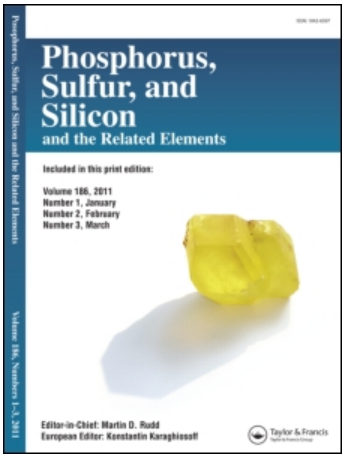

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PREPARATION OF OCTAETHYL-3-AMINO-PENTANE-1,1,5,5-TETRAKISPHOSPHONATE BY CATALYTIC HYDROGENATION OF THE CORRESPONDING 3-NITRO-COMPOUND

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The aim of this investigation was to find a convenient synthetical access to tetraethyl-3-amino-1,1-bisphosphonates, a class of chemical compounds which are useful agents in the concept of osteotic vectorisation of antitumor and antiinflammatory drugs. Base-catalyzed addition of nitroalkanes to tetraethylethenylidenebisphosphonate **1** affords the tetraethyl-3-nitro-alkane-1,1-bisphosphonates **3** and **4** and octaethyl-3-nitro-pentane-1,1,5,5-tetrakisphosphonate **2**, which can be hydrogenated to the corresponding 3-amino-alkane-1,1-bisphosphonates **6** and **7** and the title compound octaethyl-3-amino-pentane-1,1,5,5-tetrakisphosphonate **5**.

Key words: *gem*-bisphosphonates, Michael-type addition, 1,1,5,5-tetrakisphosphonate, 3-amino-1,1-bisphosphonates, drug targeting, bone malignancies.

INTRODUCTION

The structural analogy of 1,1-bisphosphonates to pyrophosphate in connection with the higher hydrolytic stability of the P—C bond—compared with the P—O—P bridge in pyrophosphate[1]—makes the *gem*-bisphosphonates very potential drugs in the treatment of bone diseases. They are used as very effective therapeutics for osteoporosis,[2] tumor-induced hypercalcemia[3] and Paget's disease[4] because of their influence on bone-metabolism and their bone-seeking properties.[5] For the same reason they are widely used in bone-tumor scintigraphy.[6]

Above all the ability of *gem*-biphosphonates to absorb to bone tissue[7] leads to a new kind of application. The *gem*-bisphosphonate moiety is used as a carrier for cytotoxic or antibiotic substances, bringing them to the bone to achieve higher concentrations for a treatment of bone tumors or inflammatory bone diseases.[8]

For that purpose conjugates must be made containing both a powerful antitumor or antibacterial agent and the 1,1-bisphosphonic acid. Tetraethyl-3-amino-1,1-bisphosphonates seemed to be the appropriate compounds for a later coupling with a drug—a small molecule, which probably can be connected without problems to various functional groups. After hydrolysis of the phosphonic ester functions the resulting molecule should have the osteotropic character of the bisphosphonate.

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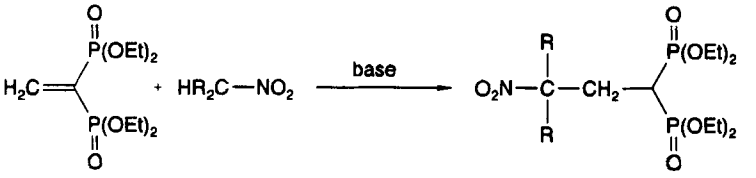
RESULTS AND DISCUSSION

A possible way for the synthesis of the desired 3-amino-1,1-bisphosphonates **6** and **7** was the hydrogenation of the corresponding 3-nitro-compounds **3** and **4**. These can be prepared by a modified method of the procedure from Sturtz and Guervenou[9] in a Michael-type addition of nitroalkanes to tetraethyl-ethenylidenebisphosphonate **1**.[10]

In trying to reproduce the results of Sturtz and Guervenou and to synthesize **3** we were able to obtain only the product of a di-addition **2**. The physical properties and the NMR-spectroscopical data for **2** are the same Sturtz and Guervenou described for the substance they made, thinking it was **3**.



