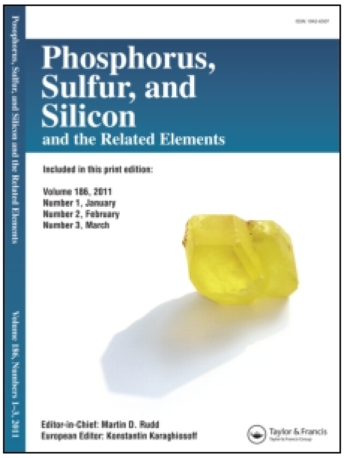

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A NOVEL REARRANGEMENT IN THE SERIES OF *GEM*-BISPHOSPHONIC ACIDS

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A NOVEL REARRANGEMENT IN THE SERIES OF *GEM*-BISPHOSPHONIC ACIDS†

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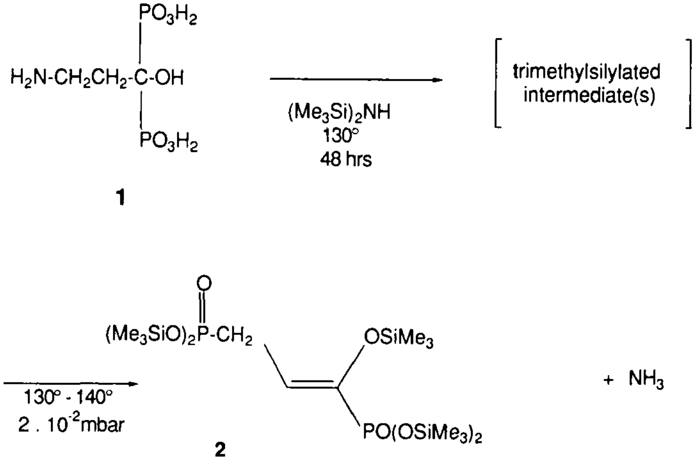
Silylated 3-amino-propane-1-hydroxy-1,1-bisphosphonic acid and some of its *N*-alkyl derivatives undergo a thermally induced rearrangement which includes elimination of the amino substituent and migration of a phosphono group. The homologue 4-aminobutane-1-hydroxy-1,1-bisphosphonic acid is converted to pyrrolidine derivatives under the same conditions. The mechanism of the observed reactions is discussed.

Key words: Substituted aminoalkane-1-hydroxy-1,1-bisphosphonic acids, trimethyl silylation, thermal rearrangement, 3-phosphono-propanoyl acid, 3-phosphono-propionic acid.

INTRODUCTION

Some bisphosphonic acids containing basic side chain substituents are compounds of pharmaceutical interest which are undergoing clinical investigation as agents for the treatment of various bone diseases. A well known member of this series is 3-amino-propane-1-hydroxy-1,1-bisphosphonic acid **1**.[1] This paper describes a novel rearrangement which is observed when **1** is trimethylsilylated and distilled at low pressure (Scheme 1).



Scheme 1.

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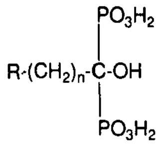
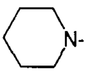
† This communication was presented in part at the XIth International Conference on Phosphorus Chemistry, Tallinn, USSR, July 1989.

RESULTS

The main fraction of the distillation was an olefinic product **2** identified as the E-isomer. No trace of the Z-olefin was observed. The yield of **2** amounted up to 60% in several runs.

In order to establish the scope and limitations of this rearrangement and to elucidate the reaction mechanism, we subjected the following derivatives of **1** to the rearrangement conditions (Scheme 2):

	R	n	Product(s)
 $R\text{-}(CH_2)_n\text{-}C(OH)(PO_3H_2)_2$	$(CH_3)_2$-N-	2	2
		2	2 + 3
	H_2N-	3	4 + 5

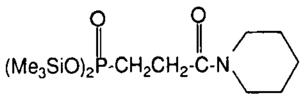
Scheme 2.

Thus in an analogous manner, **2** was also obtained from trihydrogen 3-trimethylammoniopropane-1-hydroxy-1,1-bisphosphonate which was prepared by exhaustive methylation of **1** with dimethyl sulphate. The eliminated amines were isolated as their hydrochlorides from the cold trap and identified by mass spectroscopy.

