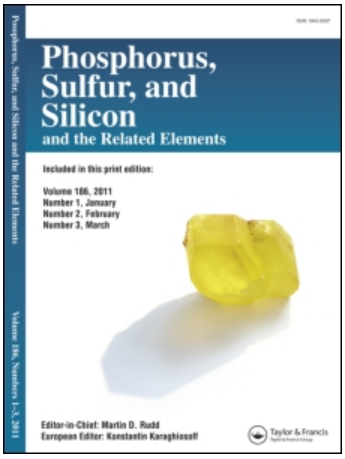


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# Aminophosphinic Acids in a Pyridine Series, Part 2: Synthesis of 2-, 3-, and 4-Pyridyl Derivatives of 1-(Benzylamino)-methyl-H-phosphinic Acids

Waldemar Goldeman[a]; Bogdan Boduszek[a]
[a] Department of Organic Chemistry, Faculty of Chemistry, Wrocław University of Technology, Wrocław, Poland

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# Aminophosphinic Acids in a Pyridine Series, Part 2: Synthesis of 2-, 3-, and 4-Pyridyl Derivatives of 1-(Benzylamino)-methyl-H-phosphinic Acids

**Waldemar Goldeman and Bogdan Boduszek**
Department of Organic Chemistry, Faculty of Chemistry, Wrocław University of Technology, Wrocław, Poland

*New 2-pyridyl, 3-pyridyl, and 4-pyridyl derivatives of 1-[*N*-(benzyl)amino]-methyl-H-phosphinic acid were prepared by the addition of bis(trimethylsilyl)phosphonite to the corresponding imines and subsequent methanolysis of the addition products. Treatment of the 2-pyridyl- and 1-(4-pyridyl)-1-(benzylamino)-methyl-H-phosphinic acids with aqueous mineral acids leads to cleavage and formation of the corresponding secondary amines and phosphorous acid ($H_3PO_3$).*

**Keywords** Aldimines; aminophoshinic acids; bis(trimethylsilyl)phosphonite (BTSP); phosphinic acids; pyridines



## INTRODUCTION

1-Aminoalkyl-H-phosphinic acids are isoelectronic and isosteric analogs of 1-aminoalkylcarboxylic acids and have interesting biological activity. For example, they are inhibitors of several enzymes, such as an angiotensin-converting enzyme (*Phosinopril*),[2] HIV protease,[3] glutamine synthetase,[4] and CN-ligase.[5] Although the C—P bond in the aminophosphonates or in aminophosphonic acids is generally believed to be stable in the basic or acidic medium, there are reports that some aminophosphonic and aminophosphinic acids are susceptible to cleavage under such conditions.

A few years ago, we described and analyzed the acidic cleavage of 2- and 4-pyridine derivatives of aminomethylphosphonic acid[6] and

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Dedicated to Professor Marian Mikołajczyk, CBMiM PAN in Łódź, Poland, on the occasion of his 70th birthday.
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Address correspondence to Bogdan Boduszek, Department of Organic Chemistry, Faculty of Chemistry, Wrocław University of Technology, Wybrzeże Wyspiańskiego 27, 50-370 Wrocław, Poland. E-mail: bogdan.boduszek@pwr.wroc.pl

their esters,[6a] aminomethyl(phenyl)-phosphinic acids,[1,7] aminophosphine oxides,[8] and some heterocyclic aminophosphonic derivatives of 2-pyrone, 2-chromone, and 4-coumarin.[9]

Pyridine derivatives of aminophosphonic and aminophosphinic acids are currently known, in contrast to pyridine derivatives of aminomethyl-H-phosphinic acids, having a P-H bond in the molecule. They are also named the phosphonous acids. Among them, only the 1-amino-1-(3-pirydyl)-methyl-H-phosphinic acid was described in the literature.[10] Therefore, we decided to prepare some new 2-, 3-, and 4-pyridyl derivatives of 1-(benzylamino)-methyl-H-phosphinic acids and examine their stability under acidic solutions.

## RESULTS AND DISCUSSION

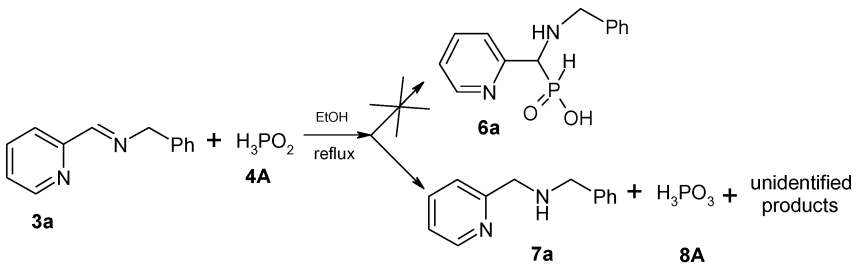
### Synthesis of Pyridine 1-Benzylamino-methyl-H-phosphinic Acids



Synthesis of *N*-substituted 1-aminoalkyl-H-phosphinic acids by addition of anhydrous hypophosphorous acid ($H_3PO_2$) to imines, likewise as the reaction of amine salts of hypophosphorous acid with carbonyl compounds, were described in 1948 by Schmidt.[11] Baylis et al.[12] applied various aldimines prepared from benzhydrylamine to receive the corresponding 1-aminoalkyl-H-phosphinic acids in a similar reaction. Addition of anhydrous hypophosphorous acid to imines, or in situ derived imines, are the most common ways to prepare 1-aminoalkyl-H-phosphinic acids.[11–14] Other methods, for example, an addition of hypophosphorous acid to bisamides[15]; Kabachnik–Fields-like reaction with use of amines, carbonyl compounds, and hypophosphorous acid[16]; and recently, an addition of ethyl diethoxymethylphosphinate to imines,[17] were also applied.

