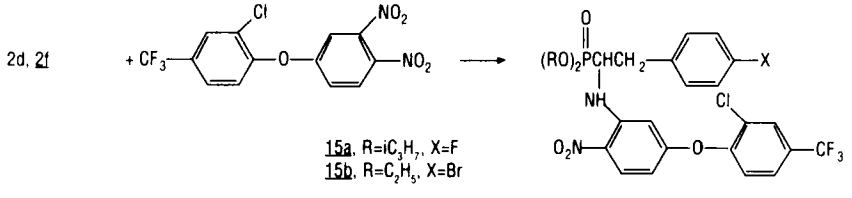




13



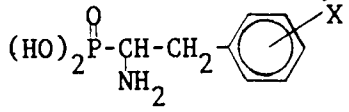
14

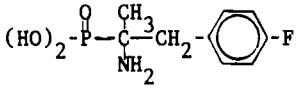
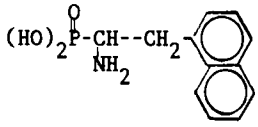
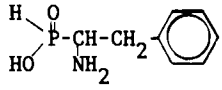
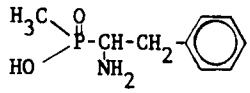
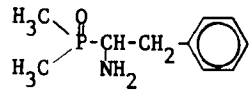


15a, R=iC_3H_7, X=F
15b, R=C_2H_5, X=Br

TABLE XII

Inhibition constants for buckwheat PAL and anthocyanin synthesis[17,21]



X	Inhibition constants for buckwheat PAL (μM)			Inhibition of anthocyanin synthesis in vivo by 1 mM
H	(R,S)	2.6	R 1.5 S 11.6	83%
2-F	(R,S)	1.6		65%
3-F	(R,S)	2.7		73%
4-F	(R,S)	3.5	(−) 2.8 (+) 13.5	87%
4-Cl	(R,S)	120		0
4-Br	(R,S)	~1100		0
4-I	(R,S)	~2200		0
2-CH_3	(R,S)	12.3		72%
3-CH_3	(R,S)	21		54%
4-CH_3	(R,S)	780		0
3-CF_3	(R,S)	200		
4-$(CH_3)_3C$	(R,S)	~2000		4%
4-OH	(R,S)	410		0
3,4-Cl_2	(R,S)	170		
2,4-Cl_2	(R,S)	380		
2,4-F_2	(R,S)	6.1		63%
2,6-F_2	(R,S)	55.0		25%
3,4-$(OH)_2$	(R,S)	260		
	(R,S)	180		4%
	(R,S)	82		0%
	(R,S)	110		0%
	(R,S)	850		11%
	(R,S)	∞		0%

In contrast, the leucyl-, tyrosyl- and valyl-*t*RNA synthetase were not inhibited by the phosphorus analogs of leucine, tyrosine and valine.[18]

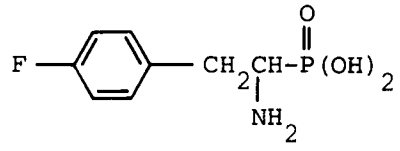
L-1-amino-2-phenyl-ethylphosphonic acid, **3a**, has been found to interact with rabbit muscle pyruvate kinase, in a mode depending on the pH and substrate concentration, exhibiting activatory and inhibitory effects at low (1–5 mM) and at high (above 5 mM) ligand concentrations, respectively[19] (Mastalerz 1981). Other biochemical interactions of **3a** include transamination with ketoglutarate in mouse tissues[20] (Simonsen 1974) and inhibition of one of the key enzymes of plant metabolism, the phenylalanine ammonia lyase[17,21] (Amrhein). In fact **3a** is the most active compound in the buckwheat-PAL inhibition test,[21] (see Table XII) of a series of 1-amino-2-substituted arylethyl-phosphonic acids. Furthermore the data in Table XII 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 shows no inhibition of PAL. The inhibition of anthocyanin synthesis in buckwheat hypocotyls is comparable with the PAL inhibition and the same order of activity seems to exist. A comparison of the activity of racemic 1-amino-2-(4-fluorophenyl)ethylphosphonic acid **3f** and racemic 4-fluorophenylalanine shows that **3f** is a better inhibitor (by two orders of magnitude) of anthocyanin synthesis than 4-fluorophenylalanine. This indicates that the inhibition is mainly due to the introduction of the phosphonic acid group.[17] We observed that many of the 1-amino-2-arylethylphosphonic acids are quite active botryticides.

