Synthesis of phosphinic analogs of sulfur-containing amino acids

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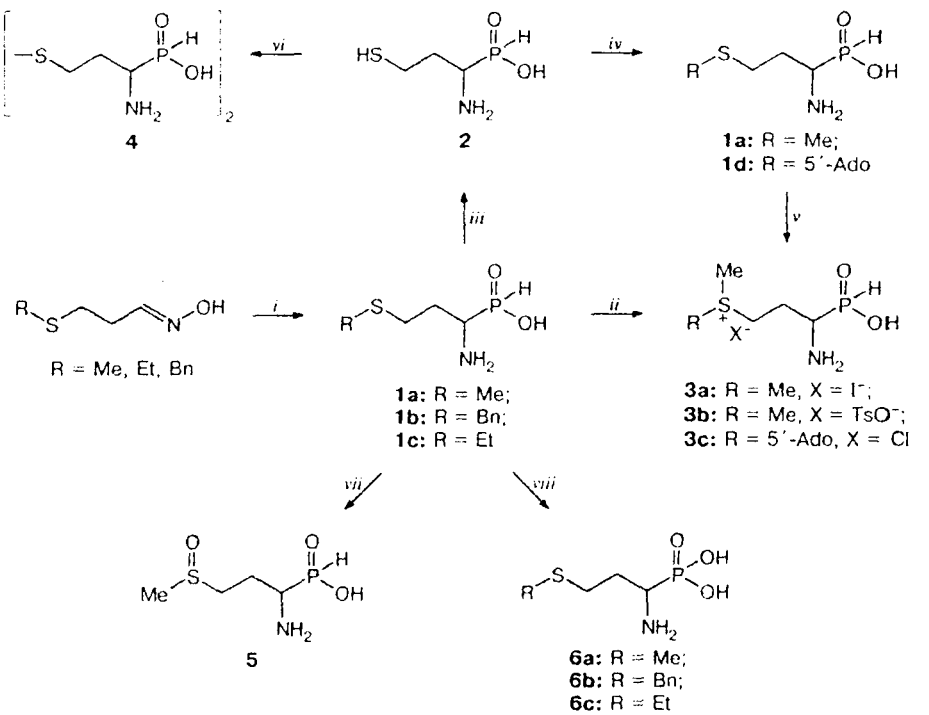
Phosphinic analogs of the key compounds of the metabolism of methionine were synthesized. The compounds obtained were selectively oxidized either at the phosphinic group or at the sulfur-containing fragment.

Key words: phosphinic and phosphonic analogs of methionine, ethionine, *S*-benzylhomocysteine, homocysteine, *S*-adenosylhomocysteine, and *S*-adenosylmethionine.

1-Amino-3-(methylthio)propylphosphinic acid (**1a**), an analog of methionine, is one of the most biologically active compounds among phosphinic analogs of amino acids. This compound possesses high antibacterial activity,[1] peptides involving **1a** have fungicidal activity,[2] and **1a** itself inhibits the initial stage of protein biosynthesis.[3] The structure—biological activity relationships of phosphinic analogs of compounds involved in methionine metabolism were not investigated systematically because analogs were not obtained or remained unavailable.

In the present work, the synthesis of phosphinic analogs of key compounds in the metabolism of methionine is discussed.

Scheme 1



Reagents and conditions: *i*. H_3PO_2/R′OH/Δ; *ii*. MeI/AcOH or MeOTs/AcOH; *iii*. Na/liquid NH_3; *iv*. MeI/liquid NH_3 or 5′-Cl-Ado/DMSO/H_2O; *v*. MeI/AcOH—HCOOH; *vi*. O_2/Fe^{3+} or I_2/NaOH/EtOH/H_2O; *vii*. H_2O_2/AcOH/+4 °C; *viii*. I_2/HI/EtOH.

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The known synthesis[4] of acid **1a** (12.8% yield) includes addition of H_3PO_2 to a Schiff base (prepared from 3-methylthiopropanal and diphenylaminomethane) with subsequent elimination of the protecting group by acidification. Another way,[5] *viz.*, the reaction of 3-methylthiopropanal oxime with anhydrous H_3PO_2 in the absence of a solvent, also yields **1a**, but our observations showed the process to be often out of control.

