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Notes

# Synthetic Sulfur-Containing Amino Acids. Inhibition of Transport Systems in S37 Ascites Tumor Cells

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The preparation of a series of synthetic sulfur-containing amino acids is described. These compounds included heterocyclic analogues of L-cysteine, DL-norcysteine, and DL-homocysteine. The amino acids were assessed for their ability to inhibit the neutral amino acid transport systems of the Sarcoma 37 ascites tumor cell and their inhibitions were compared with those of L-methionine and L-ethionine. Transport studies indicated that the amino acids synthesized were capable of inhibiting the uptake of [<sup>3</sup>H]-L-histidine in the S37 cell.

Amino acid uptake in mammalian cells may be by multiple transport systems of overlapping specificities.<sup>1</sup> In 1962 Ahmed and Scholefield<sup>2</sup> proposed the systematic use of competitive inhibitions to determine whether uptake of a given solute was by a single transport system or by several. Oxender and Christensen<sup>3</sup> utilized patterns of competitive inhibition in proposing that uptake of neutral amino acids in Ehrlich ascites tumor cells was mediated by two major transport systems, one termed the L system and one identified as the A system. An alternate approach of good utility in discriminating the amino acid transport systems of S37 ascites tumor cells from each other is based on histidine interactions with two neutral amino acid systems with disparate kinetic parameters such that biChart I



phasic double-reciprocal kinetic plots can be obtained.<sup>4,5</sup> This approach has also been utilized for transport studies in renal tubules.<sup>6,7</sup> Measurement of histidine uptake at differing analogue concentrations has the advantages that (a) small quantities of additional analogues can competitively inhibit one system and (b) the test substrate is commercially available.<sup>8</sup>

Sulfur-containing amino acids are known to affect various biological processes.<sup>7</sup> Methionine is a principal methyl group donor in vivo via S-adenosylmethionine (SAM) and is involved in the initiation of polypeptide chain synthesis as N-formylmethionine-transfer RNA.<sup>9</sup> A deranged one-carbon metabolism has been implicated in carcinogenesis including increased SAM in leukemic white cells<sup>10</sup> and neuroblastomas.<sup>11</sup> A decreased ratio of SAM synthetase/ATP, relative to adenosyl-L-methionine transferase, was observed in mouse<sup>12</sup> or Novikoff hepatoma,<sup>13</sup> and methionine has been reported to compete vigorously with histidine for uptake in the S37 cell via both the L and A transport systems.<sup>5</sup> Cysteine has demonstrated specific cellular protective effects when administered prior to various cancer chemotherapeutic agents<sup>14,15</sup> and has been observed to participate in the  $\gamma$ -glutamyl cycle<sup>16</sup> which is implicated as a major energetic support for amino acid transport in S37 cells.<sup>17</sup> A series of sulfur-containing amino acids was synthesized in an effort to ascertain their specificities for the identifiable neutral amino acid transport systems in S37 ascites tumor cells.

**Chemistry.** DL-Thiazolidinecarboxylic acid (1) was synthesized from cysteamine hydrochloride and glyoxalic acid hydrate according to the procedure of Forneau<sup>18</sup> in 74% yield. The isomeric L-4-thiazolidinecarboxylic acid 2 was obtained in improved yields from reaction of Lcysteine hydrochloride with 40% formaldehyde by modification of the procedure of Ratner and Clark.<sup>19</sup> Addition of ethanol and pyridine afforded 2 in 92% yield. Martin and Mathus<sup>20</sup> have discussed <sup>1</sup>H NMR parameters with respect to conformation equilibria of 2, L-cysteine, and S-methyl-L-cysteine. Compound 2 is a closed system analogue of DL-norcysteine. DL-Tetrahydro-1,3-thiazine-4-carboxylic acid (3) was obtained in improved yield<sup>21</sup> as the previously unreported hydrochloride salt. DL-

Table I.Effects of Sulfur-Containing Amino Acids on[³H]-L-Histidine Uptake by the A and L Neutral AminoAcid Transport Systems of S37 Ascites Tumor Cells<sup>a</sup>

compd <sup>b</sup>	uptake of [ <sup>3</sup> H]-L-histidine		
	L system (0.1 mM), <sup>c</sup> % control	A system (10 mM), <sup>c</sup> % control	
1	63	58	
2	72	74	
3	90	85	
4	51	73	
5	70	72	
6	45	68	
7	31	81	
8	52	70	
9	11	68	
10	11	63	
11	6	55	
12	16	51	
13	96	119	

<sup>a</sup> All values represent averages of duplicate runs on triplicate samples and are expressed as percent of controls  $\pm$  5%. <sup>b</sup> Concentrations of test compounds represent L = 5 mM; DL = 10 mM. <sup>c</sup> Concentrations of [<sup>3</sup>H]-L-histidine evaluated.

