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The Acidic Cleavage of Pyridylmethyl(amino)phosphonates. Formation of the Corresponding Amines.

Bogdan Boduszek

Institute of Organic Chemistry, Biochemistry and Biotechnology,
Technical University, 50-370 Wrocław, Poland

Abstract: Hydrolysis of 3-pyridylmethyl(amino)phosphonates by means of 20% aq. hydrochloric acid gave corresponding 3-pyridylmethyl(amino)phosphonic acids, as expected. However, hydrolysis of 2- and 4-pyridylmethyl(amino)phosphonates led to decomposition of the phosphonates with a cleavage of C-P bond and formation of the corresponding amines.The leaving phosphorus moiety was identified as phosphoric acid. The scope of the reaction is limited to 2- and 4-pyridylmethyl derivatives of aminophosphonic acids and their esters, as well as to the derivatives possessing similar structure. In the contrary, the basic hydrolysis of 2- and 4-pyridylmethyl(amino)phosphonates led to the corresponding monoalkyl esters of the aminophosphonates, and no a cleavage of C-P bond was observed in those cases.

INTRODUCTION

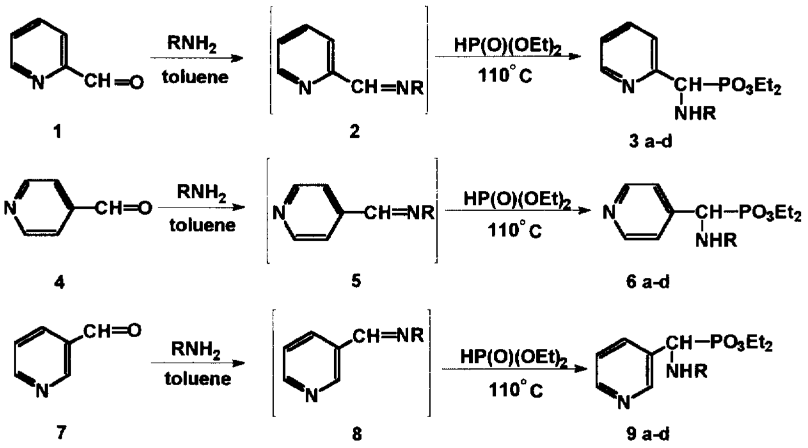
Aminophosphonates and aminophosphonic acids as analogues of natural amino acids have received their great interest due to their useful biological activity. Today, this class of compounds is a subject of several thousand papers. Aminophosphonates bearing heterocyclic moiety are surprisingly little known. At present, synthesis and study of heterocyclic aminophosphonates become a subject of a growing interest[1,5,6]. Recently, we have published a work concerning the synthesis of aminophosphonates derived from furan and thiophene[2], and also aminophosphonates being derivatives of imidazole and pyridine[3]. During synthetic work on pyridine derivatives of aminophosphonic acids we found an unexpected behaviour of pyridine aminophosphonates in acidic conditions. Usually, hydrolysis of aminophosphonates by means of aqueous hydrochloric acid leads to corresponding aminophosphonic acids.

Indeed, hydrolysis of 3-pyridylmethyl(amino)phosphonates by aq. HCl gave the corresponding 3-pyridylmethyl(amino)phosphonic acids, as expected. However, the analogous hydrolysis of 2- and 4-pyridylmethyl(amino)phosphonates led to quite unexpected products. During hydrolysis we observed a cleavage of C-P bond in phosphonates and a rearrangement of the phosphonates to corresponding amines, with rejection of phosphorus moiety[3]. This unusual reaction in the case of 2- and 4-pyridylmethyl(amino)phosphonates become a subject of our interest and detailed investigations. In order to determine the scope of this cleavage, we have synthesized some 2-, 3-, and 4-pyridylmethyl(amino)phosphonates, and also corresponding 4-quinolyl phosphonate, and studied their behavior during hydrolysis, in acidic conditions.

RESULTS AND DISCUSSION

Synthesis of Aminophosphonates.

The best method for synthesis of various pyridine aminophosphonates is a thermal addition of diethyl phosphonates to pyridine aldimines. Pyridine aldehydes 1, 4, and 7 react easily with aliphatic or aromatic amines in toluene solution to form corresponding aldimines (Schiff bases). The obtained imines were caused to react *in situ* with diethyl phosphonate to give aminophosphonate diethyl esters 3, 6 and 9.



	R
a	Bu
b	Ph
c	$CHPh_2$
d	CH_2Ph

Scheme 1

The obtained phosphonate esters were low melting solids (N-phenyl and N-benzhydryl derivatives), or thick oils (N-butyl and N-benzyl derivatives). The oily esters were purified by conversion into oxalate salts, which were obtained according to a procedure described previously[2,3]. The physical data of the obtained esters are given in Table 1.

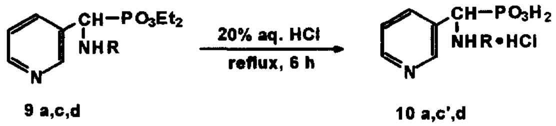
Table 1. Pyridyl Aminophosphonates **3**, **6**, **9**, **15** and Quinolyl Phosphonate **13**.