We found that **1a** is smoothly formed in 35% yield in the reaction of 3-methylthiopropanal oxime with H_3PO_2 in boiling alcohols. Similarly, compound **1b** was synthesized in 27% yield.

Aminophosphinic acid **1b** was transformed into an analog of homocysteine **2** in 43% yield by the action of sodium metal in liquid ammonia.

A phosphinic analog of *S*-adenosylhomocysteine **1d** was synthesized by alkylation of thiol **2** with 5′-chloro-5′-deoxyadenosine in liquid ammonia or aqueous DMSO; in the latter case, **1d** was obtained in 90% yield. Methylation of thiol **2** was carried out under conditions similar to those for the synthesis of isotope-labeled (on the methyl group) thioether **1a**.

Methylation of **1a** with MeOTs or MeI in AcOH or a mixture of AcOH and HCOOH did not involve the phosphinic fragment, resulting in the **3a**- and **3b**-phosphinic analog of vitamin U.

Aminophosphinic acid **1d** was transformed into **3b**, an analog of *S*-adenosylmethionine, which is the main donor of Me-groups in biological methylation, by the action of an excess of MeI in AcOH—HCOOH or HCOOH—dioxane at 20 °C with subsequent isolation of the product by ion-exchange chromatography on Dowex 50W×8 cation exchanger in the H^+ form.

Oxidative transformations of phosphinic analogs were performed so that both the hydrophosphoryl fragment and the sulfur-containing group were selectively involved. Under the conditions described earlier,[6] an ethanolic solution of I_2 and HI smoothly reacted with acids **1a**, **1b**, and **1c** to give the corresponding aminophosphonic acids with retention of the thioether group. Under the standard conditions of thiol oxidation, the mercapto group of phosphinic acid **2** was oxidized with I_2 to disulfide without involving the P—H fragment. Nor did the action of H_2O_2 in AcOH on **1a** involve the P—H fragment during the oxidation of the thioether group to the sulfoxide.

Thus, we synthesized polyfunctional phosphinic analogs of the most important sulfur-containing amino acids and developed methods for selective oxidation of the compounds obtained.

Experimental

Thin-layer chromatography was performed on Kieselgel $60F_{254}$ plates (Merck) in Pr^iOH—25% NH_4OH—H_2O, 7 : 2 : 1 (A), and Bu^nOH—AcOH—H_2O, 12 : 3 : 5 (B), and on Cellulose F_{254} plates (Merck) in Bu^nOH—AcOH—H_2O, 12 : 3 : 5 (C); spots were visualized by color reactions with ninhydrin, ammonium molybdate, and sodium nitroprusside. Ion-exchange chromatography was performed on Dowex-50W×8 cation exchanger (100—200 mesh) in the H^+ and PyH^+ forms (BioRad, USA). HPLC was carried out according to the known procedure[7] on a Hypersil ODS column (Hewlett-Packard, 5 μm, 2.1×100 mm), UV detector, λ = 257 nm. The following buffer solutions were used: (*A*) 0.1 *M* KH_2PO_4 (pH 2.5)—0.008 *M* $C_8H_{17}SO_3Na$—H_2O/CH_3CN, 94 : 6 (by volume) and (*B*) 0.1 *M* KH_2PO_4 (pH 3.2)—0.008 *M* $C_8H_{17}SO_3Na$—H_2O/CH_3CN, 70 : 30 (by volume). A mixture of buffers *A* and *B* was used as the eluent (a gradient of buffer *B* in buffer *A* from 10 to 85% was varied as follows: 10% (0 to 2 min), 10→85% (2 to 17 min), 85% (17 to 19 min), and 85→10% (19 to 20 min)), flow rate 0.5 mL min^{-1}. Melting points (decomp.) were measured on an Electrothermals instrument (UK) and are given noncorrected. ^1H NMR spectra were recorded on a Varian XL-100-15 instrument (100 MHz) in D_2O (relative to Bu^tOH); the chemical shifts are given with respect to Me_4Si. UV spectra were recorded on a Beckman 25 instrument. *S*-Alkylthiopropanal oximes were prepared according to the known procedure.[8]

