Brief Communications

Synthesis of phosphinic and phosphonic analogs of homoserine

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A convenient procedure for the synthesis of 1-amino-3-hydroxypropylphosphinic and -phosphonic acids (analogs of homoserine) was developed. The procedure involves the reaction of salts of phosphinic and phosphonic analogs of *S*-methylmethionine with AcONa/AcOH followed by hydrolysis.

Key words: analogs of homoserine, 1-amino-3-hydroxypropylphosphinic and -phosphonic acids.

Phosphinic analogs of amino acids and their metabolites exhibiting biological activities have been extensively studied in recent years. Thus α-amino-γ-methylthiopropylphosphinic acid, which is an analog of methionine, possesses high antibacterial activity.[1] However, a phosphinic analog of another γ-substituted α-amino acid, *viz.*, of homoserine, which plays a major role in metabolism of methionine and *S*-adenosylmethionine (the main donor of methyl groups), has not hitherto been known.

The present study was aimed at developing a convenient procedure for the synthesis of 1-amino-3-hydroxypropylphosphinic and -phosphonic acids (**1a** and **1b**, respectively), which are analogs of homoserine.

α-Aminoalkylphosphinic acids are generally prepared by the addition of H_3PO_2,[2] $HP(SiOMe)_2$,[3] or $(EtO)_2CHP(O)(H)OEt$ [4] at the C=N bond of *N*-substituted imines followed by deprotection as well as by reactions of oximes with H_3PO_2.[5] Previously, a phosphonic analog of homoserine **1b** has been prepared by a multistage procedure[6] involving *C*-alkylation of *N*-protected ethyl aminomethylphopshonate, which is an analog of glycine, with *O*-protected iodoethanol followed by deprotection.

However, according to our data, these procedures appeared to be of little use in the synthesis of amino acid **1a**. Thus the reaction of 3-hydroxypropanal oxime with H_3PO_2 afforded the target amino acid in a yield of only 1%.

Taking into account that salts of *S*-methylmethionine are readily converted into homoserine[7] and the fact that organophosphorus analogs of *S*-methylmethionine **3a** and **3b** are readily accessible,[8] we examined the possibility of the use of the latter for the synthesis of compounds **1a** and **1b**, respectively. Initially, the phosphinic and phosphonic analogs of methionine, *viz.*, **2a** and **2b**, were converted into sulfonium salts **3a** and **3b**, respectively. Compound **3a** was prepared according to a procedure reported previously.[8] It appeared that phosphonic acid **3b** was also more conveniently prepared by methylation of sulfide **2b** under the action of methyl *p*-toluenesulfonate according to a procedure used for the synthesis

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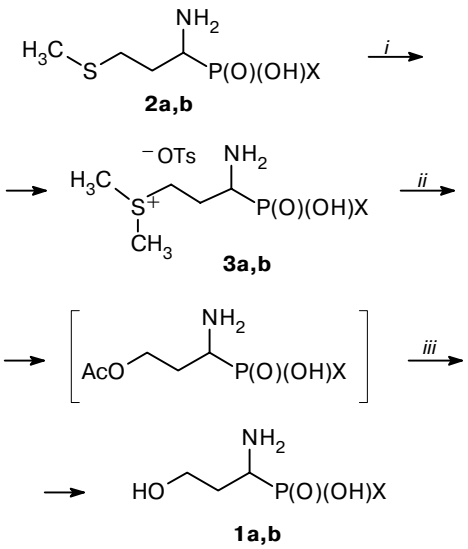
of **3a** rather than by oxidation of the corresponding phosphinic acid **3a**.[8]

Under conditions of the synthesis of homoserine from *S*-methylmethionine (heating in aqueous solutions of $NaHCO_3$), sulfonium salts **3a** and **3b** gave mixtures of products, which contained demethylation products **2a** and **2b**, respectively, whereas the target compounds **1a** and **1b** were present in insignificant amounts. Analogously, the reaction of sulfide **2a** with iodoacetamide under conditions of the formation of homoserine from methionine derivatives[9] afforded a complex mixture of products.

We found that heating of sulfonium salts **3a** and **3b** with NaOAc in AcOH followed by treatment with aqueous HCl gave rise to amino(hydroxy)alkylphosphinic and -phosphonic acids **1a** and **1b**, respectively, in 80—85% yields. Apparently, the reactions proceeded through intermediate formation of the corresponding *O*-acetyl derivatives.

Scheme 1



1, **2**, **3:** X = H (**a**), OH (**b**)

Reagents and conditions: *i.* MeOTs/AcOH—HCOOH; *ii.* NaOAc · 3 H_2O/AcOH, Δ; *iii.* HCl/H_2O.

In addition, oxidation of aminopropylphosphinic acid **1a** with Br_2 in an acidic medium afforded aminopropylphosphonic acid **1b** in 84% yield.

Experimental

Thin-layer chromatography was carried out on Silufol UV_{254} plates using the 7 : 2 : 1 Pr^iOH—25% NH_4OH—H_2O (*A*) and 12 : 3 : 5 Bu^nOH—AcOH—H_2O (*B*) systems. Compounds were visualized by color reactions with ninhydrin and ammonium molybdate. Ion-exchange chromatography was performed on Dowex-50Wx8 cation-exchange resin (100—200 mesh, H^+; BioRad, USA) using 15% aqueous Pr^iOH as the eluent. The melting points (decomposition, not corrected) were determined on an Electrothermal instrument (England). The ^1H NMR spectra were recorded on a Bruker AMX III-400 instrument in D_2O with Bu^tOH as the internal standard; the chemical shifts are given relative to Me_4Si.

