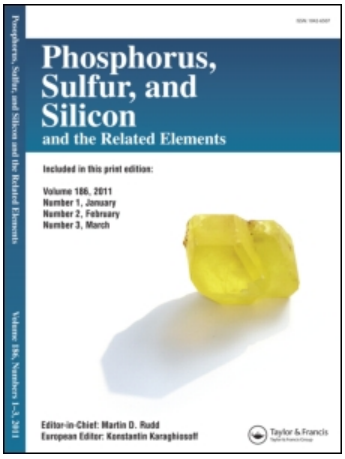

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ORGANIC PHOSPHORUS COMPOUNDS 103.[1] AMINOOXYALKYLPHOSPHINIC ACIDS AND AMINOOXYALKYLPHOSPINE OXIDES AND DERIVATIVES

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ORGANIC PHOSPHORUS COMPOUNDS 103.[1] AMINOOXYALKYLPHOSPHINIC ACIDS AND AMINOOXYALKYLPHOSPINE OXIDES AND DERIVATIVES

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Condensation of α-hydroxyalkylphosphinates, **1**, with N-hydroxy-phtalimide, using Mitsunobu's condition, yields 1-phthalimido-N-oxyalkylphosphinates, **2**, which on treatment with hydrazine give 1-aminooxyalkylphosphinates, **3**. Hydrolysis of these produces 1-aminooxyalkylphosphinic acids, **4**. Two 1-aminooxyalkyl-dimethyl-phosphine oxides, **7**, are also described. The physical properties of these compounds are listed and the biological activity of some compounds is reported.

Key words: 1-Aminooxyalkylphosphinates; 1-aminooxyalkylphosphinic acids: 1-aminooxyalkyl-dimethylphosphine oxides; NMR-spectra; biological activity.

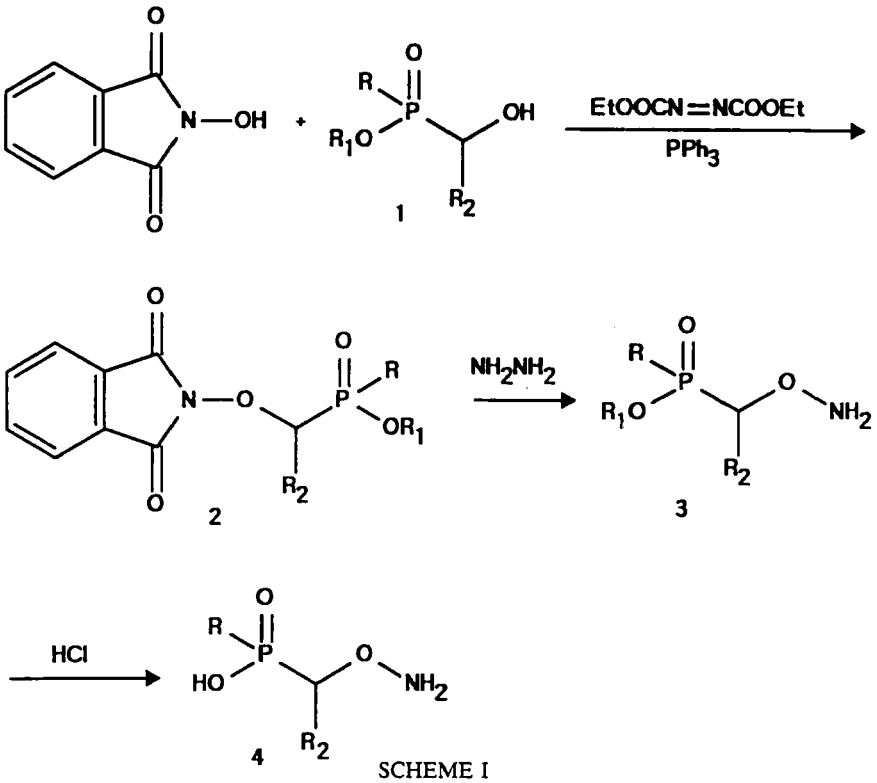
INTRODUCTION

Recently we reported on the preparation, chemical, physical, and biological properties of 1-aminooxyalkylphosphonic acids and derivatives.[1] In continuation of these studies we describe now the synthesis and properties of 1-aminooxyalkylphosphonous and -phosphinic acids as well as -phosphine oxides and derivatives.