Among the active compounds were 1-amino-2-(4-fluorophenyl)ethylphosphonic acid, **3f**, and the methyl-substituted compounds **3k**, **3l**, and **3m**. The fluoroderivative **3f** was also effective as a seed-dressing agent in barley showing a 100% protection against the fungus Fusarium nivale at 600 ppm.

1-Amino-2-(4-hydroxyphenyl)ethylphosphonic acid, **3q**, shows inhibitory properties in the tyrosyl-*t*RNA synthetase catalyzed ATP-PP_i exchange reaction. It is competitive with respect to tyrosine but binds 5-fold less effectively than tyrosine.[22] Neuzil *et al.*[23] observed that **3q** 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.[3,23] The same authors reported[3] that **3q** is one of the best competitive inhibitors of the tyrosine

TABLE XIII

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

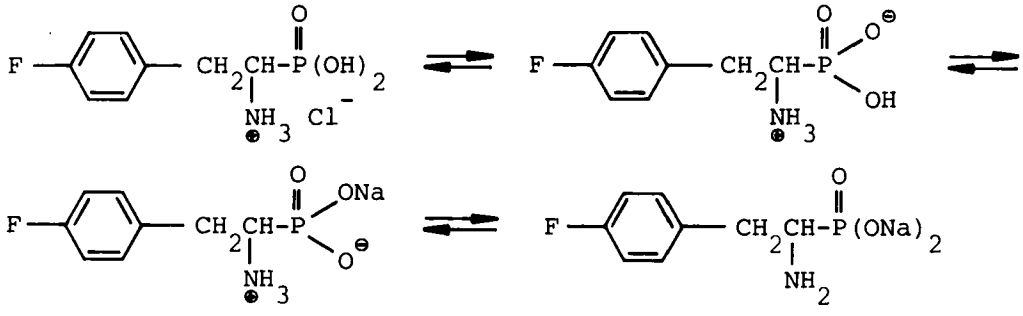


pH	1	4	7	10	11
^{31}P-chemical shift in ppm	14.12	11.16	10.97	16.83	20.28

TABLE XIV

^{1}H-NMR at 250 MHz of **1f**, **2f** and **3f**

No.	Solvent	^{1}H-NMR		
		$(CH_3)_2$	CH_2	CHP
1f	$CDCl_3$	1.35 (m)	3.16 ($^2J_{HH}$ 14; $^3J_{HH}$ 10.5; J_{HP} 7.5) 3.32 ($^2J_{HH}$ 14; $^3J_{HH}$ 3; J_{HP} 7.8)	3.7 ($^3J_{HH}$ 3; $^3J_{HH}$ 10.5; $^2J_{HP}$ 12)
2f	$CDCl_3$		2.62 (m) 3.15 (m)	3.15 (m)
3f	D_2O		2.3 ($^2J_{HH}$ 13.8; $^3J_{PH}$ 5.9) 3.0 ($^2J_{HH}$ 13.8)	2.7 (2*t*, $^3J_{HH}$; 12.5; $^2J_{HP}$ 13.6; $^3J_{HH}$ 2.5)



aminotransferase of rat liver and of tyrosine decarboyxlase extracted from Streptococcus faecalis. Three aminophosphonates i.e., **2b**, **2d**, and **2j** were active acaricides against Tetranychus cin. tol., particularly against larvae and eggs. Several of the compounds and in particular **2f***, **6c**, **6b**, **11**, **17b**, **17d** and **20** exhibited plant growth regulator properties, and **15a** and **15b** showed herbicidal activity.