Homocysteine thiolactone (13) was allowed to react with 40% formaldehyde-HCl (5:1) yielding 95% of the desired compound 3 (Chart I).

The synthesis of L-3-thiomorpholinecarboxylic acid (4) was ultimately effected by a modification of the procedure of Carson and Wong.<sup>22</sup> Compound 4 was obtained in 54% yield along with 40% of an unreported side product. The <sup>13</sup>C NMR spectrum of the side product gave three equal intensity signals in D<sub>2</sub>O at 33.73, 33.92, and 54.92 ppm relative to DSS suggesting the cysteine dimer 8. The structure of dimer 8 was confirmed by an alternative synthesis.<sup>23</sup>

The L-2-methyl-4-thiazolidinecarboxylic acid (5) was prepared in low yield (24%) after reaction of L-cysteine (12) with aqueous acetaldehyde.<sup>23</sup> L-2,2-Dimethyl-4thiazolidinecarboxylic acid hydrochloride (6) was synthesized by modification of the procedure of Riemschneider and Hoyer.<sup>24</sup> By utilizing 2,2-dimethoxypropane as a dehydrating agent, 6 was obtained as the hydrochloride salt in 96.5% yield as compared to 56% yield under the aqueous formaldehyde conditions previously reported.

The synthesis of symmetrical 4-aminotetrahydrothiopyran-4-carboxylic acid (7) was accomplished by a modified Strecker<sup>25,26</sup> synthesis from commercially available tetrahydrothiopyran-4-one (14, Aldrich Chemical Co.). Treatment of 14 in methanol with aqueous sodium cyanide and ammonium chloride afforded 4-amino-4-cyanotetrahydrothiopyran 15 in 85% yield. Acid hydrolysis of 15 followed by fractional crystallization and cellulose chromatography gave 7 in 40% yield.

**Biological Results and Discussion.** The results of biological evaluation of compounds 1-13 in ascites tumor cells are presented in Table I. The sulfur-containing amino acids were studied for their abilities to inhibit the uptake of  $[^{3}H]$ -L-histidine via the two principal neutral amino acid transport systems documented in the S37 tumor cell. L-Methionine (9) and L-ethionine (10) both compete in a similar manner with the substrate histidine in either the A or the L transport systems. Similar effects can be noted for L-cysteine (12) and DL-homocysteine (11). The amino acid 11 was the most potent inhibitor of the alicyclic analogues studied in our laboratories. As can be seen in Table I, the L system is most effectively inhibited when substrate concentration ratios are taken into consideration. It is interesting to note that thiolactone 13 had virtually no effect on the L system while demonstrating a mild stimulatory effect on the A system.

Transport studies on heterocyclic compounds 1–4 generally indicated moderate inhibitory influences on both transport systems with the 2-thiazolidine acid 1 inhibiting 40% of control uptake of radiolabeled histidine. The 2,2-dimethyl derivative (Me<sub>2</sub>-2, 6) produced a significantly greater selectivity for the L system as compared to the A system (55% inhibition of uptake vs. 32%).

Compound 6 is of further interest when compared to the monomethyl analogue 5 and the unsubstituted parent acid 2. The enhanced effectiveness of 6 may be attributed in part to increased lipophilic character or receptor specificity but is more likely due to the lability of the ring system.<sup>25,26</sup> This compound may be acting as an acylating agent or may be hydrolyzed directly to 12 which is competitive with histidine uptake in both transport systems (16% uptake vs. 51%) with greater effect noted in the L system.

Thiomorpholine derivative 4 and cysteine derivative 8 were comparable as moderate inhibitors of normal A system substrate uptake while showing some enhanced effects on the L system of the ascites tumor cells. The thiopyran derivative 7, the only analogue examined which lacked a chiral center in the molecule, was the most effective heterocycle tested for uptake inhibition of the L system and also demonstrated the greatest specificity of the cyclic derivatives tested.

