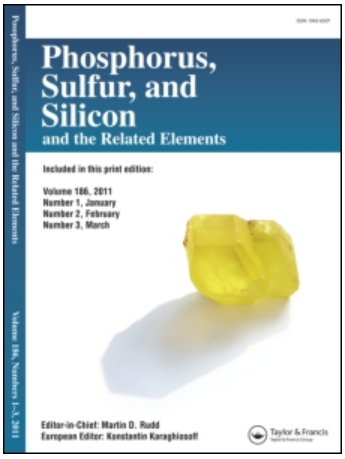

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ORGANIC PHOSPHORUS COMPOUNDS 102.[1] AMINOOXYALKYLPHOSPHONIC ACIDS AND DERIVATIVES

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ORGANIC PHOSPHORUS COMPOUNDS 102.[1] AMINOOXYALKYLPHOSPHONIC ACIDS AND DERIVATIVES

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(Received March 31, 1992)

Condensation of α-hydroxyalkylphosphonates, **1**, with N-hydroxy-phthalimide using Mitsunobu's condition yields 1-phthalimido-N-oxyalkylphosphonates, **2**, which on treatment with hydrazine give 1-aminooxyalkylphosphonates, **3**. Hydrolysis of these with HCl produces 1-aminooxyalkylphosphonic acids, **4**, in good yield. The reactions of **3** with dinitrodiphenyl ether, isocyanides, aldehydes and ketones are also reported.

1-Aminooxy-2-phenylethylphosphonic acid, **4g**, is only a weak inhibitor of PAL, but **4i** is a good inhibitor of anthocyanin synthesis. **4g** exhibits weak antifungal activity (against Botrytis cinerea) and **5a** and **5b** show herbicidal activity against dicotyledonous weeds.

Key words: 1-Aminooxyalkylphosphonates; 1-aminooxyalkylphosphonic acids; physical properties; NMR-spectra; biological activity.

INTRODUCTION

L-α-Aminooxy-β-phenylpropionic acid is a potent competitive inhibitor of phenylalanine ammonia-lyase (PAL)[2] and aminooxyacetic acid is an efficient inhibitor of anthocyanin synthesis[2,3] and of γ-aminobutyric acid-α-ketoglutaric acid transaminase in vivo,[4] but a relatively poor inhibitor of PAL.[5] Aminooxyacetic acid also reacts specifically with P-pyridoxal groups of cystathionase.[6] It seemed of interest to prepare the corresponding phosphonic and phosphinic acid analogs and to determine their biological activity.

RESULTS AND DISCUSSION

Two aminooxyalkylphosphonic acids have been described previously in the literature, i.e., aminooxymethylphosphonic acid[7,8] and β-aminooxyethylphosphonic acid.[8] Whereas Denzel et al.[7] used the Mitsunobu reaction[9] to synthesize this type of compound, Khomutov et al.[8] prepared these compounds by the interaction of acethydroximic acid and ω-haloalkylphosphonates followed by hydrolysis. Because Mitsunobu's reaction is simple to carry out and gives satisfactory yields we used this method for the synthesis of several α-aminooxyalkylphosphonic acids (Scheme I). Furthermore this procedure is also useful for the synthesis of aminooxyalkylphosphonous and -phosphinic acids.[10]

α-Hydroxyalkylphosphonates, **1**, are easily obtained by the base catalyzed addition of aldehydes to secondary phosphites.[11] Condensation of **1** with N-hydroxy-

