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AZIRIDINE-2-PHOSPHONIC ACID, THE VALUABLE SYNTHON FOR SYNTHESIS OF 1-AMINO-2-FUNCTIONALIZED ETHANEPHOSPHONIC ACIDS

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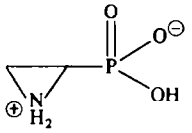
Abstract—The ring-opening of aziridine-2-phosphonic acid with a series of nucleophiles was studied. This reaction was found to proceed regioselectively and to provide a good preparative method for the synthesis of phosphonic analogs of various 2-substituted 1-aminoethanecarboxylic acids.

In the last decade, 1-aminoalkanephosphonic acids and their derivatives have been the subject of numerous reports concerning their biochemical activity.[1]

In the course of our work directed toward the study of synthesis and properties of 1-amino-2-substituted ethanephosphonic acids we have succeeded in the preparation of the phosphonic analogs of serine, cysteine, 2-chloroalanine, 1,2-diaminopropionic acid and their O-, S- and N-alkyl derivatives.

We have previously described the synthesis of aziridine-2-phosphonic acid and its conversion into 1-amino-2-hydroxyethanephosphonic acid.[2] In a preliminary communication we also reported briefly the synthesis of 1-amino-2-mercaptoethanephosphonic acid in the same way.[3]

The aim of this paper is to present the synthetic utility of zwitterionic aziridine-2-phosphonic acid with the structure **1** for the preparation of 1-amino-2-functionalized ethanephosphonic acids via regioselective ring-opening reactions.



1

The facility of the synthesis of aziridine **1** in two-pot procedure and its good tendency to undergo ring-opening reaction with a series of nucleophiles creates a preparative method for the introduction of suitable chemical function at 2 position of 1-aminoethanephosphonic acid.

It is proper to add that in recent patents aziridine-2-carboxylic acid has been synthesized[4] and transformed into serine[4e] and 2-chloroalanine;[5] its racemic[6a] and optical active form[6b] were earlier described in scientific literature.

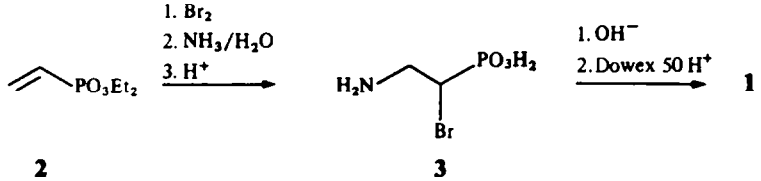
It should also be noted that free S-aziridine-2,3-dicarboxylic acid was isolated from "Streptomyces" and its antibacterial activity was reported.[7] The same kind of activity was established for the series of aziridine-2-phosphonates.[8]

RESULTS AND DISCUSSION

As we earlier described[2] aziridine-2-phosphonic acid **1** is easily prepared from 1-bromo-2-aminoethanephosphonic acid **3** formed from 1-bromovinylphosphonate. We have improved the preparation of **3** using the commercially available diethyl vinylphosphonate **2** as starting material. The fast bromination of **2** in absence of solvent and then a direct reaction of the resulting dibromo derivative with aqueous ammonia and final hydrolysis of crude diethyl ester of **3** leads in one-pot procedure to 47% of pure **3**. The cyclization of **3** in a boiling aqueous sodium hydroxide within 5 min forms the disodium salt of **1** which after passage through an ion exchange column gives 86% of pure aziridine **1** (Scheme 1).

