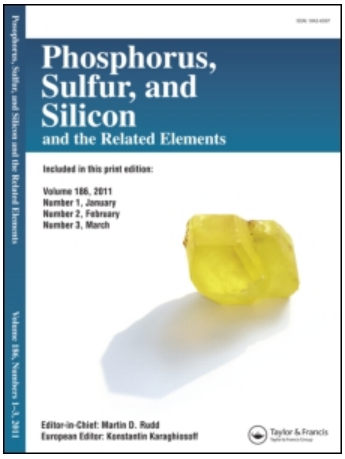

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SYNTHESIS AND CLEAVAGE OF PYRIDONE-4 AMINOPHOSPHONIC ACIDS

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*Some new pyridone aminophosphonic acids were synthesized from pyridone aldimines and tris(trimethylsilyl)phosphite. It was found that the obtained aminophosphonic acids **2** were cleaved in mineral acid solutions to form the corresponding amines **3** and phosphoric acid. Preliminary kinetic measurements were performed.*

Keywords: 1-(*N*-benzyl)-2-formyl-5-benzyloxy-pyridone-4; bromotrimethylsilane; cleavage reaction; pyridone derivatives of aminomethylphosphonic acid

Working on the chemistry of heterocyclic aminophosphonate derivatives, we found that certain pyridine,[1,2] chromone,[3] and coumarin[3] derivatives of aminomethylphosphonic acid undergo a cleavage in strong mineral acid solutions to form heterocyclic secondary amines and phosphoric acid.[1–3] In order to define the scope of these cleavages, we looked at other aminophosphonate heterocyclic systems that could demonstrate a similar behavior in acidic conditions. In our search for such compounds, our attention was drawn to pyridone-4 aminophosphonate derivatives, which should yield a similar cleavage. In order to verify such an hypothesis, we have synthesized some new pyridone-4 aminophosphonic derivatives, namely the [1-(*N*-benzyl)-5-benzyloxy-pyridone-4-yl-2]-methyl(amino)phosphonic acids (**2a–c**), and we carried out suitable reactions in acidic solutions.

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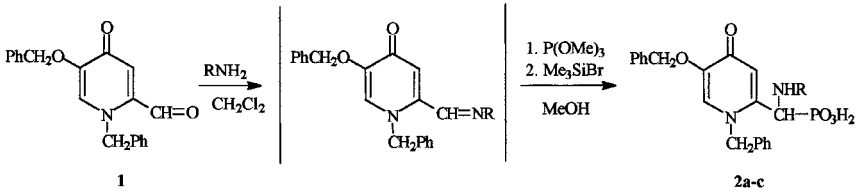
RESULTS AND DISCUSSION

Synthesis of pyridone aminophosphonic acids was limited by access to the appropriate aldehydes, which were considered as key starting materials in the synthesis of such compounds. The pyridone-4 aminophosphonic acids **2a–c** were obtained in a typical way,[4] in the following sequence of reactions (Scheme 1): A key aldehyde **1** the 1-(*N*-benzyl)-2-formyl-5-benzyloxy-pyridone-4[5] was reacted with primary amines to obtain the corresponding imines. The imines then were treated with a mixture of trimethyl phosphite and bromotrimethylsilane, what caused in situ formation of tris(trimethylsilyl)phosphite,[4] which instantly reacted with the imines, giving silylated phosphonate intermediates. Treatment of the intermediates with methanol, caused a removal of the silylated groups and the formation of the final aminophosphonic acids **2a–c** (Scheme 1).