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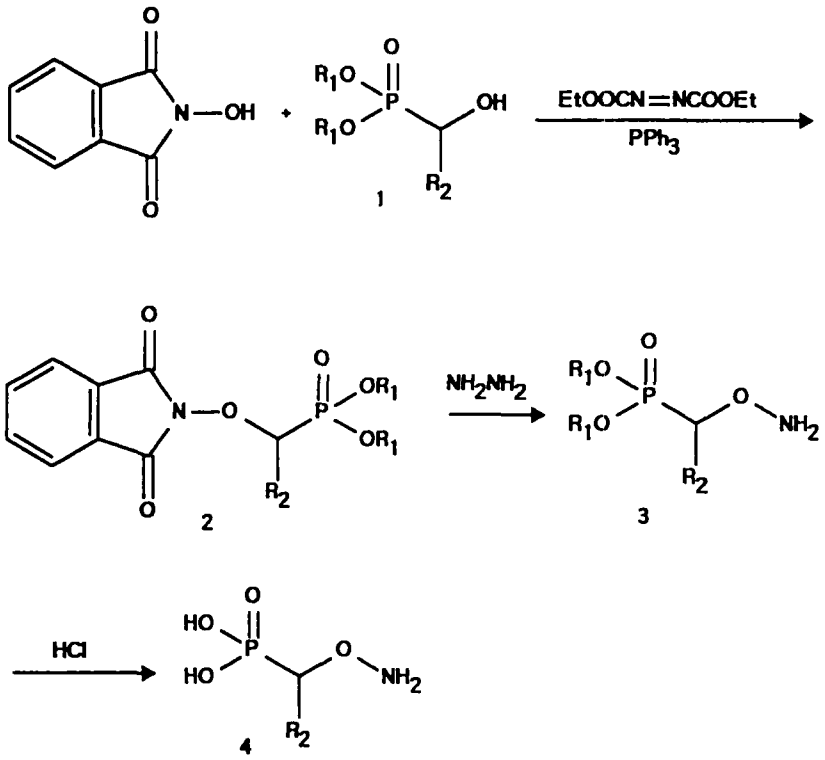


SCHEME I

phthalimide under Mitsunobu's condition produces the 1-phthalimido-N-oxyalkylphosphonates **2** in yields ranging from 40 to 100%. Treatment of **2** with hydrazine yields 1-aminooxyalkylphosphonates, **3**, in satisfactory yields.

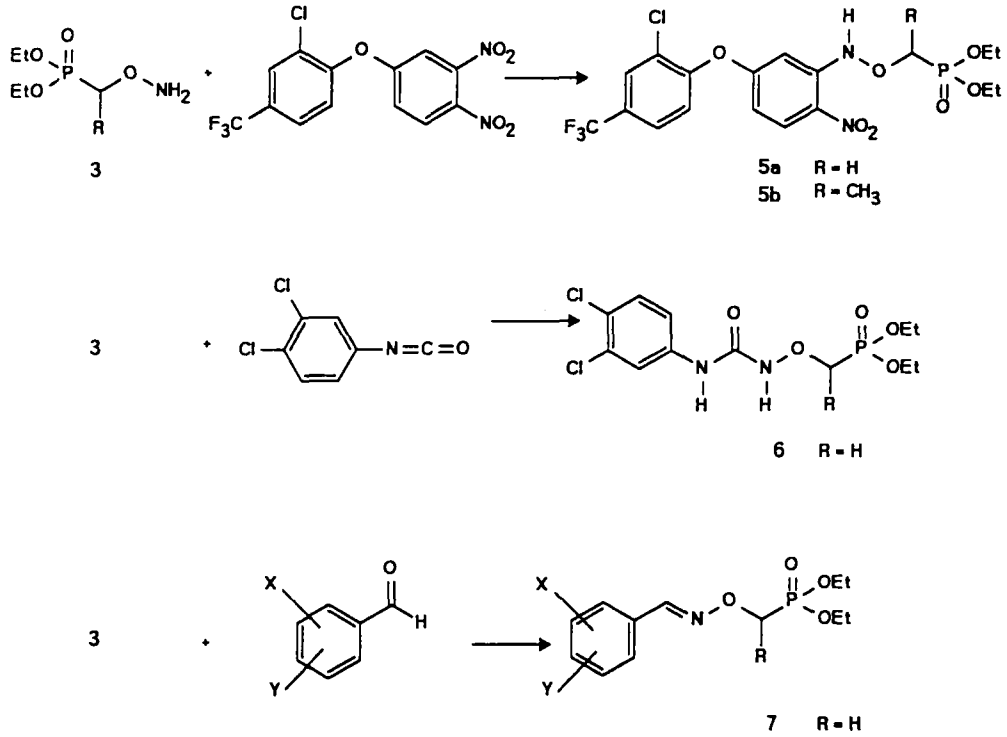
Hydrolysis of **3** with 20% aqueous hydrochloric acid under reflux gives the crystalline 1-aminooxyalkylphosphonic acids, **4**, in good yield.