1-Amino-3-(methylthio)propylphosphinic acid (1a). *A.* A solution of 3-methylthiopropanal oxime[8] (119 g, 1.0 mol) in 100 mL of MeOH was added with stirring in an atmosphere of N_2 to a boiling solution of anhydrous H_3PO_2 [9] (132 g, 2.0 mol) in 320 mL of MeOH over 1 h. The reaction mixture was refluxed for 4 h, and 150 mL of MeOH was removed. Et_3N (to pH ~ 4) and then 500 mL of boiling Pr^iOH were added to the residue. The resulting solution was kept at +4 °C for 16 h. The crystals that formed were filtered off, washed with Pr^iOH, and dried in air. The crude product (yield 77.6 g) was recrystallized from aqueous Pr^iOH to give **1a** (58.5 g, 34.6%), m.p. 229 °C (*cf.* Ref. 4: 231 °C (decomp.)). R_f 0.53 (A), R_f 0.36 (B), R_f 0.55 (C). ^1H NMR (D_2O), δ: 1.80—2.30 (m, 2 H, $C\underline{H}_2CH$); 2.14 (s, 3 H, MeS); 2.57—2.85 (m, 2 H, CH_2S); 3.12—3.44 (m, 1 H, CH); 7.02 (dd, 1 H, PH, J = 528 Hz, J = 1.5 Hz).

B. Sodium metal was added to a solution of compound **2** (1.55 g, 0.01 mol) in 40 mL of liquid NH_3 until a blue color persisted, and then freshly distilled MeI (1.9 mL, 0.03 mol) was added. The ammonia was allowed to evaporate, and the residue was concentrated *in vacuo* with water. Compound **1a** was isolated on a 75-mL column with Dowex 50W resin (H^+ form) by elution with a 15% aqueous solution of Pr^iOH. The fractions containing **1a** were concentrated *in vacuo* to dryness to give **1a** (1.5 g, 89%) that is identical with an authentic sample.

C. MeOH (1.8 mL) and MeI (0.012 mL) were added to a solution of compound **2** (31 mg, 0.2 mmol) in 0.2 mL of 2 *M* NaOH. The mixture was left for 16 h and concentrated *in vacuo* to dryness. Compound **1a** (32 mg, 95%) was isolated as described above to give a product identical with an authentic sample.

1-Amino-3-(benzylthio)propylphosphinic acid (1b). A solution of 3-benzylthiopropanal oxime[8] (104.4 g, 0.53 mol) was added with stirring in an atmosphere of N_2 to a boiling solution of anhydrous H_3PO_2 [9] (69.3 g, 1.05 mol) in 400 mL of anhydrous Pr^iOH over 1 h. The reaction mixture was refluxed for 3 h and cooled. The precipitate that formed was filtered off, washed with Pr^iOH, and dried in air to give crude product **1b** (35.1 g, 27%). The filtrates were combined and, after addition of Et_3N to pH ~4.5, left at 20 °C for 16 h to give an additional amount of **1b** (6.36 g, 4.9%). Recrystallization from H_2O afforded **1b** (36.4 g, 28%), m.p. 221 °C. R_f 0.61 (A), R_f 0.46 (B). ^1H NMR (0.25 *M* NaOD in D_2O), δ: 1.72—2.20 (m, 2 H, CH_2CH); 2.38—2.86 (m, 3 H, $S\underline{C}H_2CH_2$ and

CH); 3.86 (s, 2 H, $C\underline{H}_2C_6H_5$); 6.60 (dd, 1 H, PH, J = 486 Hz, J = 1.8 Hz); 7.21 (m, 5 H, $C_6\underline{H}_5$). Found (%): C, 48.75; H, 6.81; N, 5.43. $C_{10}H_{16}NO_2PS$. Calculated (%): C, 48.97; H, 6.57; N, 5.71.