#### **Experimental Section**

Biological Methods. All compounds tested were within 0.4% of calculated values (C, H, and N; Galbraith Laboratories, Knoxville, Tenn.). Membrane transport of amino acids was studied by methods described previously.<sup>4,5,10</sup> S37 ascites tumor cells were harvested 6-8 days following transplant of approximately 0.3 mL of a 1:10 suspension of packed tumor cells in a modified Krebs-Ringer phosphate buffer. After washing the cells three times in buffer, they were resuspended and used in test uptake incubations for 2 min at 20 °C. Incubations were terminated by pouring media containing the cells into chilled buffer. Centrifugation, followed by resuspension in chilled buffer to remove extracellular label entrained in the pellet, and two further centrifugations for 1-min periods were carried out. The supernatant was removed following each spin. Wet weights of cell pellets were determined followed by lysing in 95% EtOH. An aliquot of this solution was taken for liquid scintillation counting.

Chemical Methods. All melting points were determined on a Thomas-Hoover melting point apparatus and are uncorrected. Proton NMR and <sup>13</sup>C NMR were obtained with a Varian A-60A spectrometer or a Brucker HX90-E NMR spectrometer and are reported with respect to Me<sub>4</sub>Si or DSS; IR data were obtained with a Beckman Model 4230 spectrophotometer; optical rotations were observed with a Perkin-Elmer 241 polarimeter; analyses were supplied by Galbraith Laboratories, Knoxville, Tenn.

DL-2-Thiazolidinecarboxylic Acid (1). Compound 1 was prepared according to Fourneau:<sup>18</sup> mp 182–183 °C (lit.<sup>18</sup> mp 183 °C).

L-4-Thiazolidinecarboxylic Acid (2). L-Cysteine hydrochloride hydrate (3.5 g, 0.02 mol) and 4 mL of 40% formaldehyde were left overnight at room temperature in 10 mL of water. Addition of 10 mL of absolute EtOH and 6 mL of pyridine gave crystals which were collected, washed with EtOH and Et<sub>2</sub>O, and air-dried to give 2.45 g (92%) of 2, mp 196–197 °C (lit.<sup>19</sup> mp 196–198 °C).

DL-Tetrahydro-1,3-thiazine-4-carboxylic Acid Hydrochloride (3). DL-Homocysteine thiolactone hydrochloride (3.1 g, 0.02 mol), 40% formaldehyde (10 mL), and 2 mL of dilute HCl were combined in 100 mL of water for 2 days at room temperature. After concentration in vacuo to a white solid, recrystallization from EtOH-EtOAc gave 3.51 g (95%) of product: mp 213-216 °C dec; NMR (D<sub>2</sub>O)  $\delta$  1.6-2.9 (m, 2, CH<sub>2</sub>), 2.9-3.1 (m, 2, SCH<sub>2</sub>), L-3-Thiomorpholinecarboxylic Acid (4). Compound 4 was prepared by the method of Carson and Wong:<sup>22</sup> mp 269-270 °C dec (lit.<sup>22</sup> mp 270-271 °C dec).

L-2-Methyl-4-thiazolidinecarboxylic Acid (5). Compound 5 was prepared by the method of Blondeau:<sup>23</sup> mp 162-164 °C (lit.<sup>23</sup> mp 161-163 °C dec).

L-2,2-Dimethyl-4-thiazolidinecarboxylic Acid Hydrochloride (6). L-Cysteine hydrochloride monohydrate (3.5 g, 0.02 mol) and 50 mL of 2,2-dimethoxypropane were refluxed for 1 h in 250 mL of acetone. The resulting white platelets were collected in two crops to yield 3.83 g (96.5%): mp 161–163 °C; NMR (D<sub>2</sub>O)  $\delta$  1.85 (s, 6, 2CH<sub>3</sub>), 3.55–3.73 (m, 2, CH<sub>2</sub>), 4.93 (m, 1, CH); IR (Nujol) 1740 cm<sup>-1</sup> (br);  $[\alpha]^{24}_{D}$  –76.0° (c 0.45, MeOH). Anal. (C<sub>6</sub>H<sub>12</sub>NO<sub>2</sub>SCI) C, H, N.

