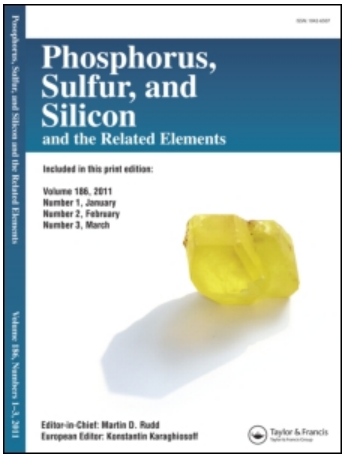

Phosphorus, Sulfur, and Silicon and the Related Elements
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713618290

A CLEAVAGE OF SOME HYDROXYBENZYL(α-AMINO)-PHOSPHONATES IN A BASIC MEDIUM

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To cite this Article Boduszek, Bogdan and Halama, Agnieszka(1998) 'A CLEAVAGE OF SOME HYDROXYBENZYL(α-AMINO)-PHOSPHONATES IN A BASIC MEDIUM', Phosphorus, Sulfur, and Silicon and the Related Elements, 143: 1, 151 — 158
To link to this Article: DOI: 10.1080/10426509808045493
URL: http://dx.doi.org/10.1080/10426509808045493

Phosphorus, Sulfur and Silicon, 1998, Vol. 143, pp. 151-158
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A CLEAVAGE OF SOME HYDROXYBENZYL(α-AMINO)-PHOSPHONATES IN A BASIC MEDIUM[1]

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(Received 01 October, 1998)

α-Aminobenzylphosphonic acids possessing the hydroxy groups in *ortho* and *para* positions, underwent a **C-P** bond cleavage during heating with aqueous NaOH solution. In the case of *o*- and *p*-hydroxy diethyl esters **1** and **3** the products of the cleavage were the corresponding aldehydes and phosphorous acid (H_3PO_3). The *m*-hydroxy derivative was not affected by a base. It has been found, that displacement of the hydroxy group by the methoxy one in the p-hydroxybenzyl(α-amino)phosphonic acid leads to a stability of such a compound towards a base; no a C-P bond cleavage was observed in this case.

Keywords: a C-P bond cleavage; *o*- and *p*-hydroxybenzyl(α-N-butylamino)phosphonates; phosphorous acid

INTRODUCTION

The C-P bond in α-aminophosphonates is considerably strong, and it usually does not undergo a cleavage in aqueous basic or acidic conditions. However, there are some examples of aminophosphonates, in which the C-P bond can be easily split by action of a basic or acidic medium. For instance, 2- and 4-pyridylmethyl(α-amino)phosphonates are split in strong acidic conditions, to form the corresponding amines and phosphoric acid[2]. Also, 2- and 4-nitrobenzyl(α-amino)phosphonates undergo a C-P bond cleavage in a strong basic solution[3,4]. Further investigations revealed, that some hydroxybenzyl aminophosphonates were also cleaved by a base.

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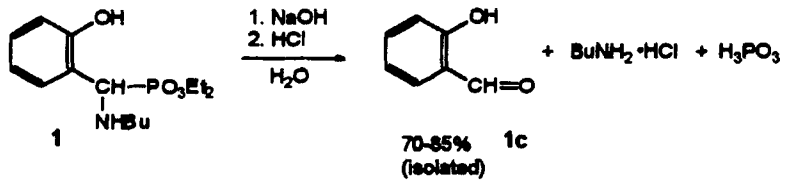
RESULTS AND DISCUSSION

The starting materials, *o*-, *p*- and *m*-hydroxybenzyl(α-N-butylamino)phosphonic acids (**1**, **3**, **5**) (and the *p*-methoxy derivative **4**) were synthesized from the corresponding aldehyde, butylamine and diethyl phosphite, following the described method[3], and characterized by the spectroscopy methods.

