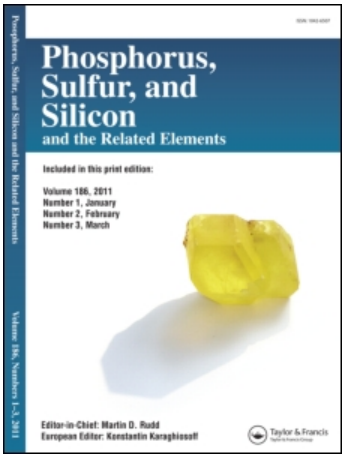

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ORGANIC PHOSPHORUS COMPOUNDS 89.[1] A NEW METHOD FOR THE PREPARATION OF AMINOMETHYLPHOSPHONIC ACID AND DERIVATIVES

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A high yield preparation of aminomethylphosphonic acid and derivatives, **1**, **2** and **3**, involves heating of N,N'N"-tris(alkoxycarbonyl)hexahydrotriazines with sec. phosphites in the presence of $BF_3 \cdot Et_2O$ as a catalyst followed by hydrolysis. Without catalyst no reaction occurs. This reaction has also been used to obtain O-ethyl N-ethoxycarbonylaminomethyl-methylphosphinate, **4**. Interaction of **1** and ethylbromoacetate in the presence of NaH, followed by hydrolysis produces glyphosate **5** in high yield.

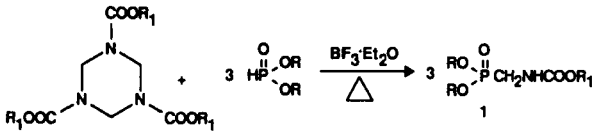
Key words: N-Alkoxycarbonylaminomethylphosphonates; aminomethylphosphinic acid; O-ethyl-N-ethoxycarbonylaminomethyl-methylphosphinate; glyphosate.

INTRODUCTION

Aminomethylphosphonic acid (AMPA) has received much attention in recent years. For example it has been reported that AMPA is a plant growth retardent[2,3] and can increase the sucrose yield of sugar cane.[4] It is also the primary metabolite in glyphosate metabolism in soil[5] and in aerobic biotreatment systems[6] and furthermore it has been used as a starting material in recent preparations of glyphosate,[7,8] a very active herbicide.[9] A number of synthetic routes to AMPA have been reported. The methods which have been published prior to 1974 have been summarized in a review article.[10] More recently some other routes have been described, such as direct amination of chloromethyl phosphonic acid with ammonia at 150°C,[2,11] catalytic debenzylation with H_2 of dibenzylaminomethylphosphonic acid,[12] cleavage of N-benzhydryl substituted aminoalkylphosphonic acids with HBr,[13,14] aminoalkylation of triphenylphosphite with benzyl N-(acetoxymethyl)-carbamate followed by hydrolysis,[15] electrochemical oxidation of nitrilotrimethylene triphosphonic acid in water,[16] interaction of phosphonomethyltriflate and ammonia,[17] treatment of N-hydroxymethylbenzamide with PCl_3 in acetic acid[18] or with a mixture of PCl_3 and $(CH_3O)_3P$,[19] heating of CH_3CN and trioxane with H_3PO_3 and PCl_3,[20] and finally phosphite addition to hexahydrotriazines followed by hydrolysis.[21] The last method is described in detail below.

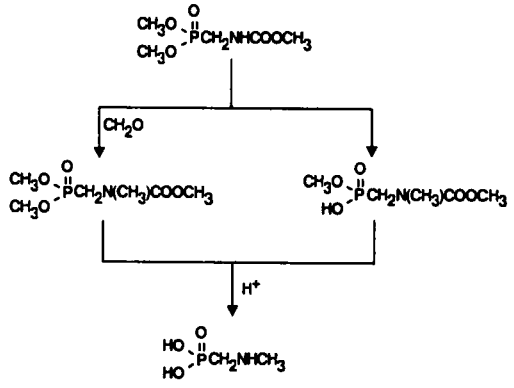
RESULTS AND DISCUSSIONS

We found that heating of *N,N',N''*-tris(alkoxycarbonyl)hexahydrotriazines with sec. phosphites produces in the presence of Lewis acids, esp. $BF_3 \cdot Et_2O$,O,O-dialkyl-N-alkoxycarbonylaminomethylphosphonates in very high yield. Without catalyst no reaction occurs.