A very specific hydrophosphinylating agent is the bis(trimethylsilyl)-phosphonite (BTSP),[24] which allows the reaction to be carried out in mild conditions. The first report on the BTSP addition to benzylidene aniline and/or benzylidenemethyl imine was written in 1984 by Romanov et al.[18] However, the first useful application of BTSP for the synthesis of amino-H-phosphinic acids was described by Grobelny.[19] This method, with applying the *N*-(diphenylmethyl)-imines, was further modified by the use of other imines, including *N*-(trityl)-imines,[10a,20] some heterocyclic imines,[21] and resin bounded imines.[10b]

In our investigations on the synthesis of 1-(N-alkylamino)methyl(n-pyridine)-phosphinic acids, we focused on modifications of the hydrophosphinylation of imines **3** by means of hypophosphorous acid (**4A**) and its derivatives, including methyl phosphinate (**4B**) and BTPS (**4C**).



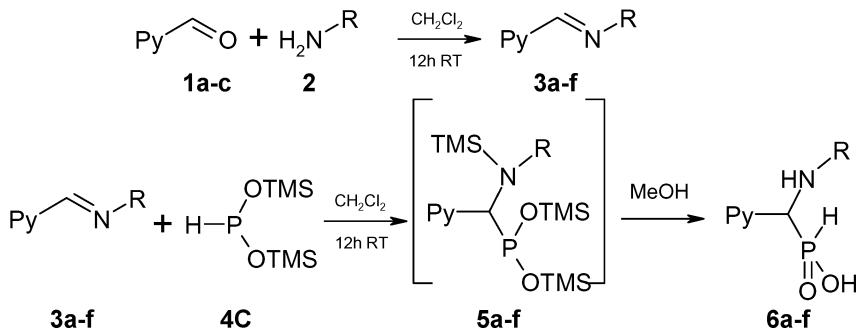

**SCHEME 1**

Thus, NMR monitoring of the reaction mixture of 2-pyridylmethylbenzylimine (**3a**) with anhydrous hypophosphorous acid (**4A**), after 2 h of reflux in absolute ethanol, revealed mainly the products of redox reaction, including phosphorous acid (**8A**) and *N*-(2-pyridylmethyl)-benzylamine (**7a**), and also some other unidentified compounds (Scheme 1). The obtained results suggested that an apparent reduction of the starting imine (**3a**) by $H_3PO_2$ (**4A**) occurred as a basic reaction under the conditions applied.

In turn, we examined the reaction of pyridine-2-carboxyaldehyde (**1a**), benzylamine hydrochloride (**2A**), and hypophosphorous acid (**4A**) in aqueous ethanol according to the procedure in the literature,[12] except that the reaction was run at room temperature (to prevent possible decompositions at higher temperature). After 3 days, the reaction mixture contained ca. 40% of 1-benzylamino-1-(2-pyridyl)-methyl-H-phosphinic acid (**6a**) and an unspecified amount of phosphorous acid (**8A**). By analogy with the data in the literature data,[22] we have assumed that the use of amine hydrochloride should prevent a possible reduction of the imine **3** by hypophosphorous acid. So, in this case, the presence of the $H_3PO_3$ clearly suggested a cleavage of the initially formed aminophosphinate **6**, according to the pattern previously described by one of us.[6a]

For this reason, we have decided to use BTSP as the hydrophosphinylating agent. Thus, the reaction of BTSP with *n*-pyridylmethylenebenzylamines **3a–c** in dichloromethane solution occurred smoothly and afforded the appropriate silyl esters **5**, easily convertible to the final amino-H-phosphinic acids **6a–c**, by methanolysis (Scheme 2). Crystallizations of **6a**–**c** were performed in acetone or acetone-diethyl ether mixtures affording the pure amino acids with average to good yields (Table I).

In continuation, we applied this procedure to prepare the pure optically active diastereomers of corresponding 1-(α-methylbenzylamino)-1-(n-pyridyl)methyl-H-phosphinic acids **6d–f**, by using




**a**:2-Py, R=$PhCH_2$; **b**:3-Py, R=$PhCH_2$; **c**:4-Py, R=$PhCH_2$;
**d**:2-Py, R=(S)-$Ph(CH_3)CH$; **e**:3-Py, R=(S)-$Ph(CH_3)CH$; **f**:4-Py, R=(S)-$Ph(CH_3)CH$

**SCHEME 2**



(*S*)-$\alpha$-methylbenzylamine for preparation of imines **3d–f**. The crude reaction mixtures of **6d–f** were found to contain the diastereomeric pairs [(*S*, *S*)-**6** and (*S*, *R*)-**6**, respectively] existing in a following molar ratio (determined by $^{31}$P NMR spectra): for **6d** (2-Py) 58:42, for **6e** (3-Py) 60:40, and for **6f** (4-Py) 61:39, respectively.