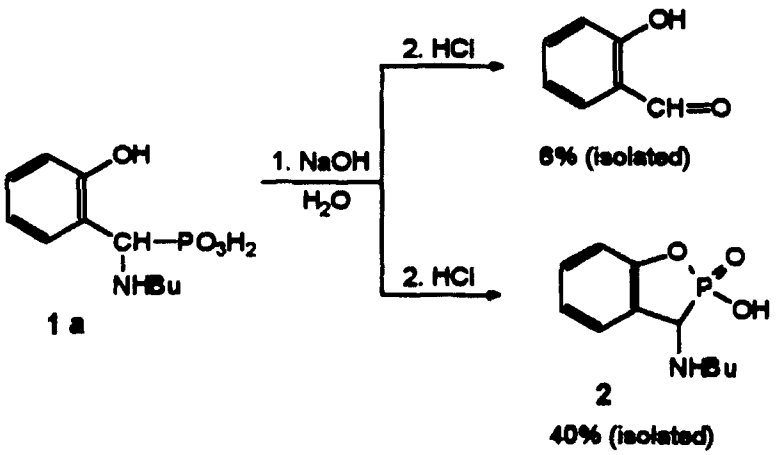
The cleavage of hydroxybenzyl phosphonic acids and esters was performed by heating of a sample of the acid (or the ester) with an excess of aqueous NaOH solution for 10 hours at 100°C, and then the reaction mixture was neutralized with aq. HCl, in order to isolate the formed products. On the basis of the obtained results, we found that diethyl *o*-hydroxybenzyl(α-N-butylamino)phosphonate **1** undergoes a cleavage in NaOH solution, to form finally the salicylaldehyde, butylamine and phosphorous acid in high yield (scheme 1). However, in the case of the corresponding acid **1a** only 6% of salicylaldehyde was isolated. The main product was in this case the cyclic phosphonic derivative **2**, which was a rather unstable compound, and it has been gradually changed to the starting material **1a**, in the presence of moisture (scheme 2). Formation of a similar cyclic phosphonic derivative was also reported[5], during synthesis of the phosphonic ester, derived from salicylaldehyde.



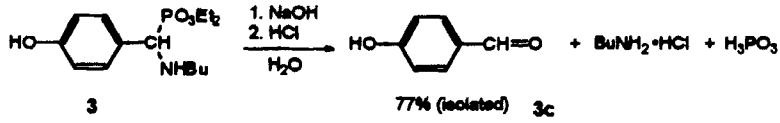
SCHEME 1

The diethyl ester **3** was also cleaved in NaOH solution, to give *p*-hydroxybenzaldehyde (in 77% yield), butylamine and phosphorous acid, respectively (scheme 3). Traces of products resulting from the Cannizzaro rearrangement of the formed aldehyde were also detected by means of ESI±Q1MS spectroscopy.

The corresponding acid **3a** when treated with aq. NaOH gave only 7% of *p*-hydroxybenzaldehyde (and butylamine in high yield) and a mixture of



SCHEME 2



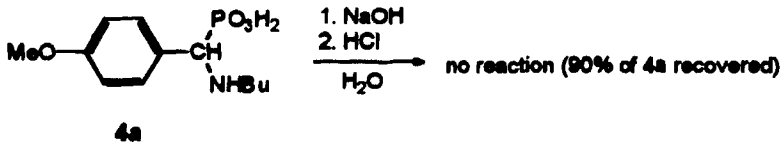
SCHEME 3

other products, in which mainly *p*-hydroxybenzyl(α-hydroxy)phosphonic acid (**3d**) has been identified by means of mass spectroscopy, and also isolated from the reaction mixture.

The *m*-hydroxybenzyl(α-N-butylamino)phosphonic acid (**5a**) heated 10 hours in aq. NaOH solution has not been affected by the base. After final neutralization with aq. HCl, the acid **5a** was recovered unchanged, in almost 90% yield.