1-Amino-3-(ethylthio)propylphosphinic acid (1c). 3-Ethylthiopropanal oxime[8] (33 g, 0.25 mol) was added with stirring in an atmosphere of N_2 to a boiling solution of anhydrous H_3PO_2 [9] (33 g, 0.5 mol) in 100 mL of Pr^{i}OH over 30 min. The reaction mixture was refluxed for 3.5 h, concentrated *in vacuo*, and washed with ether (4×150 mL). The residue was dissolved in 100 mL of MeOH, and Et_3N (to pH ~ 4.5) and then boiling Pr^{i}OH (250 mL) were added. The resulting solution was kept at +4 °C for 12 h. The crystals that formed were filtered off, washed with cold Pr^{i}OH, and dried in air to give crude product **1c** (18.3 g, 40%). The product was purified on a 1.2-L column with Dowex 50W resin (H^+ form) by elution with a 15% aqueous solution of Pr^{i}OH. Recrystallization from aqueous Pr^{i}OH gave **1c** (14.0 g, 30%), m.p. 238 °C. R_f 0.64 (A), R_f 0.44 (B). ^{1}H NMR, δ: 1.28 (m, 3 H, CH_3); 1.85–2.29 (m, 2 H, $C\underline{H}_2CH$); 2.60 (q, 2 H, $CH_3C\underline{H}_2S$, J = 7 Hz); 2.65–2.87 (m, 2 H, SCH_2); 6.98 (dd, 1 H, PH, J = 524 Hz, J = 1.5 Hz). Found (%): C, 32.43; H, 7.98; N, 7.42. $C_5H_{14}NO_2PS$. Calculated (%): C, 32.78; H, 7.70; N, 7.65.

1-Amino-3-mercaptopropylphosphinic acid (2). Sodium metal (2.42 g, 0.105 mol) was added portionwise to a solution of compound **1b** (12.3 g, 0.05 mol) in 200 mL of boiling liquid NH_3 until a blue color persisted. The reaction mixture was stirred for 30 min, and then solid NH_4Cl was added until the blue color disappeared. The ammonia was allowed to evaporate, and the residue was concentrated with H_2O *in vacuo*. Thiol **2** was isolated on a 550-mL column with Dowex 50W resin (H^+ form) by elution with a 15% aqueous solution of Pr^{i}OH. The fractions containing **2** were concentrated *in vacuo* to dryness. The residue was dried *in vacuo* over P_2O_5/KOH to give compound **2** (3.63 g, 43.4%). R_f 0.39 (A), R_f 0.23 (B). ^{1}H NMR, δ: 1.72–2.26 (m, 2 H, $C\underline{H}_2CH$); 2.40–2.78 (m, 2 H, SCH_2); 3.04–3.40 (m, 1 H, CH); 6.92 (dd, 1 H, PH, J = 527 Hz, J = 1.5 Hz). The content of HS groups in the sample was found by the method[10] to be equal to 98.7% (with respect to the theoretical yield).

1-Amino-3-(dimethylthionia)propylphosphinic acid iodide (3a). Anhydrous H_3PO_2 (0.12 g) and MeI (5.0 mL) were added to a solution of compound **1a** (1.69 g, 0.01 mol) in 10 mL of AcOH. The reaction mixture was left in the dark at 20 °C for days with periodic stirring. The precipitate that formed was filtered off and washed successively with an AcOH–Et_2O (1 : 1) mixture and Et_2O. The crude product (3.03 g) was recrystallized from aqueous ethanol to give compound **3a** (2.54 g, 81.5%), m.p. 208–209 °C. R_f 0.12 (A), R_f 0.08 (B), R_f 0.31 (C). ^{1}H NMR, δ: 2.11–2.56 (m, 2 H, $C\underline{H}_2CH$); 2.96 and 2.97 (both s, 6 H, Me_2S); 3.13–3.44 (m, 1 H, CH); 3.51 (t, 2 H, SCH_2, J = 7.5 Hz); 7.07 (dd, 1 H, PH, J = 521 Hz, J = 1.5 Hz). Found (%): C, 19.54; H, 4.54; N, 4.22. $C_5H_{15}INO_2PS$. Calculated (%): C, 19.30; H, 4.86; N, 4.50.