Compd. no.	Yield %	mp. °C	^{1}H-NMR [$CDCl_3$], δ, ppm	^{31}P-NMR δ, ppm
3a	96 47^{a}	oil 114-115^{b}	8.52(d, 1H, py-6, J= 4.3 Hz), 7.78(t, 1H, py-4, J=7.6Hz), 7.46(d, 1H, py-3, J=7.8 Hz), 7.30(t, 1H, py-5, J=6.2Hz), 4.54(d, 1H, CH-P, J=20.4 Hz), 4.03-3.74(m, 4H, 2x CH_2O), 2.53(m, 2H, CH_2N), 1.40(m, 2H, 2x CH_2), 1.15(m, 5H, CH_2, CH_3), 1.00(t, 3H, CH_3, J=7.3 Hz), 0.73(t, 3H, CH_3, J=7.1 Hz)..	20.92 (s)
3b	65	99-101 lit.^{9} 106	8.63(d, 1,H, py-6, J=4.6 Hz), 7.67(t, 1H, py-4, J=7.8 Hz), 7.53(d, 1H, py-3, J=7.8 Hz), 7.28-7.11(m, 3H, arom.),6.70(m, 3H, arom.), 5.04(d, 1H, CH-P, J=22.3 Hz), 4.17-4.04(m, 4H, 2x CH_2O), 1.28(t, 3H, CH_3, J=7.1Hz), 1.18(m, 3H, CH_3,).	22.43 (s)
3c	95	oil	8.69(d, 1H, py-6, J=4.6 Hz), 7.95(m, 1H, py-4), 7.71(m, 1H, py-3), 7.46-7.25(m, 11H, arom.), 4.71(s, 1H, $CHPh_2$), 4.27-3.96(m, 4H, 2x CH_2O), 4.20(d, 1H, CH-P, J=19.1 Hz), 1.37(t, 3H, CH_3, J=7.1 Hz),, 1.24(t, 3H, CH_3, J=7.1 Hz)..	23.50 (s)
3d	91 51^{a}	oil 101-103^{b}	8.56(d, 1H, py-6, J=4.6 Hz), 7.64(t, 1H, py-4, J=7.5 Hz), 7.42(m, 1H, py-3), 7.30-7.12(m, 6H, arom.), 4.15(d, 1H, CH-P, J=21.5 Hz), 4.10-3.86(m, 4H, CH_2O), 3.65(dd, 2H, NCH_2Ph, J=13.5 Hz), 1.20(t, 3H, CH_3), 1.11(t, 3H, CH_3).	23.23 (s)
6a	89 74^{a}	oil 127-129^{b}	8.51(d, 2H, py-2, py-6, J=4.6 Hz), 7.30(m, 2H, py-3, py-5), 4.05-3.90(m, 5H, CH-P, CH_2O), 2.40(m, 2H, CH_2N), 1.37-1.23(m, 4H, CH_2CH_2), 1.20(t, 3H, CH_3, J=7.3 Hz) 1.13(t, 3H, CH_3), 0.80(t, 3H, CH_3, J=7.1 Hz).	22.97(s)
6b	69	106-108	8.45(d, 2H, py-2, py-6, J=6.0 Hz), 7.33(m, 2H, py-3, py-5), 7.00(m, 2H, arom.), 6.62(m, 1H, arom.), 6.40(d, 2H, arom.), 4.63(d, 1H, CH-P, J=25.7 Hz), 4.05-3.76(m, 4H, 2x CH_2O), 1.19(t, 3H, CH_3, J=7.1 Hz), 1.06(t, 3H, CH_3, J=7.1 Hz).	21.92(s)
6c	58	101-103	8.62(d, 2H, py-2, py-6, J=5.8 Hz), 7.30(m, 12H, py-3, py-5, arom.), 4.67(s, 1H, $CHPh_2$), 4.24-3.87(m, 4H, 2x CH_2O), 4.00(d, 1H, CH-P, J=17.3 Hz), 1.36 (t, 3H, CH_3, J= 7.1 Hz), 1.17(t, 3H, CH_3, J= 7.1 Hz).	23.11(s)
6d	90 87^{a}	oil 145-147^{b}	8.62(d, 2H, py-2, py-6, 6.0 Hz), 7.30(m, 2H, py-3, py-5), 7.28(m, 5H, phenyl), 4.20-3.90(m, 4H, 2x CH_2O), 4.05(d, 1H, CH-P, J=21.2 Hz), 3.70(dd, 2H, $PhCH_2N$, J= 13.4 Hz),2.95(bs, 1H, NH), 1.28(t, 3H, CH_3), 1.20(t, 3H, CH_3).	22.80(s)
9a	95 90^{a}	oil 129-130^{b} lit.^{4}121-123^{b}	8.62(s, 1H, py-2), 8.52(m, 1H, py-6), 7.90(m, 1H, py-4), 7.43(dd, 1H, py-5, J= 4.8 Hz), 4.43(d, 1H, CH-P, J=20.1 Hz), 4.12-3.77(m, 4H, 2x CH_2O), 2.51(m, 2H, CH_2N), 1.43-1.24(m, 4H, CH_2CH_2), 1.22(t, 3H, CH_3, J= 7.1 Hz), 1.05(m, 3H, CH_3, J= 7.3 Hz), 0.82(t, 3H, CH_3, J= 7.3 Hz).	22.20(s)
9b	75	121-122	8.68(s, 1H, py-2), 8.49(m, 1H, py-6), 7.83(m, 1H, py-4), 7.25(m, 1H, py-5), 7.06(m, 2H, Ph), 6.70(t, 1H, Ph, J= 7.9 Hz), 6.55(d, 2H, Ph, J=7.9 Hz), 4.78(d, 1H,CH-P, J=24.0 Hz), 4.20-3.75(m, 4H, CH_2O), 1.27(t, 3H, CH_3, J=7.1 Hz), 1.13(t, 3H, CH_3, J= 7.1 Hz).	22.61(s)
9c	72	79-80	8.60(bs, 1H, py-2), 8.49bs, 1H, py-6), 7.82(m, 1H, py-4), 7.45(m, 1H, py-5), 7.38-7.22(m, 10H, Ph), 4.68(s, 1H, $CHPh_2$), 4.3-3.9(m, 4H, CH_2O), 3.98 (d,1H, CH-P, J=17.4Hz), 3.2(bs, 1H, NH), 1.37(t, 3H, CH_3,J= 7.1 Hz), 1.15(t, 3H, CH3, J= 7.1 Hz).	23.83(s)
9d	97 81^{a}	oil 181-184^{b}	8.50(m, 2H, py-2, py-6), 7.77(m, 1H, py-4), 7.28-7.15(m, 6H, py-5, phenyl) 4.06-3.86(m, 4H, 2x CH_2O), 3.99(d, 1H, CH-P, J=24.4 Hz), 3.65(dd, 2H, $PhCH_2N$, J = 12.4 Hz) , 2.52(bs, 1H, NH), 1.21(t, 3H, CH_3), 1.10(t, 3H,CH_3)	23.59(s)
13	96 86^{a}	oil 130-132^{b}	8.94(d, 1H, qu-2, J= 4.6 Hz), 8.17(t, 2H, qu-5, qu-8, J= 8.2 Hz), 7.72(m, 2H, qu-6, qu-7), 7.58(m, 1H, qu-3), 4.93(d, 1H, CH-P, J=21.2 Hz), 4.20-3.88(m, 4H, 2x CH_2O), 2.50(t,2H, CH_2N), 2.40(bs, 1H, NH), 1.45-1.25(m, 7H, CH_2CH_2, CH_3), 1.02(t,3H, CH_3, J= 7.1 Hz), 0.85(t, 3H, CH_3, J= 7.3 Hz).	23.17(s)
15	90 52^{a}	oil 111-113^{b}	8.52(d, 2H, py-2, py-6, J= 5.0 Hz), 7.41(m, 2H, py-3, py-5), 3.98(m, 4H, 2x CH_2O), 2.30(m, 2H, CH_2N), 1.69(d, 3H, CH_3-C-P, J=16.2 Hz), 1.41-1.27(m, 4H, CH_2CH_2), 1.22-1.13(m, 6H, 2xCH_3), 0.85(t, 3H, CH_3, J= 7.1 Hz).	26.16(s)

^{a}Yield of oxalate. ^{b}mp of oxalate

Acidic hydrolysis of phosphonates.