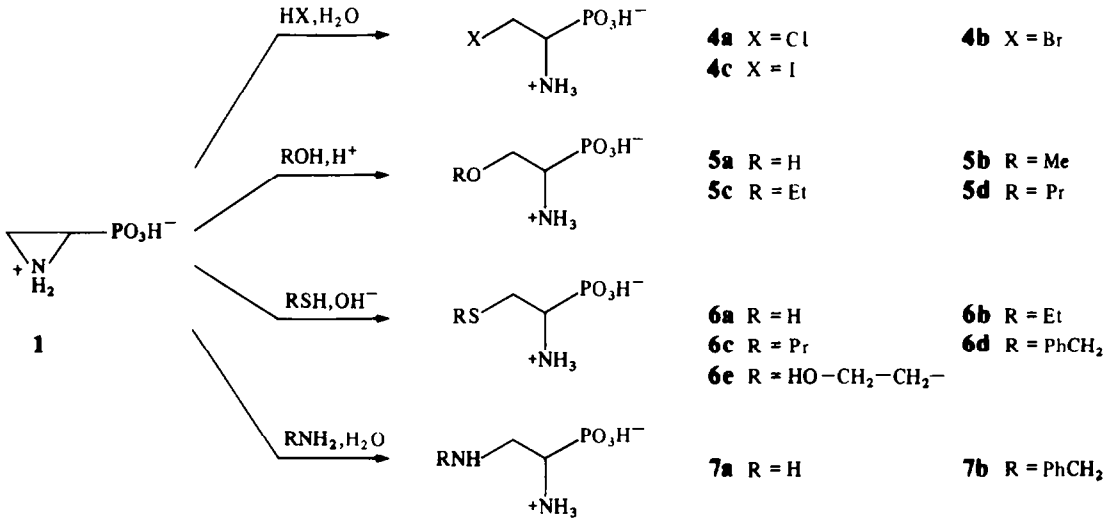
The conversion of linear system **3** to cyclic structure **1** is conveniently monitored by ^{1}H-NMR spectroscopy by performing the reaction in an NMR tube using deuterated medium NaOD/D_2O. The disappearance of two multiplets due to ethane skeleton centered at 4.12 ppm and 3.42 ppm with the concomitant appearance of new multiplet of non-protonated aziridine ring centered at 2.26 ppm was observed. This process was complete after 5 min at 100°.

As opposed to diethyl aziridine-2-phosphonate[9] which we previously used to synthesize phosphonic analogs of serine and 2-chloroalanine,[2,10a] aziridine-2-phosphonic acid **1** is a solid, crystalline, stable product, much more readily prepared and purified. Its zwitterionic structure was ascertained by comparison of ^{1}H-NMR spectrum of disodium salt of aziridine-2-phosphonic acid with the spectrum of free acid **1** (in D_2O). The complete downfield shift 0.90 ppm was



2 **3**

Scheme 1.



Scheme 2.

observed for ring protons of free acid **1** compared to its disodium salt. According to lit.[11] a downfield shift about 1 ppm was admitted from a methylene group of protonated aziridine compared to the unprotonated form.

The synthesis of 2-functionalized 1-amino-ethanephosphonic acid **4–7** was achieved by both acid-catalyzed and noncatalyzed openings of aziridine ring of **1** (Scheme 2). Treatment of aziridine **1** with conc aqueous hydrochloric, hydrobromic or hydroiodic acid led to corresponding 1-amino-2-halogenoethanephosphonic acid **4** in good yield. Unfortunately, our attempts to prepare the fluoro derivative **4** (X = F) via ring-opening of **1** with liquid HF and Olah's reagent met with failure.

The alkoxy derivatives of 1-amino-2-hydroxy-ethanephosphonic acid **5** (R = Me, Et, Pr) were formed by reaction of aziridine **1** with appropriate alcohol in the presence of sulfuric acid. The synthesis of phosphonic analog of serine **5** (R = H) via ring-opening of **1** with boiling water was described earlier.[2]

Treatment of aziridine **1** with hydrogen sulfide in alkaline solution led to formation of phosphonic analog of cysteine **6** (R = H). While the reaction of aziridine-2-phosphonic acid **1** with H_2S occurs within 2 hr at 40°, the ring-opening with mercaptanes, forming the S-alkyl derivatives **6** (R = Et, Pr, $PhCH_2$, $HOCH_2CH_2$), requires higher temperature (100°) and longer time of reaction (12–80 hr).

