Potent orally Active Inhibitors of Angiotensin-Converting Enzyme (ACE)

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1-[3-Mercaptoalkanoyl]pyroglutamic acids and 1-[3-mercaptoalkanoyl]-4-hetero(oxa,
thia and aza)pyroglutamic acids were prepared and their inhibitory activities against
angiotensin-converting enzyme (ACE) were examined.

(2S)-1-{(2S)-3-Mercapto-2-methylpropanoyl]pyroglutamic acid 2 was found to be the
most potent orally active inhibitor of ACE of rabbit lung among the derivatives synthesized
in the present study and appeared to have great potential for use as an oral antihypertensive
agent.

Keywords —— angiotensin-converting enzyme; angiotensin-converting enzyme
inhibitor; antihypertensive agent; L-pyroglutamic acid; 1-[3-mercapto-2-methylpropan-
yl]pyroglutamic acid

Recently (2S)-1-{(2S)-3-mercapto-2-methylpropanoyl]proline (SQ 14225) was found to
be a potent inhibitor of angiotensin-converting enzyme (ACE), and was considered to be potentially
useful as a therapeutic agent for renal hypertension. 1)

ACE converts the inactive decapeptide angiotensin I to the potent vasopressor octapeptide
angiotensin II and the vasodepressor nonapeptide bradykinin to the inactive heptapeptide. 2)

In our search for new inhibitors of ACE, we synthesized 1-[3-mercaptoalkanoyl]pyroglu-
tamic acids 1, 2, 3 and 4 and 1-[3-mercaptoalkanoyl]-4-hetero(oxa, thia and aza)pyroglutamic
acids 5, 6 and 7 (Table I), and examined their inhibitory activities against ACE in vitro and
in vivo.

(2S)-1-{(2S)-3-Mercapto-2-methylpropanoyl]pyroglutamic acid 2 was found to be the
most potent orally active inhibitor of ACE and was considered to have great potential for use
as an oral antihypertensive agent.

R

\[ \text{CH}_2\text{COSCH}_2\text{CHCOCI} + \text{HNCOOBu'} \]  \[ \text{CH}_2\text{COSCH}_2\text{CHCON} \text{COOBu'} \]  \[ \text{OSX} \]  \[ \text{COOH} \]

\[ \text{8a: R=H} \quad \text{9a: } X=\text{CH}_3, \text{COOBu': (S)} \]
\[ \text{8b: R=CH}_3(\text{S}) \quad \text{9b: } X=\text{CH}_3, \text{COOBu': (R)} \]
\[ \text{8c: R=CH}_3(\text{R}) \quad \text{9c: } X=\text{O}, \text{COOBu': (S)} \]
\[ \text{8d: R=CH}_3(\text{R}, \text{S}) \quad \text{9d: } X=\text{S}, \text{COOBu': (R)} \]
\[ \text{8e: } X=\text{N-THP}, \text{COOBu': (S)} \]

\[ \text{O}_{\text{8'X}} \]  \[ \text{CH}_2\text{COSCH}_2\text{CHCON} \text{COOBu'} \]

\[ \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \quad \}\]  a) NaH, THF, b) CF_3COOH, anisole, c) H_2NCH_2CH_3SH, CH_3CN

Chart 1
Chemistry

1-[3-Mercaptoalkanoyl]pyroglutamic acids 1, 2, 3 and 4 were synthesized from tert-butyl pyroglutamates 9a and 9b according to Chart 1.

Sodium salts of tert-butyl pyroglutamates 9a and 9b were treated with 3-acetylthiopropanoyl chlorides 8a, 8b and 8c\textsuperscript{5} in anhydrous THF at 0° C to afford tert-butyl 1-[3-acetylthiopropanoyl]pyroglutamates 10a, 10b, 10c and 10d in 60—80% yields. Deprotection of the acetyl group and tert-butyl group was achieved by treatment with trifluoroacetic acid and anisole at 0 °C followed by 2-mercaptoethylamine (1 eq) in acetonitrile at room temperature to afford 1-[3-mercapto propanoyl]pyroglutamic acids 1, 2, 3 and 4 in about 90% yields.