RESULTS AND DISCUSSION

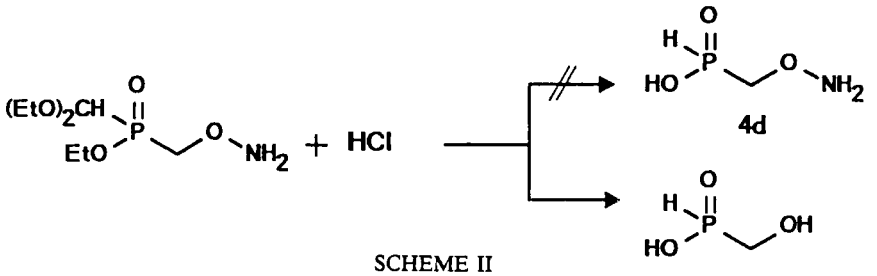
The Mitsunobu reaction,[2] which was suitable for the preparation of 1-aminooxyalkylphosphonic acids[1] was also successfully applied to the synthesis of 1-aminooxyalkylphosphinic acids and phosphine oxides (Scheme I).

α-Hydroxyalkylphosphinates, **1**, are easily obtained by the base catalyzed addition of aldehydes to phosphonite half esters.[3] O-Ethyl-diethoxymethylphosphonite was obtained from the interaction of H_3PO_2 with $HC(OC_2H_3)_3$ in the presence of p-TsOH.[4] Condensation of **1** with N-hydroxyphthalimide under Mitsunobu's condition produces the 1-phthalimido-N-oxyalkylphosphinates, **2**, in yields ranging from 64 to 100%. Treatment of **2** with hydrazine yields 1-aminooxyalkylphosphinates, **3**, in moderate yields. Hydrolysis of **3a** and **3k** with 20% aqueous HCl under reflux gives the crystalline 1-aminooxymethylphosphinic acids, **4a** and **4k** in good yields.



SCHEME I

However, when **3d** was hydrolyzed under the same conditions, 1-aminooxyalkylphosphonous acid, **4d**, was not obtained according to Scheme II:

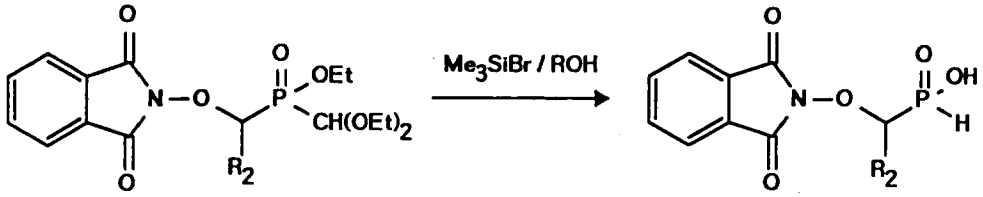


SCHEME II

Instead, cleavage of the C—O—N bond occurred simultaneously and hydroxymethylphosphonous acid was produced.

On the other hand, when **2d** and **2e** were dealkylated with trimethyl bromosilane and the silyl esters hydrolyzed with methanol, the corresponding phosphonous acids **21** and **2m** were obtained in about 50% yield (Scheme III).

1-aminooxyalkyl-dimethylphosphine oxides, **7**, were obtained starting from α-hydroxyalkyl-dimethylphosphine oxides, **5**, (Table VI) followed by condensation with N-hydroxyphthalimide to give **6** (Table VII), and hydrazinolysis of these to produce **7** (Table VIII).