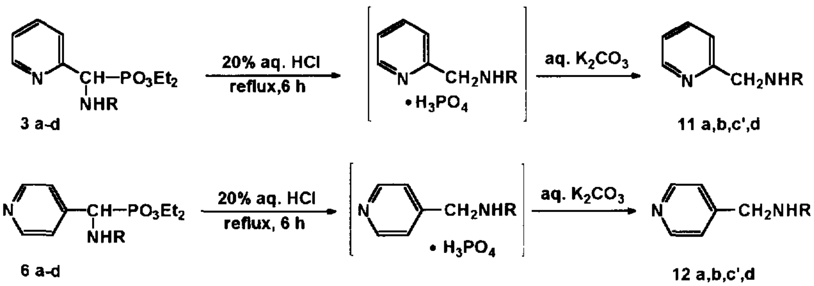
The esters **3**, **6** and **9** were hydrolyzed in standart conditions, by means of 20% aqueous hydrochloric acid. In the case of 3-pyridyl esters **9**, corresponding aminophosphonic acids **10** were isolated. Hydrolysis of benzhydryl derivative **9c** led to aminophosphonic acid **10c'**, with unsubstituted amino group, since the benzhydryl group was simultaneously removed during hydrolysis. (Scheme 2).



	R
a	Bu
c	$CHPh_2$
c'	H
d	CH_2Ph

Scheme 2

Hydrolysis of 2- and 4-pyridyl esters (**3** and **6**) by means of 20% aq. HCl proceeded by a different way. After removing of an excess of acid and water from reaction mixture a residue was obtained, which resulted to be a salt of amine **11** or **12** (phosphate salt, mixed with some hydrochloride of amine). Free amine was obtained, when the residue was neutralized with a base (aq. potassium carbonate), and the amine extracted with chloroform. The reactions are described on Scheme 3:



	R
a	Bu
b	Ph
c	$CHPh_2$
c'	H
d	CH_2Ph

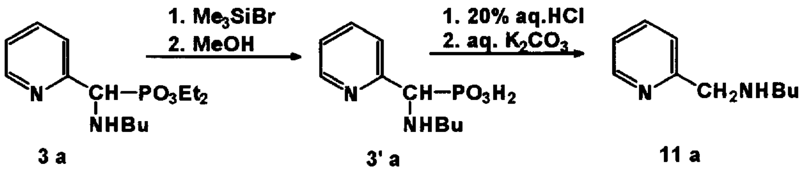
Scheme 3

As a result of hydrolysis of esters **3** and **6** a cleavage of C-P bond occurred, and the heterocyclic part of molecule rearranged to corresponding amines with expulsion of phosphorus moiety. The yield of the formed amines was good, and it usually considerably exceeded 50%. Amines have been idendified on the basis of their MS, NMR spectra, microanalysis and comparison with literature data. The physical data of the obtained amines are summarized in Table 2. The yield of amines obtained from 2-pyridyl phosphonates was higher than in the case of 4-pyridyl derivatives, what could indicate that 2-pyridyl esters are more susceptible for conversion than 4-pyridyl ones.

Some pyridyl N-alkylaminophosphonates were obtained by us previously[4]. We had also noticed a cleavage of obtained 2-pyridylmethyl(amino)phosphonates during acidic hydrolysis. Unfortunatelly, the structures of isolated products of hydrolysis were established incorrectly, as hemiaminals salts[4], not salts of amines.

Formation of phosphoric acid during hydrolysis of aminophosphonates **3** and **6** was demonstrated on the basis of ^{31}P-NMR studies. For this purpose, samples of hydrolyzed aminophosphonates (after removing of excess of water and HCl) were dissolved in D_2O and ^{31}P-NMR spectra were recorded. Analysis of the obtained spectra showed an existence of characteristical singlet for phosphoric acid with the value varying from 1.125 to 0.897 ppm, depending on a sample used (for comparison: pure phosphoric acid in D_2O exhibited the singlet at 0.984 ppm in those conditions). Also, the ^{1}H-NMR spectra of hydrolyzed aminophosphonates showed disappearance of characteristical dublet of CH-P group, and instead of this, a new singlet, originated from formed CH_2 group was observed. It was found additionally, that solution of aminophosphonate in aqueous 20% HCl can be kept for more than 24 hours at room temperature without any decomposition. But warming-up the sample to 90-95°C and keeping for 4 hours induced a cleavage and formation of amine and phosphoric acid.

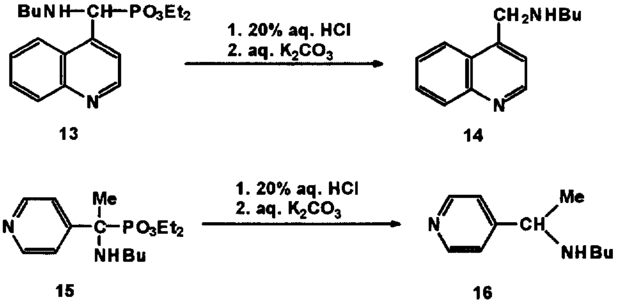
The C-P cleavage is not only characteristical for aminophosphonate esters. Also corresponding aminophosphonic acids undergo a similar cleavage. It was proved for 2-pyridylmethyl(N-butylamino)phosphonic acid (**3'a**), which was cleaved by refluxing with aq. 20% HCl for 4 hours. (The acid **3'a** was obtained by treatment of the corresponding ester **3a** with trimethylbromosilane and subsequent metanolysis, according to the procedure of silylation of phosphonates, described in[1].).