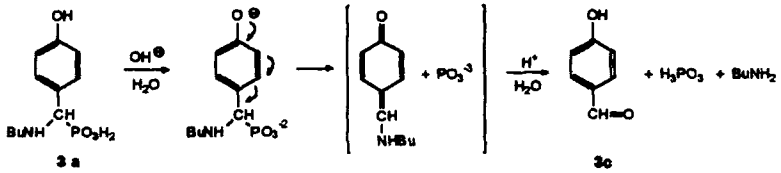
Similarly, *p*-methoxybenzyl(α-N-butylamino)phosphonic acid (**4a**) was stable during 10 hrs heating in aq. NaOH solution (scheme 4).

On the basis of obtained results, we propose a mechanism of the cleavage of *p*-hydroxybenzyl(α-amino)-phosphonates, asd shown on the following scheme:



4a

SCHEME 4

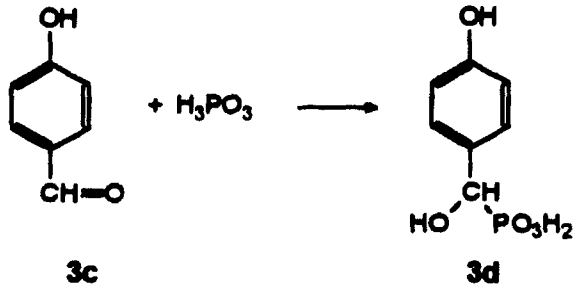


3a 3c

SCHEME 5

The mechanism of the cleavage of *o*-hydroxy derivatives seems to proceed in the same way. The by-product **2** in this case was probably formed by the intramolecular attack of the ionized hydroxy group on the phosphorus atom (scheme 2).

Formation of *p*-hydroxybenzyl(α-hydroxy)phosphonic acid (**3d**) in the case of the cleavage of the *p*-hydroxybenzyl derivative was probably caused by subsequent reaction of the formed phosphorous acid with aldehyde **3c**, during work-up of the reaction mixture (scheme 6). The authenticity of **3d** was comfirmed by an independent synthesis.



3c 3d

SCHEME 6

CONCLUSIONS

On the basis of the obtained results and previous investigations[1,2,3], it seems that the driving force leading to a cleavage of some aminobenzylphosphonates is an ability to ionization (or protonation) of certain substituents placed in *ortho* and *para* position. The ionized groups can transfer the charge to the phosphorus moiety, by means of the resonance effect, forming the conjugate bond system with the α-carbon ato in the molecule. It causes a departure of a charged phosphorus moiety. This phenomenon has also occurred for *o*- and *p*-nitrobenzyl derivatives[3,4] in a basic medium, and the similar case was observed for 2- and 4-pyridylmethyl derivatives, which were cleaved in acidic solution[2]. The *o*- and *p*-hydroxybenzyl derivatives, which are easily ionized by sodium hydroxide have also fulfilled these conditions. The proposed mechanism of the cleavage of hydroxybenzyl(amino)phosphonates is outlined in the scheme 5.

The *meta* derivative, which is also ionized in alkaline medium was not cleaved because the substituent in this position does not demonstrate a resonance effect in the molecule and therefore is not able to form a conjugate bond system with the α-carbon atom. Displacement of the hydroxy group by the methoxy one in the *para* position (compound **4a**) leads also to a stability of such a compound toward a basic medium. It is explained by the fact, that the methoxy group is not ionizable by aq. sodium hydroxide.

EXPERIMENTAL

NMR spectra were recorded on a Bruker Avance TM DRX 300 MHz spectrometer for ^{1}H and ^{31}P spectra. ESI±Q1MS spectra (electrospray ionization mode) were done on a Finnigan apparatus and were used for identification of the cleavage products.

Synthesis of starting materials

The diethyl hydroxybenzyl(α-N-butylamino)phosphonates were obtained from the corresponding aldehyde, butylamine and diethyl phosphite, following a procedure described earlier[2,3]. The products were purified as oxalate salts.