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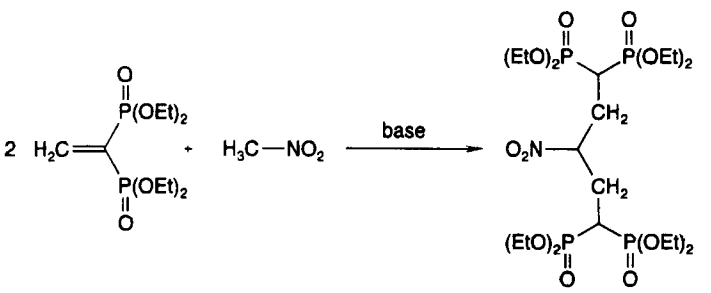
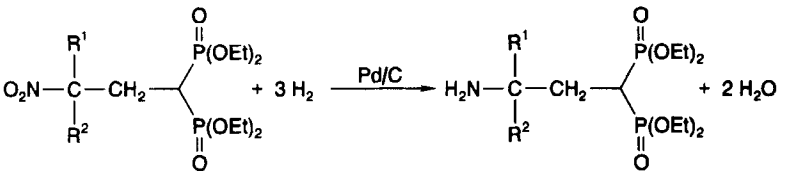
SCHEME 1



1 **2**

SCHEME 2



SCHEME 3

A satisfactory elemental analysis for both the mono-addition product **3** and the di-addition product **2** gave first evidence of the correctness of our interpretation. Moreover compounds **2** and **3** show clear differences in the NMR-spectra, above all the signals for the proton(s) and the carbon next to the nitrogen are different and characteristic. We also obtained mass spectra of all nitro-compounds **2**, **3** and **4**, which show the molepeaks and the $[M—NO_2^+]$-peaks and make it possible to decide without any doubt whether it is compound **2** or **3**. Mass spectra of the amino-compounds **5**, **6** and **7** also show $[M+H^+]$-peaks when FAB-technique is used for ionisation.

For the preparation of pure **3** not containing considerable amounts of the tetrakisphosphonate **2** a large excess of nitromethane was necessary.

The catalytical hydrogenation proceeds without any problems at room temperature and atmospheric pressure overnight if enough Pd/charcoal catalyst is used. The resulting amino-compounds **5**, **6** and **7** were purified by column chromatography on Al_2O_3 (alkaline) with ethyl acetate/ethanol (3:1).

EXPERIMENTAL

Solvents used were dried following the usual methods and afterwards stored over molecular sieves. Tetraethyl-ethenylidenebisphosphonate was prepared according to Degenhardt and Burdsall.[10] Nitroalkanes were purchased from Merck or Riedel de Haen.

All NMR spectra (^1H, ^{13}C, ^{31}P) were recorded on a Bruker WH 200 spectrometer in $CDCl_3$. Standards used: ^1H NMR: int.std. TMS, ^{13}C NMR: int.std. TMS, ^{31}P NMR: int.std. H_3PO_4 (85%). Chemical shifts δ are indicated in ppm, coupling constants J in Hz. Mass spectra were recorded on a Finnigan 8200 spectrometer at an ionisation potential of 70 eV (EI). If ionisation was achieved with FAB-technique, a 3-nitrobenzylalcohol matrix (Nibeol) was bombarded with fast Xenon atoms. Only the values for M^+ ($[M+H^+]$) and selected fragments most relevant to structural determination are mentioned.

Octaethyl-3-nitro-pentane-1,1,5,5-tetrakisphosphonate **2**. To a mixture of 0.31 g (5 mmol) of nitromethane and 0.56 g (5.5 mmol) of di-(isopropyl)amine in 20 ml of dry THF, 3 g (10 mmol) of tetraethyl-ethenylidenebisphosphonate **1** are added. After stirring at r.t. for 2 h all volatiles are removed at a rotavapor. To obtain **2** the crude reaction product, a pale yellow viscous oil, is purified by column chromatography (silica gel, 0.06–0.25 mm, ethyl acetate/ethanol 3:1). The resulting colourless oil is freed from remaining solvent at 0.02 mbar over several hours.

Yield: 2.6 g (80%); NMR: ^1H: 1.17–1.27 [m, 24 H], 2.07–2.58 [m, 6 H, $CH(PO_3ET_2)_2$ and $CH_2CH(PO_3Et_2)_2$, 4.06 [m, 16 H], 5.09 [m, 1 H, O_2NCH]; ^{13}C: 16.1 [m, 8 C], 30.0 [t, $^2J_{PC}$ = 4.5], 33.3 [t, $^1J_{PC}$ = 133.8], 62.8 [m, 8C], 84.8 [m, 1 C, O_2NC]; ^{31}P: 21.4, 21.8; M.S. (EI): m/z 661 (M^+, 5%), 615 ($[M—NO_2]^+$, 100%).