Table I. Physical Constants and Inhibitory Activities

<table>
<thead>
<tr>
<th>Compound</th>
<th>mp, °C (uncorr.)</th>
<th>$[\alpha]_D^0$, ° (MeOH)</th>
<th>IC\textsubscript{50}, nm against ACE\textsuperscript{a)}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Oil</td>
<td>−58.2 (c, 0.95)</td>
<td>60</td>
</tr>
<tr>
<td>2</td>
<td>109—110</td>
<td>−113.6 (c, 0.55)</td>
<td>3.6</td>
</tr>
<tr>
<td>3</td>
<td>108—109</td>
<td>−21.0 (c, 1.00)</td>
<td>45</td>
</tr>
<tr>
<td>4</td>
<td>110—111</td>
<td>+7.1 (c, 1.28)</td>
<td>300</td>
</tr>
<tr>
<td>5</td>
<td>101—102</td>
<td>−154.4 (c, 0.58)</td>
<td>6.4</td>
</tr>
<tr>
<td>6</td>
<td>Oil</td>
<td>−191.8 (c, 1.00)</td>
<td>20</td>
</tr>
<tr>
<td>7\textsuperscript{b)}</td>
<td>Oil</td>
<td>−45.7 (c, 0.61)</td>
<td>42</td>
</tr>
<tr>
<td>SQ 14225</td>
<td>103—105</td>
<td>−131.0 (c, 2.00)</td>
<td>23</td>
</tr>
</tbody>
</table>

\textsuperscript{a)} Inhibitory activities against ACE were determined according to the reported procedure: D.W. Cushman, H.S. Cheung, E.F. Sabo and M.A. Ondetti, \textit{Biochemistry}, \textbf{16}, 5484 (1977).

\textsuperscript{b)} A roughly 1:1 mixture of diastereomers.
An improved method for large scale preparation of optically pure 2 was developed as follows. 1) L-Pyroglutamic acid was treated with racemic 3-acetylthio-2-methylpropanoyl chloride 8d in acetonitrile in the presence of triethylamine (2 eq) at 0 °C for 2 h to afford (2S)-1-[2RS]-3-acetylthio-2-methylpropanoylpyroglutamic acid 12. 2) The dicyclohexylammonium salt of 12 was recrystallized once from acetonitrile, followed by treatment with dil. HCl to afford optically pure (2S)-1-[2(S)-3-acetylthio-2-methylpropanoyl]pyroglutamic acid 13. 3) Treatment of 13 with 2-mercaptoethylamine (2 eq) in acetonitrile at room temperature for 1 h afforded optically pure (2S)-1-[(2S)-3-mercaptop-2-methylpropanoyl]pyroglutamic acid 2.

(4S)-3-[(2S)-3-Mercapto-2-methylpropanoyl]-2-oxazolidone-4-carboxylic acid 5, (4R)-3-[(2S)-3-mercaptop-2-methylpropanoyl]-2-thiazolidone-4-carboxylic acid 6 and 3-[(2S)-3-mercaptop-2-methylpropanoyl]-2-imidazolidone-4-carboxylic acid 7 were also prepared from tert-buty1 (4S)-2-oxazolidone-4-carboxylate 9c, tert-buty1 (4R)-2-thiazolidone-4-carboxylate 9d and tert-buty1 (4S)-3-tetrahydropyranyl-2-imidazolidone-4-carboxylate 9e, respectively, according to Chart 1.

<table>
<thead>
<tr>
<th>Table II</th>
</tr>
</thead>
<tbody>
<tr>
<td>Analysis (%)</td>
</tr>
<tr>
<td>Compound</td>
</tr>
<tr>
<td>1</td>
</tr>
<tr>
<td>2</td>
</tr>
<tr>
<td>3</td>
</tr>
<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
<tr>
<td>7</td>
</tr>
</tbody>
</table>

Biological and Pharmaceutical Studies

As shown in Table I, we have tested the inhibitory activity of the above compounds against ACE of rabbit lung.