2

2l, R_2 = H

2m, R_2 = CH_3

SCHEME III

BIOLOGICAL ACTIVITY

1-Aminooxyalkylphosphinic acids, **4**, and 1-aminooxyalkyl-dimethyl-phosphine oxides, **7** are biologically less active than the corresponding phosphonic acids.[1,5] Thus **21** and **2m** are bactericides for rice, **3b** and **3f** show antifungal activity against *Cercospora arachidola and Piricularia oryzae*, respectively, **4a** exhibits immunization activity and **4b** is a weak botryticide. **21** and **4a** showed strong inhibition of anthocyanin synthesis; **2m** and **7a** were less active.[6] The results are summarized in Table I.

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.

TABLE I

Inhibition of anthocyanin synthesis

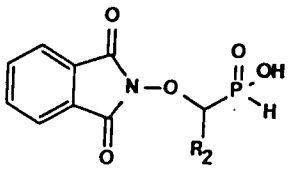
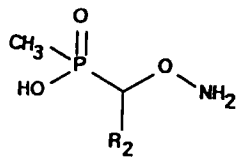
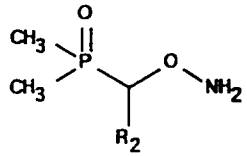
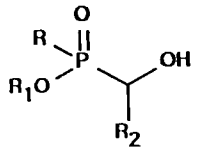
Compound		Inbibition in vivo by 1 mM
	R_2=H, **21** R_2=CH_3, **2m**	70% 13%
	R_2=H, **4a**	75%
	**7a**	23%

TABLE II

Physical properties of



1

						^{1}H - NMR in $CDCl_3$			^{31}P - NMR (85% H_3PO_4 ref.)
1	R	R_1	R_2	Yield in %	b.p. °C/torr (m.p.)	R	R_2 or PCH_2O	OH	
a	CH_3	n-C_3H_7	H	62.1	100/0.1	1.5(J14)	3.85(J6)	5.5	
b	C_2H_5	i-C_3H_7	H	82.8	103/0.2	0.9-2.1	3.9(J5)	5.73	
c	C_2H_5	i-C_3H_7	C_2H_5	73.5	80/0.1	0.9-2.1	3.75	5.07	
d	$(EtO)_2CH$	C_2H_5	H	51.8	125/0.1	4.87(J8)[a]	3.93(J4)	5.07	40.11 ; 38.9
e	$(EtO)_2CH$	C_2H_5	CH_3	89.9	110/0.08	4.87(J9)[a]	1.5(J11)	5.1	
f	$(EtO)_2CH$	C_2H_5	C_2H_5	87.5	95/0.15	4.9(J9)[a]	0.8-2.0	4.3	39.85 ; 39.16
g	$(EtO)_2CH$	C_2H_5	n-C_3H_7	84.2	95/0.05	4.9(J9)[a]	0.7-2.2	4.2	39.51 ; 38.92
h	$(EtO)_2CH$	C_2H_5	$MeSCH_2CH_2$	76.7	125/0.15	4.9(J9)[a]	2.17(SMe) 2.1(CH_2)	4.5	39.37 ; 38.79
i	$(EtO)_2CH$	C_2H_5	$PhCH_2$	79.4	150/0.08 (45-66)	4.83(J9)[a]	3.1 (CH_2) 7.23 (Ph)	4.3	38.87 ; 38.29
k	C_6H_5	i-C_3H_7	H	67.1	130/0.05 (69-73)	7.2-8.0	4.03(J4)	4.47	38.04

a) signal for OCHO

1.0-n-Propyl-hydroxymethyl-methylphosphinate, **1a**. To a solution of 73.26 g (0.6 mol) of the O-n-propyl-methylphosphonite and 8.4 ml of triethylamine is added with stirring at 60°C 19.82 g of para-formaldehyde. An exothermic reaction ensues. The mixture is stirred for one hour at 120°C and then fractionally distilled to give 56.7 g (62.1%) of **1a**, b.p. 100°C/0.1 torr.