Diethyl 2-hydroxybenzyl(α-N-butylamino)phosphonate (1) Oxalate

Yield: 60%. M.p. 132–137°C. ^{1}H NMR (D_2O) 7.42(m, 2H, arom.), 7.05(m, 2H, arom.), 4.90(d, 1H, CH-P, J=18.2 Hz), 4.15(m, 4H, OCH_2), 3.03(m, 3H, CH_2N), 1.60(m, 2H), 1.30(m, 8H), 0.87(t, 3H, CH_3). ^{31}P NMR: 18.20(s).

Diethyl 4-hydroxybenzyl(α-N-butylamino)phosphonate (3) Oxalate

Yield: 89%. M.p. 138–142°C. ^{1}H NMR (D_2O): 7.47(d, 2H, arom.0, 7.05(d, 2H, arom.), 4.83(d, 1H, CH-P, J= 17.7 Hz), 4.16(m, 4H, OCH_2), 3.02(t, 2H, CH_2N), 1.67(m, 2H), 1.32(m, 8H), 0.87(t, 3H, CH_3). ^{31}P NMR: 17.92(s).

Diethyl 4-methoxybenzyl(α-N-butylamino)phosphonate (4) Oxalate

Yield: 73%. M.p. 118–119°C. ^{1}H NMR (D_2O): 7.52(d, 2H, arom), 7.10(d, 2H, arom), 4.84(d, 1H, CH-P, J=17.9 Hz), 4.1(m, 4H, OCH_2), 3.85(s, 3H, OCH_3), 3.0(t, 2H), 1.67(m, 2H), 1.35(m, 8H), .0.84(t, 3H). ^{31}P NMR: 17.443(s).

Diethyl 3-hydroxybenzyl(α-N-butylamino)phosphonate (5) Oxalate

Yield: 53%. M.p. 127–129°C. ^{1}H NMR (D_2O): 7.32(m, 1H, arom.), 6.98(m, 3H, arom.), 4.78(d, 1H, CH-P, J= 12.8 Hz), 4.10(m, 4H, OCH_2), 2.95(m, 2H, CH_2N), 1.55(m, 2H, CH_2), 1.17(m, 8H, CH_2, CH_3), 0.80(t, 3H, CH_3). ^{31}P NMR: 17.987(s).

The hydroxybenzyl(α–N-butylamino)phosphonic acids were obtained by hydrolysis of the corresponding esters by means of 20% aq. HCl, according to the procedure[2,3], and recrystallized from water or aqueous ethanol.

2-Hydroxybenzyl(α-N-butylamino)phosphonic acid (1a)

Yield: 65%. M.p. 283–287°C (dec.). ^{1}H NMR (D_2O+D_2SO_4): 7.41(m, 2H, arom.), 7.04(m, 2H, arom.), 4.85(d, 1H, CH-P, J= 17.7 Hz), 3.03(t, 2H, CH_2N), 1.66(m, 2H), 1.31(m, 2H), 0.86(t, 3H, CH_3). ^{31}P NMR: 12.97 (s).

4-Hydroxybenzyl(α-N-butylamino)phosphonic acid (3a)

Yield: 84%. M.p. 180–185°C. ^{1}H NMR (D_2O+D_2SO_4): 7.32(d, 2H, arom.), 6.88(d, 2H, arom.), 4.22(d, 1H, CH-P, J=16.0 Hz), 2.85(m, 2H, CH_2N), 1.56(m, 2H), 1.25(m, 2H),.78(t, 3H, CH_3). ^{31}P NMR: 10.916 (s).

4-Methoxybenzyl(α-N-butylamino)phosphonic acid (4a)

Yield: 66%. M.p. 221–222 °C. ^{1}H NMR (D_2O+D_2SO_4): 7.65(d, 2H, arom.), 7.24(d, 2H, arom.), 4.74(d, 1H, CH-P, J= 17.1 Hz), 4.00(s, 3H, OCH_3), 3.12(m, 2H, CH_2N), 1.78(m, 2H), 1.42(m, 2H), 0.98(t, 3H, CH_3). ^{31}P NMR: 13.887 (s).