The 1,2-diaminoethanephosphonic acid **7** (R = H) and its 2-N-benzyl derivative **7** (R = $PhCH_2$) were produced by the action of aziridine **1** with aqueous solution of ammonia and benzylamine at 100°, respectively.

It is proper to add that the solution of disodium salt of aziridine **1**, obtained just after cyclization of **3**, can be directly used to prepare the amino **4** and **6**, instead of pure aziridine-2-phosphonic acid **1**, isolated by ion exchange column. The cyclization of **3** occurs quantitatively and no evidence of by-products was observed (NMR, TLC).

The structural assignment of 1-amino-2-functionalized ethanephosphonic acids **4–7** was initially formulated on the basis of their spectroscopic data. A more convincing evidence of structure was obtained by a comparison of spectroscopic and physical properties of some 1-amino derivatives **4–7** with samples prepared by the unambiguous chemical synthesis or with samples of appropriate isomeric 2-amino derivatives.

Thus, we established the structure of 1-amino-2-mercaptoethanephosphonic acid **6** (R = H) and its S-benzyl derivative **6** (R = $PhCH_2$) by comparison with independently synthesized samples[3] (IR, TLC, m.p.). The structure of phosphonic analog of serine **5** (R = H) and 2-bromoalanine **4** (X = Br) were well confirmed by the comparison with samples of isoserine analog[10] and 1-bromo-2-aminoethanephosphonic acid **3**, respectively (NMR, TLC, m.p.).

The acid hydrolysis of ethers **5** (R = Me, Et, Pr) leads directly to serine analog **5** (R = H).[2]

It should also be noted that according to lit. the ring-opening of aziridine-2-carboxylates by different nucleophiles in various reaction media usually proceeds regioselectively and leads to introduction of new chemical group at 2 position of 1-amino acids.[12]

We observed that ring-opening of aziridine-2-phosphonic acid **1** to products **4–7** is regiospecific and no evidence was observed for the formation of isomeric products, resulting from attack of nucleophile at C-1 position (NMR, TLC). The nucleophilic attack is generally directed to the less substituted C-2 carbon of aziridine ring.

EXPERIMENTAL

All M.ps are uncorrected and were taken on a Koeffler apparatus. IR spectra were obtained with a Perkin–Elmer 621 instrument as KBr pellets. Absorption are given in cm^{-1}.

^{1}H-NMR spectra were recorded on a Tesla BS 487 80 MHz instrument in D_2O, D_2O/D_2SO_4 or CF_3COOH solns. Chemical shifts are reported in units (ppm) downfield from the internal standard HMDS. Analytical TLC for amino acids was performed on precoated commercial (Merck, Kieselgel 60 F_{254}, 5 × 10 cm) plates and the homogeneous mixture of acetic acid : n-butanol : pyridine : water = 5 : 5 : 3 : 3 (v) was used as eluent. The analytical chromatograms were developed by spraying with a 1% soln of ninhydrine in acetone followed by heating on a hot plate.

1-Bromo-2-aminoethanephosphonic acid (**2**)