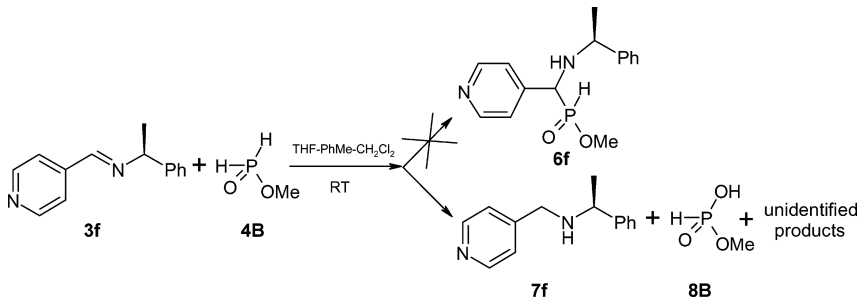
The major diastereomers of **6d–f** were isolated by crystallization from acetone or acetone-diethyl ether. Yields of all of the obtained **6d–f** are collected in the Table I.

Major diastereomers of **6d–f**, were found to possess an opposite (*R*) configuration on the tertiary $\alpha$-carbon atom, according to the $^{1}$H and $^{31}$P NMR spectra and also in line with the data in the literature of parent aminophosphine oxides.[8]

**TABLE I 1-(*N*-Benzylamino)-*n*-pyridinemethyl-H-phosphinic Acids 6a–f**

| | | | Yields [%] | |
|---|---|---|---|---|
| | *n*-Py | R | $^{31}$P NMR yields | Isolation yields |
| **6a** | 2-Py | $PhCH_2$ | not determined | 40 |
| **6b** | 3-Py | $PhCH_2$ | not determined | 79 |
| **6c** | 4-Py | $PhCH_2$ | not determined | 46 |
| **6d** | 2-Py | (*S*)-$Ph(CH_3)CH$ | 65 | 19[a] |
| **6e** | 3-Py | (*S*)-$Ph(CH_3)CH$ | 60 | 28[a] |
| **6f** | 4-Py | (*S*)-$Ph(CH_3)CH$ | 69 | 8[a] |

[a]Yield given for pure diastereomer.




**SCHEME 3**

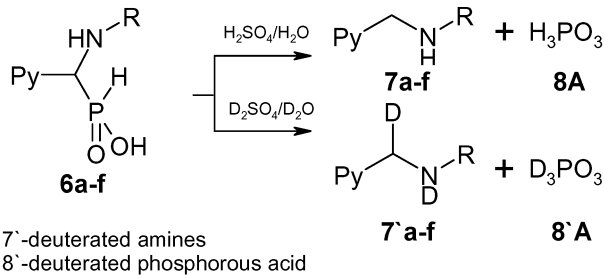
Since the diastereomerically pure pyridine aminophosphinic acids **6d–f** were obtained in low yields (Table I), we looked for alternative methods of synthesis of these compounds. However, the additions either hypophosphorous acid (**4A**) or methyl phosphonite (**4B**)[23] to **3f** were found to afford mainly the products of the redox reaction. Thus, in the latter case, methyl phosphonate (**8B**) and secondary 4-pyridyl-$\alpha$-methylbenzylamine (**7f**) (separated with 69% yield as **7f** $\times$ $C_2O_4H_2$) were found as major constituents of the reaction mixture (Scheme 3).

Structures of the obtained products **6a–f** were determined by spectroscopy methods $^1$H, $^{13}$C, $^{31}$P NMR, and IR) and by comparison with data in the literature[10,12] of similar compounds. In $^1$H NMR spectra of the products **6a–f**, there are observed the characteristic doublets at ca. 6.6–7.0 ppm with $J_{P-H} \cong 550$ Hz constants, responsible for the P-H coupling.

Our results show that the title 2-, 3-, and 4-pyridyl derivatives of 1-(benzylamino)-methyl-H-phosphinic acids **6** can be prepared by using the BTSP in fair yields. Alternative application of other hydrophosphinylating reagents, such as hypophosphorous acid (**4A**) or methyl phosphonate (**4B**), in reaction with imines **3**, caused the redox-type reactions, suggesting the domination role of the reduction of imines **3** by **4A** and/or **4B**.

