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Synthetic Studies of Bacitracin. VI.[1] Synthesis of Unprotected Thiazoline Peptides

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For a total synthesis of bacitracian A, a synthetic method to secure unprotected thiazoline peptides must be established. 2-Aminomethyl-R-Δ^2-thiazoline-4-carboxamide, 2-aminomethyl-R-Δ^2-thiazoline-4-carboxylic acid, 2-aminomethyl-R-Δ^2-thiazoline-4-carbonyl-L-leucine were synthesized by either the iminoether coupling method or by the dehydration method using *N*-benzyloxycarbonyl group and benzyl ester as protecting groups.

In the previous papers,[1,2] the syntheses of protected thiazoline peptides by either the iminoether coupling method, or by dehydration of cysteine peptide in nonaqueous medium were described. Saponification of methyl or ethyl ester of thiazoline peptide was accompanied by racemization of cysteine residue and cleavage of thiazoline ring,[2] while the thiazoline ring was stable in strong acidic condition.[3] In order to obtain the unprotected thiazoline peptide, therefore, use of *N*-benzyloxycarbonyl group and benzyl ester group, both being cleavable by hydrogen bromide in acetic acid, is required. Based on this principle, a synthetic method of the unprotected thiazoline peptide was established.

A thiazoline derivative of a dipeptide derived from L-cysteinamide was prepared as shown in Fig. 1. *N,N'*-Bisbenzyloxycarbonyl-L-cystine[4] was converted to *N,N'*-bisbenzyloxycarbonyl-L-cystinyl dichloride[5] by treatment with phosphorus pentachloride. The acid chloride was treated with ammonia to afford *N,N'*-bisbenzyloxycarbonyl-L-cystine diamide (I), which was then reduced to benzyloxycarbonyl-L-cysteinamide (II) with zinc dust and hydrochloric acid. Amide II was treated with 30% hydrogen bromide in acetic acid to give L-cysteinamide hydrobromide (III).

Coupling of III with benzyloxycarbonylaminoacetimino ethyl ether[2] gave 2-benzyloxycarbonylaminomethyl-R-Δ^2-thiazoline-4-carboxamide (IV), which was then treated with 30% hydrogen bromide in acetic acid to afford 2-aminomethyl-R-Δ^2-thiazoline-4-carboxamide (V). Product V was very hygroscopic solid and gave L-cystine by hydrolysis with hydrochloric acid followed by oxidation.

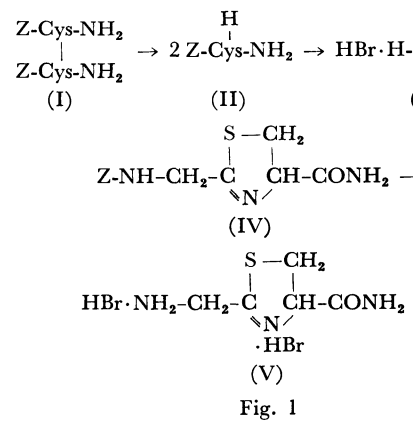

Fig. 1

Z=$C_6H_5CH_2OCO$
Cystine used is of L-configuration.

Unprotected thiazoline peptides were synthesized from di- or tripeptide involving cysteine residue by the dehydration method according to the scheme shown in Fig. 2. Coupling of benzyloxycarbonylglycine with dibenzyl L-cystinate dihydrochloride[6]

*1 This paper is dedicated to Emeritus Professor Munio Kotake in commemoration of his 75th birthday, November, 30, 1969.

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4) M. Bergmann and L. Zervas, *Ber.*, **65**, 1192 (1932).

5) V. du Vigneaud and G. L. Miller, "Biochemical Preparations," Vol. 2, p. 76 (1952).

6) L. Zervas and I. Photaki, *J. Amer. Chem. Soc.*, **84**, 3887 (1962).

using *N,N'*-dicyclohexylcarbodiimide gave *N,N'*-bisbenzyloxycarbonylglycyl-L-cystine dibenzyl ester (IV), which was then converted to benzyloxycarbonylglycyl-L-cysteine benzyl ester (VII) by reduction with zinc dust and hydrochloric acid.

A ring closure of dipeptide VII through dehydration by hydrogen chloride in chloroform afforded benzyl 2-benzyloxycarbonylaminomethyl-R-Δ^2-thiazoline-4-carboxylate hydrochloride, from which the benzyloxycarbonyl thiazoline derivative (VIII) was obtained in crystalline state by removal of hydrogen chloride by treatment with an aqueous concentrated potassium carbonate solution.

Compound VIII was treated with 30% hydrogen bromide in acetic acid at 40°C for 3 hr to give a very hygroscopic solid of 2-aminomethyl-R-Δ^2-thiazoline-4-carboxylic acid dihydrobromide (IX).