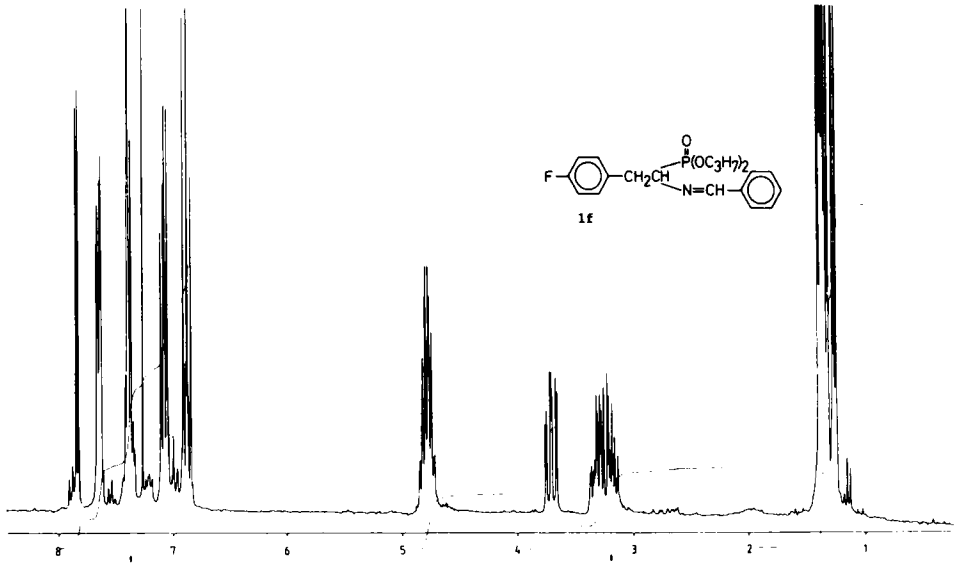


FIGURE 1 ^{1}H-NMR spectra of **1f**, **2f** and **3f** at 250 MHz.

