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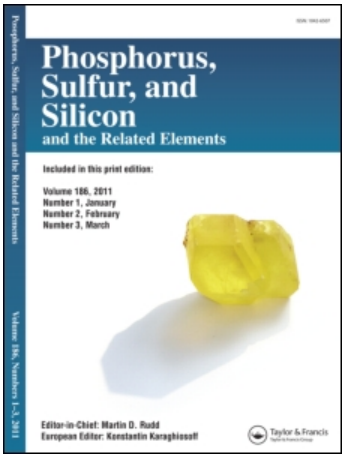

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ORGANIC PHOSPHORUS COMPOUNDS 94[1] PREPARATION, PHYSICAL AND BIOLOGICAL PROPERTIES OF AMINO-ARYLMETHYLPHOSPHONIC- AND-PHOSPHONOUS ACIDS

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ORGANIC PHOSPHORUS COMPOUNDS 94[1] PREPARATION, PHYSICAL AND BIOLOGICAL PROPERTIES OF AMINO-ARYLMETHYLPHOSPHONIC- AND -PHOSPHONOUS ACIDS

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(Received August 20, 1990)

The preparation, physical and spectroscopic properties of amino-arylmethylphosphonic- and -phosphonous acids, the phosphorus analogues of phenylglycine, are described. It is shown that several of the compounds prepared exhibit antifungal activity at 200 ppm. Thus **1e**, **1f**, **1g** and **1h** showed activity against Erysiphe (barley), **2a** against Puccinia (wheat) and **6a** against Botrytis (apple). Of particular interest is the high gameticidal activity of **3a** in the greenhouse.

Key words: Amino-arylmethylphosphonic- and -phosphonous acids; preparation; properties; biological activity.

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INTRODUCTION

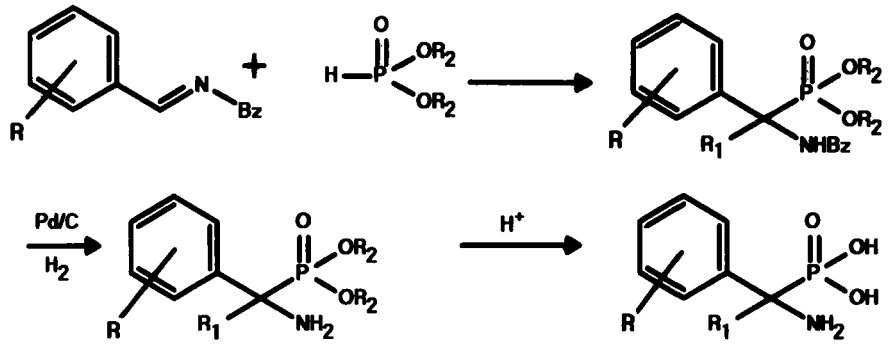
Recently we reported on the preparation and biological properties of 1-amino-2-arylmethylphosphonic acids.[2] It was shown that some of the derivatives were strong inhibitors of PAL and anthocyanin synthesis and also showed high fungicidal activity especially against Botrytis cinerea and Fusarium nivale. It seemed of interest to prepare homologues of the above series and determine their biological activity.

In this paper we report on the synthesis and biological activity of amino-arylmethylphosphonic- and -phosphonous acids.

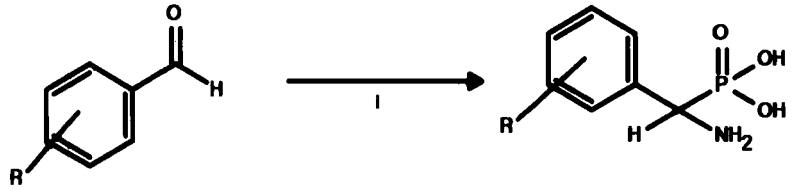
RESULTS AND DISCUSSION

Several methods have been reported in the literature for the preparation of amino-arylmethylphosphonic-, -phosphonous and -phosphinic acids (for reviews see References 3–6). Among these the simplest ones seem to be the addition of a P—H function to Schiff bases, prepared from aldehydes and benzylamine, followed by debenzylation and hydrolysis[7,8] (method A, Scheme 1) and the amidoalkylation of phosphorous chloride with aldehydes and amides[9] or benzylcarbamate[10] (method B, Scheme 2). Generally the yields are higher (see Table III) when using method A (Scheme 1) for the preparation of amino-arylmethylphosphonic acids. Furthermore this method has the advantage that the esters of amino-arylmethylphosphonic acids are produced as intermediates which are isolable (see Table II) and may be used for further synthesis.