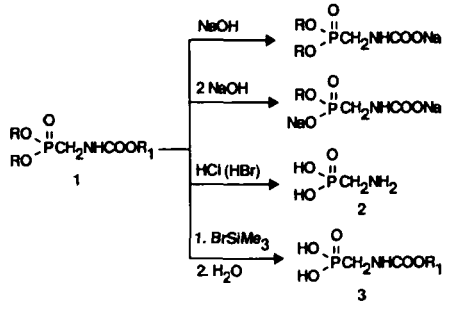


The hexahydrotriazines used as starting material can be produced in a simple manner and in excellent yield by reaction of the corresponding urethanes with formaldehyde in an aqueous-hydrochloric acid medium,[22] or by reaction of the urethane with paraformaldehyde in the presence of p-toluenesulfonic acid as catalyst in toluene as solvent.[23]

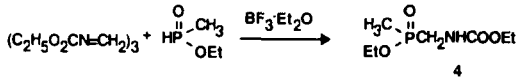
Although AMPA 2, can be prepared directly by acid hydrolysis of the crude esters **1** it is best to first purify the triesters **1** by thin layer distillation. While 5 hours reflux time were sufficient to hydrolyse the triester **1a** with HBr-solution (48%), a period of 20 hrs. was necessary for complete hydrolysis with 20% HCl. Addition of 1 Mol% KI shortened the hydrolysis time to 10 hrs. Furthermore complete hydrolysis of the trimethylester **1c** required only 6 hrs. reflux time with 20% HCl. When the crude not distilled trimethylester **1c** was hydrolyzed with 20% HCl a product was obtained which was difficult to crystallize. In the ^{1}H-NMR spectrum a signal was seen which indicated the presence of a N—CH_3 group. This N—CH_3 group could have been formed either by reaction of the carbamate with formaldehyde or by an alkylation through the P-OCH_3 ester:



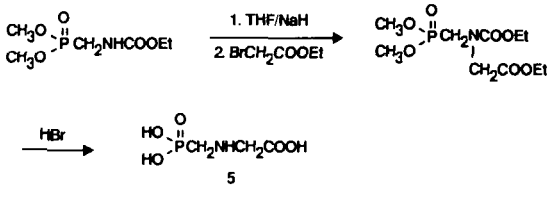
Whereas partial hydrolysis of the triester **1** with NaOH produced only impure products, dealkylation with trimethylbromosilane followed by hydrolysis gave high yields of N-alkoxycarbonyl-aminomethyl-phosphonic acids, **3**, as shown in the following scheme:



The tris(alkoxycarbonyl)hexahydrotriazines could also be cleaved by phosphonite half esters to give N-alkoxycarbonylaminomethyl-alkylphosphinates, **4**, e.g.



Finally the phosphonates **1** are useful starting materials for the preparation of glyphosate, **5**, according to:



thus when using **1d** as a starting material **5** was siolated in 73.4% yield. A similar process was claimed in an European patent application[24] in which the formyl group was used as the protecting group.

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.

N,N',N''-Tris(ethoxycarbonyl)-hexahydro-1,3,5-triazine, ^{1}H-NMR ($CDCl_3$) $\delta = CH_3$ 1.3 (t, 3H); OCH_2 4.23 (qu, 2H); NCH_2 (4.9 (m, 2H) and *N,N'N''*-tris(methoxycarbonyl)-hexahydro-1,3,5-triazine, ^{1}H-NMR ($CDCl_3$) $\delta = CH_3O$ 3.75 (s, 9H); NCH_2 4.9 (m, 6H), were prepared as described in the literature.[22,23]

1. *O,O-Diethyl-N-ethoxycarbonylaminomethylphosphonate*, **1a**. To a stirred mixture of 20.22 g (0.066 mol) of $(EtO_2C\text{-}NCH_2)_3$ and 28.4 ml (0.22 mol) of diethylphosphite is added at 125°C 2 ml of boron trifluoride etherate. The temperature of the reaction mixture is then raised to 150°C. After one hour heating a further 2 ml of $BF_3\cdot Et_2O$ is added, in the course of which the temperature in the reaction mixture falls temporarily to 105°C and subsequently slowly rises again to 150°C. After a further hour stirring at 150°C the reaction is finished. The readily volatile material is then distilled off in the high vacuum. As a residue is obtained 48 g (100%) of crude **1a**. The product can be used