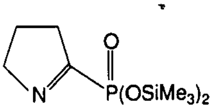
When 3-piperidino-propane-1-hydroxy-1,1-bisphosphonic acid was subjected to the rearrangement conditions, compound **3** was obtained as the main product; in addition, a minor amount of **2** was formed.

4-Aminobutane-1-hydroxy-1,1-bisphosphonic acid reacted in a different fashion to afford the ring-closed products **4** and **5**, the latter compound was not obtainable in a pure state, but was contaminated with minor amounts of **4**.

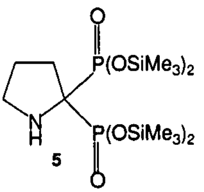
Based on their spectroscopic data, the products isolated were assigned the following structures:



3

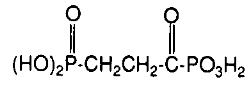


4



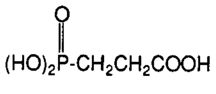
5

Treatment of compound **2** with 2-propanol and subsequent addition of tert. butylamine furnished three compounds (**6**, **7** and **8**) as their mono-tert. butylamine salts:



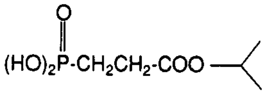
$(HO)_2P(=O)-CH_2CH_2-C(=O)-PO_3H_2$

6



$(HO)_2P(=O)-CH_2CH_2COOH$

7

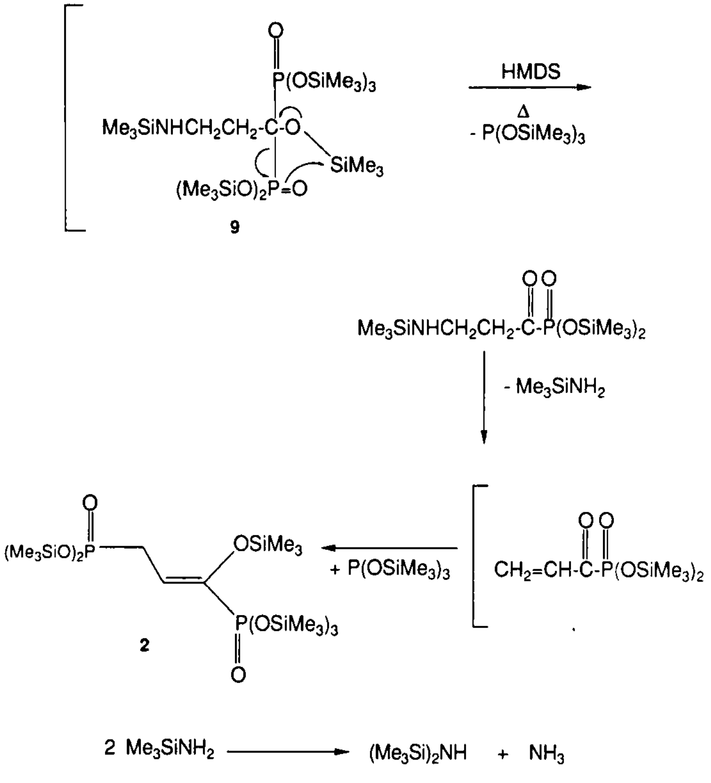


8

The formation of **7** may be explained by the presence of moisture during work-up. Only **8** could be isolated as an analytically pure compound.

DISCUSSION

On the basis of the structures of the observed products, we propose the following reaction mechanism (Scheme 3):