REACTIONS OF 1-AMINOOXYALKYLPHOSPHONATES

The 1-aminooxyalkylphosphonates, **3**, give all the reactions typical for O-alkylhydroxylamines. Thus the interaction of **3a** and 3,4-dinitro-2′-chloro-4′-trifluoromethyl-diphenyl ether gives O,O-diethyl-2-nitro-5-(2′-chloro-4′-trifluoromethylphenoxy)-phenyl-aminooxymethylphosphonate, **5a**, with isocyanates an urea derivative **6** is obtained, and oximes, **7**, are produced when **3** is treated with aldehydes or ketones (Scheme II). Dealkylation of **6** and **7** with trimethylbromosilane followed by hydrolysis yields the corresponding acids (Table V).

BIOLOGICAL ACTIVITY

In contrast to 1-amino-2-phenylethylphosphonic acid,[12] 1-aminooxy-2-phenylethylphosphonic acid, **4g**, is only a weak inhibitor of PAL,[13] but the inhibition of



SCHEME II

anthocyanin synthesis in vivo by 1 mM of 1-aminooxy-3-phenylpropylphosphonic acid, **4i**, is 68%.[13] **4g** exhibits weak antifungal activity. More pronounced is the selective herbicidal activity of **5a** against dicotyledonous weeds in cereals and rice. At a concentration of 500 g/ha the control of seven dicotyledonous weeds was 79%; **5b** is less active (59%) than **5a**.

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. Me_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.

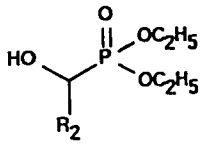
1. O,O-Diethyl-1-hydroxyethylphosphonate, **1b**. At room temperature, 292 ml of acetaldehyde is added dropwise to a stirred solution of 658.5 ml of diethylphosphite in 60 ml of triethylamine. The reaction is exothermic and the temperature rises to 70°C. After the addition is complete, the reaction mixture is kept for 14 hours at room temperature. Then the volatile parts are removed in a rotatory evaporator and the residue is distilled to give 283.5 g (75%) of **1b**, b.p. 114–116°C/0.2 mbar; (lit.[11] b.p. 116–119°C/1.5 torr).

^{1}H-NMR (in $CDCl_3$) δ: 1.35 (t, CH_3, 6H); 1.5 (2d, C—CH_3, J18, 3H); 4.2 (qui, m, OCH_2, CHP, 5H); 5.15 (s, OH, 1H).
The compounds listed in Table I have been prepared similarly.

2. O,O-Diethyl-(1-phthalimido)-N-oxyethylphosphonate, **2b**. An amount of 32.32 g (0.2 mol) of azodicarbonic acid diethyl ester is added dropwise, at a temperature of 0 to 5°C to a mixture of 36.34 g

TABLE I

Physical properties of



1

1	R_2	Boiling point °C/mbar	Yield %	^{1}H-NMR in $CDCl_3$				
				R_2	CH_3	OCH_2	PCH	OH
a	H	110/o.1[a]	85.5	-	1.32	4.2	3.9 (J6)	5.15
b	CH_3	114-116/0.2[b]	75	1.5	1.35	4.2	4.2(m)	5.15
c	C_2H_5	111-113/0.1[c]	55.6	0.8-2.0	1.3	4.13	3.8	5.1
d	n-C_3H_7	109-112/0.06[d]	40.9	0.7-2.0	1.3	4.15	3.8	4.93
e	i-C_3H_7	96-102/0.06	60.9	1.43	1.33	4.23	3.37	4.8
f	n-C_4H_9	112-115/0.06	67.4	0.7-2.3	1.4	4.2	3.9	5
g	$C_6H_5CH_2$	135/0.15	60.6	7.3+3.1	1.3	4.15	4	4.6
h	$CH_3SC_2H_4$	115/0.2	70.6	2.1(SCH_3) 2.0:2.7	1.4	4.2	4.2	4.9
i	$C_6H_5CH_2CH_2$	130-135/0.1	84.2	7.23 2.03:2.8	1.3	4.17	3.8	5.3
k	n-$C_3H_7(CH_3)CH$	95/0.1	86.1	0.7-2.2	1.3	4.2	3.7	4.4
l	n-C_9H_{19}	154/0.03 (m.p.42-45)	78.3	0.7-2.0	1.3	4.2	3.8	3.6

a) lit.[11] 103-105°C/0.2torr; b) lit.[11] 116-119°C/1.5torr; c) lit.[11] 120-121°C/1.5torr; d) lit[11] 111-112°C/0.3torr