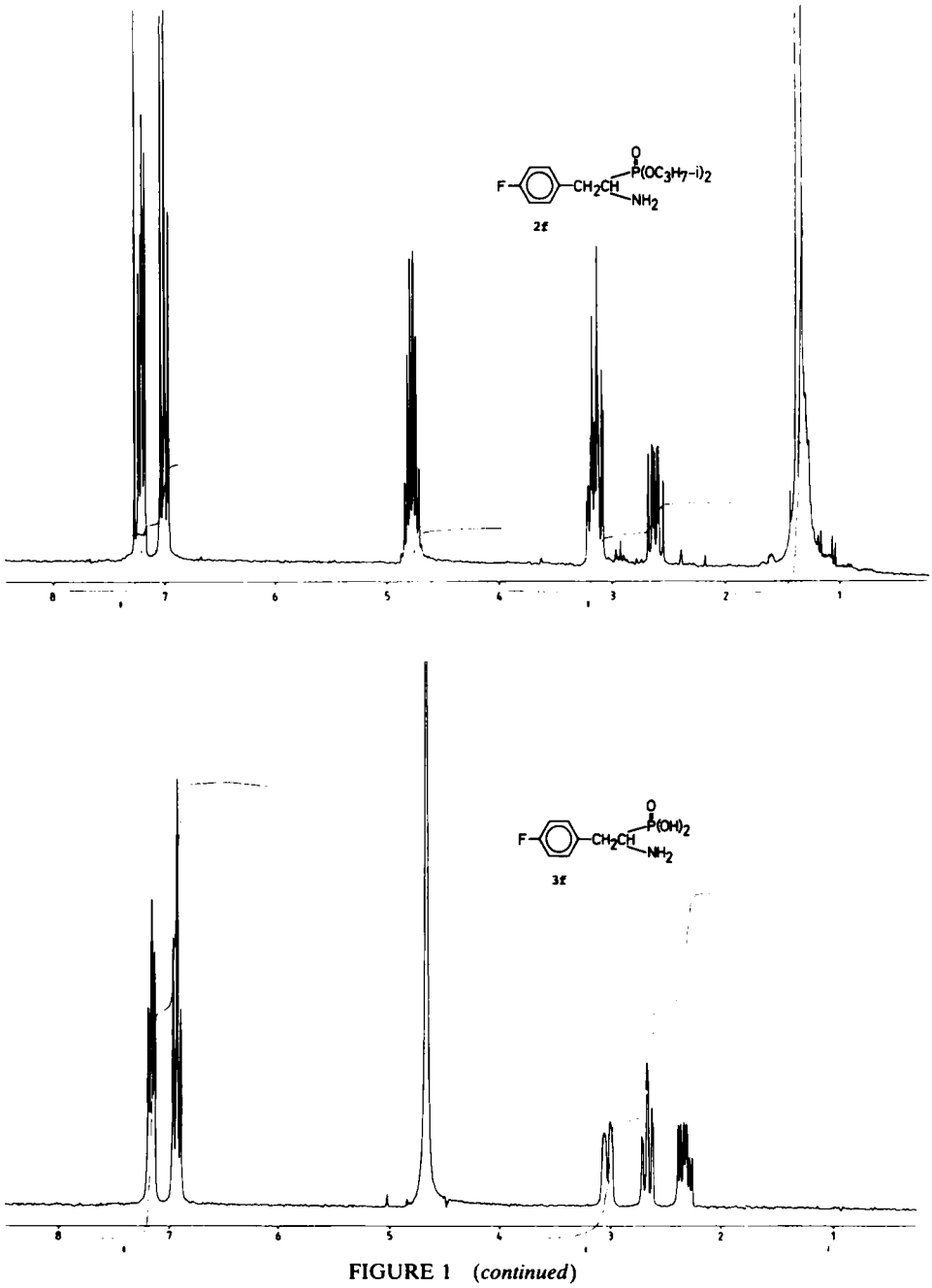


FIGURE 1 (*continued*)

Spectroscopic studies

Like in other aminosubstituted phosphonic acid compounds[24] the ^{31}P-chemical shift of 1-amino-2-aryl-ethylphosphonic acids is strongly dependent on the pH of the solution (Table XIII). Very likely all acids possess the betaine structure, and on neutralization with sodium hydroxide produce the disodium salts.

The ^{1}H-NMR spectra of **1f**, **2f** and **3f** at 250 MHz are shown in Fig. 1. The more interesting shifts and coupling constants are summarized in Table XIV.

ACKNOWLEDGEMENT

I wish to thank Ciba–Geigy's Central Function Research for the hydrogenation experiments, the combustion analysis and for the ^{31}P and ^{13}C NMR spectra, Dr. G. Rist for valuable discussions and Mr. H. Spoerri for experimental help. I particularly want to thank Professor N. Amrhein for determining the PAL and anthocyanin synthesis inhibition constants.

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 the reactions were run under an atmosphere of argon.

The starting material $PhCH{=}NCH_2P(O)(OR)_2$ (**A**, R = C_2H_5; **B**, R = i-C_3H_7) was prepared by the interaction of $(PhCH_2NCH_2)_3$ and sec. phosphites followed by catalytic debenzylation and reaction with benzaldehyde as described in the literature.[14]

The substituted benzylbromides were prepared from the corresponding substituted toluenes by bromination with NBS in CCl_4 using AIBN as a catalyst. The 2- and 4-methoxy substituted benzyl bromides had to be used shortly after their preparation, because they decomposed on standing at room temperature. Attempts to obtain 3-methoxy benzyl bromide from 3-methoxy toluene and NBS in CCl_4 + AIBN failed. In this case bromination in the ring occurred and 2-bromo-5-methoxy toluene was isolated.

1. O,O-Diisopropyl-1-N-benzylidenamino-2-(4-fluorophenyl)ethylphosphonate (**1f**). To a solution of 113.4 g (0.8 mol) of $(i\text{-}C_3H_7)_2NH$ in 750 of THF is added with stirring and cooling 500 ml (1.6 = molar = 0.8 mol) of n-butyllithium. Then the mixture is cooled to −75°C and within 1 h is added a solution of 226.6 g (0.8 mol) of **B** in 600 ml of THF. After further stirring for 1 h a solution of 151.2 g (0.8 mol) of 4-fluorobenzyl bromide in 150 ml of THF is dropwise added and stirring continued for 1 h. After standing over night at ambient temperature the solvent is evaporated on a rotavapor and the residue dissolved in 1 l. of CH_2Cl_2, washed three times with 200 ml of H_2O each, the organic phase dried with Na_2SO_4 and the solvent evaporated to give 286.3 g (=91.4%) of crude **1f** which on distillation with a wiped wall molecular still gives 261.2 g (= 83.4%) of pure **1f**, b.p. 160°C/0.8 Torr. The compounds listed in Table I, IV, VII and X were prepared similarly.

Method A (Debenzylation)

2. O,O-Diisopropyl-1-amino-2-(4-fluorophenyl)ethylphosphonate (**2f**). To a solution of 19.6 g (0.05 mol) of **1f** in 200 ml of isopropanol is added 2 g of Pd/C (5% Pd) and the mixture hydrogenated at 20–25°C. After 62% hydrogen uptake another 2 g of Pd/C and after 90% H_2-uptake again 2 g of Pd/C is added. After 19 hours hydrogen uptake stops. The mixture is filtered and the filtrate evaporated on a rotavapor. The residue (15 g = 98.9%) is kugelrohr distilled to give 12.6 g (= 83.1%) of **2f**, a colorless oil, b.p. 170°C/0.6 Torr.

