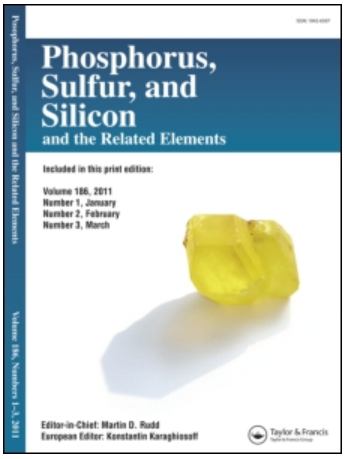

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PREPARATION OF TETRAETHYL-4-HYDROXYPHENYLMETHYLENE-1,1-BISPHOSPHONATE BY HYDROXY-DE-DIAZONIATION OF THE CORRESPONDING DIAZONIUM SALT OF TETRAETHYL-4-AMINOPHENYLMETHYLENE-1,1-BISPHOSPHONATE

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Bisphosphonates are widely used in diagnosis and therapy of different bone diseases. They are useful agents in osteotic vectorization of antitumor and antiinflammatory drugs because of their potential to accumulate in the inorganic bone matrix hydroxylapatite. Hence, there is great interest in alkyl-bisphosphonates, containing functional groups advantageous for further synthetic modification, as structural units for coupling with the drug. We report on the synthesis of tetraethyl-4-hydroxyphenylmethylene-1,1-bisphosphonate **8** by hydroxy-de-diazoniation of the diazonium salt **7**, prepared by diazotation of the corresponding amine tetraethyl-4-aminophenylmethylene-1,1-bisphosphonate **6**.

Keywords: bisphosphonates; hydroxy-de-diazoniation; drug targeting; bone malignancies

INTRODUCTION

Bisphosphonates, especially *gem*-bisphosphonates, show high affinity towards bone and other calcified tissues[1]. They are used in diagnosis and therapy of osteoporosis[2,3], tumor-induced hypercalcemia[4,5] and Paget's disease[6,7], due to their influence on bone metabolism and bone-seeking

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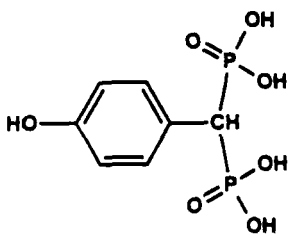
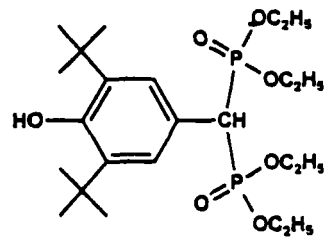
properties[8]. Their great potential to accumulate in the inorganic bone matrix hydroxylapatite makes them useful as carriers for cytotoxic or antibiotic substances, increasing the concentration of the drug in bone tissue. This drug targeting with bisphosphonates should result in an improved therapy of several bone malignancies. According to this concept, alkyl-bisphosphonates containing functional groups are useful structural units for coupling with the drug.

RESULTS AND DISCUSSION

Several alkyl-bisphosphonates containing an amino- or hydroxy-function have been synthesized[9–11]. Nevertheless, unsubstituted 4-hydroxy- or 4-aminophenylmethylene-tetraalkyl-1,1-bisphosphonates can't be found in the literature. The synthesis of the free bisphosphonic acid **1** (see Scheme 1) was described by Gross and Oszegowski[12], but they obtained 4-hydroxyphenylmethylene-1,1-bisphosphonate **1** by silylation and subsequent hydrolysis of 3,5-di-tert-butyl-4-hydroxyphenylmethylene-1,1-bisphosphonate **2**, derived from 3,5-di-tert-butyl-4-hydroxybenzaldehyde. The tert-butyl groups are necessary for conversion of the aldehyde into the bisphosphonate. They are removed during hydrolysis. A direct synthesis of the corresponding alkylester of **1** was not possible and esterification of **1** with triethylorthoformiate led to the 4-ethoxyphenylmethylene derivative.



1

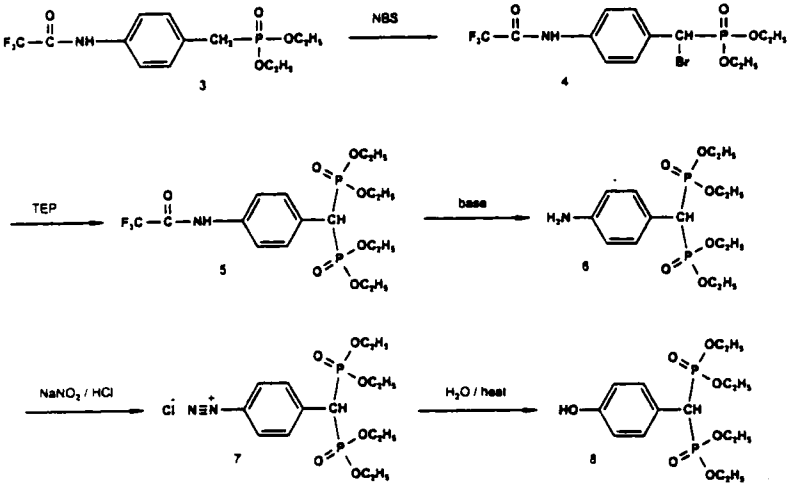


2

SCHEME 1

A convenient, direct synthesis of the corresponding ethylester of **1**, the title compound **8**, was found by hydroxy-de-diazoniation of the diazonium