Scheme 4

The products of the hydrolysis of **3'a** were 2-(N-butylaminomethyl)pyridine (**11a**) and phosphoric acid, which was identified by ^{31}P-NMR spectrum. (Singlet for phosphoric acid at 0.897 ppm was found in the reaction mixture). The amine **11a** was isolated by usual way (neutralisation with potassium carbonate and extraction with chloroform), and identified by G.C. and NMR spectra.

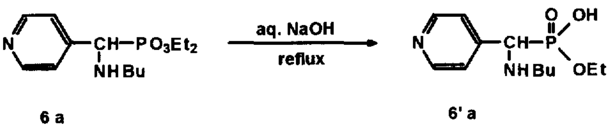
The cleavage of aminophosphonates is not only limited to 2- and 4-pyridylmethyl derivatives. It was found that 4-quinolylmethyl(N-butylamino)phosphonate diethyl ester (**13**) during hydrolysis yielded corresponding amine **14**. Similarly, the phosphonate **15** obtained from 4-acetylpyridine has been hydrolyzed to the amine **16**:



Scheme 5

The cleavage of 4-quinolyl phosphonate **13** is presumably caused by the same reason as in the case of 4-pyridyl derivatives. There is obvious structural resemblance in both of these compounds (i.e. 4-quinolyl and 4-pyridyl phosphonates).

The cleavage of 2- and 4-pyridyl aminophosphonates and formation of amines occurs exclusively during acidic hydrolysis only. Basic hydrolysis (by means of aq. sodium hydroxide) does not cause a cleavage of C-P bond in the phosphonates. It was proved by refluxing of the phosphonate **6a** with 3 equivalents of aq. NaOH, where the monoester **6'a** was only isolated:



Scheme 6

Free aminophosphonic acid **3'a** was also not affected during treatment with aqueous sodium hydroxide. Upon refluxing with aq. NaOH for 4 hours, followed by acidification, the acid was recovered unchanged. These experiments demonstrated unequivocally that a cleavage of 2- and 4-pyridyl aminophosphonates took a course only in acidic medium.

Table 2. Pyridyl And Quinolyl Amines Obtained From Aminophosphonates

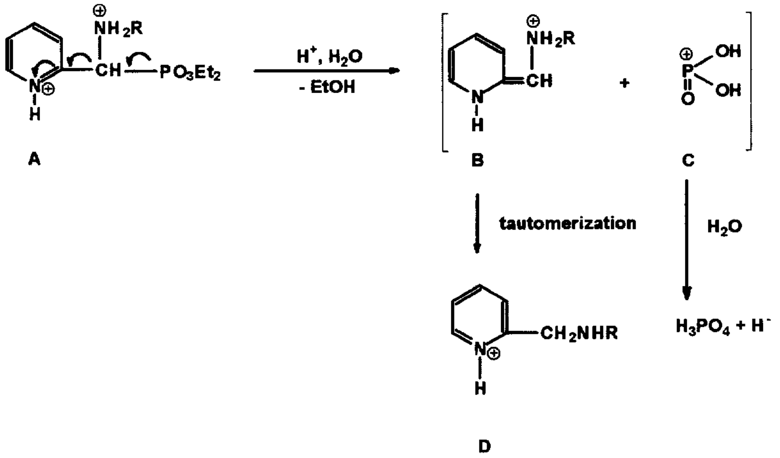
Compd. no.	Yield %	mp °C	^{1}H-NMR (CDCl$_3$), δ, ppm	G.C.-M.S. m/e, (%)
11a	85	oil[11] 199-200^b	8.52(d, 1H, py-6, J= 6.6 Hz), 7.60(m, 1H, py-4), 7.28(m, 1H, py-3), 7.13(m, 1H, py-3), 3.88(s, 2H, pyCH$_2$N), 2.63(t, 3H,CH$_2$N, J=7.1 Hz) 2.35(s, 1H, NH), 1.55-1.29(m, 4H, 2x CH$_2$), 0.88(t, 3H, CH$_3$,J=7.3 Hz).	163 (1.8) M-1 121 (22.8) 93 (100)
11b	72	47-49 lit.[11]48-49	8.61(d, 1H, py-6, J= 4.7 Hz), 7.65(m, 1H, py-4), 7.36(m, 1H, py-3), 7.20 (m,3H, py-5, Ph), 6.72(m, 3H, Ph), 4.63(bs, 1H, NH), 4.49 (s, 2H,pyCH$_2$N).	---
11c'	72	oil[13] 162-164^b lit.[12] 167^b	8.43(d, 1H, py-6, J= 4.7 Hz), 7.52(m, 1H, py-4), 7.16(m, 1H, py-3), 7.03(m, 1H, py-5), 3.86(s, 2H, pyCH$_2$N), 2.25(bs, 2H, NH$_2$).	108 (60.6), M 107 (45), M-1 80 (100).
11d	74	oil[11] 182-184^b	8.57(d, 1H, py-6, J= 4.7 Hz), 7.65(m, 1H, py-4), 7.40-7.16(m, 7H, py-3, py-5, Ph), 3.96(s, 2H, pyCH$_2$N), 3.88(s, 2H, CH$_2$Ph), 2.83(bs, 1H, NH).	197 (1.5) M-1 106 (45) 93 (100)
12a	56	oil 190-191^b	8.45(d, 2H, py-2, py-6, J= 6.0 Hz), 7.19(m, 2H, py-3, py-5), 3.73(s, 2H, pyCH$_2$N), 2.54(t, 2H, CH$_2$N, J= 7.0 Hz), 1.91(bs, 1H, NH), 1.45-1.24(m, 4H, 2xCH$_2$), 0.83(t, 3H, CH$_3$, J= 7.2 Hz).	164 (6.6) M 121 (100) 92 (40.4)
12b	55	98-99 108-112^b	8.57(d, 2H, py-2, py-6, J= 6.0 Hz), 7.31(m, 2H, py-3, py-5), 7.19(m, 2H, Ph), 6.77(m, 1H, Ph), 6.60(m, 2H, Ph), 4.40(s, 2H, pyCH$_2$N).	---
12c'	61	oil[13] 174-175^b	8.53(d, 2H, py-2, py-6, J= 7.0 Hz), 7.26(m, 2H, py-3, py-5), 3.90(s, 2H, pyCH$_2$N), 2.51(bs, 2H, NH$_2$).	108 (13.4) M 107 (17.9) 80 (100)
12d	38	oil 214-216^b	8.54(dd, 2H, py-2, py-6, J= 1.6 Hz), 7.38-7.26(m, 7H, py-3, py-5, Ph) 3.85(s, 2H, pyCH$_2$N), 3.82(s, 2H, NCH$_2$Ph), 2,24(bs, 1H, NH).	198 (13.4) M 197 (24.) M-1 121 (14.3)
14	84	oil 182-183^b	8.86(d, 1H, qu-2, J= 4.4 Hz), 8.08(dd, 2H, qu-5, qu-8, J= 8.3 Hz), 7.70(m, 1H, qu-7), 7.56(m, 1H, qu-6), 7.44(d, 1H, qu-3, J=4.4 Hz), 4.26(s, 2H, quCH$_2$N), 2.74(t, 2H, CH$_2$N, J= 7.1 Hz), 1.80(bs, 1H, NH), 1.55-1.37(m, 4H, 2xCH$_2$), 0.93(t, 3H, CH$_3$, J= 7.3 Hz).	---
16	34	oil 156-158^b	8.49(d, 2H, py-2, py-6, J= 6.1 Hz), 7.22(m, 2H, py-3, py-5) 3.69(q, 1H, py-CH-Me, J= 6.6 Hz), 2.41(m, 2H, CH$_2$N), 1.80(bs, 1H, NH), 1.43-1.23(m, 4H, 2xCH$_2$), 1.29(d, 3H, py-C-CH$_3$, J= 6.6 Hz), 0.83(t, 3H, CH$_3$, J= 7.3 Hz).	178 (3.0) M 163 (55.0) 135 (52.5) 106 (100).