Br_2 (32 ml, 0.61 M) was dropwise added to well stirred diethyl vinylphosphonate (Aldrich) (100 g, 0.61 M) over 30 min at 15–20° (ice water-bath). After the addition was complete the stirring was continued for 2 hr at room temp and conc NH_4OH (200 ml) was added at 50–60° (exothermic reaction!) over 5–10 min. The mixture was stirred at the same temp for another 10 min and the resulting homogeneous soln was gently conc *in vacuo* to give a semi-solid residue. To this conc HCl (200 ml) was added and the acid soln after separation of the inorganic salt was refluxed for 6 hr. The resulting hydrolyzate was evaporated *in vacuo*, the thick oil was dissolved in EtOH and an insoluble material was removed by filtration. The filtrate was treated with propylene oxide (to pH of 5–6) and after several hours the solid amino acid was filtered (83.0 g). Crystallization of this material from water–EtOH provided pure **2** (58.7 g, 47%), m.p. 218–222°.[2] IR (KBr): 3700–1900 (CH, NH_3^+, PO_3H^-), 1640 (NH), 1140 and 1030 (PO_3H^-); 560 (C–Br). ^{1}H-NMR (D_2O–D_2SO_4): 3.50–4.42 (m, 2H, C$\underline{H}_2$–CH), 4.72 (dt, 1H, J^2_{PH} = 10 Hz, J^3_{HH} = 10 Hz and 4 Hz, CH_2–C$\underline{H}$). (Found: N, 6.8; P, 15.3; Br, 39.3. Calc for $C_2H_7BrNO_3P$: N, 6.8; P, 15.2; Br, 39.2%.)

Aziridine-2-phosphonic acid (**1**)

To a suspension of **2** (7.0 g, 34 mM) in 20 ml of water was added NaOH aq (4.1 g, 102 mM) in 30 ml of water. The homogeneous resulting soln was gently refluxed for 5 min, concentrated *in vacuo* and applied to the Dowex 50 H^+ column. The column was washed with water, the ninhydrine-positive fractions were collected and conc *in vacuo* below 40° (10–15 ml). To this EtOH was added and the slightly turbid soln was allowed to stand overnight. The white crystals (3.0 g) of product were separated by filtration. To the filtrate EtOH was added and the mother liquors from the above crystallization gave an additional amount of pure **1** (0.6 g). Thus the total yield of **1** was 3.6 g (86%), m.p. 224–226°.[2] IR (KBr): 3700–1900 (CH, NH_2^+, PO_3H^-), 1605 (NH), 1770 and 1085 (PO_3H^-). ^{1}H-NMR (D_2O): 2.75–3.58 (m, ABX, C$\underline{H}$–C$\underline{H}_2$). (Found: N, 11.5; P, 25.1. Calc for $C_2H_6NO_3P$: N, 11.4; P, 25.2%.)

1-Amino-2-chloroethanephosphonic acid (**4a**)

The soln of **1** (1.0 g, 8 mM) in 20 ml of conc HCl was refluxed for 20 min. The mixture was evaporated *in vacuo* to dryness, the residue was dissolved in EtOH and the resulting soln was treated with propylene oxide (to pH of 5–6). The ppt was filtered off (1.18 g) and crystallized from water–EtOH to give 0.98 g (77%) white crystals of pure **4a**, m.p. 202–208°.[10a] IR (KBr): 3700–2000 (CH, NH_3^+, PO_3H^-), 1625 and 1600 (NH), 1170 and 1070 (PO_3H^-), 750 (C–Cl). ^{1}H-NMR (CF_3COOH): 3.70–5.00 (m, ABX, 3H, C$\underline{H}_2$–C$\underline{H}$), 7.67 (broad, 2.8 H, NH_3^+). (Found: N, 8.7; P, 19.6; Cl, 21.9. Calc for $C_2H_7ClNO_3P$: N, 8.8; P, 19.4; Cl, 22.2%.)

1-Amino-2-bromoethanephosphonic acid (**4b**)

The same procedure was used as described for **4a** using conc HBr instead of HCl; the crude product (1.56 g) was crystallized from water–EtOH to give 1.22 g (75%) white crystals of pure **4b**, m.p. 171–173°. IR (KBr): 3700–1900 (CH, NH_3^+, PO_3H^-), 1595 (NH), 1165 and 1060 (PO_3H^-), 560 (C–Br). ^{1}H-NMR (D_2O–D_2SO_4): 3.83–4.75 (m, ABX, C$\underline{H}$–C$\underline{H}_2$). (Found: N, 6.4; P, 15.1; Br, 39.2. Calc for $C_2H_7BrNO_3P$: N, 6.8; P, 15.2; Br, 39.2%.)