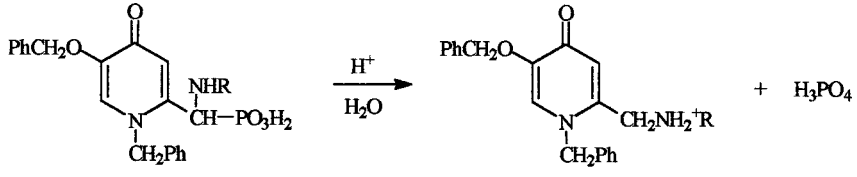


1 **2a-c**

a: R = Ph_2CH, **b**: R = $PhCH_2$, **c**: R = Bu

SCHEME 1

The obtained compounds were tested for prospective cleavage of a C—P bond in acidic conditions. Indeed, pyridone-4 aminophosphonic acids **2a–c** undergo such a cleavage during heating with mineral acid solutions (H_2SO_4, HCl), as it was observed in the case of 2- and 4-pyridylmethyl phosphonate derivatives, reported earlier.[1,2] Likewise, as in the previous case, products of the cleavage were amines, in this case the pyridone-4 benzylamines **3** and phosphoric acid (Scheme 2). The *N*-benzhydryl derivative **2a**, besides the cleavage, underwent



2a-c **3a'-c**

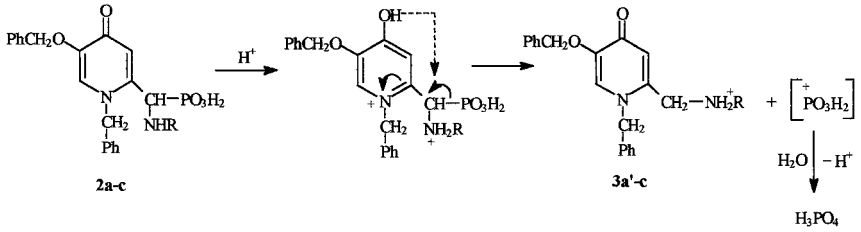
a: R = Ph_2CH, **a'**: R = H, **b**: R = $PhCH_2$, **c**: R = Bu

SCHEME 2

furthermore the reaction of removal of the benzhydryl group in these acidic conditions, giving the pyridone amine **3a′**, with an unsubstituted amino group (Scheme 2).

The formed heterocyclic amines (**3a′–c**) were isolated from the reaction mixture by alkalization and extraction, then characterized by spectroscopy methods.

The mechanism of the cleavage of **2a–c** seems to be similar, as that one which was proposed for the cleavage of related pyridyl aminophosphonic acids.[2] Likewise, as in the previous cases,[2,3] a driving force causing the cleavage is an electrophilic attack of the hydronium ion (H_3O^+) on the protonated aminophosphonate **2** (Scheme 3), and in consequence, the leaving of a phosphonate group as a protonated metaphosphate ($^+PO_3H_2$). The formed metaphosphate is a very reactive species and reacts immediately with water to produce H_3PO_4 and to regenerate a proton (Scheme 3).



SCHEME 3

Additional evidence for the proposed mechanism came from some kinetic data obtained from these cleavages. Kinetic data are given in Table I.

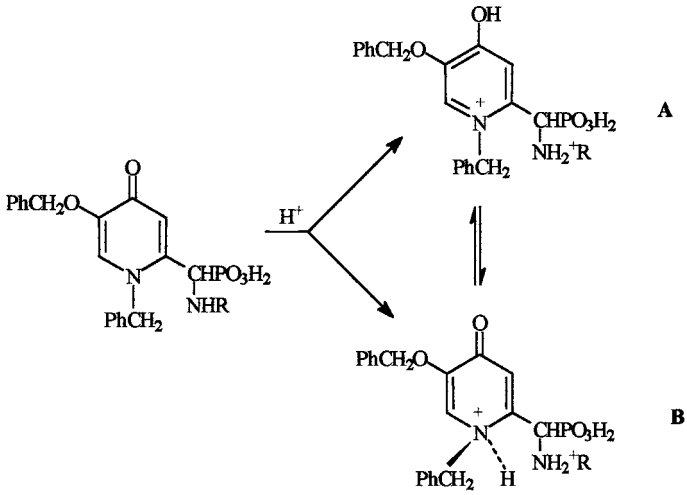
TABLE I Kinetics for Acid-Catalyzed Cleavage of **2b,c** in aq. H_2SO_4/D_2SO_4 at 95 ± 0.5°C