^{b}mp of oxalate

Proposed Mechanism of the Acidic Cleavage of 2- And 4-Pyridyl Aminophosphonates.

There is no doubt that a chemical character and electronic structure of 2- and 4-pyridyl moieties is responsible for acidic cleavage of 2- and 4-pyridylmethyl(amino)phosphonates. When pyridine nitrogen is protonated in phosphonate molecule, one can postulated a delocalisation of a positive charge on 2- and 4-position of the molecule. In the case of 2- and 4-pyridylphosphonates, it is accompanied with the formation of conjugate double bonds between CH group and pyridine ring (pyridone or enamine-like structure **B**). Formation of the species **B** is facilitated and possible when phosphorous moiety is removed as positively charged group. The "positive" phosphorus moiety (**C**) can react simultaneously with solvent (water) in reaction conditions, forming phosphate (phosphoric acid). The species **B**, which resembles an enamine can tautomerize to more stable form, such as amine **D**, easily. Protonation of amine group is an additional force for the breaking bond between carbon and phosphorus. Accumulation of positive charges in the molecule facilitate cleavage of the C-P bond and make possible the departure of phosphorus moiety with a positive charge. It is sure, that the protonation of amine group is substantial for the cleavage of C-P bond, since the corresponding 2- and 4-pyridylmethyl(hydroxy)phosphonates do not undergo a cleavage during acidic hydrolysis, but form corresponding hydroxyphosphonic acids. (Scheme 8).

The proposed mechanism of a cleavage of 2-pyridyl aminophosphonates is illustrated on Scheme 7.



Scheme 7

An analogous mechanism may be proposed for hydrolysis of 4-pyridylmethyl(amino)phosphonates. It is obvious, that the similar mechanism of a cleavage for 3-pyridyl derivatives cannot be written down, because of lack of possibility of formation of pyridone-like structure.

The cleavage of pyridyl aminophosphonates appears to be a concerted process, not two-step one. The species **B** and **C**, shown on the scheme 7 are rather representing the canonical forms of postulated intermediates, not really existing ones. There is an evidence for formation of enamine **B**, as an intermediate in this reaction. During hydrolysis, the solution of aminophosphonate usually turned to be dark-red, what is characteristical for some compounds possessing conjugate double bonds.

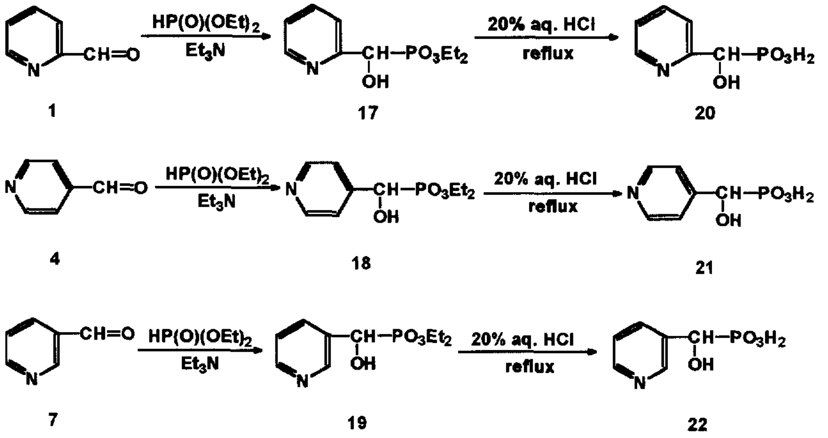
The described cleavage of pyridyl aminophosphonates resembles in some aspects a phosphonate-phosphate rearrangement, known in the case of some hydroxyphosphonates[14], and also aminophosphine oxides[15].

It is worth to mention, that homologues having additional CH_2 group in aliphatic chain such as 2-, 3- and 4-pyridylethyl(amino)phosphonates[7], were easily hydrolysed to corresponding pyridylethyl(amino)phosphonic acids, and no cleavage of C-P bond was reported[7].

Synthesis And Hydrolysis of Pyridylmethyl(hydroxy)phosphonates.

Synthesis of some 2-, 3- and 4-pyridylmethyl(hydroxy)phosphonates was performed in order to determine their behaviour during acidic hydrolysis. The hydroxyphosphonates synthesized were corresponding ones to the previously used aminophosphonates. They were obtained easily from the corresponding pyridine aldehydes **1**, **4** and **7** and diethyl phosphite in toluene solution, in a presence of equimolar amount of triethylamine as a catalyst. The yields of products **17**, **18** and **19** were almost quantitative, and their physical data were in a good agreement with the literature ones[8,9].