salt **7**, derived from the new tetraethyl-4-amino-phenylmethylene-1,1-bisphosphonate **6** (see Scheme 2). Compound **6** was synthesized by radical bromination of the diethyl-4-(trifluoracetylamino)phenylmethyl-phosphonate **3**, using N-bromosuccinimide (NBS), and subsequent Michaelis-Arbuzov reaction of the resulting diethyl-bromo-[4-(trifluoracetylamino)phenyl]methylene-phosphonate **4** with triethylorthophosphite (TEP), leading to the trifluoracetyl-protected amine **5**. Basic hydrolysis affords **6**, which can be used for further synthesis.



SCHEME 2

6 is a white solid that changes color to brown during storage. The trifluoracetyl-group is advantageous for storage, purification and also for protection of the amino-function during synthesis.

Thus, the title compounds **6** and **8**, as well as the diazonium salt **7**, are useful agents for further synthesis, especially in the field of osteotic vectorization of diverse drugs.

EXPERIMENTAL

The solvents used were dried following the usual methods. Diethyl-4-aminophenylmethyl-phosphonate was prepared by Arbuzov reaction of TEP with 4-nitrophenylmethylbromide (purchased from Merck) and subsequent catalytic hydrogenation.

All NMR spectra (^{1}H, ^{13}C, ^{31}P) were recorded on a Bruker WH 200 MHz spectrometer in dmso-d6. TMS and H_3PO_4were used as internal standards.

Elemental analysis were performed using a Hearaeus C,H,N-Rapid system. P was determined as magnesium pyrophosphate.

Diethyl-4-(trifluoracetylamino)phenylmethyl-phosphonate **3**. Diethyl-4-aminophenylmethyl-phosphonate (5.0 g), 0.02 mol) was dissolved in 25 ml of dry tetrahydrofuran. Trifluoracetic anhydride (4.2 g, 0.02 mol) was added dropwise. After stirring for one hour at room temperature 30 ml of water were poured in and the mixture was concentrated at the rotavapor to about half of the volume. On standing, the product precipitated as clear, colorless crystals (m.p. 141°C).

Yield: 5.5 g (81%); **NMR** (in dmso-d6): ^{31}**P**: 26.6; ^{1}**H**: 1.15 [t, ^{3}J = 7.1 Hz, 6 H], 3.21 [d, ^{2}J = 21.5 Hz, 2 H], 3.92 [m, 4 H], 7.29 [d, ^{3}J = 8.4 Hz, 2 H], 7.60 [d, ^{3}J = 8.4 Hz, 2 H], 11.25 [s, **1** H]; ^{13}**C**: 16.18 [d, $^{3}J_{PC}$ = 5.7 Hz], 46.70 [d, $^{1}J_{PG}$ = 135.2 Hz], 61.42 [d, $^{2}J_{PC}$ = 6.5 Hz], 115.85 [q, $^{1}J_{FC}$= 288.6 Hz], 120.97 [d, $^{4}J_{PC}$ = 2.5 Hz], 129.71 [d, $^{2}J_{PC}$ = 9.1 Hz], 130.26 [d, $^{3}J_{PC}$ = 6.7 Hz], 134.84 [m, $^{4}J_{FC}$ = 3.7 Hz], 154.45 [q, $^{2}J_{FC}$= 36.8 Hz].

Tetraethyl-4-(trifluoracetylamino)phenylmethylene-1,1-bisphosphonate **5**. To a hot solution of 3.0 g (0.009 mol) of **3** in dry CCl_4 (60 ml) N-bromosuccinimide (1.76 g, 0.009 mol) was added. The mixture was refluxed and irradiated with a 500 W light bulb for three hours. After filtration of succinimide the filtrate was concentrated and 3.0 g of crude diethyl-bromo-[4-(trifluoracetylamino)phenyl]methylene-phosphonate **4** precipitates. **4** was dissolved, without further purification, in 20 ml of dry tetrahydrofuran. After addition of 1.2 g (0.007 mol) of triethylphosphite (TEP) the mixture was refluxed for eight hours. Subsequently, all volatiles were removed in the vacuum and the resulting residue was treated with ether and filtered to give **5** as a white solid (m.p. 165°C).