TABLE I

Physical and spectral properties of O, Odialkyl-N-alkoxycarbonylaminomethylphosphonates, **1**

No	R	R_1	Yield %†	b.p. °C/torr	^{1}H-NMR ($CDCl_3$) C—CH_3	CH_2P	OCH_3	OCH_2	NH
a	C_2H_5	C_2H_5	58.7	130/0.15	1.25 and 1.33	3.6 (J11)		4.15 (qui.)	5.6 (br. t)
b	C_2H_5	CH_3	42.9	130/0.08	1.3	3.6 (J11)	3.65 (s)	4.12 (qui.)	5.8 (br. t)
c	CH_3	CH_3	76.5	115/0.1		3.65 (J11)	3.7 (s) 3.8 (d, J11)		6.2 (br.)
d	CH_3	C_2H_5	46.9	130/0.1	1.23 (t)	3.63 (J11)	3.77 (J11)	4.13 (qu.)	5.87 (br.)
e‡	i-C_3H_7	CH_2Ph	48	m.p. 75–76°C	1.33 (d)	3.60 (J12)	4.75 (m, CH)	5.17 (s)	5.45 (br.)

† Yield of distilled product; the crude yield was in every case nearly a 100 per cent.

‡ Obtained from the interaction of $(i\text{-}C_3H_7O)_2P(O)CH_2NH_2$ and $ClCO_2CH_2Ph$ in the presence of Et_3N[25].

without further purification directly for the following hydrolysis. A part of **1** is purified by thin layer distillation, b.p. 130°C/0.15 torr, yield 58.7% (of crude material).

^{1}H-NMR ($CDCl_3$) δ = 1.25 and 1.33 (2t, CH_3, 9H); 3.6 (2d, J_{PCH} 11Hz, J_{NHCH} 6Hz, CH_2P, 2H); 4.15 (qui, OCH_2, 4H); 5.6 (br, NH, 1H) (ppm)

$C_8H_{18}NO_5P$ (239.2) calc.: C 40.17 H 7.59 N 5.86%
found: C 39.8 H 7.5 N 6.1%

The compounds listed in Table I have been prepared similarly.

2. *Aminomethylphosphonic acid,* **2**. (a) From crude **1a**. A mixture of 50.6 g (0.2 mol) of crude **1a** and 250 ml of HBr (48%) in H_2O is refluxed for 5 h whereby ethylbromide is distilled off. The slightly brown, clear solution is evaporated on a rotavapor and the residue (40.8 g) recrystallized from water/aceton to give 16 g (72%) of **2**.

(b) From distilled **1a**. A mixture of 23.92 g (0.1 mol) of distilled **1a** and 100 ml of HCl (20%) is refluxed for 20 h. Then the clear solution is evaporated on a rotavapor to give 12.6 g crude **2** which on recrystallization from water/acetone yields 9.4 g (84.7%) of pure **2**, white crystals, m.p. 277–281°C dec.).

^{1}H-NMR (D_2O) δ = 3.03 (d, J_{PCH}12Hz, CH_2P, 2H); 4.7 (s, OH, NH, 4H) (ppm).

CH_6NO_3P (110.98) calc.: C 10.82 H 5.45 N 12.62%
found: C 10.90 H 5.54 N 12.56%

Equivalent weight found 112, calculated 111; pK_1 = <2.5; pK_2 = 5.57; pK_3 = 10.2.

3. *N-Ethoxycarbonylaminomethylphosphonic acid,* **3a**. (A) O,O-Bis(trimethylsilyl)-N-ethoxycarbonylaminomethylphosphonate, **A**. To 14.35 g (0.06 mol) of **1a** is added 39.1 ml of trimethylbromosilane and the mixture stirred at 20°C for 15 hrs. The slightly turbid solution is filtered and the filtrate evaporated on a rotavapor. The residue is purified by thin layer distillation, yield 6.2 g (31.9%) b.p. 115°C/0.12 torr. The material solidifies at 20°C.