Hydrolysis of hydroxyphosphonates **17**, **18** and **19** by means of 20% aq. hydrochloric acid gave corresponding hydroxyphosphonic acids **20**, **21** and **22**, in high yields.



Scheme 8

There was no cleavage of bond observed in the case of pyridylmethyl(hydroxy)phosphonates. This observation has additionally confirmed, that an existence of a group able to protonation (as e.g. amine group) is for the indispensable occurrence of a cleavage of C-P bond in the case of 2- and 4-pyridylmethylaminophosphonates.

The cleavage of aminophosphonates, described here, is unusual reaction, because of a strength of single C-P bond, which is comparable with a strength of single C-C bond (energy value for C-P bond is about 63 kcal/mole[10]), and therefore the reactions of its cleavage are rarely reported in literature.

EXPERIMENTAL

Materials and Methods.

NMR spectra were recorded on a Bruker Avance TM DRX 300 MHz spectrometer in $CDCl_3$, DMSO and D_2O solutions, using 300.13 MHz for ^{1}H-NMR spectra, and 121.51 MHz for ^{31}P-NMR spectra, respectively. G.C.-M.S. analyses were carried out with a Hewlett Packard HP 5971A apparatus, at an ionization potential of 70 eV, equipped with HP-1, capillary column, 25 m. Elemental analyses were performed in the Laboratory of Instrumental Analysis, in the Institute. Melting points were measured on a Digital Melting Point Apparatus Electrothermal 9200, and are uncorrected. All commercially available reagents were used as received from the supplier (Aldrich Company).

Preparation of Diethyl Aminophosphonates 3, 6, 9, 13 and 15.

To a solution of pyridine aldehyde **1**, **4**, or **7**, or quinoline-4-carboxaldehyde, or 4-acetylpyridine (10 mmol) in toluene (50 mL), corresponding amine was added (10 mmol). In the case of n-butylamine twofold excess of amine (20 mmol) was used. The mixture was refluxed for 1 hr, then the solvent was evaporated *in vacuo*. The resulted crude imine was mixed with diethyl phosphonate (1.4 g, 10 mmol) and the mixture was heated under nitrogen at 100-110°C for 30 min. in the case of **3b**, **6b** and **9b** (or for 1-1.5 hrs in the remaining cases), and cooled. The obtained crude products (solids): **3b**, **6b**, **6c**, **9b**, and **9c** were purified by crystallization from a mixture of hexane-toluene. The remaining oily esters were purified by transformation into oxalate salts, according to the procedure described in[2,3]. Free esters were liberated from oxalates by aq. potassium carbonate and extracted with chloroform[2]. The physical data of esters are given in table 1.

Anal. calcd. for **3a**· oxalate,: $C_{14}H_{25}N_2O_3P\cdot(COOH)_2\cdot 2H_2O$: N, 6.57; P, 7.26; found: N, 6.62, P, 7.31.
Anal. calcd. for **3b**,: $C_{16}H_{21}N_2O_3P$: N, 8.75; P, 9.67 ; found: N, 8.81; P, 9.35.
Anal. calcd. for **3c**,: $C_{23}H_{27}N_2O_3P$: N, 6.83; P, 7.55; found: N, 6.54; P, 7.41.
Anal. calcd. for **3d**· oxalate,: $C_{17}H_{23}N_2O_3P\cdot (COOH)_2\cdot 2H_2O$: N, 6.08; P, 6.73; found: N, 6.01; P, 6.62.
Anal. calcd. for **6a**· oxalate,: $C_{14}H_{25}N_2O_3P\cdot (COOH)_2\cdot 2H_2O$: N, 6.57, P, 7.26; found: N, 6.60,; P, 6.92.
Anal. calcd. for **6b**,: $C_{16}H_{21}N_2O_3P$: N, 8.75; P, 9.67; found: N, 8.26; P, 10.02.
Anal. calcd. for **6c**, : $C_{23}H_{27}N_2O_3P$: N, 6.83; P, 7.55; found: N, 6.81; P, 7.82.
Anal. calcd. for **6d** ·oxalate,: $C_{17}H_{23}N_2O_3P\cdot (COOH)_2\cdot 2H_2O$: N, 6.08; P, 6.73; found: N, 5.81; P, 6.80.
Anal. calcd. for **9a**· oxalate,: $C_{14}H_{25}N_2O_3P\cdot (COOH)_2\cdot 2H_2O$: N, 6.57; P, 7.26; found: N, 6.80; P, 7.40.
Anal. calcd. for **9b**,: $C_{16}H_{21}N_2O_3P$: N, 8.75; P, 9.67, found: N, 8.74; P, 10.00.
Anal. calcd. for **9c**, : $C_{23}H_{27}N_2O_3P$: N, 6.83; P, 7.55; found: N, 6.72, P, 7.64.
Anal. calcd. for **9d**· oxalate, : $C_{17}H_{23}N_2O_3P\cdot (COOH)_2\cdot 2H_2O$: N, 6.08; P, 6.73; found: N, 5.41; P, 6.77.
Anal. calcd. for **13**· oxalate,: $C_{18}H_{27}N_2O_3P\cdot (COOH)_2\cdot 2H_2O$: N, 5.88; P, 6.50; found: N, 6.08; P, 6.50.
Anal. calcd. for **15**· oxalate,: $C_{15}H_{27}N_2O_3P\cdot (COOH)_2\cdot 2H_2O$: N, 6.36; P, 7.03; found: N, 6.01; P, 6.83.

Preparation of Amines 11a-d, 12a-d, 14 and 16, by Acidic Hydrolysis of Aminophosphonates 3, 6, 13, 15.

The appropriate aminophosphonate (5 mmol) was dissolved in 20% aq. HCl (50 mL), the solution was refluxed for 6 hrs, and evaporated *in vacuo* to dryness, to give a solid residue.(In the case of hydrolysis the **3c** and **6c**, prior to evaporation, the mixture was extracted with 50 mL chloroform, in order to remove the formed benzhydrol). A sample of the residue (0.03 g) was taken, dissolved in D_2O and ^1H- and ^{31}P-NMR spectra were recorded. The remaining residue was made alkaline with an excess of aq. potassium carbonate, and extracted with chloroform (50 mL). The chloroform extract was dried (anh. K_2CO_3), filtered and evaporated to give crude amine. Amines were purified as oxalate salts, obtained according to the procedure described in[2]. Free amines were obtained from oxalates by alkalization and extraction with chloroform. The solid amines **11b** and **12b** were purified by crystallization from toluene. The physical data of amines are collected in table 2.