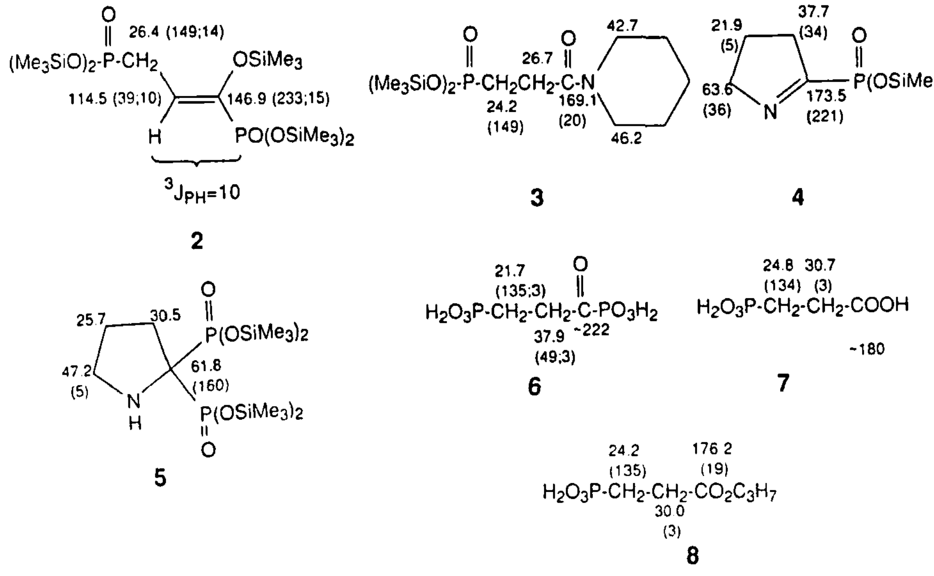


Scheme 3.

Trimethylsilylation of **1** may result in the transient formation of intermediate **9** which is finally converted to **2** as shown in scheme 3. Primary amines of structures similar to **1** usually form the monosilylamino derivatives under the conditions used.[2] Silylation of α-hydroxy phosphonates followed by thermal elimination of tris-(trimethylsilyl) phosphite is known to cause P—C-bond cleavage resulting in re-generation of the original carbonyl species.[3] In the case of bisphosphonates this process leads to an α-acyl phosphonate. Subsequent β-elimination of trimethylsilylated amine affords a conjugated double bond which reacts further with the generated tris(trimethylsilyl) phosphite[4] to produce the observed product **2**. A six-membered transition state has been postulated to occur during the addition to 1,2-unsaturated carbonyl compounds in which the silicon atom participates by binding simultaneously to both the enolic and the phosphonyl oxygen, thus resulting in the formation of a product with uniform geometry.[5] The reaction sequence terminates with the transfer of a trimethylsilyl group from the phosphite moiety to the enolic oxygen atom.[6]

Compound **3** is apparently formed from an acyl phosphonate intermediate by reaction with the eliminated piperidine. The reaction of acyl phosphonates with nucleophiles as e.g., amines is well known.[7] **4** and **5** are formed from the butane homolog of **1** by ring closure since elimination is not likely to occur in a ketone substituted in the γ-position. In addition, some polymerisation takes place.

The rearrangement described above has hitherto not been reported in the series of *gem*-bisphosphonic acids. Known rearrangements in this series are the phosphonate-phosphate rearrangement[8] and the rearrangement of 2-chloro 1-hydroxy-ethane-1,1-bisphosphonic acid and its amino analogue.[9]



Scheme 4. ^{13}C-NMR chemical shifts and J_{CP} coupling constants (in brackets) of 2-8. Essential data.

EXPERIMENTAL

NMR-spectra were recorded using a Bruker AM 300 (^{1}H-NMR) and a Varian XL 300 (^{13}C-NMR) spectrometer. The essential data of the ^{13}C-NMR chemical shifts and J_{CP} coupling constants are shown in scheme 4.

E-1,3-Di[bis(trimethylsilyloxy)-phosphonyl]-1-trimethylsilyoxy-prop-1-ene **2**. In a typical experiment, 117.5 g 3-amino-propane-1-hydroxy-1,1-bisphosphonic acid (0.50 Mol) was added in portions to 624 ml hexamethyl disilazane heated to 60°. The reaction mixture was heated to reflux for 42 hours under stirring when a clear solution was obtained. Ammonia evolved during the reflux period. The excess hexamethyl disilazane was removed by distillation and the residual oil was subjected to a bulb-to-bulb distillation in vacuo. A main fraction was obtained at an external temperature of 140–180° and a pressure range of 6.10^{-2} to 4.10^{-2} mbar as a slightly yellow, viscous oil. Redistillation on a 10 cm Vigreux distillation head furnished 168.4 g of **2**, bp. 119–121° at 3.10^{-2} mbar.