4-Amino-4-cyanotetrahydrothiopyran (15). To a solution of 1.0 g (0.02 mol) of NaCN in 4.0 mL of water was added 1.18 g (0.022 mol) of ammonium chloride. The mixture was stirred until a clear solution was obtained and a solution of ketone 14 (2.32 g, 0.02 mol) in 5 mL of MeOH was added. The reaction was refluxed for 14 h, 15 mL of water was added, and the solution was adjusted to pH 12 with Na<sub>2</sub>CO<sub>3</sub>. The product was extracted with Et<sub>2</sub>O (3 × 150 mL), the organic layer dried (Na<sub>2</sub>SO<sub>4</sub>), and 15 precipitated as the hydrochloride salt by addition of ethereal HCl. Compound 15 (2.86 g, 85%) was isolated as a white crystalline solid: mp 203–205 °C; IR (KBr) 2230 cm<sup>-1</sup> (strong, CN); NMR (D<sub>2</sub>O)  $\delta$  2.0–2.4 (m, 4 H), 2.6–3.0 (m, 4 H). Anal. (C<sub>6</sub>H<sub>11</sub>N<sub>2</sub>SCl) C, H, N.

4-Aminotetrahydrothiopyran-4-carboxylic Acid Hydrochloride (7). Compound 15 (1.80 g, 0.01 mol) was refluxed in 6 N HCl (150 mL) for 24 h. The reaction mixture was evaporated to dryness under reduced pressure, and the solid residue was dissolved in 100 mL of EtOH, boiled with C, filtered, and crystallized giving 7 plus NH<sub>4</sub>Cl. Multiple recrystallization from MeOH followed by cellulose chromatography (Avicel powder, 1:60) eluted with EtOAc-MeOH (9:1) gave 800 mg (40%) of 7 as a white solid. Recrystallization from MeOH gave pure 7 as white plates: mp 250-251 °C dec; NMR (D<sub>2</sub>O)  $\delta$  2.6-3.0 (m); IR (KBr) 1735 cm<sup>-1</sup> (C=O). Anal. (C<sub>6</sub>H<sub>12</sub>NO<sub>2</sub>SCl) C, H, N.

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# Synthesis of Potential Hypolipidemic Agents. Reaction of Substituted Phenyl 2,3-Epoxypropyl Ethers with Adenine, Uracil, and Thymine

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Three adenine derivatives were found to be active hypolipidemic agents at 10 mg/kg/day. The most active compound was 9-(*p*-chlorophenoxy-2-hydroxypropyl)adenine (5). Compound 5 significantly lowered serum triglyceride and cholesterol content in male Sprague–Dawley rats and inhibited hepatic phosphatidate phosphohydrolase activity in vitro. The synthesis of these agents involved reacting adenine, uracil, and thymine with a series of substituted phenyl 2,3-epoxypropyl ethers.

Previous work in our laboratories has shown that a series of 1,3-bis(substituted phenoxy)-2-propanones possessed excellent hypocholesterolemic activity.<sup>1</sup> A further extension of this work is described and is based on structure-activity studies<sup>2</sup> performed on eritadenine (I), a



naturally occurring substance isolated from the Japenese mushroom, shiitake (Lentinus edodes), and other purine analogues<sup>3</sup> which show good hypolipidemic activity. We prepared for testing a number of 9-substituted adenine and 1-substituted pyrimidine derivatives which incorporated the phenoxy-2-propanol moiety. These derivatives were synthesized by reacting the appropriate epoxide with adenine (Scheme I), uracil, or thymine (Scheme II) in the presence of  $K_2CO_3$  in Me<sub>2</sub>SO. We found this method to be superior to the one using NaOH with DMF as solvent.<sup>4</sup> Fewer side products were observed by TLC. The epoxides were originally prepared according to standard literature procedures.<sup>5</sup> In an effort to improve yields we used the phase-transfer catalysis procedure (Scheme III) described by McKillop and co-workers<sup>6</sup> with one modification in that no organic solvent was used. We found that the reaction proceeded faster in the absence of methylene chloride and also eliminated the possibility of diaryloxymethane formation.11

## **Experimental Section**

All melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The NMR spectra were taken in Me<sub>2</sub>SO- $d_6$  with tetramethylsilane as an internal standard on a Jeolco C60-HL spectrometer. The IR absorptions were obtained with a Perkin-Elmer 257 spectrophotometer and the UV spectra were determined in H<sub>2</sub>O with a Cary Model 15 spectrophotometer. The spectral data were as expected and therefore only representative data are reported. TLC refers to microslides coated with Merck silica gel GF-254 and visualized







Scheme III



by ultraviolet light. Elemental analyses agreed with the theoretical values within  $\pm 0.4\%$  and were obtained from Atlantic Microlab,