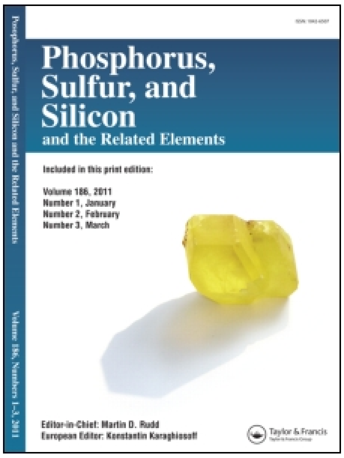

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ORGANIC PHOSPHORUS COMPOUNDS 99.[1] SYNTHESIS AND PROPERTIES OF N-PHOSPHONOMETHYL-AMINOACETALDEHYDE

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Interaction of methylene aminoacetaldehyde dimethylacetal and dimethylphosphite produces the phosphonomethyl-substituted aminoacetaldehyde acetal **1**. Using bis(trimethylsilyl)phosphite in this reaction and hydrolyzing the reaction mixture with alcohol gives the stable crystalline N-dihydroxyphosphonylmethyl-aminoacetaldehyde acetals **3a** and **3b**. Complete hydrolysis of **3a** and **3b** with HCl produces N-dihydroxyphosphonylmethyl-aminoacetaldehyde hydrate, **4**, as shown by ^{13}C-NMR spectroscopy. None of the compounds exhibited biological activity.

Key words: N-Diethoxyphosphonylmethyl-aminoacetaldehyde dimethylacetal; N-dihydroxyphosphonylmethyl-aminoacetaldehyde acetals; N-dihydroxyphosphonylmethyl-aminoacetaldehyde hydrate; ^{13}C-NMR spectra of acetals.

INTRODUCTION

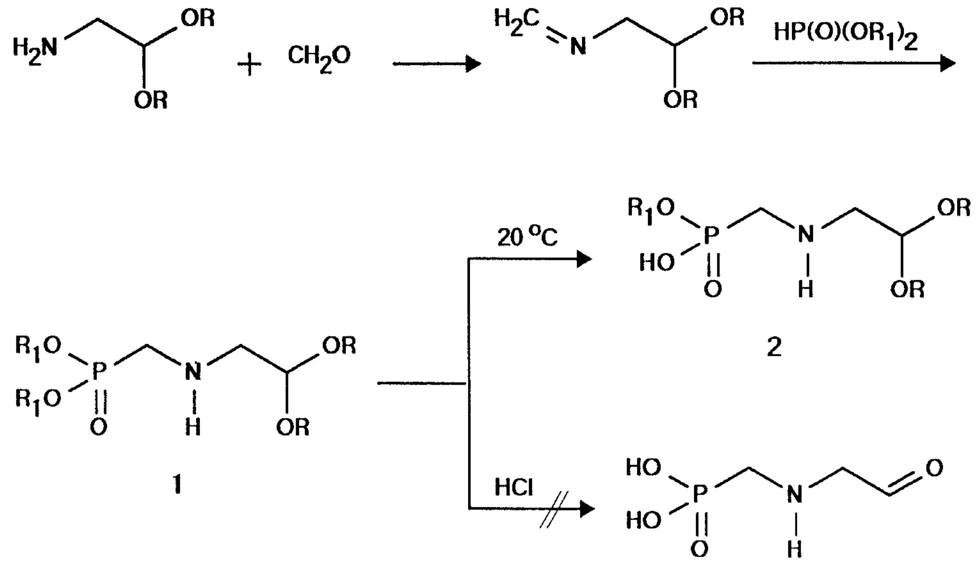
N-Phosphonylmethyl- and N-alkylphosphinylmethylglycines were intensively investigated in the past twenty years, since some of these compounds such as glyphosate,[2] glyphosine,[3] N-alkylphosphinylglycines[4–6] and some others[7–9] possess herbicidal or plant growth regulating properties. It seemed of interest to us to prepare the aldehyde of glyphosate i.e., N-dihydroxyphosphonylmethyl-aminoacetaldehyde and to determine its biological activity.