(0.2 mol) of hydroxyphthalimide, 36.43 g (0.2 mol) of **1b** and 52.45 g (0.2 mol) of triphenylphosphine in 400 ml of tetrahydrofuran. The reaction is exothermic and a clear solution forms. After the addition is complete, the solution is kept for 14 hours at room temperature, then the volatile parts are removed in a rotatory evaporator. The residue is taken up in 200 ml of diethyl ether and stirred for one hour, filtered and the filtrate is again concentrated. Thin layer distillation of the residue yields 80.6 g (100%) of **2b**, a yellow oil, b.p. 175°C/0.08 mbar.

^{1}H-NMR (in $CDCl_3$) δ: 1.3 (2t, CH_3, 6H); 1.6 (2d, C—CH_3, J16, 3H); 4.15 (qui, OCH_2) and 4.7 (2q, OCH) (5H); 7.3–7.8 (m, aryl, 4H).
The compounds listed in Table II have been prepared similarly.

3. O,O-Diethyl-1-aminooxyethylphosphonate, **3b**. 8.94 g (0.18 mol) of hydrazine are added dropwise while stirring to an ice-cold solution of 40.3 g (0.1 mol) of **2b** in 150 ml of methylene dichloride. The reaction is exothermic and a thick suspension forms. After the addition is complete, the suspension is stirred for one hour at 0 to 5°C and then filtered. The filtrate is dried over sodium sulfate and evaporated. The residue is 27.8 g of a red oil which is purified by thin layer distillation. The main fraction (11.8 g) distills at 65°C/0.06 mbar. It is distilled again to yield 9.1 g-(46.1%) of pure **3b**, a clear oil, b.p. 77–80°C/0.02 mbar.

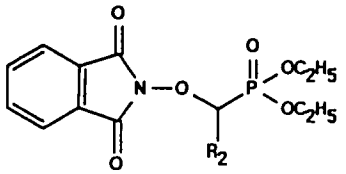
^{1}H-NMR (in $CHCl_3$) δ: 1.35 (t, CH_3, 6H); 1.5 (2d, J16, C—CH_3, 3H); 4.2 (qui, OCH_2, OCH, 5H); 5.9 (s, NH_2, 2H).
^{31}P-NMR (in $CHCl_3$) 24.26 ppm.

$C_6H_{16}NO_4P$ (197.17) calc.: C 36.55 H 8.18 N 7.10 P 15.71%
found: C 37.2 H 8.1 N 6.1 P 15.2%

The compounds listed in Table III have been prepared similarly.

TABLE II

Physical properties of



2

Z	R_2	Boiling point °C/mbar	Yield%	^{1}H-NMR in $CDCl_3$				
				R_2	CH_3	OCH_2	PCH	C_6H_4
a	H	chromatographed[a]	70.2	-	1.4	4.3	4.57 (J9)	7.4 - 8.0
b	CH_3	175/0.08	100	1.6	1.3	4.15	4.7	7.3 - 7.8
c	C_2H_5	175/0.06	69.6	1.0 - 2.3	1.3	4.17	4.7	7.3 - 8.0
d	n-C_3H_7	crude,further processed		0.8 - 2.2	1.3	4.2	4.7	7.5 - 7.8
e	i-C_3H_7	crude,further processed						
f	n-C_4H_9	crude,further processed						
g	$C_6H_5CH_2$	180/0.1	56.3	7.4 + 3.33	1.33	4.2	5.1	7.0 - 7.5
h	$CH_3SCH_2CH_2$	resin	38.5	2.03 (SCH_3) 2.0:2.7	1.3	4.1	4.7	7.3 - 8.0
i	$C_6H_5CH_2CH_2$	resin	100	1.8 - 3.4 7.0 - 8.0	1.35	4.2	4.7	7.0 - 8.0
k	n-$C_3H_7CH(CH_3)$	150/0.02	90.1	0.8 - 2.3	1.3	4.1	4.7	7.3 - 7.9
l	n-C_9H_{19}	190/0.06	74.4	0.8 - 2.5	1.3	4.2	4.7	7.4 - 8.0

a) lit.[7] m.p. 80 - 85 °C

4. 1-Aminooxyethylphosphonic acid, **4b**. A mixture of 5.92 g (0.03 mol) of **3b** in 50 ml of 20% aqueous hydrochloric acid is heated under reflux for four hours. Then the reaction mixture is concentrated and the resinous residue is taken up in methanol and brought to boiling. A solution forms which crystallizes upon cooling. The precipitate is filtered off, dried and gives 3.7 g (73.3%) of **4b**, white crystals, m.p. 187–189°C (dec.).