## Acidic Cleavage of Pyridine 1-Benzylamino-methyl-H-phosphinic Acids

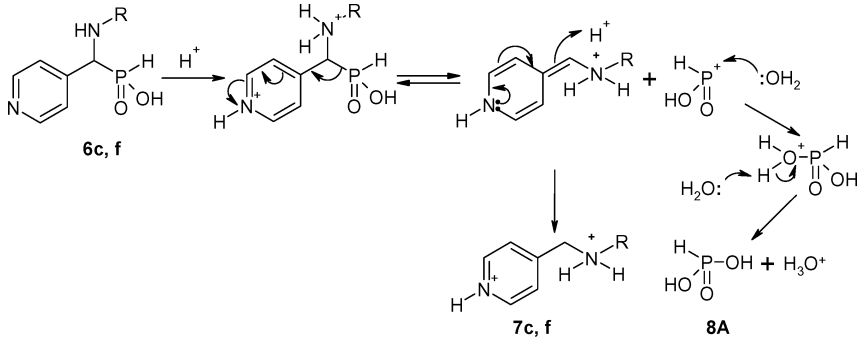
Preliminary tests performed in the NMR tubes show that 1-benzylamino-2-pyridylmethyl-H-phosphinic **6a**,**d** and 1-benzylamino-4-pyridylmethyl-H-phosphinic acids **6c**,**f** are exceptionally easily cleaved in 1M $H_2SO_4/H_2O$ (1M $D_2SO_4/D_2O$) solutions at room temperature. In fact, after dissolving of amino acids **6a**,**d**,**e**,**f** in 1M $H_2SO_4/H_2O$



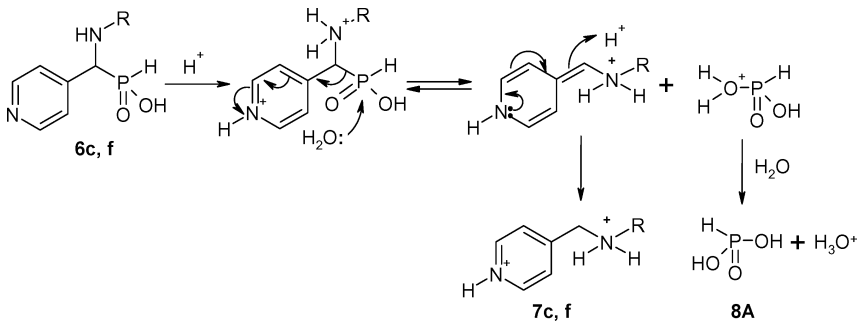

**SCHEME 4**

(1M $D_2SO_4/D_2O$) solutions, these compounds **6**, according to $^{31}P$ and $^{1}H$ NMR data, practically disappeared in a few minutes of exposition. The $^{31}P$ NMR spectra of these solutions showed new peaks attributed to phosphorous acid (**8A**), and $^{1}H$ NMR spectra signals attributed to the formed corresponding *N*-(n-pyridylmethyl)-benzylamines **7**. A presence of the formed products **7** and **8A** indicates that the examined aminomethyl-H-phosphinic acids **6** are exceptionally susceptible to breaking the C—P bond under acidic conditions applied (Scheme 4).

In contrary, the corresponding 3-pyridyl derivatives **6b**,**e** were also cleaved, but more slowly and/or at considerably higher temperature (ca ~95°C). It was estimated that rates of the cleavage of 1-(3-pyridyl)-1-(benzylamino)-methyl-H-phosphinic acids **6b**,**e** were several hundred times smaller at 95°C than these of corresponding 2- or 4-pyridyl derivatives, easily cleaved at room temperature. Since corresponding aminophosphonic analogs are stable at acidic conditions, even at elevated temperatures,[6a,b] the susceptibility of




**SCHEME 5**




**SCHEME 6**

1-(3-pyridyl)-1-(benzylamino)-methyl-H-phosphinic acids **6b**,**e** to cleave was observed for the first time in our case.

These findings on the cleavage of all amino acids **6** examined are in accordance with the data in the literature on the acidic cleavage mechanisms of pyridine aminophosphonic acids,[6] aminophosphinic acids,[7] aminophosphine oxides,[8] and also for 1-(hydroxyimino)-methylphosphonates.[25]

By analogy with the data on the literature,[6–8,25] two mechanisms of cleavage of amino-H-phosphinic acids **6a–f**, shown in Schemes 5 and 6, respectively, are proposed.

Thus, the first mechanism drawn for the **6c**,**f** (Scheme 5) is a dissociative-type [$S_N1(P)$], which assumes that after protonation of the nitrogen atom, a cleavage of the C—P bond occurs and the metaphosphate-like moiety is departed, which then reacts with a nucleophilic solvent to form the products.

The second one (Scheme 6) is an associative-type mechanism [$S_N2(P)$], which assumes first a nucleophilic attack of water (solvent) molecule on the phosphorous atom, that consequently leads to breaking of a C—P bond.

Detailed kinetic and mechanistic studies on the cleavage of a series of 2-, 3-, and 4-pyridine derivatives of aminomethyl-H-phosphinic acids **6** will be the subject of a separate article.

## CONCLUSIONS

A series of new pyridine 1-*N*-(benzyl)amino-methyl-H-phosphinic acids was synthesized by using bis(trimethylsilyl)-phosphonite (BTSP) in reaction with pyridine imines in moderate yields. It was found that the BTSP is a reagent of choice for the synthesis of these acids.

The pyridine 1-*N*-(benzyl)amino-methyl-H-phosphinic acids were extremely unstable in acidic conditions. The sulfuric acid solutions of the acids **6a–f** decomposed quickly to form secondary pyridyl-benzylamines and phosphorous acid. On the basis of the data in the literature, two alternative mechanisms of the cleavage were proposed.