$C_{21}H_{47}NO_{14}P_4$ (661.50)	calc.	C 38.13	H 7.16	N 2.12	P 18.73%
	found	C 38.05	H 7.32	N 1.95	P 18.41%

Tetraethyl-3-nitro-propane-1,1-bisphosphonate **3**. 54 mg (1 mmol) of sodiummethylate are dissolved in nitromethane (21.6 g, 0.35 mol) and 20 ml of dry THF are added. After stirring for 1 h, 3 g (10 mmol) of **1** are added to the mixture very quickly. After stirring for two additional hours at r.t. 20 ml of a saturated NH_4Cl-solution are poured in and then nitromethane and THF are removed at the rotavapor. Precipitations are dissolved by adding water. The aqueous solution is now extracted with chloroform (4 × 20 ml). The organic phase is dried over Na_2SO_4 and the solvent evaporated. The crude product, a pale yellow oil, is purified by column chromatography (silica gel, 0.06–0.25 mm, ethyl acetate/ethanol 3:1) to obtain satisfactory elemental analysis. Pure **3** is a nearly colourless oil, which has to be evaporated at 0.02 mbar over a long time to remove all the solvent.

Yield: 3.3 g (91.5%); NMR: ^1H: 1.24 [t, ^3J = 7.1, 12 H], 2.28–2.56 [m, 3 H, $CH(PO_3Et_2)_2$ and $CH_2CH(PO_3Et_2)_2$, 4.08 [m, ^3J = 7.1, 8 H], 4.59 [t, ^3J = 6.8, 2 H, O_2NCH_2]; ^{13}C: 16.1 (d, $^3J_{PC}$ = 6.2, 4 C], 23.3 [t, $^2J_{PC}$ = 4.9], 33.6 [t, $^1J_{PC}$ = 134.0], 62.8 [m, 4 C], 73.0 [t, $^3J_{PC}$ = 7.2]; ^{31}P: 21.6; M.S. (EI): m/z 361 (M^+, 4%), 315 ($[M—NO_2]^+$, 100%).

$C_{11}H_{25}NO_8P_2$ (361.27)	calc.	C 36.57	H 6.98	N 3.88	P 17.15%
	found	C 36.84	H 7.00	N 3.82	P 16.96%

Tetraethyl-3-methyl-3-nitro-butane-1,1-bisphosphonate **4**. 2-nitropropane (0.89 g, 10 mmol) is mixed with 25 ml of dry THF, di-(isopropyl)amine (1.11 g, 11 mmol) and **1** (3 g, 10 mmol). The solution is refluxed with stirring for 2 d and after cooling to r.t. neutralized with 0.5 n hydrochloric acid. After evaporation to 15–20 ml the solution is extracted 4× with 20 ml of $CHCl_3$. The combined organic layers are dried over Na_2SO_4 and evaporated. The crude yellow oil is purified by chromatography on silica column (0.06–0.25 mm, ethyl acetate/ethanol 3:1) to obtain a nearly colourless viscous liquid.

Yield 3.19 g (82%); NMR: ^{1}H: 1.23 [t, ^3J = 7.1, 12 H], 1.52 [s, 6 H], 2.28–2.54 [m, 3 H, $CH_2CH(PO_3Et_2)_2$ and $CH(PO_3Et_2)_2$], 4.06 [m, ^3J = 7.1, 8 H]; ^{13}C: 16.1 [d, $^3J_{PC}$ = 6.1, 4 C], 25.6 [s, 2 C], 32.3 [t, $^1J_{PC}$ = 134.6], 35.1 [t, $^2J_{PC}$ = 4.3], 62.8 [m, 4 C], 86.8 [t, $^3J_{PC}$ = 5.2]; ^{31}P: 22.8; M.S. (EI): m/z 343 ([M—NO_2]$^+$, 100%)

$C_{13}H_{29}NO_8P_2$ (389.32)	calc.	C 40.11	H 7.51	N 3.60	P 15.91%
	found	C 40.10	H 7.60	N 3.50	P 15.90%

Hydrogenation of **2**, **3** *and* **4**: *Preparation of* **5**, **6** *and* **7**: *Typical procedure*. The nitro compound (6 mmol: 3.97 g **2**, 2.17 g **3** or 2.34 g **4**) is dissolved in 25 ml of methanol containing a few drops of water and 1 g of the catalyst (20% Pd on charcoal, containing 51% H_2O (DEGUSSA)) is added. The reaction proceeds at r.t. and atmospheric pressure and takes between 6 h for **3** and **4** and about 18 h for **2**, if the mixture is stirred vigorously. After that the catalyst is filtered off and the resulting solution is evaporated until crude **5**, **6** or **7** remains as pale green or yellow oil. For purification, column chromatography is necessary (Al_2O_3, alkaline). Ethyl acetate/ethanol mixtures were used as eluent, starting with 3:1 to remove educt and other impurities, then 1:1 and at last pure ethanol to eluate the product from the column. We were not able to purify compound **6** in this way without decomposition (on silica) or strong decrease in yield (alox). Therefore we purified **3** very carefully to obtain nearly pure **6** after hydrogenation without further purification.