RESULTS AND DISCUSSION

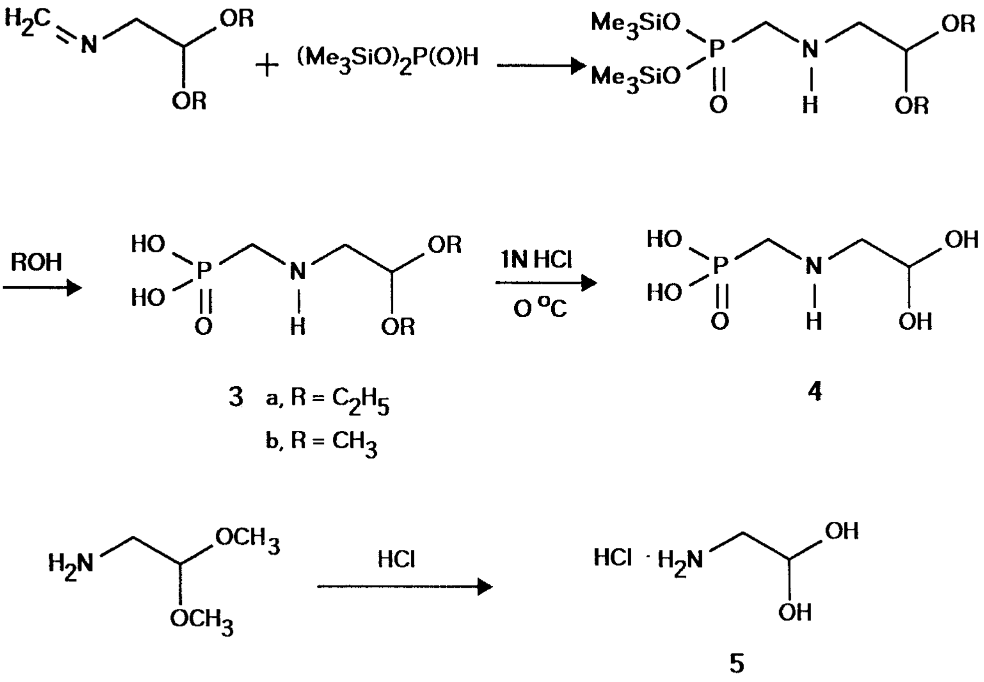
The Mannich type reaction[10] was used for the synthesis of N-phosphonosubstituted aminoacetaldehyde acetals. Thus when methylene aminoacetaldehyde dimethylacetal was heated with diethylphosphite to 120°C, a 72.8% yield of N-diethoxyphosphonylmethyl-aminoacetaldehyde dimethylacetal, **1**, was obtained (Scheme I). This compound, on standing at 20°C for extended periods of time, precipitated the crystalline halfester **2**. Attempts to hydrolyze **1** with HCl to N-dihydroxyphosphonylmethyl-aminoacetaldehyde failed. Complete destruction of the molecule occurred and a black tar was formed.

Therefore the addition reaction of bis(trimethylsilyl)phosphite to methylene-aminoacetaldehyde acetals was used to prepare the silyl esters which could readily be hydrolyzed by alcohol/water to the corresponding acids **3a** and **3b** (Scheme II).

Treatment of **3b** with HCl, first at 0°C then at 15°C and evaporation of the reaction solution in the high vacuum at 40°C, gave the N-phosphonomethyl-aminoacetaldehyde as a brown resin which has the hydrate structure **4**.



SCHEME I

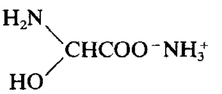


SCHEME II

In this connection it is of interest to note that aminoacetaldehyde, obtained from aminoacetaldehyde dimethylacetal and HCl[11], possesses ^1H- and ^{13}C-NMR spectra very similar to those of **4** and has, consequently, also a hydrate structure (**5**, Scheme II) in aqueous solution.