Under the same conditions, compound **2** was also obtained when 3-dimethylamino-propane-1-hydroxy-1,1-bisphosphonic acid[10] or trihydrogen 3-trimethyl ammonio-propane-1-hydroxy-1,1-bisphosphonate was used as the starting material.

^{1}H-NMR ($CDCl_3$): 5.65 (ddt, $J_{H,P-C=} = 10.1$, $J_{H,PCH2} = 8.3$, $J_{H,CH2} = 7.5$, vinyl H); 2.56 (ddd, $^2J_{HP} = 22.3$, $^3J_{H,H} = 7.5$, $^4J_{HP} = 3.3$, CH_2); 0.29 ($SiCH_3$).

^{13}C-NMR ($CDCl_3$): 146.9 ($J_{CP} = 233$ & 15, subst. vinyl C); 114.5 ($J_{CP} = 39$ & 10, vinyl CH); 26.4 ($J_{CP} = 149$ & 14, CH_2).

EI-MS: 578 (M). FD-MS: 579 (M + H) HR-MS of m/z 506: $C_{15}H_{40}O_7P_2Si_4$ (506 is a hydrolysis product of 578 formed during mass spectral analysis).

3-[Bis(trimethylsilyloxy)-phosphonyl]-propionic piperidide **3**. 3-Piperidino-propane-1-hydroxy-1,1-bisphosphonic acid[11] was treated with hexamethyl disilazane as in the foregoing experiments. **3** was obtained as a colourless oil, bp. 119–122°/3.10^{-2} mbar. In the forerunning fraction, traces of **2** were detected by NMR spectroscopy.

^{1}H-NMR ($CDCl_3$): 3.55 & 3.37 (NCH_2); 2.57 ($CH_2C{=}O$); 2.02 (PCH_2); 1.63 & 1.56 (remaining piperidine CH_2); 0.28 ($SiCH_3$).

^{13}C-NMR ($CDCl_3$): 169.1 ($J_{CP} = 20$, C=O); 46.2 (piperidine C(6)); 42.7 (piperidine C(2)); 26.7 ($\underline{C}H_2$-C=O); 26.2, 25.3 & 24.3 (piperidine C(3)), C(4), C(5)); 24.2 ($J_{CP} = 149$, PCH_2); 0.8 (CH_3).

EI-MS: 365 (M); FD-MS: 366 (M + H).

2-[Bis(trimethylsilyloxy)-phosphonyl]-pyrrolenine **4**. 4-Aminobutane-1-hydroxy-1,1-bisphosphonic acid[9] was treated as described above. Distillation of the reaction products gave a fraction boiling at 67–71°/4.10^{-2} mbar, consisting of pure **4**. A further fraction boiling at 80–93°/4.10^{-2} mbar was found to be a mixture of **4** and *2,2-di-[bis(trimethylsilyloxy)-phosphonyl]-pyrrolidine* **5** as the main component.

4: ^{1}H-NMR ($CDCl_3$): 4.05 (H_2-C(5)); 2.78 (H_2-C(3)); 1.90 (H_2-C(4)); 0.31 (CH_3).
^{13}C-NMR ($CDCl_3$): 173.5 ($J_{CP} = 221$, C(2)); 63.6 ($J_{CP} = 36$, C(5)); 37.7 ($J_{CP} = 34$ C(3)); 21.8 ($J_{CP} = 5$, C(4) = 5, C(4)); 0.8 (CH_3).
DCI-MS (NH_3): Pos. 294, neg. 292.

5: ^{1}H-NMR ($CDCl_3$): 3.06 (H_2-C(5)); 2.21 (H_2-C(3)); 2.03 (NH); 1.87 (H_2-C(4)); 0.31 (CH_3).
^{13}C-NMR ($CDCl_3$): 61.8 ($J_{CP} = 160$, C(2)); 47.2 ($J_{CP} = 5$, C(5)); 30.5 C(3)); 25.7 C(4)); 1.2 (CH_3).
DCI-MS (NH_3): Pos. 520, neg. 519.