1-Amino-2-iodoethanephosphonic acid (**4c**)

The soln of **1** (1.0 g, 8 mM) in 10 ml of 50% HI was allowed to stand for 24 hr at room temp. The resulting mixture was neutralized with 5% Na_2CO_3 aq and applied to the Dowex 50 H^+ column. The column was washed with water, the ninhydrine-positive fractions were collected and evaporated to dryness furnished pure crystalline product, 1.40 g (70%), m.p. 182–184°. IR (KBr): 3700–1800 (CH, NH_3^+, PO_3H^-), 1600 and 1590 (NH), 1180 and 1060 (PO_3H^-), 530 (C–I). ^{1}H-NMR (D_2O–D_2SO_4): 3.66–4.75 (m, ABX, C$\underline{H}_2$–C$\underline{H}$). (Found: N, 5.4; P, 12.2; I, 49.4. Calc for $C_2H_7INO_3P$: N, 5.6; P, 12.3; I, 50.6%.)

1-Amino-2-alkoxyethanephosphonic acids (**5**)

General procedure. The suspension of powdered **1** (1.0 g, 8 mM) in 100 ml of appropriate alcohol was homogenized by addition of about 10 ml of conc H_2SO_4 and the resulting soln was refluxed for 3 hr. The mixture was then cooled, neutralized with NH_4OH and evaporated to dryness. The residual solid was dissolved in a minimum amount of water and applied to the Dowex 50 H^+ column. The column was washed with water, the ninhydrine-positive fractions were collected and evaporated to dryness. Crystallization from water–ethanol furnished pure, crystalline products **5**.

1-Amino-2-methoxyethanephosphonic acid (**5b**). Yield 65%, m.p. 235–238°.[10a] IR (KBr): 3700–2000 (CH, NH_3^+, PO_3H^-), 1630 and 1520 (NH), 1180 and 1030 (PO_3H^-). ^{1}H-NMR (D_2O–D_2SO_4): 3.75 (s, 3H, C$\underline{H}_3$), 3.80–4.50 (m, ABX, 3H, C$\underline{H}_2$–C$\underline{H}$). (Found: N, 9.0; P, 19.6. Calc for $C_3H_{10}NO_4P$: N, 9.0; P, 20.0%.)

1-Amino-2-ethoxyethanephosphonic acid (**5c**). Yield 60%, m.p. 244–247°. IR (KBr): 3700–1900 (CH, NH_3^+, PO_3H^-), 1640 and 1630 (NH), 1180 and 1060 (PO_3H^-). ^{1}H-NMR (D_2O–D_2SO_4): 1.55 (t, 3H, J^3_{HH} = 7 Hz, C$\underline{H}_3$), 3.98 (q, 2H, J^3_{HH} = 7 Hz, $CH_3C\underline{H}_2O$), 4.08–4.58 (m, ABX, 3H, C$\underline{H}_2$–C$\underline{H}$). (Found: N, 8.0; P, 18.7. Calc for $C_4H_{12}NO_4P$: N, 8.3; P, 18.3%.)

1-Amino-2-propoxyethanephosphonic acid (**5d**). Yield 55%, m.p. 256–260°. IR (KBr): 3700–1900 (CH, NH_3^+, PO_3H^-), 1640–1590 (NH), 1175 and 1030 (PO_3H^-). ^{1}H-NMR (D_2O–D_2SO_4): 1.28 (t, 3H, J^3_{HH} = 7 Hz, C$\underline{H}_3$), 2.01 (sext, 2H, J^3_{HH} = 7 Hz, $CH_3C\underline{H}_2CH_2$), 3.96 (t, 2H, J^3_{HH} = 7 Hz, $CH_3CH_2C\underline{H}_2O$), 4.08–4.58 (m, ABX, 3H, C$\underline{H}_2$–C$\underline{H}$). (Found: N, 7.8; P, 16.8. Calc for $C_5H_{14}NO_4P$: N, 7.6; P, 16.9%.)