Yield: 1.9 g (57%); **NMR** (in dmso-d6): ^{31}**P**: 19.3; ^{1}**H**: 1.03 [t, ^{3}J = 7.1 Hz, 6 H], 1.18 [d, ^{3}J = 7.1 Hz, 6 H], 3.85 [m, 4 H], 4.05 [m, 4 H],

4.34 [t, $^2J_{PH}$ = 24.8 Hz, 1 H], 7.52 [d, ^3J = 8.6 Hz, 2 H], 7.61 [d, ^3J = 8.6 Hz, 2 H]; **^{13}C**: 12.83 [m], 42.71 [t, $^1J_{PC}$ = 126.8 Hz], 62.29 [m], 115.76 [q, $^1J_{FC}$ = 288.5 Hz], 120.73, 128.03 [t, $^2J_{PC}$ = 7.8 Hz], 130.95 [t, $^3J_{PC}$ = 6.2 Hz], 135.39 [m, $^4J_{FC}$ = 2.6 Hz], 154.44 [q, $^2J_{FC}$ = 36.9 Hz].

$C_{15}H_{26}F_3NO_7P_2$(475.34) calc.: C 42.96, H 5.51, N 2.95, P 13.03, found: C 43.12, H 5.60, N 3.08, P 13.29.

Tetraethyl-4-aminophenylmethylene-1,1-bisphosphonate **6**. 1.9 g [0.004 mol) of **5** were added to 50 ml of 0.1 M aqueous NaOH. After stirring at 100°C for three hours, the solution was extracted several times with CH_2CL_2. The combined organic layers were dried with Na_2SO_4 and the solvent was removed. The resulting oil crystallized and 1.3 g of a white solid were obtained (m.p. 92°C).

Yield: 1.3 g (88%); **NMR** (in dmso-d6): **^{31}P**: 18.8; **^{1}H**: 1.01 [t, ^3J = 7.0 Hz, 6 H], 1.18 [d, ^3J = 7.0 Hz, 6 H], 3.81 [m, 4 H], 3.93 [t, $^2J_{PH}$= 24.8 Hz, 1 H], 3.99 [m, 4 H], 5.06 [s, 2H], 6.47 [d, ^3J = 8.3 Hz, 2 H], 7.10 [dt, ^3J = 8.3 Hz, $^4J_{PH}$ = 2.0 Hz, 2 H]; **^{13}C**: 15.91 [m], 42.51 [t, $^1J_{PC}$ = 131.7 Hz], 61.93 [m], 113.49, 116.42 [t, $^2J_{PC}$ = 7.9 Hz], 130.92 [t, $^3J_{PC}$ = 6.2 Hz], 147.63.

$C_{15}H_{27}NO_6P_2$ (379.37) calc.: C 47.50, H 7.17, N 3.69, P 16.33, found: C 47.47, H 7.16, N 3.62, P 16.17.

Tetraethyl-4-hydroxyphenylmethylene-1,1-bisphosphonate **8**. 1.0 g (0.0026 mol) of **6** was dissolved in 2.5 ml of semi-concentrated hydrochloric acid. $NaNO_2$ (0.18 g, 0.0026 mol) in 1 ml of water was added within 10 minutes, while the temperature was kept below −10°C. The resulting diazonium salt **7**solution was diluted with 5 ml of water and heated for two hours at 100°C under generation of nitrogen. Then the yellow solution was extracted several times with CH_2Cl_2. The combined organic layers were washed with water and dried with Na_2SO_4. The solvent was removed and the resulting oil crystallized slowly. The product was recrystallized from ether, yielding a light yellow solid (m.p. 89°C).

Yield: 0.5 g (50%); **NMR** (in dmso-d6): **^{31}P**: 19.2; **^{1}H**: 1.01 [t, ^3J = 7.0 Hz, 6 H], 1.18 [d, ^3J = 7.0 Hz, 6 H], 3.81 [m, 4 H], 4.00 [m, 4 H], 4.08 [t, $^2J_{PH}$ = 25.1 Hz, 1 H], 6.68 [d, ^3J = 8.5 Hz, 2 H], 7.26 [dt, ^3J = 8.5 Hz, $^4J_{PH}$= 2.0 Hz, 2 H], 9.37 [s, 1 H]; **^{13}C**: 16.00 [m], 42.34 [t, $^1J_{PC}$ = 131.2 Hz], 62.11 [m], 114.89, 120.30 [t, $^2J_{PC}$ = 7.9 Hz], 131.51 [t, $^3J_{PC}$ = 6.2 Hz], 156.57.

$C_{15}H_{26}O_7P_2$ (380.31) calc.: C 47.37, H 6.89, P 16.29, found: C 47.24, H 6.93, P 16.04.

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