Furthermore this method is also adaptable to the preparation of phosphinates

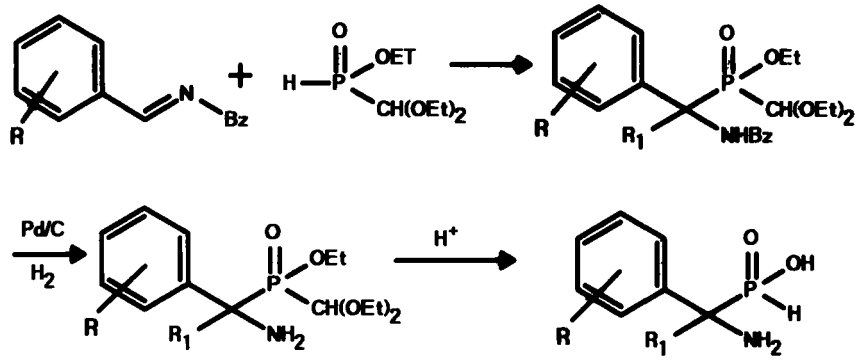


Scheme 1



I: $BzOCONH_2$ / PCl_3 /AcOH /HCl

Scheme 2



Scheme 3

(Table V) and phosphonous acids[11] (Table VI, Scheme 3). The starting material O-ethyl-diethoxymethylphosphonite is easily prepared according to the literature.[12] The yields are in the region of 60–90%.

Biological Activity

The divers and interesting biological and biochemical properties of 1-aminophosphonic acids have been described in detail in a review article.[13] More recently it

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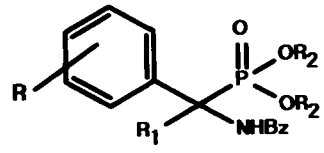
TABLE I

Physical properties of

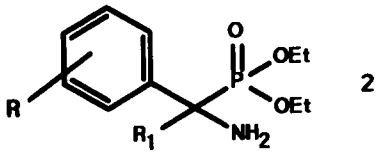


1

No	R	R_1	R_2	yield in %	b.p. °C/torr n_d^{20}	^{1}H-NMR in $CDCl_3$			^{31}P-chem. shift (85% H_3PO_4 ref. in $CDCl_3$)
						R_1	CH_2	NH	
a	4-F	H	CH_3	81.4	1,5364	4.0 (J20)	3.6	2.6 (br.)	
b	4-F	H	C_2H_5	95.3	1.5170	3.6–4.2 (m)		2.37 (br.)	
c	4-F	H	i-C_3H_7	47.4	130/0.2	3.9 (J19)	3.6 (J7)	2.6 (br.)	
d	4-CH_3	H	C_2H_5	95.7	1,5280	3.6–4.3 (m)		2.6 (br.)	
e	3-iC_3H_7	H	C_2H_5	100	1,5207	3.6–4.3 (m)		2.4 (br.)	
f	3-iC_3H_7	CH_3	C_2H_5	99.8	1,5012	1.9 (J16)	3.6 (m)	2.7 (br.)	
g	4-iC_3H_7	H	C_2H_5	100	1,5181	3.6–4.4 (m)		2.4 (br.)	23.84
h	4-iC_3H_7	CH_3	C_2H_5	100	1,5229	1.8 (J16)	3.6	2.7 (br.)	
i	2,3-OCF_2O	H	C_2H_5	94.3		3.6–4.4 (m)		2.6 (br.)	
k	3,4-$(CH_3O)_2$	H	C_2H_5	89.5	resin	3.6–4.4 (m)		2.6 (br.)	
l	3-(4-FC_6H_4O)	H	C_2H_5	94	1,5439	3.8	3.5 (J12, 1H) 3.8 (J12, 1H)	2.5 (br.)	
m	3-(4-ClC_6H_4O)	H	C_2H_5	96	1.5574	3.8	3.55 (J12, 1H) 3.82 (J12, 1H)	2.3 (br.)	23.03