(2S)-1-[3-Mercaptopropanoyl]pyroglutamic acid 1 has an IC₉₀ value of 60 nm, being 2.5 times less active than SQ 14225. However, the introduction of a 2-methyl substituent with S configuration enhanced the inhibitory potency, whereas a 2-methyl substituent with R configuration had no effect on the potency. (2S)-1-[2(S)-3-Mercapto-2-methylpropanoyl]pyroglutamic acid 2 was 20 times more active as an inhibitor of ACE than the unsubstituted analog 1, but (2S)-1-[2(R)-3-mercaptop-2-methylpropanoyl]pyroglutamic acid 3 has almost the same activity as the unsubstituted analog 1.6

Insertion of a hetero atom (oxygen, nitrogen and sulfur) into the ring of (2S)-1-[(2S)-3-mercaptop-2-methylpropanoyl]pyroglutamic acid 2 weakened the inhibitory potencies against ACE by 2—12 times. The 4-oxa, 4-thia and 4-aza analogs 5, 6 and 7 of 2 were 2, 6 and 12 times, respectively, less active than the parent compound. Their increasing polarities probably cause their affinities to the enzyme to be weakened.

The most potent compound 2 among the derivatives has a Kᵢ value of 6.16 nm (Kᵢ value of SQ 14225 = 38.9 nm) and showed reversible competitive inhibition of ACE of rabbit lung. Compound 2 also had an inhibitory effect (IC₉₀ = 15 nm) against Kininase II of rabbit lung (IC₉₀ of SQ 14225 = 17 nm) and inhibited the vasopressor response of angiotensin I (0.3 μg/kg, i.v.) in the normotensive anesthetized rat after oral administration (0.5 mg/kg).

Moreover, compound 2 showed a significant vasodepressor effect on 2-kidney Goldblatt RHR (acute phase) at 3 mg/kg, p.o. and on 2-kidney Goldblatt RHR (chronic phase) at 100 mg/kg, p.o.6
Experimental

Melting points are uncorrected. Nuclear magnetic resonance (NMR) spectra were recorded on a Varian XL-100 machine and signals are given in δ units downfield from TMS as an internal standard. Infrared (IR) spectra were measured on a Hitachi 269-30 spectrometer. Mass spectrum (MS) and specific rotations (25°C) were taken on JMS-01SG and JASCO DIP-4 machines, respectively.

Preparation of 2. Method A: tert-Butyl (2S)-1-[(2S)-3-acetythio-2-methylpropanoyl]pyrogalactum 10b — A solution of 914 mg of tert-butyl L-pyrogalactum in 16 ml of anhydrous THF was treated with 180 mg of 63% NaH under cooling in an ice bath. The mixture was stirred for 20 min, then 891 mg of (2S)-3-acetythio-2-methyl-propanoyl chloride (prepared from (2S)-3-acetythio-2-methylpropiophenon with thionyl chloride in anhydrous benzene at room temperature for 20 h) in 8 ml of anhydrous THF was added at 0°C, and then the reaction mixture was stirred at 1.5 h at 0°C and for 2 h at room temperature. The contents were diluted with EtOAc, washed with water, dried and concentrated in vacuo.

The residue was separated by column chromatography on silica gel (EtOAc: cyclohexane/4:1) to give 1.13 g (54% yield) of the title compound. [α]D = -97.8° (c, 1.61, MeOH). NMR (CDCl3) ppm: 1.26 (3H, d, J = 6.9 Hz), 1.47 (9H, s), 2.31 (3H, s), 2.0-2.7 (4H, m), 3.08-3.22 (2H, m), 3.70-4.05 (1H, m), 4.62 (1H, dd, J = 3.0, 8.5 Hz). MS m/z: 329 (M+), 286, 273, 256, 230, 213, 198. IR (film) cm⁻¹: 1745, 1695.