3-Hydroxybenzyl(α-N-butylamino)phosphonic acid (5a)

Yield: 62%. M.p. 240–244°C (dec.). ^{1}H NMR (D_2O+D_2SO_4): 7.40(m, 1H, arom.), 7.05(m, 3H, arom.), 4.62(d, 1H, CH-P, J= 17.4 Hz), 3.0(m, 2H, CH_2N), 1.65(m, 2H), 1.26(m, 2H), 0.80(t, 3H, CH_3). ^{31}P NMR: 8.759(s).

Cleavage of hydroxybenzyl(α-N-butylamino)phosphonates: 1, 3

A sample of aminophosphonate (5 mmol) and sodium hydroxide (2.0g, 50 mmol) were dissolved in 50 mL water and the solution was refluxed for 10 hrs, then neutralized with aq. HCl to pH≈2. The formed products (aldehydes **1c** and **3c**) were extracted with methylene chloride, the extract was dried and evaporated to give the aldehyde **1c** or **3c**. Authenticity of the formed aldehydes was confirmed by NMR data and comparison with an authentic sample. The remained aqueous layer was evaporated to dryness and the residue was treated with 50 mL absolute ethanol. The undissolved material (sodium chloride) was discarded and the ethanolic solution was evaporated to dryness to give a mixture of butylamine hydrochloride and H_3PO_3. The residue was analysed by means of ^{1}H, ^{31}P NMR and ESI±Q1MS spectroscopy methods.

The cleavage of acids **1a** and **3a** and isolation of the products were performed on the similar way.

Isolation of the by-product 2

A sample of acid **1a** (1.3g, 5 mmol) was dissolved in 50 mL water, containing 2.0g (50 mmol) of sodium hydroxide. The solution was refluxed for 5 hrs, cooled and neutralized with aq. HCl to pH ≈ 2. The mixture was evaporated to dryness and extracted with absolute ethanol (50 mL). The ethanolic extract was evaporated to give a crude product **2** (0.48g). The crude product **2** was analysed by means of NMR and mass spectroscopy (ESI+Q1MS). Attempts of purification of the product **2** have failed, because of the hygroscopic nature of **2.** During long storage the **2** has been

transformed gradually into the starting material **1a**, and other undefined products.

^{31}P NMR(D_2O) Two main singlets of ^{31}P were observed in the spectrum: 21.656 ppm, related to the cyclic phosphonate derivative **2**, and 11.516 ppm corresponded to the regenerated starting material **1a**.

ESI-Q1MS: 517.5 (dimer of **1a**, 2xM-1), 481.3 (dimer of **2**, 2×M-1), 258.3 (**1a**, M-1), 240.3 (**2**, M-1).

Isolation of the acid 3d

A sample of acid **3a** (1.3g, 5 mmol) was cleaved by aq. NaOH, by the same way as described above, for the cleavage of **1a**. After neutralization with aq. HCl, the mixture was evaporated to a small volume (~ 10 mL) and allowed to stand for several hours. The separated crystals of **3a** were collected by filtration and dried. The obtained product was extremely little soluble in water and organic solvents.

Yield: 10÷20%. M.p.:The product does not melt up, but it carbonize above 300°C. ESI-Q1MS: 202.2 (M-2), 225.1 (M-1+Na). ESI+Q1MS: 204.9 (M+1). ^1H NMR (D_2O): 7.37(bs, 2H, arom), 6.93(bs, 2H, arom), 4.40(d, 1H, CH-P, J= 13.2 Hz). ^{31}P NMR: 11.968(s).

The synthesis of p-hydroxybenzyl(α-hydroxy)phosphonic acid (3d)

A mixture of *p*-hydroxybenzaldehyde (2.4g, 20 mmol), and phosphorous acid (1.7g, 20 mmol) in 50 mL aq. 20% HCl was refluxed for 6 hrs and allowed to stand for 24 hrs at room temp. The precipitated reddish material was collected by filtration, washed with water and acetone and dried.

Yield : 0.65g. The data for the obtained product were in agreement with the data of the product obtained by the cleavage of **3a**.

Acknowledgements

This work received financial support from Wroclaw University of Technology

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