## EXPERIMENTAL

$^{1}H$, $^{31}P$ and $^{13}C$ NMR spectra were measured on a Bruker Avance 300 MHz spectrometer using TMS as an internal standard. IR spectra were recorded on a Perkin Elmer 1600 FTIR spectrophotometer. Melting points were determined using an Electrothermal 9200 apparatus and a Boetius hot-stage apparatus and were uncorrected. Elemental analyses were done in Department of Chemistry, University of Wroclaw, Wrocław, Poland. Reagents used were obtained from the Sigma–Aldrich Company (Poznań, Poland). Solvents were of commercial quality and purchased from a local supplier (POCh Gliwice, Poland).



### Synthesis of 1-(Alkylamino)-pyridylphosphinic Acids 6a–f: General Procedure

To a solution of benzyl- or (*S*)-$\alpha$-methylbenzylamine (30 mmol) in dichloromethane (25 mL), the appropriate pyridine aldehyde (30 mmol) was added at 0°C and the mixture was stirred overnight at room temperature over the anhydrous sodium sulfate. The mixture was filtered and washed with dichloromethane (3 × 5 mL), and the solution of crude imine was cooled to 0°C. Bis(trimethylsilyl) phosphonite (30 mmol) in dry dichloromethane (25 mL) was added dropwise, and the mixture was stirred at room temperature for 2 h and left overnight. Then the solvent was evaporated, and the residue was treated with cold methanol (30 mL). Addition of methanol caused separation of a precipitate, which after 10 min dissolved. The solution was again evaporated under reduced pressure, giving a crude product as thick oil. The crude product was crystallized from the appropriate solvent (the 3-pyridyl derivatives crystallized from cold acetone, in contrary to the 2- and 4-derivatives, which were crystallized from mixture of acetone and diethyl ether or methanol/diethyl ether at –20°C).

*NOTE: All 2- and 4-pyridyl derivatives should be stored in a refrigerator under inert gas due to decomposition under prolonged influence of moisture.*

### *1-Benzylamino-1-(2-pyridyl)-methyl-H-phosphinic Acid (6a)*

It was obtained as colorless crystals: yield 40%; mp 155–156 C. $^{31}P\{^1H\}$ NMR ($D_2O$): $\delta = 17.6$ (s). $^1H$ NMR ($D_2O$): $\delta = 8.52$ (d, $J =$ 4.5 Hz, 1H, 6-Py*H*); 7.80 (t, $J = 7.7$ Hz, 1H, 4-Py*H*); 7.27-7.37 (m,7H, *Ph*$CH_2$, Py*H*); 7.00 (d, $J = 557.0$ Hz, 1H, P-H); 4.33 (d, $J = 13.5$ Hz, 1H, *CH*P); 4.17 (s, 2H, Ph*CH*$_2$). $^{13}C$ NMR ($D_2O$+NaOD): $\delta = 50.8$ (d, $^3J_{PC} = 5.6$ Hz, Ph*C*); 61.8 (d, $J_{PC} = 80.2$ Hz, PyC); 124.1; 124.7 (d, $J =$ 3.0 Hz); 129.0; 129.6; 130.0; 138.3; 148.6 (d, $J_{PC} = 4.6$ Hz); 149.3; 149.9. FTIR, $\nu_{max}$ (KBr [$cm^{-1}$]): 3410, 3039, 2950, 2737, 2551, 2403, 2307 (H-P), 1602, 1587, 1476, 1436, 1200 (P=O), 1169, 1070 (P-OH), 1022 (H-P), 975, 911, 889, 854, 793, 749, 693, 643, 600, 559, 534, 509, 481. Elemental anal. for **6a**, Calcd.: C, 59.53; H, 5.77; N, 10.68. Found: C, 59.45; H, 5.98; N, 10.59%.

### *1-Benzylamino-1-(3-pyridyl)-methyl-H-phosphinic Acid (6b)*

It was obtained as colorless crystals: yield 79%; mp 214–216°C. $^{31}P\{^1H\}$ NMR ($D_2O$): $\delta = 18.0$ (s). $^1H$ NMR ($D_2O$): $\delta = 8.52$ (d, $J =$ 5.0 Hz, 1H, 4-Py); 8.43 (s, 1H, 2-Py); 7.93 (d, $J = 8.0$ Hz, 1H, 6-Py,); 7.54 (dd, $J = 5.0$ Hz, $J = 8.0$ Hz, 1H, 5-Py,); 7.35 (m, 3H, *Ph*$CH_2$); 7.24–7.27 (m, 2H, *Ph*$CH_2$); 7.03 (d, $J = 550.3$ Hz, 1H, P-H); 4.28 (d, $J = 12.9$ Hz, 1H, *CH*P); 4.14 (s, 2H, Ph*CH*$_2$). $^{13}C$ NMR ($D_2O$+NaOD): $\delta = 50.6$ (d, $^3J_{PC} = 14.2$ Hz, Ph*C*); 59.9 (d, $J_{PC} = 96.2$ Hz, PyC); 124.2; 127.4; 128.6 (d, $J = 5.0$ Hz); 132.1; 132.2; 137.1 (d, $J_{PC} = 5.1$ Hz); 138.0; 147.7; 147.7. FTIR, $\nu_{max}$ (KBr [$cm^{-1}$]): 3445, 3409, 3034, 2979, 2742, 2596, 2326 (H-P), 1616, 1575, 1479, 1456, 1425, 1361, 1182, 1162 (P=O), 1080 (P-OH), 1056 (H-P), 1024, 988, 959, 913, 852, 813, 787, 752, 711, 698, 645, 615, 593, 550, 479. Elemental anal. for **6b**, Calcd.: C, 59.53; H, 5.77; N, 10.68. Found: C, 59.65; H, 6.03; N, 10.41%.