Method B (cleavage with HCl)

3. O,O-Diethyl-1-amino-2-(4-bromophenyl)ethylphosphonate (**2d**). A solution of 76.4 g (0.18 mol) of O,O-diethyl-1-N-benzyliden-amino-2-(4-bromophenyl)ethylphosphonate **1d** in 500 ml of CH_2Cl_2 is treated with 200 ml of 1N HCl at 20°C and stirred for one hour at that temperature. Then the organic phase is separated and the aqueous phase extracted twice with 100 ml of CH_2Cl_2 each and the organic phase discarded. The aqueous phase is neutralized with soda and extracted three times with 200 ml of CH_2Cl_2 each. The organic phase is dried with Na_2SO_4, the solvent evaporated and the residue molecularly distilled to give 37.1 g (=61.3%) of **2d**, b.p. 125°C/0.04 Torr.

$C_{12}H_{19}BrNO_3P$ (336.17)

calc'd: C 42.88 H 5.70 N 4.17 P 9.21%
found: C 43.5 H 5.70 N 4.2 P 8.9%

The compounds listed in Tables II, V, VIII and IX were prepared either by method A or B.

4. 1-Amino-2-(4-fluorophenyl)ethylphosphonic acid (**3f**). A mixture of 227.5 g (0.75 mol) of **2f** and 750 ml of 20%-HCl solution is refluxed with stirring for 5 hours and stirring continued at room temperature for 10 hours. Then 500 ml of H_2O are added and the precipitate filtered and washed with 250 ml of H_2O and 500 ml of methanol to give after drying 103.3 g of **3f**. The filtrate is evaporated and the residue recrystallized from methanol/propylen oxide to give another 43.3 g. Yield 146.6 g (=98.2%) of **3f**, a white solid, m.p. 266–270°C (dec.).

^{1}H-NMR (in D_2O/NaOD): CH_2 2.3 (3d, $^3J_{HH}$ 2.5, $^2J_{HH}$ 13.8, $^2J_{PH}$ 5.9); CH 2.70 (3d, $^3J_{HH}$ 2.5, $^3J_{HH} \sim 12$, $^2J_{HP}$ 13.6); CH_2 3.0 (broad d, J 13); NH_2, OH 4.65; aromat. H 6.9 (2d) and 7.15 (2d). ^{31}P 16.83 ppm (in D_2O/NaOD, pH 10)

$C_8H_{11}FNO_3P$ (219.15)

calc'd: C 49.85 H 5.86 N 6.39 F 8.67 P 14.13%
found: C 49.9 H 5.2 N 6.4 F 8.4 P 14.2%

Aequiv. weight found 220, calc'd 219 (addition of excess NaOH and back titration with 0.1 N HCl; $pK_1 < 2.5$; $pK_2 = 5.58$; $pK_3 = 9.83$.)

5. O,O-Diethyl-1-N-benzylamino-1-methyl-2-phenyl-ethyl-phosphonate (**7**).
(a) starting material $PhCH_2N{=}\underset{\displaystyle CH_3}{\underset{|}{C}}{-}CH_2C_6H_5$ (**C**)

A mixture of 73.5 g (0.5 mol) of methyl-benzylketone and 54.5 ml (0.5 mol) of benzylamin in 250 ml of toluene is refluxed for 2 h with aceotropic removal of water. Then the solvent is evaporated and the residue distilled to give 69.9 g (= 62.7%) of **C**, b.p. 215–130°C/0.02 Torr.
(b) Preparation of **7**
A mixture of 22.3 g (0.1 mol) of **C** and 13.8 g of diethyl-phosphite is heated with stirring at 110°C for one hour and then chromatographed on kieselgel with ethylacetate: hexane = 7:3 to give 21.3 g (=59%) of **7**, a yellow oil.

^{1}H-NMR (in $CDCl_3$): 1.3 (m; CH_3 + NH, 10H); 3.1 (2d, J_{PCCH} 9 Hz, C—CH_2, 2H); 4.03 (br s, N—CH_2, 2H); 4.2 (qui, OCH_2, 4H); 7.3 (s, C_6H_5, 10H).