1-Amino-2-mercaptoethanephosphonic acid (**6a**)

Into a stirred soln prepared from **1** (3.0 g, 24 mM), NaOH (2.0 g, 50 mM) and 100 ml freshly distilled water, H_2S was bubbled for 2 hr at 40–45°. The mixture was then immediately acidified with conc HCl and evaporated *in vacuo* to dryness. The solid residue was dissolved in a minimum amount of water and applied to the Dowex 50 H^+ column. The column was washed with water, the nitroprusside-positive fractions were collected (5% soln of nitroprusside sodium salt in aqueous ammonia) and evaporated *in vacuo* to dryness to give 2.2 g (58%) of crystalline product **6a**, t. top. 228–234°[3] (251.5–252.5°).[13b] IR (KBr): 3700–1800 (CH, NH_3^+, PO_3H^-, SH), 1605 and 1520 (NH), 1180 and 1030 (PO_3H^-). ^{1}H-NMR (D_2O–D_2SO_4): 2.87–4.50 (m, ABX, C$\underline{H}_2$–C$\underline{H}$). (Found: N, 8.9; P, 19.6; S, 20.2. Calc for $C_2H_8NO_3PS$: N, 8.9; P, 19.7; S, 20.4%.)

1-Amino-2-S-alkylethanephosphonic acids (**6**)

General procedure. The mixture of **1** (1 g, 8 mM) and 16 mM appropriate mercaptane in 2 ml of water was homogenized with 60% NaOH aq and the resulting soln was heated in a sealed tube for 12 hr (**6e**) or 80 hr (**6b, c, d**) at 100°. The mixture was then cooled, neutralized with HCl and evaporated *in vacuo* to dryness. The residue was dissolved in water, the resulting soln was refluxed with activated charcoal and filtered. The filtrate was applied to the Dowex 50 H^+ column, which was washed with water and the ninhydrine-positive fractions were collected. After evaporation of water, the crystalline products **6** were obtained.

1-Amino-2-S-ethyloethanephosphonic acid (**6b**). Yield 53%, m.p. 254–256° (257–259.5°).[13a] IR (KBr): 3700–1800 (CH, NH_3^+, PO_3H^-), 1600 and 1515 (NH), 1170 and 1020 (PO_3H^-). ^{1}H-NMR (D_2O–D_2SO_4): 1.58 (t, 3H, J^3_{HH} = 7 Hz, C$\underline{H}_3$), 2.96 (q, 2H, J^3_{HH} = 7 Hz, $CH_3C\underline{H}_2$), 3.06–4.33 (m, ABX, 3H, C$\underline{H}_2$C$\underline{H}$). (Found: N, 7.3; P, 16.7; S, 17.5. Calc for $C_4H_{12}NO_3PS$: N, 7.5; P, 16.7; S, 17.3%.)

1-Amino-2-S-propyloethanephosphonic acid (**6c**). Yield 50%, m.p. 251–253° (251–252°).[13a] IR (KBr): 3700–1800 (CH, NH_3^+, PO_3H^-), 1600 and 1505 (NH), 1170 and 1015 (PO_3H^-).

^{1}H-NMR (D_2O–D_2SO_4): 1.36 (t, 3H, J^3_{HH} = 7 Hz, $C\underline{H}_3$), 2.01 (sext, 2H, J^3_{HH} = 7 Hz, $CH_3C\underline{H}_2$), 3.00 (t, 2H, J^3_{HH} = 7 Hz, $CH_3CH_2C\underline{H}_2$), 3.11–4.41 (m, ABX, 3H, $C\underline{H}_2C\underline{H}$). (Found: N, 7.1; P, 15.6; S, 16.0. Calc for $C_5H_{14}NO_3P$: N, 7.0; P, 15.6; S, 16.1%.)