Anal. calcd. for **11a**.oxalate: $C_{10}H_{16}N_2\cdot(COOH)_2$: C, 56.68; H, 7.13; N, 11.02;
found: C, 56.68; H, 7.11, N, 11.00.
Anal. calcd. for **11b**: $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21; found: C, 78.01; H, 6.83, N, 15.14.
Anal. calcd. for **11d**· oxalate: $C_{13}H_{14}N_2\cdot 2\cdot(COOH)_2$: C, 53.96; H, 4.80; N, 7.40;
found: C, 53.58; H, 4.93; N, 7.02.
Anal. calcd. for **12a**. oxalate: $C_{10}H_{16}N_2.\ 2(COOH)_2$: C, 44.21; H, 5.30; N, 7.36;
found: C, 44.00; H, 5.81; N, 7.23.
Anal. calcd. for **12b**: $C_{12}H_{12}N_2$: C, 78.23; H, 6.57; N, 15.21; found: C, 78.11; H, 6.58; N, 14.78.
Anal. calcd. for **12d**· oxalate: $C_{13}H_{14}N_2\cdot 2\cdot(COOH)_2$: C, 53.96; H, 4.80; N, 7.40;
found: C, 53.38; H, 5.59; N, 7.34.
Anal. calcd. for **14**· oxalate: $C_{14}H_{18}N_2\cdot(COOH)_2\cdot 2H_2O$: C, 56.46; H, 7.11; N, 8.23;
found: C, 56.18; H, 6.98; N, 7.95.
Anal. calcd. for **16**· oxalate: $C_{11}H_{18}N_2\cdot(COOH)_2\cdot 2H_2O$: C, 51,13; H, 7.92; N, 9.17;
found: C, 50.87; H, 7.99; N, 8.89.

Hydrolysis of Aminophosphonates 9a,c,d: Preparation of Aminophosphonic Acids 10a,c',d.

The appropriate aminophosphonate (5 mmol) was dissolved in 20% aq. HCl (50 mL) and refluxed for 6 hrs. Then the mixture was evaporated *in vacuo* to dryness to give crude aminophosphonic acids. (In the case of hydrolysis of **10c**, prior to evaporation, the solution was extracted with 50 mL chloroform in order to remove the formed benzhydrol). The acids **10a,c',d** were purified by crystallization from aqueous ethanol.

3-Pyridylmethyl(N-butylamino)phosphonic Acid, Hydrochloride (**10a**): Yield 86%. M.p dec> 175°C; ^{1}H-NMR(DMSO): 8.90(s, 1H, py-2), 8.71(d, 1H, py-6, J= 5.0 Hz), 8.37(d,1H, py-4, J= 7.6 Hz), 7.73(m, 1H, py-5), 4.73(d, 1H, CH-P, J=26.5 Hz), 2.90(m, 2H, CH_2N), 1.67(m, 2H, CH_2), 1.25(m, 2H, CH_2), 0.83(t, 3H, CH_3, J= 7.1 Hz) .^{31}P-NMR: 9.97(s).; Anal. calcd. for $C_{10}H_{18}N_2O_3PCl$: N, 9.98; P, 11.04; Cl^- 12.63; found: N, 9.91; P, 11.22, Cl, 12.48.

3-Pyridylmethyl(amino)phosphonic Acid, Hydrochloride (**10c'**): Yield 51%. M.p. 242-245°C (dec). Lit[3]. m.p. 260-265°C (dec.) ^{1}H-NMR(D_2O): The spectrum was in agreement with literature one[3].

3-Pyridylmethyl(N-benzylamino)phosphonic Acid, Hydrochloride (**10d**): Yield 60%. M.p. 235-240°C. Lit.[3] m.p. 235-240°C (dec.). ^{1}H-NMR :The spectrum was identical with literature one[3].

Preparation of 2-Pyridylmethyl(N-butylamino)phosphonic Acid (3'a):

2-Pyridyl ester **3a** (1.5 g, 5 mmol) was dissolved in dry chloroform (10 mL), and bromotrimethylsilane (3.8 g, 25 mmol) was added. The solution was kept for 24 hrs at room temp. (protected against moisture), and then evaporated. The residue was dissolved in a mixture of methanol-diethyl ether (1:1) (20 mL), and refrigerated. The separated crystals of acid **3'a** were collected by filtration and dried. Yield: 56%. M.p. 244-246°C. ^{1}H-NMR(D_2O): 8.52(d, 1H, py-6, J= 4.9 Hz), 7.84(t, 1H, py-4, J= 7.8 Hz), 7.48(d, 1H, py-3, J= 8.0 Hz), 7.39(t, 1H, py-5, J= 5.0 Hz), 4.53(d, 1H, CH-P, J=16.3 Hz), 3.00(m, 2H, CH_2N), 1.60(m, 2H, CH_2), 1.26(m,2H, CH_2), 0.78(t, 3H, CH_3, J= 7.3 Hz.) ^{31}P-NMR: 6.63(s). Anal. calcd. for $C_{10}H_{17}N_2O_3P$: N, 11.47; P, 12.68; found: N, 11.39; P, 12.72.

Acidic Cleavage of 2-Pyridylmethyl(N-butylamino)phosphonic Acid (3'a): Formation of Amine 11a.

A sample of acid **3'a** (0.46 g, 1.88 mmol) was dissolved in 20% HCl (25 mL), and refluxed for 6 hrs, then the solution evaporated to dryness. A sample of residue was taken for NMR studies. The remained product was alkalized with aq. K_2CO_3, and extracted with chloroform (25 mL). After evaporation of extract an oil was obtained, which resulted to be the amine **11a**. Yield: 0.22 g, (71%). ^{1}H-NMR spectrum was identical with the spectrum of amine **11a**, obtained from ester **3a**.