$C_{20}H_{28}NO_3P$ (361.42)

calc'd: C 66.47 H 7.81 N 3.88 P 8.57%
found: C 66.2 H 7.5 N 3.7 P 8.4%

6. O,O-Diethyl-1-amino-1-methyl-2-phenyl-ethylphosphonate (**5e**). From 20.5 g (0.057 mol) of **7** in 200 ml of EtOH, 10 g of Pd/C (5%) and H_2 as described in 2 is obtained 14.4 g (= 93.5%) of **5e**, an oil.

^{1}H-NMR (in $CDCl_3$): C—CH_3 1.10 (d, J_{PCCH} 16 Hz), CH_3 1.33 (t,), NH_2 1.63 (s) 11 H; CH_2 2.97 (d, J_{PCCH} 9 Hz, 2H); OCH_2 4.17 (qui, 4H); C_6H_5 7.3 (s, 5H).

7. 1-Amino-1-methyl-2-phenyl-ethylphosphonic acid (**6e**). A mixture of 10.9g (0.04 mol) of **5e** and 100 ml of HCl (20%) is refluxed for 5 h and worked-up as described for **3f**. There is obtained 5.5 g (= 64%) of **6e**, m.p. 245–7°C (dec.).

^{1}H-NMR (in DCl/D_2O): CH_3 1.53 (d, J_{PCCH} 15 Hz, 3 H); CH_2 3.25 (d, J_{PCCH} 9 Hz, 2H); OH, NH_2 7.2 (s); C_6H_5 7.4 (s, 5H).

$C_9H_{14}NO_3P \times H_2O$ (233.19)

calc'd: C 46.3 H 6.9 N 6.0 P 13.3%
found: C 46.3 H 6.9 N 6.0 P 13.3%

8. O,O-Diisopropyl-1-N-dimethylaminomethylidenamino-2-(4-fluorophenyl)-ethylphosphonate (**8a**). A mixture of 6.07 g (= 0.02 mol) of **2f** and 2.93 ml of $(CH_3)_2NCH(OCH_3)_2$ in 40 ml of THF is refluxed with stirring for 2 hours. Then the volatiles are evaporated and the residue is kugelkohr distilled to give 6 g (= 83.7%) of **8a**, a colorless oil, b.p. 160°C/0.06 Torr.

^{1}H-NMR (in $CDCl_3$): $(CH_3)_2$ 1.3 (d, 12 H); $(CH_3)_2N$ 2.7 (s, 6H); PCHCH$_2$ 2.8–3.7 (m, 3 H); OCH 4.7 (m, 2 H); C_6H_4 + N = CH 6.7–7.2 (m, 5 H).

O,O-Diethyl-1-N-dimethylaminomethylidenamino-2-(4-bromo-phenyl-ethylphosphonate (**8b**) was similarly prepared in 76.7% yield, b.p. 160–170°C/0.08 Torr.

^{1}H-NMR ($CDCl_3$): CH_3 1.3 (t, 6 H); $N(CH_3)_2$ 2.77 (s, 6 H) $PCHCH_2$ 2.9–3.7 (m, 3 H) OCH_2 4.2 (qui, 4 H) C_6H_4 + N = CH 6.9–7.5 (m, 5 H).

9. O,O-Diisopropyl-1-N-(3,4-dichlorophenylaminocarbonyl)-2-(4-fluorophenyl)-ethylphosphonate (**9**). To a solution of 6.07 g (= 0.02 mol) of **2f** in 25 ml of ether is added with stirring at 5–10°C a solution of 3.76 (0.02 mol) of 3,4-dichlorophenylisocyanate in 25 ml of Et_2O. After stirring for a further hour the solid is filtered off, washed with ether and dried to give 8.3 g (= 84.4%) of **9**, m.p. 191–3°C.

^{1}H-NMR ($CDCl_3$): $(CH_3)_2$ 1.33 (12 H); CH_2 2.6–3.2 (m, 2 H); PCH + OCH 4.5 (m, 3 H); aromat. CH + CNH 6.3–7.4 (m, 8 H); NH aryl 8.6 (s, 1 H).

10. O,O-Diisopropyl-1-N-formylamino-2-(4-fluorophenyl)ethylphosphonate (**10**). From 6.07 g (0.02 mol) of **2f** and 5 ml of $HCO_2C_2H_5$ under reflux for 20 h is obtained 5 g (= 75.4%) of **10**, b.p. 160–170°C/0.04 Torr.