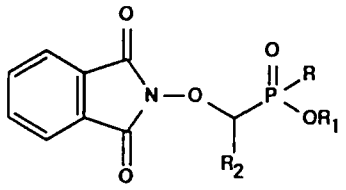
^{1}H-NMR (in $CDCl_3$) δ: 0.95 (*t*, C—CH_3); 1.5 (*d*, J14, PCH_3); 1.6 (*m*, C—CH_2); 3.8 (*d*, J4, PCH_2O); 3.95 (2*t*, OCH_2); 5.55 (*s*, OH). The compounds listed in Table II have been prepared similarly. The starting material for the preparation of **1d** and **1i**, i.e., O-ethyl-diethoxymethylphosphonite was obtained from the interaction of H_3PO_2, p-TsOH and $CH(OC_2H_5)_3$ according to the literature.[4]

2. O-Ethyl-(1-phthalimido-N-oxymethyl)-diethoxymethylphosphinate, **2d**. To 45.24 g (0.2 mol) of **1d**, 52.46 g (0.2 mol) of triphenylphosphine and 32.62 g of N-hydroxyphthalimide in 400 ml of THF are added with stirring and ice cooling 38.32 g of azodicarbonic acid diethyl ester, dissolved in 100 ml of THF. A slightly exothermic reaction ensues. The mixture is stirred for 12 h at 20°C and then evaporated on a rotavapor. The residue is treated with 200 ml of diethyl ether, stirred for one hour, filtered, and the filtrate evaporated to give crude **2d**. This is flash-chromatographed on silica gel using ethyl acetate/petrol ether (1:1), then ethyl acetate and finally methanol as eluents. From the methanol fractions are obtained 42.5 g (57.2%) of **2d**, which is recrystallized form 900 ml of diisopropyl ether to give 26.6 g (35.8%) of pure **2d**, white crystals, m.p. 72–76°C.

^{1}H-NMR (in $CDCl_3$) δ: 1.3 and 1.4 (*t*, CH_3, 9H); 4.0 (2*q*, OCH_2, 4H); 4.4 (qui, $POCH_2$, 2H); 4.7 (*d*, J6, PCH_2O, 2H); 5.23 (*d*, J9, PCH, 1H); 7.9 (*s*, aryl, 4H).
The compounds listed in Table III have been prepared similarly.

TABLE III

Physical properties of



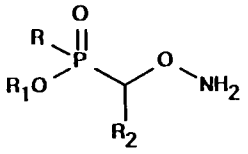
2

						^{1}H - NMR in $CDCl_3$		
2	R	R_1	R_2	yield in %	b.p. °C/torr (m.p.)	R	PCHO	R_2
a	CH_3	n-C_3H_7	H			1.8(J15)	4.6	
b	C_2H_5	i-C_3H_7	H	87.7	oil	0.8-2.3	4.55	
c	C_2H_5	i-C_3H_7	C_2H_5	87.2	180/0.09	0.8-2.4	4.5	0.8-2.4
d	$(EtO)_2CH$	C_2H_5	H	64.4	(72-76)	5.23(J9)[a]	4.7(J6)	
e	$(EtO)_2CH$	C_2H_5	CH_3	93.4	(64)	5.3(J10)[a]	4.6	1.7(J14)
f	$(EtO)_2CH$	C_2H_5	C_2H_5	100	oil	5.1(J10)[a]	4.5	0.8-2.3
g	$(EtO)_2CH$	C_2H_5	n-C_3H_7	100	resin	5.1(J10)[a]	4.6	0.8-2.3
h	$(EtO)_2CH$	C_2H_5	$CH_3SCH_2CH_2$	100	resin	5.05(J10)[a]	4.7	2.1(SCH_3) 2.6(CH_2)
i	$(EtO)_2CH$	C_2H_5	$C_6H_5CH_2$	100	resin	5.2(J10)[a]	4.4	3.4(CH_2) 7.0-7.7(Ar)
k	C_6H_5	i-C_3H_7	H	100	resin	7.5-8.0	4.7	
l	H	H	H	58	(176-177)	6.87(d,J528)	3.65(J7.5)	
m	H	H	CH_3	47	(186-188)			