TABLE I

^{13}C-chemical shifts[a] and $^{1}J_{CH}$ coupling constants of acetal C atoms in D_2O

Entry	Structure	δ	$^{1}J_{CH}$
3a	$H_2O_3PCH_2NHCH_2CH(OEt)_2$	98.7	164
3b	$H_2O_3PCH_2NHCH_2CH(OCH_3)_2$	100.8	165
4	$H_2O_3PCH_2NHCH(OH)_2$	85.9	165
6	$(HO)_2CHCOO^-NH_3^+$	88.9	165
7	$(EtO)_2CHCO_2Et$[b]	97.9	
8	$(HO)_2CHCOOH$[c]	87.1	
9	$CH_2(OEt)_2$[d]		161
10	 $(H_2N)(HO)CHCOO^-NH_3^+$	71.8	149

[a] The full ^{13}C NMR spectra of **3a**, **3b**, and **4** are reported in the experimental part, compounds **6** and **10** represent unpublished work of our laboratory.

[b] In $CDCl_3$, lit.[13], spectrum No 12 612.

[c] Lit.[13], spectrum No 2998.

[d] Lit.[14]

This structure is based upon the chemical shift and the $^{1}J_{CH}$ coupling constant of the acetal C atom listed in Table I together with the values of various reference compounds. A comparison of the acetal C chemical shift of glyoxylic acid diethylacetal **7** with glyoxylic acid hydrate **8** shows a high field shift of ca. 11 ppm very similar to that observed for **4** versus **3a**. The $^{1}J_{CH}$ coupling constant is dependent on substituent electronegativity, and this substituent effect is moderately additive.[12] The value measured for **4** is 165 Hz, precisely in the range of the dihydroxy or dialkyoxy substitution (see e.g. entry **3a**, **3b**, **6** and **9** in Table I). The coupling constant of an aminoacetal is significantly smaller (cf **10**, 149 Hz) excluding an also possible aminoacetal structure formed by dimerization.

BIOLOGICAL ACTIVITY

None of the compounds described in this report showed any biological activity.

EXPERIMENTAL

General see lit.[1] The ^{13}C-NMR spectra were recorded with a Varian XL 300 NMR spectrometer (D_2O or D_2O/DCl solutions referenced against internal dioxane (67.4 ppm)).

N-Diethoxyphosphonylmethyl-aminoacetaldehyde dimethylacetal, **1**. A mixture of 9.9 g (0.077 mol) of diethylphosphite and 9 g (0.077 mol) of $CH_2{=}NCH_2CH(OCH_3)_2$ is heated for 1 h to 120°C. Kugelrohr distillation of the dark-colored reaction product yields 14.3 g (72.8%) of **1**, a slightly yellow oil, b.p. 127–133°C/0.1 torr.

^{1}H-NMR (in $CDCl_3$) δ: 1.3 (t, CH_3, 6H); 2.47 (s, NH, 1H); 2.8 (m, CH_2NCH_2, 4H); 3.33 (s, OCH_3, 6H); 4.1 (qui, OCH_2, 4H); 4.43 (t, J = 5, OCHO, 1H).

N-Ethoxy-hydroxyphosphonylmethyl-aminoacetaldehyde dimethylacetal, **2**. 41 g of **1** were kept for 2 years at 20°C. After this period, crystals had precipitated. These were filtered off, washed with acetone and dried to give 10.8 g of **2**, white crystals, m.p. 145–146°C (dec.).
^{1}H-NMR (in D_2O) δ: 1.57 (t, CH_3, 3H); 3.5 (d, J = 13, CH_2P, 2H); 3.6 (d, J = 5, NCH_2, 2H); 3.8 (s, OCH_3, 6H); 4.3 (qui, OCH_2, 2H); 5.05 (t, J = 5, OCHO, 1H); 5.1 (s, HDO).