### *1-Benzylamino-1-(4-pyridyl)-methyl-H-phosphinic Acid (6c)*

It was obtained as colorless crystals: yield 46%; mp 105–106°C. $^{31}P\{^1H\}$ NMR ($D_2O$): $\delta = 19.4$ (s). $^1H$ NMR ($D_2O$): $\delta = 8.52$ (d, $J = 4.7$ Hz, 2H, 2-,6-Py); 7.53 (d, $J = 4.7$ Hz, 2H, 3-,5-Py); 7.27–7.32 (m, 3H, *Ph*$CH_2$); 7.20–7.26 (m, 2H, *Ph*$CH_2$); 6.92 (d, $J = 551.8$ Hz, 1H, P-H); 4.20 (d, $J = 14.5$ Hz, 1H, *CH*P); 4.00 (s, 2H, Ph*CH*$_2$). $^{13}C$ NMR ($D_2O$+NaOD): $\delta = 50.8$ (d, $^3J_{PC} = 14.2$ Hz, Ph*C*); 62.7 (d, $J_{PC} = 92.3$ Hz, PyC); 124.0 (d, $J_{PC} = 4.6$ Hz); 124.4 (d, $J_{PC} = 4.2$ Hz); 127.5; 128.6; 128.7; 138.0; 148.7. FTIR, $\nu_{max}$ (KBr [$cm^{-1}$]): 3425, 3032, 3008, 2974, 2746, 2585, 2343 (H-P), 2296, 1641, 1607, 1562, 1497, 1480, 1456, 1428, 1417, 1382, 1349, 1227 (P=O), 1164 (P-OH), 1075 (H-P), 1044, 1006, 975, 913, 870, 855, 822, 798, 752, 698, 630, 599, 549, 504, 492, 477, 464, 428. Elemental anal. for **6c**, Calcd.: C, 59.53; H, 5.77; N, 10.68. Found: C, 59.37; H, 6.08; N, 10.39%.

### *1-[(S)-α-(Methylbenzylamino)]-1-(R)-(2-pyridyl)-methyl-H -phosphinic Acid (6d)*

It was obtained as colorless crystals. The isolated yield of pure diastereoisomer: 19%; mp 166–168°C ($^{31}$P NMR yield of crude **6d**: 65%). $^{31}P\{^1H\}$ NMR ($D_2O$): $\delta = 18.0$ (s). $^1$H NMR ($D_2O$): $\delta = 8.40$ (d, $J = 4.0$ Hz, 1H, 6-Py*H*); 7.66 (t, $J = 7.5$ Hz, 1H, 4-Py*H*); 7.22 (m,6H, *Ph*, 5-Py*H*); 7.12 (d, $J = 7.6$ Hz, 1H, 3-Py*H*); 6.95 (d, $J = 557.4$ Hz, 1H, P-H); 4.41 (q, $J = 6.6$ Hz, 1H, *CH*$CH_3$); 4.26 (d, 1H, $J = 13.7$ Hz, *CH*P); 1.56 (d, $J = 6.6$ Hz, 3H, $CH_3$). $^{13}$C NMR ($D_2O$+NaOD): $\delta = 21.0$ ($CH_3$); 57.0 (d, $^3J_{PC} = 12.1$ Hz, $CH_3$*C*); 60.1 (d, $J_{PC} = 93.1$ Hz, PyC); 122.6; 123.6 (d, $J_{PC} = 3.8$ Hz); 126.8; 127.1; 128.3; 137.4; 143.9; 148.2; 156.1. FTIR, $\nu_{max}$ (KBr [$cm^{-1}$]): 3425, 3052, 3011, 2973, 2933, 2640, 2437, 2311 (H-P), 2193, 1964, 1606, 1591, 1572, 1515, 1499, 1481, 1471, 1433, 1376, 1355, 1318, 1267, 1228, 1207 (P=O), 1171 (P-OH), 1154, 1094, 1084, 1060 (H-P), 1016, 1005, 984, 940, 921, 895, 846, 790, 763, 745, 698, 649, 617, 596, 546, 510, 481, 452. Elemental anal. for **6d**, Calcd.: C, 60.86; H, 6.20; N, 10.14. Found: C, 60.37; H, 6.18; N, 10.20%.