(2S)-1-[(2S)-3-Acetythio-2-methylpropanoyl]pyrogalactum Acid 13 — A mixture of a solution of 990 mg of tert-butyl (2S)-1-[(2S)-3-acetythio-2-methylpropanoyl]pyrogalactum in 10 ml of trifluoroacetic acid and 5 ml of anisole was stirred for 1 h at room temperature then concentrated in vacuo to afford 830 mg (100% yield) of the title compound. [α]D = -100° (c, 1.65, MeOH). NMR (CDCl3) ppm: 1.24 (3H, d, J = 7.0 Hz), 2.30 (3H, s), 2.10-2.90 (4H, m), 3.05 (1H, dd, J = 7.0, 14.0 Hz), 3.21 (1H, dd, J = 5.5, 14.5 Hz), 3.70-4.05 (1H, m), 4.76 (1H, dd, J = 4.0, 8.0 Hz). MS m/z: 273 (M+), 256, 231, 213, 198. IR (film) cm⁻¹: 1750, 1695.

Method B: (2S)-1-[(2RS)-3-Acetythio-2-methylpropanoyl]pyrogalactum Acid 12 — A solution of 12.9 g of L-pyrogalactum acid in 300 ml of acetonitrile and 20.2 g of NET₄ at 0°C was treated dropwise with 18 g of (2RS)-3-acetythio-2-methylpropanoyl chloride. The mixture was stirred for 1 h at room temperature, then concentrated in vacuo. The residue was dissolved in 200 ml of H₂O and washed with EtOAc. The aqueous layer was acidified with 1 N HCl and extracted with EtOAc. The combined organic layer was dried over Na₂SO₄ and concentrated in vacuo.

The residue was purified by column chromatography on silica gel (CHCl₃: THF: AcOH/100: 10: 1) to afford 16.3 g (60% yield) of the title compound. MS m/z: 273 (M+), 256, 231, 213, 198. IR (KBr) cm⁻¹: 1754, 1695.

(2S)-1-[(2S)-3-Acetythio-2-methylpropanoyl]pyrogalactum Acid 13 — A solution of 103 mg of (2S)-1-[(2S)-3-acetythio-2-methylpropanoyl]pyrogalactum acid in 0.7 ml of acetonitrile was treated with 0.075 ml of dicyclohexylamine. The crystalline precipitates were collected and recrystallized from acetonitrile to give 70 mg of (2S)-1-[(2S)-3-acetythio-2-methylpropanoyl]pyrogalactum acid-dicyclohexylamine salt, mp 185-187°C, [α]D = -72.6° (c, 0.46, MeOH).

A solution of 347 mg of the salt in H₂O was acidified with 0.5 N HCl and extracted with EtOAc. The extracts were dried over Na₂SO₄ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (CHCl₃: THF: AcOH/10: 2: 1) to afford 217 mg (42% yield) of the title compound.

(2S)-1-[(2S)-3-Mercapto-2-methylpropanoyl]pyrogalactum Acid 2 — 2-Mercaptoethylamine (338 mg) was added to a solution of 546 mg of (2S)-1-[(2S)-3-mercapto-2-methylpropanoyl]pyrogalactum acid in 10 ml of acetonitrile under argon. A solution of 10 ml of 1% HCI was added in vacuo. The residue was treated with 10 ml of 1% HCl and the resulting aqueous mixture was extracted 3 times with EtOAc. A solution of 217 mg of the title compound was added to 217 mg of 2-Mercaptoethylamine (338 mg) and the reaction mixture was heated at 65°C for 1 h. The mixture was concentrated in vacuo and the residue was purified by column chromatography on silica gel (CHCl₃: THF: AcOH/10: 2: 1) to afford 217 mg of the title compound. [α]D = -57.8° (c, 0.97, MeOH). NMR (CDCl₃) ppm: 1.24 (3H, d, J = 6.5 Hz), 1.52 (1H, t, J = 9.0 Hz), 2.0-3.0 (6H, m), 3.70-4.10 (1H, m), 4.83 (1H, dd, J = 4.0, 8.5 Hz), 8.78 (1H, br s). MS m/z: 231 (M+), 198, 190. Calcd for C₁₂H₁₁NO₄S: 217.04927. Obsd 217.0495.