TABLE II

Physical properties of



2

No	R	R_1	yield in %	b.p. °C/torr n_D^{20}	^{1}H-NMR in $CDCl_3$		^{31}P-chem. shift (85% H_3PO_4 ref. in $CDCl_3$)
					R_1	NH_2	
a	3-iC_3H_7	CH_3	65.8	165–70/0.04	1.7 (J16)	2.3 (br.)	26.7
b	4-F	H	91	105/0.1	4.25 (J16)	1.9	
c	4-CH_3	H	78.4	115/0.1[a]	4.1 (J16)	1.9	
d	3-iC_3H_7	H	27.6	180/0.04	4.15 (J16)	2.43	24.94
e	2,3-OCF_2O	H	75.8	135/0.04	4.45 (J18)	2.1	
f	3,4-$(CH_3O)_2$	H	68.2	150/0.12	4.3 (J16)	2.1	
g	3-(4-FC_6H_4O)	H	92	1,5361	4.18 (J17)	1.9	
h	3-(4-ClC_6H_4O)	H	36	1,5490	4.18 (J17)	1.9	

[a]Lit.[15] isolated as hydrochloride m.p. 161°C.

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has been shown[14] that amino-3,4-dihydroxyphenylmethylphosphonic acid is one of the most powerful known inhibitors of mushroom tyrosinase.

We have found that several of the compounds listed in Tables I–VI exhibited antifungal activity at 200 ppm. Thus **1e**, **1f**, **1g** and **1h** showed activity against Erysiphe graminis on barley, **2a**, against Puccinia recondita on wheat, and **6a** against Botrytis cinerea on apple. Of particular interest is the high gameticidal activity of **3a** in the greenhouse, i.e., it sterilizes male anthers in plants.

EXPERIMENTAL

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

The Schiff bases were all prepared from aldehyde and benzylamine by splitting off water according to the following example:

N-(4-Fluorophenylmethylene)-benzylamine, **A**

To 54.6 ml (0.5 mol) of benzylamine in 400 ml of CH_2Cl_2 is added with stirring and ice-cooling 52.8 ml (0.5 mol) of para-fluorobenzaldehyde dissolved in 100 ml of CH_2Cl_2. Then Na_2SO_4 is added until a clear organic phase is formed. The mixture is stirred for 1 h at ambient temperature, filtered and the filtrate fractionally distilled to give 94.5 g (88.6%) of **A**, b.p. 112–114°C/0.1 torr.

1. *0,0-Diethyl-N-benzylamino-4-fluorophenylmethylphosphonate*, **1b**. To 30 g (0.14 mol) of **A** dissolved in 200 ml of Et_2O is added 1.5 ml of $BF_3 \times Et_2O$ and the formed suspension cooled with ice. Upon addition of 21.3 g (0.154 mol) of diethylphosphite an exothermic reaction ensues and the mixture becomes clear. After stirring the mixture for 14 h at 20°C the mixture is extracted three times with 100 ml of H_2O each and the organic phase dried with Na_2SO_4 filtered and the filtrate evaporated on a rotavapor. There is obtained 45.26 g (95.3%) of **1b**, a colorless, viscous oil, $n_D^{20} = 1.5170$.

^{1}H-NMR (in $CDCl_3$) δ:	1.1 and 1.3 (t, CH_3, 6H); 2.37 (s, NH, 1H); 3.6–4.2 (m, CHP, CH_2, OCH_2, 7H); 6.93–7.6 (m, C_6H_5, C_6H_4, 9H)
$C_{18}H_{23}FNO_3P$ (351.36):	calc.: C 61.53 H 6.59 N 3.98 P 8.81%
	found: C 60.7 H 6.6 N 4.0 P 8.6%

The compounds listed in Table I and V c, d, have been obtained in the same way.