### *1-[(S)-α-(Methylbenzylamino)]-1-(R)-(3-pyridyl)-methyl-H -phosphinic Acid (6e)*

It was obtained as colorless crystals. The isolated yield of pure diastereoisomer: 28%; mp 242–243°C ($^{31}$P NMR yield of crude **6e**: 60%). $^{31}P\{^1H\}$ NMR ($D_2O$): $\delta = 18.6$ (s). $^1$H NMR ($D_2O$): $\delta = 8.39$ (d, $J = 5.2$ Hz, 1H, 4-Py); 8.22 (s, 1H, 2-Py); 7.79 (d, $J = 7.8$ Hz, 1H, 6-Py); 7.42 (dd, $J = 7.8$ Hz, $J = 5.2$ Hz, 1H, 5-Py); 7.25 (s, 5H, Ph); 7.03 (d, $J = 549.5$ Hz, 1H, P-H); 4.41 (q, $J = 6.8$ Hz, 1H, *CH*$CH_3$); 4.17 (d, $J = 13.6$ Hz, 1H, *CH*P); 1.54 (d, $J = 6.8$ Hz, 3H, $CH_3$). $^{13}$C NMR ($D_2O$+NaOD): $\delta = 21.0$ ($CH_3$); 56.9 (d, $^3J_{PC} = 11.7$ Hz, $CH_3$*C*); 59.9 (d, $J_{PC} = 94.4$ Hz, PyC); 123.9; 126.9; 127.2; 128.4; 132.9 (d, $J_{PC} = 3.2$ Hz); 136.9 (d, $J_{PC} = 5.1$ Hz); 143.8; 147.2; 148.5 (d, $J_{PC} = 6.0$ Hz). FTIR, $\nu_{max}$ (KBr [$cm^{-1}$]): 3431, 3059, 3046, 3009, 2938, 2939, 2794, 2759, 2641, 2439, 2363, 2317 (H-P), 2195, 1968, 1898, 1726, 1607, 1583, 1574, 1511, 1500, 1481, 1456, 1426, 1379, 1359, 1340, 1318, 1303, 1275, 1215 (P=O), 1192 (P-OH), 1168, 1123, 1102, 1086, 1061 (H-P), 1036, 1025, 1016, 1004, 964, 957, 945, 922, 839, 810, 766, 703, 657, 649, 614, 567, 548, 511, 480, 452. Elemental anal. for **6e**, Calcd.: C, 60.86; H, 6.20; N, 10.14. Found: C, 60.57; H, 6.22; N, 9.89%.

### *1-[(S)-α-(Methylbenzylamino)]-1-(R)-(4-pyridyl)-methyl-H-phosphinic Acid (6f)*

It was obtained as colorless crystals: The isolated yield of pure diastereoisomer: 8%; mp 139–141°C ($^{31}$P NMR yield of crude **6f**: 69%).

$^{31}P\{^{1}H\}$ NMR ($D_2O$): $\delta = 18.7$ (s). $^{1}H$ NMR ($D_2O$): $\delta = 8.26$ (d, $J = 6.2$ Hz, 2H, 2-,6-Py); 7.30 (d, $J = 6.2$ Hz, 2H, 3-,5-Py); 7.09 (5H, *Ph*); 6.84 (d, $J = 549.6$ Hz, 1H, P-H); 4.08 (q, $J = 6.7$ Hz, 1H, *CH*$CH_3$); 4.04 (d, $J = 15.3$ Hz, 1H, *CH*P); 1.39 (d, $J = 6.7$ Hz, 3H, $CH_3$). $^{13}C$ NMR ($D_2O$+NaOD): $\delta = 21.2$ ($CH_3$); 57.2 (d, $^{3}J_{PC} = 11.4$ Hz, $CH_3$*C*); 60.4 (d, $J_{PC} = 94.3$ Hz, PyC); 123.9; 127.3; 128.5; 130,2; 137.0 (d, $J_{PC} = 4.9$ Hz); 143.8; 148.6 (d, $J_{PC} = 6.0$ Hz). FTIR, $\nu_{max}$ (KBr [$cm^{-1}$]): 3411, 3057, 3029, 2979, 2934, 2791, 2756, 2635, 2448, 2319 (H-P), 2190, 1599, 1560, 1500, 1478, 1455, 1433, 1418, 1378, 1350, 1320, 1273, 1231, 1206 (P=O), 1169 (P-OH), 1124, 1086, 1059 (H-P), 1017, 992, 981, 916, 847, 830, 822, 768, 750, 701, 665, 628, 616, 588, 548, 524, 479, 454. Elemental anal. for **6f**, Calcd.: C, 60.86; H, 6.20; N, 10.14. Found: C, 60.55; H, 6.28; N, 9.98%.

## Cleavage in Sulfuric Acid Solution

A sample of pyridine aminophosphinic acid **6a**,**c**,**d**,**f** (1.5 mmol) was dissolved in 1M $H_2SO_4/H_2O$ solution (8 mL) and kept at room temperature for 15–20 min. In the case of 3-pyridyl derivatives **6b,e** (8 mL, 1.5 mmol), the solution was heated at 95°C (water bath) for 3 h. Then the mixture was alkalized with an excess of 5% aqueous sodium bicarbonate solution and extracted with methylene chloride (1 × 10 mL and 3 × 5 mL). Organic layers were collected, dried (anhydr. $Na_2SO_4$), and evaporated to dryness to give the free amines. The amine was dissolved in acetone (5 mL), oxalic acid [$(COOH)_2 \cdot 2\ H_2O$; 0,19 g, 1.5 mmol] in acetone (5 mL) was added, and the mixture was refrigerated overnight. Separated precipitate was filtered off, washed with acetone (5 × 2 mL), and dried on air.