Compound	Conc. of Compd. mol · L^{-1}	Acid	Conc. of Acid mol · L^{-1}	$10^5 \cdot k_{obs}$ [a] s^{-1}	k_H/k_D
2b	0.037	H_2SO_4	0.5	1.44 ± 0.07	
	0.038	H_2SO_4	1.0	2.50 ± 0.12	
	0.038	H_2SO_4	2.0	2.87 ± 0.15	
	0.038	D_2SO_4	1.0	2.06 ± 0.10	1.21
2c	0.015	H_2SO_4	0.5	1.53 ± 0.08	
	0.015	H_2SO_4	1.0	2.62 ± 0.13	
	0.015	H_2SO_4	2.0	2.20 ± 0.11	
	0.022	D_2SO_4	1.0	1.88 ± 0.09	1.39

[a]Rates reproducible to ±5%.

Kinetics were measured only for acids **2b,c**, because the *N*-benzhydryl derivative (**2a**) decomposed in the applied conditions, which might give up inaccurate kinetic results for **2a**. Because the cleavages can be monitored easily by means of ^{31}P NMR, we calculated pseudo-first-order constants (k_{obs}), on the basis of the concentrations of unreacted aminophosphonic acids and formed phosphoric acid. A dependence of the k_{obs} on the concentration of the H^+ was found. Results (see Table I) show that k_{obs} depends on the $[H^+]$. Hence, the cleavage is an acid-catalyzed reaction and the protons play a crucial role in the cleavage. For D_2SO_4 solutions rates were slower markedly in comparison with H_2SO_4 solutions, at the same concentrations. Observed kinetic isotope effects (for **2b**; $k_H/k_D = 1.21$, and for **2c**; $k_H/k_D = 1.39$) were rather small, but existence of the $k_H/k_D > 1$, indicated that protons were involved in the rate-determining step.[2]

The ^{31}P NMR spectra of the phosphonic acids **2a–c** in aqueous solutions of sulphuric acid showed two phosphorus signals for each individual compound. NMR spectra of **2a–c** in DMSO showed only one signal for phosphorus. Occurrence of two close signals, after adding of sulphuric acid to the sample, gives evidence that there are two protonated species formed from the pyridone aminophosphonic acids **2a–c** under influence of a strong mineral acid. As seen from the pyridone structure (Scheme 4), there are two possible sites able for protonation in the pyridone ring.



SCHEME 4

Protonation of oxygen in the pyridone ring gives form **A**, but protonation of the heterocyclic nitrogen may give form **B** (Scheme 4).

Pyridones are weak bases and protonation of heterocyclic nitrogen (or oxygen) occurs in the presence of strong acids.[7] In this case (the formula **2a–c**), there are two nitrogen atoms able to be protonated. Amino groups are considerably stronger bases than heterocyclic nitrogen (or oxygen) atoms and therefore they are protonated, first, to make additionally difficult the further protonation of the molecule. However, the entire protonation of the **2a–c** might be achieved in the presence of very strong acids. Such an appearance of two forms **A** and **B** is very characteristic for sulphuric acid solutions of the **2a–c**. The forms **A** are situated at higher fields and have lower values of ^{31}P NMR shifts (the difference is about 0.25 ppm). It seems that the forms **A** are responsible for the cleavage of aminophosphonic acids **2a–c**.[3] ^{31}P NMR spectra of the **2a–c** showed that a ^{31}P signal attributed to **A** disappeared quickly when the sample was heated, leaving an unchanged **B** signal. However, further heating of the sample causes gradual disappearance of a signal attributed to **B**, and an enlarged a signal for a product (H_3PO_4). One can say that cleavage of the **2a–c** is the result of the tautomeric change of **B** to **A**, the form that is responsible for cleavage of the molecule. Obtained kinetic data (see Table I) reflects tautomeric equilibrium between these forms at cleavage conditions.