(2S)-1-[(2R)-3-Mercapto-2-methylpropanoyl]pyrogalactum Acid 3 — The title compound was prepared from tert-butyl L-pyrogalactum and (2R)-3-mercapto-2-methylpropanoyl chloride according to the procedure described for 2. mp 105-109°C. [α]D = -21.0° (c, 1.00, MeOH). NMR (CDCl₃) ppm: 1.23 (3H, d, J = 7.0 Hz), 1.54 (1H, t, J = 9.0 Hz), 2.0-3.1 (6H, m), 3.90 (1H, m), 4.60 (1H, dd, J = 5.0, 8.5 Hz), 9.55 (1H, br s). MS m/z: 231 (M+), 198. Calcd for C₁₂H₁₁NO₄S: 217.04927. Obsd 217.0496. IR (KBr) cm⁻¹: 1750, 1680.

(2R)-1-[(2S)-3-Mercapto-2-methylpropanoyl]pyrogalactum Acid 4 — The title compound was prepared from tert-butyl L-pyrogalactum and (2S)-3-mercapto-2-methylpropanoyl chloride according to the procedure described for 2. mp 110-111°C. [α]D = +7.1° (c, 1.28, MeOH). NMR (CDCl₃) ppm: 1.24 (3H, d, J = 7.0 Hz), 2.0-3.0 (6H, m), 3.70-4.10 (1H, m), 4.83 (1H, dd, J = 4.0, 8.5 Hz), 8.78 (1H, br s). MS m/z: 231 (M+), 198, 190. Calcd for C₁₂H₁₁NO₄S: 217.04927. Obsd 217.0495.

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1.55 (1H, t, J = 8.0 Hz), 2.0–3.1 (6H, m), 3.90 (1H, m), 4.80 (1H, dd, J = 5.0, 8.5 Hz), 9.5 (1H, br s). MS m/z: 231 (M^−), 198. Calcd for C_{10}H_{15}NO_{3}S: 231.0565. Obsd 231.0555. IR (KBr) cm⁻¹: 1740, 1690.

tert-Butyl (4S)-3-[(2S)-3-Acetyltio-2-methylpropionyl]-2-thiazolidone-4-carboxylate 10e—A solution of 374 mg of tert-butyl (4S)-2-oxazolidone-4-carboxylate in 3 ml of anhydrous THF was added to a mixture of 76 mg of 63% NaH in 5 ml of anhydrous THF at 0°C. The whole was stirred for 20 min at 0°C, then 360 mg of (2S)-3-acetyltio-2-methylpropionyl chloride was added at 0°C. The reaction mixture was stirred for 1 h at room temperature, diluted with EtOAc, washed with H₂O and dried over Na₂SO₄.

The organic solution was concentrated in vacuo to afford the residue, which was purified by column chromatography on silica gel (cyclohexane: EtOAc=5:1) to give 419 mg (63% yield) of the title compound. NMR (CDCl₃) ppm: 1.30 (3H, d, J = 7.0 Hz), 1.50 (9H, s), 2.27 (3H, s), 3.0–3.2 (2H, m), 3.6–4.1 (1H, m), 4.1–4.9 (3H, m). MS m/z: 331 (M^+), 275.

The following compounds were also prepared according to the procedure described above.

tert-Butyl (4R)-3-[(2S)-3-Acetyltio-2-methylpropionyl]-2-thiazolidone-4-carboxylate 10f—NMR (CDCl₃) ppm: 1.20 (3H, d, J = 8.0 Hz), 1.40 (9H, s), 2.30 (3H, s), 3.0–4.0 (5H, m), 4.95 (1H, dd, J = 9.2 Hz). MS m/z: 347 (M^+), 291.

**tert-Butyl 3-[(2S)-3-Acetyltio-2-methylpropionyl]-1-tetrahydropropyl-2-imidazolidine-4-carboxylate 10g**—Epimerization of the carbonyl group occurred during the course of the reaction and the product was a roughly 1:1 mixture of diastereomers as judged from the NMR spectrum.