^{1}H-NMR (in D_2O/DCl) δ: 1.7 (2d, J14, CH_3, 3H); 4.55 (2q, J8, CHP, 1H); 5.2 (s, OH, NH_2, 4H)

$C_2H_8NO_4P$ (141.05) calc.: C 17.03 H 6.72 N 9.93 P 21.96%
found: C 17.0 H 5.7 N 9.6 P 21.8%

The compounds listed in Table IV have been prepared similarly.

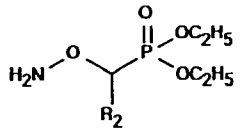
5. O,O-Diethyl-2-nitro-5-(2'-chloro-4'-trifluoromethylphenoxy)-phenyl-aminooxymethylphosphonate, **5a**. A mixture of 9.16 g (0.05 mol) of **3a** and 9.07 g (0.025 mol) of 3,4-dinitro-2'-chloro-4'-trifluoromethyl-diphenyl ether in 50 ml of toluene is refluxed for 24 h. Then the mixture is evaporated on a rotavapor and the residue flash chromatographed on silica-gel using ethyl acetate as eluent. There is obtained 4.2 g (33.7%) of **5a**, a brown resin.

^{1}H-NMR (in $CDCl_3$) δ: 1.4 (t, CH_3, 6H); 4.2 (qui, OCH_2) and 4.25 (d, J8, CH_2P) (6H); 6.3–8.27 (m, aryl, 6H); 10.2 (s, ONH, 1H). **5b**, a yellow solid, m.p. 66–69°C (yield 30%) was similarly obtained. ^{1}H-NMR (in $CDCl_3$) δ: 1.4 (t, CH_3) and 1.5 (2d, J16, C—CH_3) (9H); 4.23 (OCH_2, OCH, 5H); 6.3–8.3 (m, aryl, 6H); 10.3 (s, ONH, 1H).

6. O,O-Diethyl-N-(3,4-dichlorophenylaminocarbonyl)-aminooxymethylphosphonate, **6**. To a solution of 9.2 g (0.05 mol) of **3a** in 50 ml of diethyl ether is added dropwise with ice-cooling a solution of 10.3 g (0.05 mol) of 3,4-dichlorophenylisocyanate in 50 ml of diethyl ether. A slightly exothermic reaction ensues. The clear solution is evaporated on a rotavapor and the residue flash-chromatographed on

TABLE III

Physical properties of



3

3	R_2	Boiling point °C/mbar	Yield %	^{1}H - NMR in $CDCl_3$					^{31}P - NMR in $CDCl_3$ (ref. 85% H_3PO_4)
				R_2	CH_3	OCH_2 OCH	OCH_2P OCHR	NH_2	
a	H	130/0.4[a]	71	-	1.35	4.18	4.07 (J6)	5.93	21.87
b	CH_3	77 - 80 / 0.02	46.1	1.5	1.35	4.2	4	5.9	24.26
c	C_2H_5	86 - 90 / 0.04[c]	61.3	1.0 - 1.8	1.3	4.2	3.8	5.9	24.33
d	n-C_3H_7	110 / 0.06	32.6	0.7 - 2.0	1.35	4.2	3.8	5.7	
e	i-C_3H_7	120 / 0.01	60.5	1.1	1.3	4.2	3.67	5.7	
f	n-C_4H_9	100 / 0.06	7.3	0.5 - 2.0	1.3	4.17	3.8	5.8	
g	$C_6H_5CH_2$	150 /0.06[g]	12.4	7.27 + 3.03	1.3	4.17		5.57	
h	$CH_3SCH_2CH_2$	120/0.01[h]	38.5	2.08 SCH_3 2.0 : 2.7	1.37	4.2		6	
i	$C_6H_5CH_2CH_2$	132 / 0.03	49.8	7.25 2.1 : 2.7	1.3	4.1		5.73	
k	n-$C_3H_7CH(CH_3)$	150-155/0.08	9.9	0.7 - 2.5	1.33	4.2	3.8	5.43	24.8
l	n-C_9H_{19}	oil	26	0.7 - 2.0	1.3	4.2	3.8	5.9	24.6