N-Dihydroxyphosphonylmethyl-aminoacetaldehyde diethylacetal, **3a**. A mixture of 33.83 g (0.15 mol) of bis(trimethylsilyl)phosphite and 21.7 g (0.15 mol of $CH_2{=}NCH_2CH(OEt)_2$ is heated for 3 h to 110°C, cooled, and then slowly added to 150 ml of ethanol. A slightly yellow solution forms, from which white crystals precipitate, yield 17.4 g (51.3%) of **3a**, m.p. 191°C (dec.).
^{1}H-NMR (in D_2O) δ: 1.3 (t, CH_3); 3.25 (d, J = 12, CH_2P); 3.4 (d, J = 5, C—CH_2N); 3.8 (m, OCH_2); 4.8 (s, HDO); 5.0 (t, J = 5, OCHO). ^{13}C-NMR (in D_2O/DCl) δ: 15.1 (s, CH_3); 44.9 (d, J_{PC} = 139, PCH_2); 50.9 (d, J_{PC} = 5, NCH_2C); 65.5 (s, OCH_2); 98.7 (s, OCHO).

$C_7H_{18}NO_5P$ (227.2) calc.: C 37.01 H 7.99 N 6.17 P 13.63%
found: C 36.72 H 7.66 N 6.26 P 13.64%

N-Dihydroxyphosphonylmethyl-aminoacetaldehyde dimethylacetal, **3b**, was similarly obtained from bis(trimethylsilyl)phosphite and methylene aminoacetaldehyde dimethylacetal, yield 81%, white crystals, m.p. 187–188°C (dec.) (black melt, which produces bubbles).
^{1}H-NMR (in D_2O/DCl) δ: 3.35 (d, J = 5, CH_2N, 2H); 3.45 (d, J = 14, CH_2P, 2H); 3.47 (s, OCH_3, 6H); 4.83 (t, J = 5, OCHO, 1H); 5.6 (s, HDO).
^{13}C-NMR (in D_2O/DCl) δ: 44.4 (d, J_{PC} = 142, PCH_2); 50.1 (d, J_{PC} = 6, NCH_2C); 56.3 (s, OCH_3); 100.8 (s, OCHO).

$C_5H_{14}NO_5P$ (199.14) calc.: C 30.16 H 7.09 N 7.04 P 15.56%
found: C 29.87 H 7.21 N 7.03 P 16.38%

Equiv. weight found: 200.

N-Dihydroxyphosphonylmethyl-aminoacetaldehyde hydrate, **4**. To 4.8 g of **3b** is added 1 ml of water and 18 ml of HCl (32%) at 0°C. Then the mixture is kept for 15 h at 15°C and the solution evaporated at 40°C in the high vacuum. There is obtained 3.9 g (91.3%) of **4**, a brown resin.
^{1}H-NMR (in D_2O) δ: 3.28 (d, J = 5.5, NCH_2); 3.37 (d, J = 13, PCH_2); 5.0 (s, HDO); 5.4 (t, J = 5, OCHO).
^{13}C-NMR (in D_2O) δ: 44.2 (d, J_{PC} = 143, PCH_2); 53.4 (d, J_{PC} = 6, NCH_2); 85.9 (s, OCHO):

$C_3H_8NO_4P$/HCl H_2O (207.55) calc.: C 17.36 H 5.34 N 6.75 Cl 17.08 P 14.92%
found: C 17.6 H 5.3 N 6.9 Cl 13.7 P 16.1%

An aqueous solution of **4** precipitates a black solid after some weeks standing at 20°C. The black solid is not soluble anymore.

Aminoacetaldehyde hydrate, **5**. **5** was obtained from aminoacetaldehyde diethylacetal and HCl as described in the literature.[11]

C_2H_5NO/H_2O/HCl (113.54) calc.: C 21.15 H 7.10 N 12.33 Cl 31.22%
found: C 22.6 H 7.0 N 12.7 Cl 33.1%

^{1}H-NMR (in D_2O) δ: 3.05 (d, CH_2, 2H); 4.6 (s, HDO); 5.25 (t, OCHO, 1H).
^{13}C-NMR (in D_2O) δ: 44.8 (NCH_2); 86.8 (OCHO).

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