Basic Hydrolysis of Diethyl 4-Pyridylmethyl(N-butylamino)phosphonate (6a). Formation of the monoester 6'a:

4-Pyridyl ester **6a** (2.70 g, 8.9 mmol) was dissolved in 100 mL water, containing sodium hydroxide (1.1 g, 27.5 mmol), and refluxed for 4 hrs. Then the reddish solution was neutralized with aq. HCl to pH ≅ 3, and evaporated to dryness. The residue, (composed with sodium chloride and the product **6'a**) was treated with abs. ethanol (50 mL), (in order to extract the **6'a** from the mixture) and stirred. The ethanolic extract was filtered, evaporated and the residue was reextracted again with a fresh portion of ethanol. The final extract was evaporated to a small volume (15 mL) and acetone was added (15 mL). After refrigeration, the product **6'a** (white solid) was separated, which was collected by filtration and dried. Yield : 1.58 g (66%). M.p. 203-205°C (dec.). ^{1}H-NMR(D_2O): 8.79(d, 2H, py-2, py-6, J= 5.1 Hz), 8.09(d, 2H, py-3, py-5, J= 5.0 Hz), 4.81(d, 1H, CH-P, J=16.7 Hz), 3.88(m, 2H, CH_2O), 3.22-2.96(m, 2H, CH_2N), 1.62(m, 2H, CH_2), 1.24(m, 2H, CH_2), 1.15(m, 3H, CH_3), 0.80(t,3H, CH_3, J=7.3 Hz). ^{31}P-NMR: 8.07 (s). Anal. calcd. for $C_{12}H_{21}N_2O_3P\cdot H_2O$: N, 9.65; P, 10.67. found: N, 9.44; P, 10.65.

Preparation of Diethyl Pyridylmethyl(hydroxy)phoshonates 17, 18 and 19:

A solution of pyridyl aldehyde **1**, **4**, or **7** (2.15 g, 20 mmol), diethyl phosphonate (2.8 g, 20 mmol) and triethylamine (2.0 g, 20 mmol) in benzene (100 mL) was kept for 24 hrs at room temp., and evaporated to give the crude hydroxyphosphonates, as yellow oils. The esters **18** and **19** solidified after several hours, and were recrystallized from a mixture of hexane and diethyl ether.

Diethyl 2-Pyridylmethyl(hydroxy)phosphonate (**17**): Yield: 92%. Oil. lit[9].Oil. ^{1}H-NMR($CDCl_3$): 8.54(d, 1H, py-6, J= 4.9 Hz), 7.69(m, 1H, py-4), 7.55(m, 1H, py-3), 7.28(m, 1H, py-5), 5.09(d, 1H, CH-P, J=11.4 Hz), 4.7(bs, 1H, OH), 4.15(m, 4H, 2xCH_2O), 1.32(m, 6H, 2xCH_3). ^{31}P-NMR: 20.79 (s).

Diethyl 4-Pyridylmethyl(hydroxy)phosphonate (**18**): Yield: 95%. M.p. 68-70°C. ^{1}H-NMR($CDCl_3$): 8.52(d, 2H, py-2, py-6, J= 5.4 Hz), 7.40(m, 2H, py-3, py-5), 6.4(bs, 1H, OH), 5.03(d, 1H, CH-P, J=15.5 Hz), 3.98(m, 4H, 2xCH_2O), 1.15(m, 6H, 2xCH_3). ^{31}P-NMR: 21.63 (s). Anal. calcd. for $C_{10}H_{16}NO_4P$: N, 5.71; P, 12.63; found: N, 5.62; P, 12.67.

Diethyl 3-Pyridylmethyl(hydroxy)phosphonate (**19**): Yield: 96%. M.p. 74-77°C. ^{1}H-NMR($CDCl_3$): 8.61(s, 1H, py-2), 8.46(d, 1H, py-6, J= 4.8 Hz), 7.87(m, 1H, py-4), 7.27(m, 1H, py-5), 5.1(bs, 1H, OH), 5.04(d, 1H, CH-P, J=11.9 Hz), 4.05(m, 4H, 2xCH_2O), 1.23(m, 6H, 2xCH_3). ^{31}P-NMR: 21.67 (s). Anal. calcd. for $C_{10}H_{16}NO_4P$: N, 5.71; P, 12.63. found: N, 5.59; P, 12.70.

Preparation of Pyridylmethyl(hydroxy)phosphonic Acids 20, 21 and 22:

Ester **17**, **18** or **19** (2.5 g, 10 mmol) was dissolved in 20% aq. HCl (50 mL) and refluxed for 6 hrs. After evaporation of solvent, crude hydroxyphosphonic acid was obtained, as glass-like solid. The obtained products were purified by crystallization from aqueous methanol (1:1), to give white, lustrous crystals.

2-Pyridylmethyl(hydroxy)phosphonic Acid (**20**): Yield : 58%. M.p. 195-208°C. ^{1}H-NMR(D_2O): 8.59(d, 1H, py-6, J= 5.9 Hz), 8.43(t, 1H, py-4, J= 7.9 Hz), 7.97(d, 1H, py-3, J=8.0 Hz), 7.85(t, 1H, py-5, J= 5.9 Hz), 5.26(d, 1H, CH-P, J=17.0 Hz). ^{31}P-NMR: 12.67 (s). Anal. calcd. for $C_6H_8NO_4P$ 1.5·H_2O .; N, 6.48; P, 14.33. found: N, 6.24; P, 14.49.

4-Pyridylmethyl(hydroxy)phosphonic Acid (**21**): Yield: 76%. M.p. 240-243°C. ^{1}H-NMR(D_2O+D_2SO_4): 8.81(d, 2H, py-2, py-6, J= 5.0 Hz), 8.18(m, 2H, py-3, py-5), 5.50(d, 1H, CH-P, J=18.8 Hz). ^{31}P-NMR: 15.70 (s). Anal. calcd. for $C_6H_8NO_4P\cdot H_2O$: N, 6.76; P, 14.95. found: N, 6.59; P, 15.05.

3-Pyridylmethyl(hydroxy)phosphonic Acid (**22**): Yield: 61%. M.p. 257-260°C.(dec.) Lit.[8b] m.p. 258-260°C. ^{1}H-NMR(D_2O): 8.71(s, 1H, py-2), 8.60(d, 1H, py-6, J= 5.7 Hz), 8.55(d, 1H, py-4, J= 8.0 Hz), 7.96(t, 1H, py-5, J= 6.0 Hz), 5.05(d, 1H, CH-P, J=14.6 Hz). ^{31}P-NMR: 14.68 (s). Anal. calcd. for $C_6H_8NO_4P\cdot H_2O$: N, 6.76; P, 14.95; found; N, 6.64; P, 15.09.

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