^{1}H-NMR (CCl_4) δ = 0.2 (s, $(CH_3)_3Si$, 18H); 1.15 (t, CH_3, 3H); 3.35 (2d, J_{PCH} 11Hz, J_{NHCH} 6Hz, CH_2P, 2H); 4.0 (qu, OCH_2, 2H); 6.87 (t, J_{NHCH} 6Hz, NH, 1H)(ppm)

(B) N-Ethoxycarbonylaminomethylphosphonic acid, **3a**. A mixture of 5.9 g (0.018 mol) of **A** in 18 ml of ethanol is refluxed for 12 hrs. The clear solution is evaporated on a rotavapor to afford 4.3 g of crude **3a**, a yellow resin. This is dissolved in 14 ml of ethanol and 1.2 ml of isopropylamine. The clear solution is evaporated on a rotavapor to give 2.2 g (100%) of **3a**·$H_2NCH(CH_3)_2$, a white solid, m.p. 150–153°C (dec.)

^{1}H-NMR (D_2O) δ = 1.2 (d, $(CH_3)_2$), 1.15 (t, CH_3)(9H); 3.15 (d, J_{PCH} 12Hz, CH_2); 3.37 (m, CH), (3H); 4.0 (qu, OCH_2, 2H); 4.63 (s, OH, NH, 5H)(ppm).

Similarly obtained were: $[(CH_3)_3SiO]_2P(O)CH_2NHCO_2CH_3$, a clear colorless oil, b.p. 130–140°C/0.1 torr, yield 45.3%.

^{1}H-NMR (CCl_4) δ = 0.2 (s, $(CH_3)_3Si$, 18H); 3.33 (2d, J_{PCH}, 11.4 Hz, J_{NHCH} 6 Hz, CH_2P, 2H); 3.53 (s, OCH_3, 3H); 6.87 (t, J_{NHCH} 6 Hz, NH, 1H) (ppm).

$(HO)_2P(O)CH_2NHCO_2CH_3 \cdot H_2NCH(CH_3)_2$, **3b**, a white solid, m.p. 177–179°C (dec.)

^{1}H-NMR (D_2O) $\delta = 1.4$ (d, $(CH_3)_2$, 6H); 3.35 (d, J_{PCH} 11.5 Hz, CH_2P); 3.5 (m, CH)(3H); 3.8 (s, OCH_3, 3H); 4.83 (s, OH, NH, 5H)(ppm).

$C_3H_8NO_5P \cdot H_2NCH(CH_3)_2$ (228.19) calc.: C 31.58 H 7.51 N 12.28%
found: C 32.0 H 7.60 N 12.29%

4. O-Ethyl-N-ethoxycarbonylaminomethyl-methylphosphinate, **4**. From 20.22 g (0.066 mol) of $(EtO_2C\text{-}NCH_2)_3$, 23.8 g (0.22 mol) of O-ethyl-methylphosphonite and $BF_3 \cdot Et_2O$ as described in 1. The crude product was purified by thin-layer distillation, b.p. 135°C/0.04 torr, yield 49.2%, a clear colorless oil.

^{1}H-NMR ($CDCl_3$) $\delta = 1.25$ (t, CH_3); 1.5 (d, J_{PCH} 14 Hz, CH_3P)(9H); 3.55 (2d, J_{PCH} 7 Hz, J_{NHCH} 6 Hz, CH_2P), 3.55 and 4.1 (m, OCH_2)(6h); 6.5 (t, NH, 1H)(ppm).

5. *N-dihydroxyphosphonylmethyl-glycine*, **5**. To a suspension of 2.4 g (55–60%) of NaH in 50 ml of THF is added 10.56 g (0.05 mol) of **1d** and then dropwise 5.57 ml of ethyl-bromoacetate. An exothermic reaction ensues. The mixture is refluxed for 12 hrs., filtered, and the filtrate evaporated on a rotavapor. The residue is dissolved in 50 ml of HBr conc. and the mixture refluxed for 12 hrs. The brown solution is evaporated on a rotavapor, the residue dissolved in hot water, methanol and propylene oxide added until the solution turned turbid. On standing crystalline **5** precipitates. This is filtered, washed with acetone and dried to give 6.2 g (73.4%) **5**, m.p. 220°C (dec.)

1H-NMR (D_2O/NaOD) $\delta = 2.6$ (d, J_{PCH} 14 Hz, CH_2P, 2H); 3.33 (s, CH_2CO, 2H); 4.82 (s, OH, NH)(ppm).

Acquiv. weight found 176, calc.: 169; $pK_1 < 2.5$; $pK_2 = 2.6$; $pK_3 = 5.77$, $pK_4 = 10.34$.

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