1-Amino-3-(dimethylthionia)propylphosphinic acid tosylate (3b). MeOTs (5.58 g, 0.03 mol) was added to a solution of compound **1b** (3.28 g, 0.02 mol) in a mixture of 25 mL of AcOH and 25 mL of HCOOH. The reaction mixture was left at 20 °C for two weeks and then concentrated *in vacuo* to dryness. To the residue 35 mL of Pr^{i}OH was added and concentrated. The residue was dissolved in 10 mL of Pr^{i}OH and poured into 150 mL of Et_2O. The precipitate that formed was washed with Et_2O and dried *in vacuo* over P_2O_5/KOH. The crude product (7 g) was recrystallized from MeOH–Pr^{i}OH to give compound **3b** (5.88 g, 83%), m.p. 194 °C. R_f 0.12 (A), R_f 0.08 (B), R_f 0.31 (C). ^{1}H NMR, δ: 2.09–2.56 (m, 2 H, $C\underline{H}_2CH$); 2.39 (s, 3 H, $\underline{Me}Ph$); 2.94 and 2.95 (both s, 6 H, Me_2S); 3.14–3.45 (m, 1 H, CH); 3.50 (t, 2 H, SCH_2, J = 8 Hz); 7.06 (dd, 1 H, PH, J = 522 Hz, J = 1.5 Hz); 7.09–7.26 and 7.39–7.54 (both m, 4 H, C_6H_4). Found (%): C, 40.83; H, 6.09; N, 3.58. $C_{12}H_{22}NO_5PS_2$. Calculated (%): C, 40.55; H, 6.24; N, 3.94.

5′-[3-Amino-3-(hydrohydroxyphosphoryl)propylthio]-5′-deoxyadenosine (1d). DMSO (18 mL) and a solution of 5′-chloro-5′-deoxyadenosine[11] (1.0 g, 3.5 mmol) in 6 mL of DMSO were successively added to a solution of compound **2** (0.89 g, 5.75 mmol) in 5.8 mL of 2 *M* NaOH at 20 °C. The reaction mixture was left at 20 °C for 18 h and then poured into 150 mL of water. Crude **1d** was isolated on a 55-mL column with Dowex 50W resin (H^+ form) by washing with water (400 mL) and elution with 1 *M* NH_4OH. The fractions containing **1d** were concentrated *in vacuo*. The residue was dissolved in 1% aqueous Py. The product was isolated on a 200-mL column with Dowex 50W resin (Py^+ form) by elution with 1% aqueous Py. The fractions containing **1d** were concentrated *in vacuo*. To the residue water (4×5 mL) was added and concentrated and then EtOH (3×30 mL) was added and concentrated. The residue was dried *in vacuo* over P_2O_5/KOH to give compound **1d** (1.3 g, 92%). R_f 0.47 (A), R_f 0.17 (B), R_f 0.26 (C). ^{1}H NMR, δ: 1.82–2.29 (m, 2 H, $C\underline{H}_2CH$); 2.67–2.87 (m, 2 H, $SC\underline{H}_2CH_2$); 2.95–3.07 (m, 2 H, 5′-CH_2S); 3.10–3.40 (m, 1 H, $C\underline{H}CH_2$); 5.96 (m, 1 H, H-1′), 7.00 (dd, 1 H, PH, J = 523 Hz, J = 1.5 Hz); 8.08 (s, 1 H, H-2); 8.19 (s, 1 H, H-8). The sample obtained was of 99.9% purity (HPLC), elution time 2.51 min.

5′-{*S*-[3-amino-3-(hydrohydroxyphosphoryl)propyl]-*S*-methylthionia}-5′-deoxyadenosine chloride (3c). A mixture of HCOOH (1.5 mL) and dioxane (4.5 mL), anhydrous H_3PO_2 (110 mg), and MeI (1.5 mL) were added to a solution of compound **1d** (315 mg, 0.78 mmol) in 5 mL of anhydrous HCOOH. The reaction mixture was stirred in the dark at 20 °C for 2 days and then concentrated *in vacuo* to dryness. The residue was dissolved in 0.05 *M* HCl and applied on a 5.5-mL column with Dowex 50W resin (H^+ form). The column was washed with 0.5 *M* HCl (500 mL) and 1.0 *M* HCl (300 mL), and the product was eluted with 2.0 *M* HCl. The fractions containing **3c** were concentrated *in vacuo* to dryness. To the residue water and EtOH were added and concentrated. The residue was dried *in vacuo* over P_2O_5/KOH to give compound **3c** (176 mg, 50%). R_f 0.12 (A), R_f 0.04 (B), R_f 0.17 (C). UV (H_2O), λ_{max}/nm: 259, λ_{min}/nm: 228, $\lambda_{280}/\lambda_{260}$: 0.21. ^{1}H NMR, δ: 2.07–2.54 (m, 2 H, $C\underline{H}_2CH$); 2.96 and 2.99 (both s, 6 H, Me_2S); 3.13–3.30 (m, 1 H, $C\underline{H}CH_2$); 3.45–3.72 (m, 2 H, $SC\underline{H}_2CH_2$); 3.84–3.99 (m, 2 H, 5′-CH_2S); 6.04 (m, 1 H, H-1′); 6.94 (dd, 1 H, PH, J = 531 Hz, J = 1.5 Hz); 8.24 and 8.26 (both s, 1 H, H-2 and 1 H, H-8). The sample obtained was of 99.7% purity (HPLC), elution time 4.99 min.