(4S)-3-[(2S)-3-Mercapto-2-methylpropionyl]-2-oxazolidone-4-carboxylic Acid 5—A solution of 903 mg of tert-butyl (4S)-3-[(2S)-3-acetyltio-2-methylpropionyl]-2-oxazolidone-4-carboxylate in 5.0 ml of trifluoroacetic acid and 2.5 ml of anisole was stirred at room temperature for 40 min, then concentrated in vacuo to afford the residue, which was used for the next reaction without purification.

2-Mercaptoethylamine (460 mg) was added to a solution of the above residue in 12 ml of acetonitrile. The reaction mixture was stirred for 2.5 h at room temperature then concentrated in vacuo. The residue was dissolved in EtOAc, and the solution was washed with dil. HCl, dried over Na₂SO₄ and concentrated in vacuo to afford the crude product, which was purified by column chromatography on silica gel (CHCl₃:THF: AcOH/100: 10: 1) to give 483 mg (76% yield) of the title compound. NMR (CDCl₃) ppm: 1.27 (3H, d, J = 6.5 Hz), 2.4–3.0 (3H, m), 3.7–4.1 (1H, m), 4.39 (1H, dd, J = 4.0, 9.0 Hz), 4.64 (1H, t, J = 9.0 Hz), 4.97 (1H, dd, J = 4.0, 9.0 Hz). MS m/z: 233 (M^+), 200, 132. Calcd for C₂H₁₄N₂O₄S: 233.03579. Obsd 233.0355. IR (KBr) cm⁻¹: 1800, 1740, 1690.

The following compounds were also prepared according to the procedure described above.

(4R)-3-[(2S)-3-Mercapto-2-methylpropionyl]-2-thiazolidone-4-carboxylic Acid 6—NMR (CDCl₃) ppm: 1.25 (3H, d, J = 8.0 Hz), 1.53 (1H, t, J = 9.0 Hz), 2.40–3.05 (2H, m), 3.44 (1H, dd, J = 2.0, 12.0 Hz), 3.75 (1H, dd, J = 8.5, 12.0 Hz), 3.6–4.0 (1H, m), 5.00 (1H, dd, J = 2.0, 8.5 Hz), 9.57 (1H, br s). MS m/z: 249 (M^+), 216. Calcd for C_{10}H_{15}NO_{3}S: 249.01294. Obsd 249.01420. IR (film) cm⁻¹: 1740, 1680.

3-[(2S)-3-Mercapto-2-methylpropionyl]-2-imidazolidine-4-carboxylic Acid 7—The NMR spectrum showed the presence of a roughly 1:1 mixture of diastereomers. MS m/z: 232 (M^+), 217, 214, 199, 186. Calcd for C₂H₁₄N₂O₄S: 232.05177. Obsd 232.05221. IR (film) cm⁻¹: 1740, 1690.

References and Notes


3) The optical resolution of racemic 3-acetyltio-2-methylpropionic acid was achieved by recrystallization of its cinchonidine salt to afford the (2S)-isomer, [a]D = -33.3° (c, 1.00, EtOH), according to J. Iwao, M. Oya, E. Kato, and T. Watanabe, Japan Patent 151912 (1979).

4) Epimerization of the carbonyl group of tert-butyl (4S)-3-tetrahydropropyl-2-imidazolidine-4-carboxylate 9e occurred during the course of the reaction. 7 was a roughly 1:1 mixture of diastereomers as judged from the NMR spectrum.

5) (8S)-1-[(2S)-3-Mercapto-2-methylpropionyl]-2-piperidone-6-carboxylic acid 14 and (2S)-1-[(2S)-3-acetyltio-2-methylpropionyl]pyroglutamic acid 13 were also prepared. 14 showed an IC₅₀ value of 130 nm. 13 had almost none of the activity of 2 in *vitro*, but showed the same effect on pressor response induced by angiotensin I in conscious rats (administered orally).

6) The results of detailed pharmacological evaluations will be published elsewhere.

7) This compound was prepared from (4S)-2-oxazolidone-4-carboxylic acid [T. Kaneko and T. Inui, *Nippon Kagaku Zasshi*, 82, 1075 (1961)] and isobutene in the presence of conc. H₂SO₄ in dioxane.