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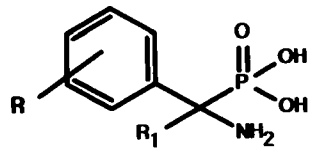
TABLE III

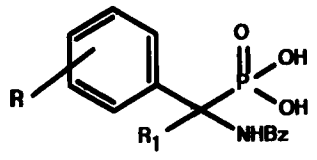
Physical properties of  3

No	R	R_1	Method[a]	yield in %	m.p. °C	solvent	^{1}H-NMR in $CDCl_3$	
							R_1	OH, NH_2
a	4-F	H	A	90.3	>300	D_2O/NaOD	3.83 (J16)	5.0
b	4-CH_3	H	A	86.3	266–7 (dec.)[b]	D_2O/DCl	4.3 (J17)	5.0
c	3-iC_3H_7	H	A	97	97 (dec.)	CD_3OD	3.7	4.5
d	3-iC_3H_7	CH_3	A	82.7	90–2 (dec.)	CD_3OD	1.6 (J14)	5.2
e	4-iC_3H_7	H	A	21.5	>300	D_2O/NaOD	3.75 (J14)	4.75
f	3,4-$(HO)_2$	H	A	98	>300[c]	D_2O/NaOD	3.4 (J14)	4.75
g	3-CH_3O, 2-OH	H	A	85.6	210 (dec.)	CD_3OD	3.3	4.55
h	3,4-$(CH_3O)_2$	H	A	78.9	252–5 (dec.)[d]	D_2O/NaOD	3.5	4.8
i	2-HO, 3,4-Cl_2	H	B	54	311–14 (dec.)			
k	4-HO, 3,5-(t-$C_4H_9)_2$	H	B	42	215 (dec.)			
l	3-C_6H_5O	H	B	62	266–8 (dec.)			
m	3-(4-FC_6H_4O)	H	A	75	275–7 (dec.)			
n	3-(4-ClC_6H_4O)	H	B	27	271–2 (dec.)			
o	3-(4-BrC_6H_4O)	H	B	59	267–70 (dec.)			

[a]Method A: from ester and HCl (Scheme 1); Method B: from aldehyde, PCl_3 and benzylurethane (Scheme 2).
[b]Lit.[16] m.p. 274–77°C.
[c]Lit.[14] m.p. 281–84°C (dec.).
[d]Lit.[14] m.p. 258–62°C (dec.).

TABLE IV

Physical properties of



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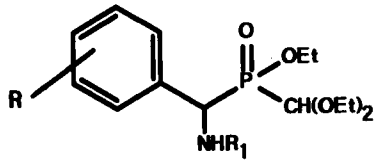
No	R	yield in %	m.p. (dec.)	solvent	^{1}H-NMR in $CDCl_3$ CH	CH_2	OH, NH_2
a	4-F	43.6	162–4				
b	4-CH_3	82.5	162	D_2O/NaOD	3.4 (J17)	3.2 (J3)	4.6
c	3-iC_3H_7	71.5	174	CD_3OD/NaOD	3.23 (J17)	3.0 (J3)	4.5
d	4-iC_3H_7	38.5	175	CD_3OD	4.1 (J17)	3.85 (J3)	5.7

TABLE V

Physical properties of



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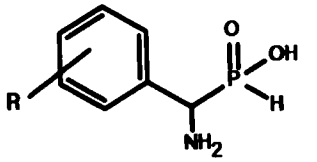
No	R	R_1	yield in %	m.p. °C n_D^{20}	^{1}H-NMR in $CDCl_3$ PCHO	NH
a	4-F	H	95.3	oil	4.8 (J10)	2.15 (br.)
b	4-CH_3	H	93.3	1,5025	4.8 (J9)	2.5 (br.)
c	4-F	$C_6H_5CH_2$	55.2	63–5	4.8 (J10)	2.5 (br.)
d	4-CH_3	$C_6H_5CH_2$	85.7	1,5241	4.9 (J10)	2.6 (br.)

TABLE VI

Physical properties of



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No	R	yield in %	m.p. °C	solvent	^{1}H-NMR PCH-N	NH_2, OH	^{31}P-chem. shift (85% H_3PO_4 ref.)
a	4-F	78.6	>300	D_2O/DCl	4.45 (J14)	5.5	23.2 (J_{PD} 91)[b]
b	4-CH_3	65.7	227 (dec.)[a]	D_2O/DCl			24.03 (J_{PD} 91)[b]

[a]Lit.[17] m.p. 237–238°C; Lit.[18] m.p. 239–240°C (dec.).
[b]Formed through P-H–P-D exchange with the solvent.