Alcoholysis products. 9.91 g of **2** was dissolved in 90 ml 2-propanol and heated to reflux for 20 hours. Evaporation of the solvent under reduced pressure gave an oil which was dissolved in methanol and treated with an excess of tert. butylamine.

Addition of 2-propanol afforded 2.5 g of a colourless crystalline precipitate which was filtered off and recrystallized from a mixture of methanol and 2-propanol.

This product consisted of a mixture of the *mono-tert. butylamine salts of 3-phosphono-propanoyl phosphonic acid* **6** and *3-phosphono-propionic acid* **7** in a ratio of 4:1 parts by weight (measured by ^{1}H-NMR). Concentration of the filtrate furnished 1.6 g of a second crop which, after recrystallisation from the same solvents, consisted of the *mono-tert. butylamine salt of 2-propyl 3-phosphono-propionate* **8**, mp. 197–198°.

6: ^{1}H-NMR (D_2O): 2.97 ($CH_2C{=}O$); 1.72 (PCH_2).
^{13}C-NMR (D_2O): ~222 (J_{CP} ~157, C=O); 37.9 (J_{CP} 49 & 3, $\underline{C}H_2$ C=O); 21.7 (J_{CP} 135 & 3, PCH_2); 52.7 & 27.5 ($(CH_3)_3$ $CNH_3^{\oplus}$).

7: ^{1}H-NMR (D_2O): 2.43 ($CH_2C{=}O$); 1.74 (PCH_2).
^{13}C-NMR (D_2O): ~180 (COOH); 30.7 ($J_{CP} = 3$, CH_2CO); 24.8 ($J_{CP} = 134$, PCH_2); 52.7 & 27.5 ($(CH_3)_3$ $CNH_3^{\oplus}$).

8: ^{1}H-NMR (D_2O): 4.96 (CH isopr.); 2.52 (CH_2 C=O); 1.82 (PCH_2); 1.34 (CH_3 *t*-butyl); 1.22 (CH_3 isopr.).
^{13}C-NMR (D_2O): 176.2 ($J_{CP} = 19$, C=O); 70.6 (OCH); 30.0 ($J_{CP} = 3$, CH_2CO); 24.2 ($J_{CP} = 135$, PCH_2); 21.8 ($(\underline{C}H_3)_2CH$); 52.7 & 27.5 ($(CH_3)_3$ $CNH_3^{\oplus}$).

$C_{10}H_{24}NO_5P$ (269.28) calc. C 44.60 H 8.98 N 5.20 P 11.50%
found C 43.90 H 8.70 N 5.00 P 11.90%

Since t.l.c. examination unveiled a contamination by phosphorous acid, this was taken in account for the following calculation:

$C_{10}H_{24}NO_5P \times 0.05\ H_3PO_3$ (273.37) calc. C 43.90 H 8.90 N 5.12 P 11.89%

Trihydrogen 3-trimethylammonio-propan-1-hydroxy-1,1-bisphosphonate. 18.8 g (0.080 Mol) 3-Amino-propane-1-hydroxy-1,1-bisphosphonic acid **1** was dissolved in 200 ml 5N sodium hydroxide solution and cooled to 0–5°C. 30.3 g dimethyl sulphate was added dropwise under stirring. The reaction solution was kept at 20–22°C for 72 hours when it was acidified with concentrated nitric acid to pH 6 and a solution of 54.4 g silver nitrate in 60 ml water was added. The precipitate obtained was filtered off, washed thoroughly and suspended in 400 ml water. Hydrogen sulfide was passed through the suspension until the uptake ceased. After filtration from the sulfide precipitate, the filtrate was evaporated under reduced pressure to a viscous oil. Crystallisation from methanol afforded 13.8 g colourless crystals, m.p. 251–252° (dec.).

$C_6H_{17}NO_7P_2 \times 0.1\ H_2O$ (278.95) calc. C 25.83 H 6.21 N 5.02 P 22.20%
found C 25.42 H 6.10 N 5.14 P 22.40%

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