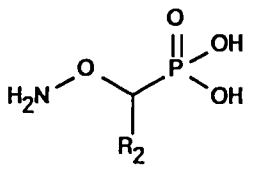
a) lit.[7] b.p. 150 °C/0.003 mbar
$C_5H_{14}NO_4P$ calc: C 32.80 H 7.11 N 7.65 P 16.92 %
(183.14) found: C 32.4 H 7.6 N 8.0 P 15.6 %

c) $C_7H_{18}NO_4P$ calc: C 39.81 H 8.39 N 6.63 P 14.67 %
(211.2) found: C 40.9 H 8.6 N 4.8 P 14.5 %

g) $C_{12}H_{20}NO_4P$ calc: C 52.75 H 7.38 N 5.13 P 11.34 %
(273.27) found: C 52.0 H 7.3 N 6.2 P 10.3 %

h) $C_8H_{20}NO_4PS$ calc: C 37.35 H 7.84 N 5.44 P 12.04 S 12.46 %
(257.29) found: C 37.8 H 7.8 N 5.1 P 11.7 S 12.1 %

TABLE IV
Physical properties of



4

4	R_2	Melting point °C	Yield %	^{1}H - NMR in D_2O/DCl		
				R_2	CH_2 : CHP	OH : NH_2
a	H	189-190 dec.[a]	75.6	-	4.7(J10)	5.6
b	CH_3	187-189 dec.	73.3	1.4(J14)	4.55(J8)	5.2
c	C_2H_5	184-185 dec.[c]	51.6	1.23-2.0	4.45(m)	5.47
				^{1}H - NMR in NaOD		
g	$C_6H_5CH_2$	172-176 dec.[g]	67.7	7.2	2.5-3.3	4.9
i	$C_6H_5CH_2CH_2$	180–190 dec.[i]	30.3	7.1 1.8 2.6	3.0-3.5	4.75

a) lit.[7] m.p. 161-163 °C(dec.); lit.[8] m.p. 207-208 °C(dec.)

CH_6NO_4P calc: C 9.46 H 4.76 N 11.93 P 24.38 %
(127.4) found: C 9.8 H 4.8 N 10.6 P 23.8 %
aequiv. weight found 130; pK_1 = 4.29 pK_2 = 6.86

c) $C_3H_{10}NO_4P$ calc: C 23.23 H 6.50 N 9.04 P 19.97 %
(155.09) found: C 23.0 H 6.4 N 8.9 P 20.0 %
aequiv. weight found 158; pK_1 = 4.62 pK_2 = 7.42

g) $C_8H_{12}NO_4P$ calc: C 44.25 H 5.57 N 6.45 P 14.25 %
(217.16) found: C 43.9 H 5.7 N 6.5 P 14.2 %

l) $C_9H_{14}NO_4P$ calc: C 46.76 H 6.11 N 6.06 P 13.40 %
(231.19) found: C 46.8 H 6.3 N 6.2 P 13.3 %
aequiv. weight found 238; $pK_1 < 2.5$ pK_2 = 4.43 pK_3 = 7.35

silica-gel using ethyl acetate/n-hexane (2:1) as eluent. There is obtained 8.4 g (45.4%) of **6**, m.p. 63–69°C.

^{1}H-NMR (in $CDCl_3$) δ: 1.33 (t, CH_3, 6H); 4.2 (qui, OCH_2) and 4.25 (d, J8, CH_2P) (6H); 7.4 (br.) and 7.9 (m, aryl) (3H); 8.3 (s, NH, 1H); 9.2 (s, NHO, 1H).

$C_{12}H_{17}Cl_2N_2O_5P$ (371.16) calc.: C 38.83 H 4.62 N 7.55 P 8.35%
found: C 39.2 H 4.7 N 7.5 P 8.4%

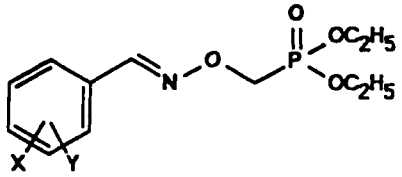
Dealkylation of **6** with trimethylbromosilane followed by hydrolysis yields the corresponding free phosphonic acid of **6**, m.p. 156°C, yield 80.3%.
^{1}H-NMR (in CD_3OD) δ: 3.9 (d, J8, CH_2P, 2H); 5.2 (s, OH, NH); 7.03 and 7.45 (aryl, 3H).