Octaethyl-3-amino-pentane-1,1,5,5-tetrakisphosphonate **5**. A nearly colourless, highly viscous oil. (Pure **5** is very hygroscopic and could only be obtained by drying in vacuo at 80°C; it was not possible to obtain a satisfactory elemental analysis of the water-free product. We were able to analyze the much less hygroscopic monohydrate without any problem, which is formed by dissolving **5** in moist methanol and removing the solvent again.)

Yield: 3.68 g (97%); NMR: ^{1}H: 1.28 [t, ^3J = 7.1, 24 H], 1.81–2.07 [m, broad, 4 H, $CH_2CH(PO_3Et_2)_2$], 2.91 [m, 2 H, $CH_2CH(PO_3Et_2)_2$], 3.20 [m, broad, 1 H], 3.38 [m, 2 H, H_2N], 4.13 [m, ^3J = 7.1, 16 H]; ^{13}C: 16.2 [d, $^3J_{PC}$ = 6.1], 33.37 [t, $^1J_{PC}$ = 133.8], 33.39 [m, 2 C], 48.9 [m, 1 C], 62.6 [m, 8 C]; ^{31}P: 23.7, 24.2; M.S. (FAB): m/z 632 ([M+H]$^+$, 100%).

$C_{21}H_{49}NO_{12}P_4 \cdot H_2O$ (649.53)	calc.	C 38.83	H 7.91	N 2.16	P 19.08%
	found	C 38.86	H 7.86	N 1.97	P 19.12%

Tetraethyl-3-amino-propane-1,1-bisphosphonate **6**. Nearly colourless, viscous oil.

Yield: 1.82 g (91.5%); NMR: ^{1}H: 1.22 [t, ^3J = 7.05, 12 H], 2.02 [m, 2 H, $CH_2CH(PO_3Et_2)_2$], 2.47 [tt, $^2J_{PH}$ = 24.1, 1 H], 2.84 [m, 2 H, H_2NCH_2], 3.29 [s, broad, 2 H, H_2N], 4.06 [m, ^3J = 7.05, 8 H]; ^{13}C: 16.2 [d, $^3J_{PC}$ = 6.0], 28.3 [t, 1 C, $H_2NCH_2CH_2$], 33.6 [t, $^1J_{PC}$ = 134.0], 40.1 [t, $^3J_{PC}$ = 7.3, 1 C, $H_2NCH_2CH_2$], 62.4 [m, 4 C]; ^{31}P: 23.8; M.S. (FAB): m/z 332 ([M+H]$^+$, 100%)

$C_{11}H_{27}NO_6P_2$ (331.29)	calc.	C 39.88	H 8.22	N 4.23	P 18.70%
	found	C 39.71	H 8.35	N 4.00	P 18.49%

Tetraethyl-3-amino-3-methyl-butane-1,1-bisphosphonate **7**. Nearly colourless, viscous liquid.

Yield: 1.65 g (76.6%); NMR: ^{1}H: 0.98 [s, 6 H], 1.17 [t, ^3J = 7.1, 12 H], 1.88 [dt, 2 H, $CH_2CH(PO_3Et_2)_2$], 2.49 [tt, 1 H, $CH_2CH(PO_3Et_2)_2$], 2.65 [s, broad, 2 H, H_2N], 4.00 [m, ^3J = 7.1, 8 H]; ^{13}C: 16.1 [d, $^3J_{PC}$ = 6.6], 30.3 [s, 2 C $H_2NC(CH_3)_2$], 31.9 [t, $^1J_{PC}$ = 134.0], 37.0 [t, $^2J_{PC}$ = 4.3], 49.4 [t, $^3J_{PC}$ = 4.7, H_2NC], 62.3 [m, 4 C]; ^{31}P: 25.5; M.S. (FAB): m/z 360 ([M+H], 100%).

$C_{13}H_{31}NO_6P_2$ (359.34)	calc.	C 43.45	H 8.70	N 3.90	P 17.24%
	found	C 43.17	H 8.62	N 3.81	P 17.21%

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