a) Signal for OCHO

TABLE IV

Physical properties of



3

3	R	R_1	R_2	yield in %	b.p. °C/torr	^{1}H - NMR in $CDCl_3$ R	PCHO	R_2	NH_2	^{31}P-NMR 85% H_3PO_4 ref
a	CH_3	n-C_3H_7	H	80.2	125/0.02	1.5(J14)	4.0(J4)		5.95	
b	C_2H_5	i-C_3H_7	H	32.7	115-125/0.02	0.8-2.2	4.05(J4.5)		6	
c	C_2H_5	i-C_3H_7	C_2H_5	46.6	120-125/0.08	0.8-2.1	3.7(m)	0.8-2.1	5.7	
d	$(EtO)_2CH$	C_2H_5	H	40.2	120-125/0.05	4.83(J8)[a]	4.1(J4)		5.9	b
e	$(EtO)_2CH$	C_2H_5	CH_3	66	125/0.03	4.87(J8)[a]	3.83	1.45	5.8	c
f	$(EtO)_2CH$	C_2H_5	C_2H_5	46.4	120/0.1	4.9(J8)[a]	3.8	0.8-2.2	5.67	
g	$(EtO)_2CH$	C_2H_5	n-C_3H_7	48.7	130/0.1	4.9(J9)[a]	3.8	0.7-2.0	5.77	d
h	$(EtO)_2CH$	C_2H_5	$CH_3SCH_2CH_2$	44.7	108/0.1	4.9(J8)[a]	3.7(m)	2.1(SCH_3) 2.65(CH_2)	5.8	e
i	$(EtO)_2CH$	C_2H_5	$C_6H_5CH_2$	24.8	oil	4.8(J9)[a]	3.8(m)	7.3(Ph) 3.1(CH_2)	5.3	f
k	C_6H_5	i-C_3H_7	H	74.2	160/0.03	7.3-8.1	4.17(J5)		5.83	

a) Signal for OCHO b) 39.42/39.10 1.1 c) 39.19/38.72 8:2 d) 39.55/39.1 2:1 e) 39.17/38.45 1:1 f) 38.77/38.33 1.1

3. O-n-Propyl-aminooxymethyl-methylphosphinate, **3a**. To 33.8 g (0.1 mol) of **2a**, dissolved in 150 ml of methylene dichloride are added dropwise at 5–10°C 8.68 ml of hydrazine hydrate. The reaction is exothermic and a thick suspension forms. After stirring for one hour at 20°C, the mixture is filtered, the filtrate dried with sodium sulfate and evaporated to give crude **3a** which is purified by kugelrohr distillation to give 13.4 g (80.2%) of pure **3a**, a colorless liquid, b.p. 125°C/0.02 torr.

^{1}H-NMR (in $CDCl_3$): 0.8–2 (*m*, C_2H_5); 1.5 (*d*, J14, PCH_3); 4.0 (*d*, J4, PCH_2O); 4.07 (2*t*, $POCH_2$); 5.95 (*s*, NH_2).

The compounds listed in Table IV have been prepared similarly.

4. Aminooxymethyl-methylphosphinic acid, **4a**. A mixture of 6.69 g (0.04 mol) of **3a** in 40 ml of 20% aqueous HCl is refluxed for 4 hours. Then the clear solution is evaporated and the residue recrystallized from methanol/propylene oxide to give 3.4 g (68%) of **4a**, white crystals, m.p. 166–169°C (dec.). ^{1}H-NMR (in D_2O) δ: 1.3 (*d*, J14, CH_3P, 3H); 4.1 (*d*, J8, OCH_2P); 4.97 (*s*, OH, NH_2, 3H).

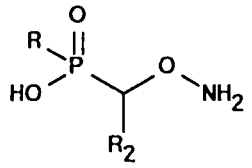
Aminooxymethyl-phenylphosphinic acid, **4k**, has been obtained similarly from **3k** and HCl in 58.8% yield, white crystals, m.p. 184°C (dec.) (Table V).

^{1}H-NMR (in D_2O/NaOD) δ: 3.7 (*d*, J8, OCH_2P): 4.8 (*s*, OH, NH); 7.1–7.7 (*m*, aryl).