EXPERIMENTAL SECTION

NMR spectra were recorded on a Bruker Avance TM DRX 300 MHz in DMSO-d_6, D_2O and in $CDCl_3$, using 300.13 MHz for ^{1}H NMR, and 121.51 MHz for ^{31}P NMR spectra. Melting points were measured on a Digital Melting Point Apparatus Electrothermal 9200. Elemental analyses were done in the Laboratory of Instrumental Analysis in the Institute.

1-(*N*-Benzyl)-2-formyl-5-benzyloxy-pyridone-4 (**1**) was obtained by oxidation of the 1-(*N*-Benzyl)-2-hydroxymethyl-5-benzyloxy-pyridone-4 with SeO_2, according to a typical procedure described in.[5] White powder, m.p. 73–75°C; ^{1}H NMR($CDCl_3$): 9.54 (s, 1H, C**H**=O), 7.33–6.90 (m, 10H, 2x Ph), 7.09 (s, 1H, 6-py), 6.99 (s, 1H, 3-py), 5.42 (s, 2H, PhC$\mathbf{H}_2$O), 5.21 (s, 2H, PhC$\mathbf{H}_2$-N).

Procedure for Preparation of the Pyridone Aminophosphonic Acids 2a–c

The procedure for the preparation of aminophosphonic acids was followed:[4,6] 1-(*N*-Benzyl)-2-formyl-5-benzyloxy-pyridone-4 (**1**) (0.64 g, 2.0 mmol) was dissolved in methylene chloride (25 mL) and the

appropriate amine was added (2.1 mmol). The mixture was left for 3 days, then anh. sodium sulfate was added, filtered, and to the filtrate, trimethyl phosphite was added (0.3 g, 2.4 mmol), followed by bromotrimethylsilane (1.5 g, 9.8 mmol). The mixture was left for 24 h and evaporated to dryness. A residue remained, which was dissolved in methanol (5 mL) and refrigerated. Next day the solvent was evaporated and the residue was treated with acetone (10 mL), followed by diethyl ether (10 mL) and refrigerated. The separated product was collected by filtration and crystallized from acetone to give the pyridone aminophosphonic acids **2a–c**, as white, amorphous solids.

[1-(*N*-Benzyl)-5-benzyloxy-pyridone-4-yl-2]-methyl(*N*-benzhydrylamino)phosphonic acid (**2a**): Yield 63%, m.p. 162–164°C, ^{1}H NMR(DMSO), δ, ppm: 8.69 (s, 1H, py-6), 7.74 (s, 1H, py-3), 7.45–6.80 (m., 20H, Ph's), 5.74 and 5.47 (dd, 2H, PhC**H**$_2$O, J = 16.2 Hz), 5.25 (s, 2H, PhC**H**$_2$N), 4.50 (s, 1H, C**H**Ph$_2$), 4.20 (d, 1H, C**H**-P, J = 20.4 Hz). ^{31}P NMR, δ, ppm: 14.32(s). Elemental Anal. for **2a**: Calc. N 4.94, P 5.47; Found: N 4.78, P 5.52.

[1-(*N*-Benzyl)-5-benzyloxy-pyridone-4-yl-2]-methyl(*N*-benzylamino)-phosphonic acid (**2b)**: Yield 48%, m.p. 171–173°C, ^{1}H NMR(DMSO), δ, ppm: 8.39 (s, 1H, py-6), 7.75 (s, 1H, py-3), 7.37–7.00 (m., 15H, Ph's), 5.54 (dd, 2H, PhC**H**$_2$O), 5.12 (s, 2H, PhC**H**$_2$N), 4.22 (s, 1H, C**H**-P, J = 17.5 Hz), 3.71 and 3.46 (dd, 2H, PhC**H**$_2$NH, J = 13.2 Hz). ^{31}P NMR, δ, ppm: 8.57(s). Elemental Anal. for **2b**: Calc. N 5.71, P 6.32; Found: N 5.61, P 6.38.