### *N-(2-Pyridylmethyl)-benzylamine Oxalate (7a × $C_2O_4H_2$)*

Colorless solid: yield 84%; mp 208–210°C (lit. 182–194 °C[6a]).

Free amine **7a**: $^{1}H$ NMR spectroscopic data consistent with that reported.[6a] $^{13}C$ NMR ($D_2O$): $\delta = 50.1$ (PyC); 51.0 (PhC); 124.6; 124.9; 129.4; 129.9; 130.0; 130.5 (1-Ph); 139.4 (5-Py); 149.0 (3-Py); 149.7 (1-Py); 165.7 [$(COOH)_2$].

### *N-(3-Pyridylmethyl)-benzylamine Oxalate (7b × $C_2O_4H_2$)*

Colorless solid: yield 89%; mp 233–235°C. $^{1}H$ NMR ($D_2O$): $\delta = 8.70$ (s, 1H, 2-Py*H*); 8,67 (d, $J = 5.6$ Hz, 1H, 4-Py*H*); 8.35 (d, $J = 7.8$ Hz, 1H, 6-Py*H*); 7.84 (dd, $J = 5.6$ Hz, $J = 7.8$ Hz, 1H, 5-Py*H*); 7.40 (s, 5H, *Ph*); 4.40 (s, 2H, Py*CH2*); 4.28 (s, 2H, Ph*CH2*). $^{13}C$ NMR ($D_2O$): $\delta = 47.0$ (PyC); 51.3 (PhC); 126.9; 129.3; 129.8; 129.9; 130.0 (1-Ph); 144.5; 144.6; 145.4 (1-Py); 145.5; 165.6 [$(COOH)_2$].

### *N-(4-Pyridylmethyl)-benzylamine Oxalate (7c × $C_2O_4H_2$)*

Colorless solid: yield 97%; mp 227–228°C. (lit. 214–216°C[6a]).

Free amine **7c**: $^1$H NMR spectroscopic data are consistent with that reported.[6a] $^{13}$C NMR ($D_2O$): 48.8 (PyC); 51.8 (PhC); 127.3 (2-,6-Py); 129.5 (2-,6-Ph); 130.0 (1-Ph); 130.1 (4-Ph); 130.2 (3-,5-Ph); 142.3 (3-,5-Py); 151.3 (1-Py); 165.6 [$(COOH)_2$].

### *N-(2-Pyridylmethyl)-(S)-α-methylbenzylamine Oxalate (7d × $C_2O_4H_2$)*

Colorless solid: yield 77%; mp 128–131°C. (lit. 135–137°C[8]). $^1$H NMR spectroscopic data are consistent with that reported.[8] $^{13}$C NMR ($D_2O$): 18.3 ($CH_3$); 48.1 (PyC); 58.8 (PhC); 125.1; 125.3; 127.7; 129.4; 129.8; 135.1 (1-Ph); 140.9 (5-Py); 147.5 (3-Py); 148.7 (1-Py); 165.7 [$(COOH)_2$].

### *N-(3-Pyridylmethyl)-(S)-α-methylbenzylamine Oxalate (7e × $C_2O_4H_2$)*

Colorless solid: yield 93%; mp 184–186°C. $^1$H NMR ($D_2O$): 8.62 (d, $J$ = 5.5 Hz, 1H, 4-Py*H*); 8.54 (s, 1H, 2-Py*H*); 8.27 (d, $J$ = 8.1 Hz, 1H, 6-Py*H*), 7.80 (dd, $J$ = 8.1 Hz, $J$ = 5.5 Hz, 1H, 5-Py*H*); 7.38 (s, 5H, Ph); 4.44 (q, $J$ = 7.0 Hz, 1H, C*H*$CH_3$); 4.30 (d, $J$ = 14.1 Hz, 1H, PhC$H_2$); 4.10 (d, $J$ = 14.1 Hz, 1H, PhC$H_2$); 1.61 (d, $J$ = 7.0 Hz, 3H, $CH_3$). $^{13}$C NMR ($D_2O$): 18.5 ($CH_3$); 45.7 (PyC); 59.2 (PhC); 127.0; 127.8; 129.6; 130.0; 130.6 (1-Ph); 135.1 (1-Py); 143.9; 143.9; 145.8; 166.3 [$(COOH)_2$].

### *N-(4-Pyridylmethyl)-(S)-α-methylbenzylamine Oxalate (7f × $C_2O_4H_2$)*

Colorless solid: solid: yield 93%; mp 189–192°C (lit. 178–181°C[8]). $^1$H NMR spectroscopic data are consistent with that reported.[8] $^{13}$C NMR ($D_2O$): $\delta$ = 18.2 ($CH_3$); 47.5 (PyC); 59.7 (PhC); 127.0 (2-,6-Py); 127.9 (2-,6-Ph); 129.5 (4-Ph); 130.1 (3-,5-Ph); 134.8 (1-Ph); 142.3 (3-,5-Py); 151.0 (1-Py); 165.7 [$(COOH)_2$].

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