1-Amino-3-methylthiopropylphosphinic acid (2a), 1-amino-3-methylthiopropylphosphonic (2b) acid,[8] (3-amino-3-hydro(hydroxy)phosphorylpropyl) dimethylsulfonium *p*-toluenesulfonate (3a),[8] and 3-hydroxypropanal oxime[10] were prepared according to procedures reported previously.

All compounds used and described in the present study were racemates.

(3-Amino-3-dihydroxyphosphorylpropyl) dimethylsulfonium *p*-toluenesulfonate (3b). MeOTs (0.558 g, 3 mmol) was added to a solution of sulfide **2b** (370 mg, 2 mmol) in a mixture of AcOH (2 mL) and HCOOH (2 mL). The reaction mixture was kept at 20 °C for two weeks and then concentrated to dryness *in vacuo*, and Pr^iOH (5 mL) was added to, and distilled from, the residue, which was then recrystallized from aqueous EtOH and dried *in vacuo* over P_2O_5/KOH. Compound **3b** was obtained in a yield of 0.48 g (65%), m.p. 214 °C. R_f 0.12 (*A*), R_f 0.08 (*B*). ^1H NMR, δ: 2.20—2.32 (m, 2 H, $C\underline{H}_2CH$); 2.36 (s, 3 H, $C\underline{H}_3C_6H_4$); 2.92 (s, 6 H, Me_2S^+); 3.35—3.42 (m, 1 H, CH); 3.50 (t, 2 H, $^+SCH_2$, J = 8 Hz); 7.33—7.35 and 7.65—7.67 (both d, 4 H, C_6H_4). Found (%): C, 38.73; H, 5.98; N, 3.74. $C_{12}H_{22}NO_6PS_2$. Calculated (%): C, 38.80; H, 5.97; N, 3.77.

1-Amino-3-hydroxypropylphosphinic acid (1a). ***A***. 3-Hydroxypropanal oxime (13.8 g, 0.155 mol) was added portionwise with stirring to a boiling solution of anhydrous H_3PO_2 (33 g, 0.5 mol) in Pr^iOH (250 mL) under an atmosphere of N_2 over 30 min. Then the mixture was refluxed for 2 h and concentrated *in vacuo*. Compound **1a** was isolated by ion-exchange chromatography. After recrystallization from aqueous EtOH and drying *in vacuo* over P_2O_5/KOH, compound **1a** was obtained in a yield of 215 mg (1%), m.p. 193 °C. R_f 0.41 (*A*), R_f 0.17 (*B*). ^1H NMR, δ: 1.88—2.29 (m, 2 H, $C\underline{H}_2CH$); 3.83—3.95 (t, 2 H, OCH_2); 3.32—3.45 (m, 1 H, CH); 6.92 (d, 1 H, PH, J = 527 Hz). Found (%): C, 25.71; H, 7.14; N, 9.91. $C_3H_{10}NO_3P$. Calculated (%): C, 25.90; H, 7.24; N, 10.06.

B. A solution of sulfonium salt **3a** (175 mg, 0.5 mmol) and NaOAc · 3 H_2O (68 mg, 0.5 mmol) in AcOH (5 mL) was refluxed for 5 h. The reaction mixture was concentrated to dryness *in vacuo*. The residue was dissolved in 5 *M* HCl (5 mL) and refluxed for 30 min. The solution was concentrated to dryness *in vacuo*, and water was added to, and distilled from, the residue. The target product **1a** was isolated by ion-exchange chromatography. After recrystallization from aqueous EtOH and drying *in vacuo* over P_2O_5/KOH, compound **1a**, which was identical with the authentic sample prepared according to procedure *A*, was obtained in a yield of 60 mg (85%).

1-Amino-3-hydroxypropylphosphonic acid (1b). ***A***. A solution of sulfonium salt **3b** (185 mg, 0.5 mmol) and NaOAc · 3 H_2O (68 mg, 0.5 mmol) in AcOH (5 mL) was refluxed for 7 h. Then the reaction mixture was worked up and the product was isolated as described above. Acid **1b** was obtained in a yield of 62 mg (80%), m.p. 237 °C. R_f 0.12 (*A*), R_f 0.17 (*B*). ^1H NMR, δ: 1.92—2.30 (m, 2 H, $C\underline{H}_2CH$); 3.82—3.93 (t, 2 H, OCH_2); 3.41—3.55 (m, 1 H, CH). Found (%): C, 22.94; H, 6.45; N, 8.93. $C_3H_{10}NO_4P$. Calculated (%): C, 23.08; H, 6.46; N, 8.97.

B. Bromine (0.15 mL) was added to a stirred solution of phosphinic acid **1a** (278 mg, 2 mmol) in a mixture of concentrated HBr (1 mL) and EtOH (5 mL). Then the reaction mixture was stirred at 20 °C for 30 min, propylene oxide was

added, and the mixture was kept at +4 °C for 2 h. The precipitate that formed was filtered off and washed with EtOH. After recrystallization from aqueous EtOH and drying *in vacuo* over P_2O_5/KOH, phosphonic acid **1b**, which was identical with the authentic sample prepared according to a procedure *A*, was obtained in a yield of 260 mg (84%).

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