7. O,O-Diethyl-N-benzylidene-aminooxymethylphosphonate, **7a**. A solution of 9.15 g (0.05 mol) of **3a** and 5 ml of benzaldehyde in 50 ml of ether is stirred for one hour and then sodium sulfate added, filtered and the filtrate kugelrohr distilled at 140°C/0.2 torr. The distillate is flash-chromatographed over silica-gel and eluded with ethyl acetate: n-hexane (2:1) to give 8.7 g (64.4%) of **7a**, b.p. 145°C/0.1 torr, n_D^{20} = 1.5172.

^{1}H-NMR (in $CDCl_3$) δ: 1.33 (t, CH_3, 6H); 4.2 (qui, OCH_2, 4H); 4.55 (d, J8, PCH_2O, 2H); 7.4 (m, aryl, 5H); 8.15 (s, CH=N, 1H).
The compounds listed in Table V have been prepared similarly.

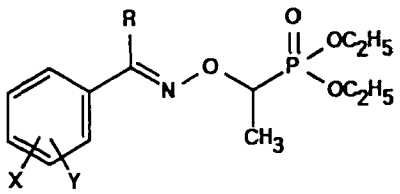
TABLE V

Physical properties of



7

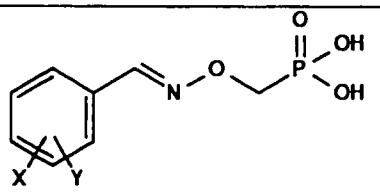
7	X	Y	Yield %	(m.p. °C) b.p. °C/torr	^{1}H - NMR in $CDCl_3$	
					PCH_2	N=CH
a	H	H	64.4	145/0.1	4.55(J8)	8.15
b	2-Cl	4-Cl	68.8	155/0.1	4.57(J8)	8.5
c	3-Cl	4-Cl	63.5	180/0.02	4.4(J8)	8.1
d	H	2-NO_2	64.5	n_D^{20}1.5303	4.55(J7)	8.75
e	H	3-NO_2	74	n_D^{20}1.5296	4.63(J7.5)	8.55
f	H	4-NO_2	48.7	(68-70)	4.57(J7)	8.3
g	H	4-F	74	175/0.1	4.55(J8)	8.17



7

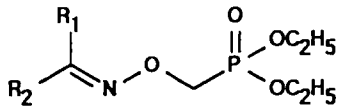
7	R	X	Y	Yield %	(m.p.) b.p. °C/torr	^{1}H - NMR in CD_3OD		
						C-CH_3	PCH	N=CH
h	H	2-Cl	4-Cl	61	(53-56)	1.53(2d,J16)	4.55(J8)	8.43
i	CH_3	3-CF_3	H	65.3	153/0.08			

TABLE V (*continued*)



7

7	X	Y	yiel %	m.p. °C	^{1}H - NMR in CD_3OD		
					PCH_2	N=CH	OH
k	2-Cl	4-Cl	35.2	154-157	4.05(J7)	8.07	4.65
l	3-Cl	4-Cl	40.5	126-131	4.05(J8)	7.7	4.9
m	H	4-F	22.5	114-122	3.87(J8)	7.63	4.7



7

7	R^1	R^2	Yield %	b.p. °C/torr	^{1}H - NMR in $CDCl_3$
					PCH_2
n	C_2H_5	C_2H_5	79.6	92-95/0.06	4.25(J8)
o	CH_3	C_2H_5	79.3	90-92/0.04	4.3(J8)
p	$-(CH_2)_4-$		80.7	110-113/0.04	4.25(J8)
q	$-(CH_2)_5-$		45.2	122-125/0.07	4.3(J8)

Dealkylation of **7b** with trimethylbromosilane followed by hydrolysis yields the free phosphonic acid **7k**, m.p. 154–157°C, yield 35.2%.
^{1}H-NMR (in CD_3OD) δ: 4.05 (d, J7, CH_2P, 2H); 4.65 (s, OH); 6.7–7.5 (m, aryl, 3H); 8.07 (s, CH=N, 1H).
7l and **7m** (Table V) have been prepared similarly.

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