1,1′-Diamino-3,3′-(dithiobis)dipropylphosphinic acid (4). *A.* 0.5 *M* I_2 in Pr^{i}OH was added to a solution of compound **2** (0.31 g, 2 mmol) in 4 mL of H_2O at 20 °C until the HS groups disappeared (negative reaction with sodium nitroprusside). Then propylene oxide was added to pH ~ 5. The precipitate that formed was filtered off, washed with Pr^{i}OH, and dried *in vacuo* over P_2O_5/KOH to give disulfide **4** (240 mg, 78%), decomp.p. 216 °C. R_f 0.38 (A), R_f 0.11 (B). ^{1}H NMR, δ: 1.93–2.49 (m, 2 H, $C\underline{H}_2CH$); 2.74–3.07 (m, 2 H, CH_2S); 3.09–3.47 (m, 1 H, CH); 7.04 (dd, 1 H, PH, J = 527 Hz, J = 1.5 Hz). Found (%): C, 23.16; H, 6.11; N, 8.78. $C_6H_{18}N_2O_4P_2S_2$. Calculated (%): C, 23.38; H, 5.89; N, 9.09.

B. A weak flow of air was passed at pH ~ 8 through a solution of compound **2** (155 mg, 1 mmol) in 5 mL of H_2O

with one drop of 0.5% $FeCl_3$ for 5 h until the HS groups disappeared. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo* and applied on a 5-mL column with Dowex 50W resin (H^+ form). The column was washed with water, and the product was eluted with 1 *M* NH_4OH. The fractions containing disulfide **4** were concentrated *in vacuo* and dried *in vacuo* over P_2O_5/KOH to give compound **4** (146 mg, 95%).

1-Amino-3-(methylsulfinyl)propylphosphinic acid (5). 30% aqueous H_2O_2 (0.7 mL) was added with stirring to a suspension of compound **1a** (0.91 g, 5.4 mmol) in 10 mL of AcOH at +4 °C for 15 min. The reaction mixture was stirred at this temperature for an additional 10 min and concentrated *in vacuo*. To the residue toluene was added and twice concentrated *in vacuo*. The residue was dissolved in MeOH, and acetone was added. The precipitate that formed was filtered off, washed with acetone, and dried in air to give crude **5** (0.95 g). Recrystallization from a H_2O—EtOH—Pr^iOH mixture gave compound **5** (0.82 g, 82%), m.p. 201—201.5 °C. R_f 0.41 (A), R_f 0.1 (B). ^1H NMR, δ: 2.01—2.49 (m, 2 H, CH_2CH); 2.74 and 2.75 (both s, 3 H, MeSO); 2.96—3.44 (m, 3 H, CH_2S and CH); 7.04 (dd, 1 H, PH, J = 532 Hz, J = 1.5 Hz). Found (%): C, 25.68; H, 6.83; N, 7.21. $C_4H_{12}NO_3PS$. Calculated (%): C, 25.94; H, 6.53; N, 7.56.

1-Aminoalkylphosphonic acids (6a—c). 1 *N* I_2 in EtOH (10.5 mL) was added dropwise with stirring to a solution of compounds **1a—c** (10 mmol) in a mixture of conc. HI (2.5 mL) and EtOH (10 mL). The reaction mixture was stirred at 20 °C for 1 h and, after addition of propylene oxide, kept at +4 °C for 2 h. The precipitate that formed was filtered off, washed with EtOH, and recrystallized from aqueous EtOH to give acids **6a—c**, in 80—95% yields, that are identical with authentic samples.

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