1-*Amino*-2-S-*benzyloethanephosphonic acid* (**6d**). Yield 57%, m.p. 263–265°.[3] IR (KBr): 3700–1800 (CH, NH_3^+, PO_3H^-), 1600 and 1510 (NH), 1150 and 1015 (PO_3H^-). ^{1}H-NMR (D_2O–D_2SO_4): 2.91–4.06 (m, ABX, 3H, $C\underline{H}_2C\underline{H}$), 4.15 (s, 2H, $PhC\underline{H}_2$), 7.71 (s, 5H, Ph). (Found: N, 5.5; P, 12.9; S, 13.0. Calc for $C_9H_{14}NO_3PS$: N, 5.6; P, 12.5; S, 12.9%.)

1-*Amino*-2-S(2-*hydroxyethane*)*ethanephosphonic acid* (**6e**). Yield 56%, m.p. 212–215°. IR (KBr): 3700–1900 (CH, NH_3^+, OH, PO_3H^-), 1620 and 1500 (NH), 1150 and 1065 (PO_3H^-). ^{1}H-NMR (D_2O–D_2SO_4): 3.25 (t, 2H, J^3_{HH} = 7 Hz, $HOCH_2C\underline{H}_2S$), 3.00–4.33 (m, ABX, 3H, $C\underline{H}_2C\underline{H}$), 4.25 (t, 2H, J^3_{HH} = 7 Hz, $HOC\underline{H}_2$). (Found: N, 7.1; P, 15.4; S, 16.0. Calc for $C_4H_{12}NO_4PS$: N, 6.9; P, 15.4; S, 15.9%.)

1,2-*Diaminoethanephosphonic acid* (**7a**) *as monohydrate*

To a soln of **1** (1.0 g, 8 mM) in 5 ml of water was added 10 ml of conc NH_4OH and the resulting mixture was heated in a sealed tube for 2 hr at 100°. The mixture was then cooled and evaporated to dryness. The yellow solid residue was crystallized from water furnished colorless crystalline product, 0.7 g (55%), m.p. 269–271°. IR (KBr): 3700–1800 (CH, NH_3^+, PO_3H^-, OH^-), 1630 and 1590 (NH), 1180 and 1040 (PO_3H^-). ^{1}H-NMR (CF_3COOH): 3.62–4.50 (m, ABX, 3H, $C\underline{H}_2C\underline{H}$), 7.21–7.85 (m, 2 × NH_3^+, 5H). (Found: N, 17.7; P, 19.5. Calc for $C_2H_9N_2O_3P \cdot H_2O$: N, 17.7; P, 19.6%.)

1-*Amino*-2-N-*benzyloethanephosphonic acid* (**7b**)

The soln of **1** (1.0 g, 8 mM) and benzylamine (3.4 g, 32 mM) in 15 ml of water was refluxed for 2 hr. The resulting mixture was cooled, treated with 10 ml of conc HCl and evaporated *in vacuo* to dryness. The residue was dissolved in MeOH and the soln was treated with propylene oxide (to pH of 5–6). The ppt was separated by filtration and crystallized from water to give pure product, 0.8 g (43%), m.p. 202–205°. IR (KBr): 3700–1900 (CH, NH_3^+, PO_3H^-), 1620 and 1540 (NH), 1170 and 1050 (PO_3H^-). ^{1}H-NMR (D_2O–D_2SO_4): 3.60–4.40 (m, ABX, 3H, $C\underline{H}_2C\underline{H}$), 4.65 (s, 2H, $PhC\underline{H}_2$), 7.80 (s, 5H, Ph). (Found: N, 12.2; P, 13.6. Calc for $C_9H_{15}N_2O_3P$: N, 12.2; P, 13.5%.)

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