2. *0,0-Diethyl-amino-4-fluorophenylmethylphosphonate*, **2b**. To 242.2 g (0.69 mol) of **1b** dissolved in 2.5 liters of ethanol is added 64 g Pd/C (5%) and the mixture hydrogenated at 20–25°C and normal pressure. After 30 h H_2-uptake stopped (uptake 102%). The catalyst is filtered off and from the filtrate the solvent removed on a rotavapor. The residue is purified by thin-layer distillation, b.p. 105°C/0.1 torr; yield of **2b**: 64 g (91.0%), a colorless oil.

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^{1}H-NMR (in $CDCl_3$) δ:	1.2 and 1.3 (t, CH_3, 6H); 1.9 (s, NH_2, 2H); 4.1 (2 qui, OCH_2, 4H); 4.3 (d, J_{PCH} 12 Hz, CHP, 1H); 6.9–7.7 (m, C_6H_4, 4H)
$C_{11}H_{17}FNO_3P$ (261.23):	calc.: C 50.58 H 6.56 N 5.36 P 11.86%
	found: C 50.3 H 6.5 N 5.1 P 11.2%

The compounds listed in Table II and Table V a, b, have been obtained in the same way.

3. *Amino-4-fluorophenylmethylphosphonic acid,* **3a** *(Method A).* A mixture of 130.62 g (0.5 mol) of **2b** and 500 ml of HCl (20%) is refluxed for 5 h and then the solution evaporated on a rotavapor. The viscous yellow residue is dissolved in methanol and the solution treated with propylene oxide. A thick white suspension forms. The solid is filtered off and dried at 80° in vacuo. There is obtained 92.6 g (90.3%) of **3a**, a white solid, m.p. > 300°C.

^{1}H-NMR (in D_2O-NaOD) δ:	3.83 (d, J_{PCH} 16 Hz, 1H); 5.0 (s, NH_2, OH); 6.9–7.6 (m, C_6H_4, 4H)
$C_7H_9FNO_3P$ (205.13):	calc.: C 40.99 H 4.42 N 6.82 P 15.10%
	found: C 40.8 H 4.6 N 6.8 P 14.6%

Equiv. weight found 208; calc. 205; $pK_1 < 2.5$; $pK_2 = 5.69$; $pK_3 = 9.47$.
The compounds listed in Table III and Table VI have been obtained in the same way.

4. *N-Benzylamino-4-fluorophenylmethylphosphonic acid,* **4a**. To 9.23 g (27 mmol) of **1b** dissolved in 50 ml of $CHCl_3$ is added 9.16 g (59 mmol) of $(CH_3)_3SiBr$ and the mixture stirred for 14 h at 20°. Then the clear solution is evaporated to give 11.8 g (99.3%) 0,0-bis-trimethylsilyl-N-benzylamino-4-fluorophenylmethylphosphonate, a slightly yellow resin. This is treated with 100 ml of ethanol and stirred for 2 h at 20°C. A thick, white suspension forms. The solid is filtered and dried at 80° in the vacuum to give 3.4 g (43.6%) of **4a**, a white solid, m.p. 162–164°C (dec.).

5. *Amino-[3-(4-bromophenoxy)-phenyl]methylphosphonic acid (Method B),* **3o**. To a solution of 5.4 g (0.036 mol) of benzylcarbamate in 20 ml of acetic acid is added 3.2 ml (0.036 mol) of PCl_3. Then 15 g (0.054 mol) of 3-(4-bromophenoxy)-benzaldehyde are added dropwise. Thereby the temperature increases to 33°C. The reaction mixture is stirred for 12 hrs at 20°C, then 30 ml of 6N HCl are added and the mixture refluxed for 30 min. After cooling to 20°C the mixture is extracted 3 times with ether and the aqueous phase evaporated on a rotavapor. The residue is dried over P_2O_5 to give 13.5 g crude **3o**, as an amorphous solid. This is dissolved in 50 ml of methanol, 5 ml of propylene oxide are added and the precipitate filtered, washed with H_2O and dried over P_2O_5 to give 7.6 g (58.9%) of **3o**, colorless crystals, m.p. 267–270°C (dec.).

$C_{13}H_{13}BrNO_4P \times H_2O$ (376.9):	calc.:	C 41.48	H 3.98	Br 21.27	N 3.72	P 8.24	H_2O 4.81%
	found:	C 42.1	H 4.0	Br 21.2	N 3.7	P 8.2	H_2O 5.3%

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