[1-(*N*-Benzyl)-5-benzyloxy-pyridone-4-yl-2]-methyl(*N*-butylamino)-phosphonic acid (**2c**): Yield 84%, m.p. 204–205°C, ^{1}H NMR(DMSO), δ, ppm: 8.73 (s, 1H, py-6), 7.97 (s, 1H, py-3), 7.4–7.2 (m., 10H, Ph's), 5.71 (dd, 2H, PhC**H**$_2$O), 5.18 (dd, 2H, PhC**H**$_2$N), 4.46 (d, 1H, C**H**-P, J = 15.1 Hz), 2.71 (m., 2H, NHC**H**$_2$), 1.37–1.12 (m., 4H, CH_2CH_2), 0.73 (t, 3H, CH_3, J = 7.1 Hz). ^{31}P NMR, δ, ppm: 3.86(s). Elemental Anal. for **2c**: Calc. N 6.14, P 6.79; Found: N 6.05, P 6.82.

Cleavage of the 2a–c and Isolation of the Amines 3a′–c

A sample of aminophosphonic acid (**2a–c**) (0.5 mmol) was mixed with 20% aq. HCl (10 mL) and the mixture was refluxed for 12 h. Then solution was evaporated to dryness and the residue was made alkaline by treatment with an excess of 5% aq. sodium bicarbonate solution. The oily product that separated was extracted three times with chloroform (3×25 mL); the extract was dried (anh. Na_2SO_4), filtered, and evaporated to give the amines **3a′–c**, as orange-yellow solids. Amine **3a′**: yield: 52%, m.p. 88–92°C, ^{1}H NMR($CDCl_3$): 7.30–6.95 (m, 12H, arom.), 5.14 (bs, 2H, O**CH**$_2$),3.79 (bs, 2H, **CH**$_2$N), 2.60 (bs, 2H),

Amine **3b**: yield: 63%, ^{1}H NMR($CDCl_3$): 7.45–7.08 (m, 17H, arom.), 5.25 (bs, 2H), 3.79 (bs, 2H), 3.57 (bs, 2H), 3.49 (bs, 2H), m.p. of oxalate of **3b**: 220–223°C (dec.).

Amine **3c**: yield: 55%, m.p. 117–118°C, ^{1}H NMR($CDCl_3$): 7.28–6.98 (m, 10H, arom.), 6.39 (s, 1H, py-3), 5.27 (bs, 2H, OC**H**$_2$), 3.91 (bs, 2H, C**H**$_2$N), 3.51 (bs, 2H, C**H**$_2$NH), 2.51 (m, 2H, NC**H**$_2$), 1.35–1.18 (m, 4H, CH_2CH_2), 0.81 (t, 3H, CH_3).

Procedure for Kinetic Runs

Stock aqueous solutions of sulphuric acid (with the conc. of H_2SO_4): c = 0.5, 1.0, and 2.0 mol · L^{-1} and a solution of deuterated sulphuric acid in D_2O with conc. of D_2SO_4 c = 1.0 mol · L^{-1} were prepared. Samples of aminophosphonic acid **2b,c** (10 ± 0.1 mg) and sulphuric acid solution (0.5 mL) were mixed together in NMR tubes and thermostated at 95°C for a specified period of time (3, 6, 9, and 12 h). The NMR tubes were then cooled and ^{31}P NMR spectra were recorded. The pseudo-first-order rate constants (k_{obs}) were determined from ^{31}P NMR spectra by plotting dependence of *log(a-x)* on time (where the "*a-x*" represents an actual concentration of non-reacted aminophosphonic acid). Kinetic runs were repeated three times. In most cases, a dependence of *log(a-x)* on time was obeyed very well.

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