$C_7H_{10}NO_3P$ (187.14) calc.: C 44.93 H 5.39 N 7.49 P 16.55%
found: C 45.1 H 5.4 N 7.6 P 16.6%

TABLE V

Physical properties of

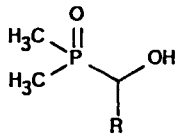


4

					^{1}H - NMR		
4	R	yield in %	m.p. °C	solvent	R	PCH_2	OH/NH_2
a	CH_3	68	166-168(dec)	D_2O	1.3(J14)	4.1(J8)	4.97
k	C_6H_5	58.8	184(dec)	D_2O/NaOD	7.1-7.7	3.7(J8)	4.8

TABLE VI

Physical properties of

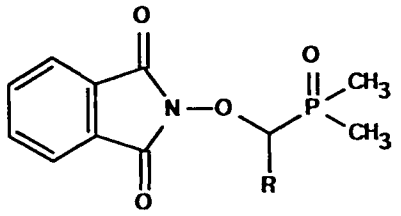


5

				^{1}H - NMR in $CDCl_3$				^{31}P-NMR 85% H_3PO_4 ref.
5	R	yield in %	b.p. °C/torr (m.p.)	PCH_3	PCHO	R	OH	
a	H	54.8	110/0.1 (72-76)	1.53(d,J12)	3.87(d,J4)		6.1	46.37
b	CH_3	82	160-165/0.06	1.5(J16)	3.97(2q)	1.4(2d)	6.23	50.46
c	n-C_3H_7	74.2	150/0.04 (63-70)	1.5(J12)	3.73(m)	1.0-2.3	4.9	49.24

TABLE VII

Physical properties of

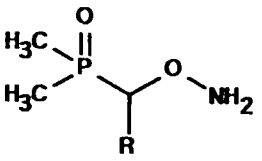


6

				^{1}H - NMR in CD_3OD			
6	R	yield in %	m.p.	PCH_3	PCHO	R	C_6H_4
a	H	68	resin	1.77(J14)	4.6(J8)		7.87
b	CH_3	64.6	resin	1.3(J12)	4.4(m)	1.4	7.45

TABLE VIII

Physical properties of



7

				^{1}H - NMR in $CDCl_3$			
7	R	yield in %	b.p. °C/torr	PCH_3	PCHO	R	NH_2
a	H	52.5	170/0.04[a] (solidifies)	1.55(J13.5)	4.05(J5.5)		5.97
b	CH_3	22.6	150/0.02	1.5(J13)	3.97(2q,J6)	1.4	5.77

a) $C_3H_7NO_2P$ (123.09) calc.: C 29.28 H 8.19 N 11.38 P 25.17 %
found: C 30.7 H 8.2 N 10.6 P 23.6 %

Equiv. weight found: 190; pK_1 2.5; pK_2 = 4.35

Dealkylation of **2d** with trimethylbromosilane in chloroform solution followed by hydrolysis with methanol produces 1-phthalimido-N-oxymethylphosphonous acid, **21**, in 58% yield, m.p. 176–177°C.

^{1}H-NMR (in D_2O/NaOD) δ: 3.65 (*d*, J7.5, OCH_2P); 4.6 (*s*, OH); 6.87 (*d*, J528, P—H); 7.1 (*s*, aryl).
^{31}P-NMR (D_2O/NaOD) δ: 21.14 (J_{PH}528).

$C_9H_8NO_5P$ (241.14) calc.: C 44.83 H 3.35 N 5.81 P 12.85%
found: C 44.9 H 3.5 N 5.9 P 11.9%

Dealkylation of **2e** with trimethylbromosilane gave similary **2m**, a white solid, in 47% yield, m.p. 186–188°C (Table III).

^{1}H-NMR (D_2O/NaOD) δ: 1.3 (2*d*, J_{PCCH}15, J_{HH}7); 4.0 (*m*, NOCH); 4.9 (*s*, OH); 7.0 (*d*, J_{PH}518); 7.35–7.55 (*m*, C_6H_4).
^{31}P-NMR (D_2O/NaOD) δ: 26.56

$C_{10}H_{10}NO_5P$ (255.17) calc.: C 47.07 H 3.95 N 5.49 P 12.14%
found: C 46.6 H 4.0 N 5.5 P 11.9%

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