^{1}H-NMR (in $CDCl_3$): $(CH_3)_2$ 1.33 (12 H); CH_2 2.5–3.3 (m, 2 H); OCH + PCH 4.4–5.0 (m, 3 H) C_6H_4 + NH 6.8–7.3 (m, 5 H); CHO 8.1 (s, 1 H).

The oxalylderivative **11** is similarly obtained from **2f** and diethyloxalate in CH_3OH, yield 51.3 %, m.p. 131–5°C.

^{1}H-NMR (in $CDCl_3$): $(CH_3)_2$ 1.35 (d, 12 H); CH_2 2.5–3.4 (m, 2 H); OCH_3 3.87 (s, 3 H); PCH + OCH 4.4–5.0 (m, 3 H); C_6H_4 + NH 6.7–7.5 (m, 5 H).

The chloroacetylderivative **12** is similarly obtained from **2f** and chloroacetic anhydride in methylen dichloride in 69.5% yield, m.p. 121–3°C (from ethylacetate/diisopropylether).

^{1}H-NMR (in $CDCl_3$): $(CH_3)_2$ 1.33 (12 H); CH_2 2.7–3.3 (m, 2 H); CH_2Cl 3.95 (s, 2 H); CHO + PCH 4.4–5.1 (m, 3 H); C_6H_4 + NH 6.8–7.4 (m, 5 H).

11. O,O-Diisopropyl-1-N(2,6-dinitro-4-trifluoromethylphenylamino)-2-(4-fluorophenyl)ethylphosphonate (**13**). A mixture of 6.07 g (0.02 mol) of **2f**, 6 g of 2,6-dinitro-4-trifluoromethyl-chlorobenzene, 1.8 ml of pyridine and 20 ml of toluene is refluxed for 4 hours. Then the mixture is diluted with 100 ml of ethylacetate, washed twice with 50 ml of H_2O each, dried, and the solvent evaporated. The residue is flash chromatographed using hexane: ethylacetate = 6:4 as eluent. There is obtained 6.8 g (= 63.3 %) of **13**, a resin.

(^{1}H-NMR) (in $CDCl_3$): $(CH_3)_2$ 1.2 (12): $PCHCH_2$ 2.8–4.2 (m, 3 H); OCH 4.7 (m, 2H); C_6H_4 6.8–7.4 (m, 4 H); C_6H_2 + NH 8.3–8.4 (m, 3 H).

12. O,O-Diisopropyl-1-N-(Z-L-alanylamino)-2-(4-fluorophenyl) ethylphosphonate (**14**). To a solution of 5.58 g (0.025 mol) of Z-L-alanine and 7.58 g (0.025 mol) of **2f** in 50 ml of CH_2Cl_2 is added with stirring at 5°C a solution of 5.67 g (0.028 mol) of dicyclohexylcarbodiimid in 50 ml of CH_2Cl_2. The mixture is stirred for 12 h at 20°C, the precipitated urea filtered and the filtrate evaporated. The residue is recrystallized from ethylacetate to give 12 g (= 94.4 %) of **14**, a white solid, m.p. 178–182°C.

13. O,O-Diisopropyl-1-N-[2-nitro-5-(2'-chloro-4'-trifluoromethylphenoxy)-phenylamino]-2-(4-fluorophenyl)ethylphosphonate (**15a**). To a solution of 1.81 g (0.005 mol) of 3,4-dinitro-2'-chloro-4'-trifluoromethyl-diphenylether in 10 ml of toluene is added with stirring 3.03 g (0.005 mol) of **2f** and the mixture stirred for 12 hours at 20°C. The solvent is evaporated and the residue chromatographed on Al_2O_3 using ethylacetate as solvent. There is obtained 1.8 g (= 58.3 %) of **15a**, a yellow resin.

^{1}H-NMR (in $CDCl_3$): $(CH_3)_2$ 1.2 (12 H); $PCHCH_2$ 2.7–4.0 (m, 3 H); OCH 4.7 (m, 2 H); aromat. H + NH 6–8.5 (m, 11 H).

15b is similarly obtained using 2d in 55.3 % yield, also a yellow resin.

^{1}H-NMR (in $CDCl_3$): (CH_3) 1.33 (2t, 6 H); $PCHCH_2$ 2.8–3.8 (m, 3 H); OCH_2 4.2 (qui, 4 H); aromat. H + NH 6.1–8.6 (m, 11 H).

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