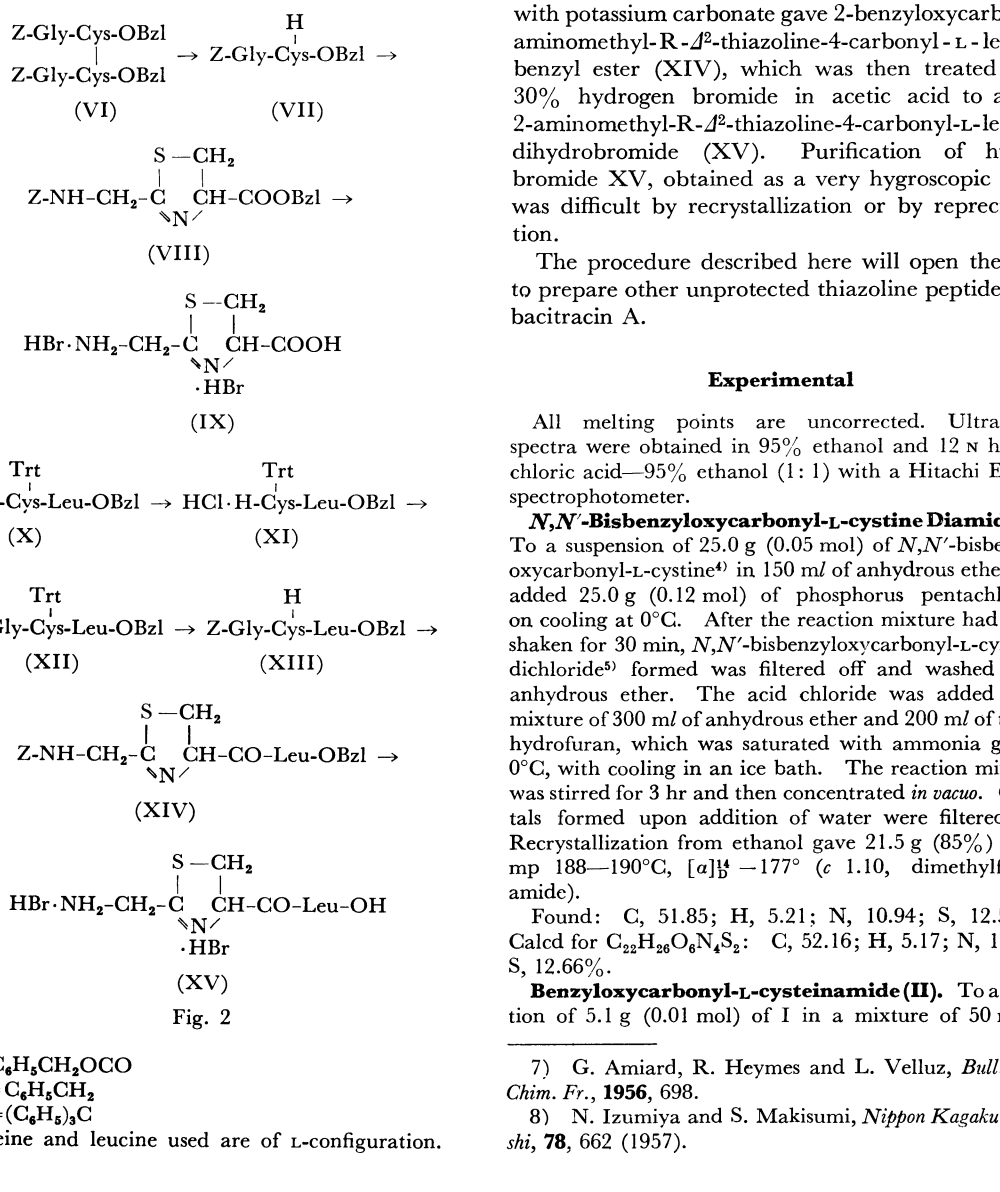

Fig. 2

Z=$C_6H_5CH_2OCO$
Bzl=$C_6H_5CH_2$
Trt=$(C_6H_5)_3C$
Cysteine and leucine used are of L-configuration.

A tripeptide containing the thiazoline ring was also prepared as follows. Condensation of *N,S*-ditrityl-L-cysteine diethylamine salt[7] with benzyl L-leucinate *p*-toluenesulfonate[8] by the carbodiimide method gave *N,S*-ditrityl-L-cysteinyl-L-leucine benzyl ester (X), which was then treated with hydrochloric acid in acetone to give benzyl *S*-trityl-L-cysteinyl-L-leucinate hydrochloride (XI). Coupling of XI with benzyloxycarbonylglycine by carbodiimide method gave benzyloxycarbonylglycyl-*S*-trityl-L-cysteinyl-L-leucine benzyl ester (XII). The *S*-trityl tripeptide XII was converted to the silver mercaptide by treatment with silver nitrate and pyridine. Removal of silver from the mercaptide by hydrochloric acid gave benzyloxycarbonylglycyl-L-cysteinyl-L-leucine benzyl ester (XIII). Compound XIII was cyclized to the thiazoline derivative by the action of hydrogen chloride in chloroform. Treatment of the product with potassium carbonate gave 2-benzyloxycarbonylaminomethyl-R-Δ^2-thiazoline-4-carbonyl-L-leucine benzyl ester (XIV), which was then treated with 30% hydrogen bromide in acetic acid to afford 2-aminomethyl-R-Δ^2-thiazoline-4-carbonyl-L-leucine dihydrobromide (XV). Purification of hydrobromide XV, obtained as a very hygroscopic solid, was difficult by recrystallization or by reprecipitation.

The procedure described here will open the way to prepare other unprotected thiazoline peptides like bacitracin A.

Experimental

All melting points are uncorrected. Ultraviolet spectra were obtained in 95% ethanol and 12 N hydrochloric acid—95% ethanol (1: 1) with a Hitachi EPS-3 spectrophotometer.

N,N'-Bisbenzyloxycarbonyl-L-cystine Diamide (I). To a suspension of 25.0 g (0.05 mol) of *N,N'*-bisbenzyloxycarbonyl-L-cystine[4] in 150 m*l* of anhydrous ether was added 25.0 g (0.12 mol) of phosphorus pentachloride on cooling at 0°C. After the reaction mixture had been shaken for 30 min, *N,N'*-bisbenzyloxycarbonyl-L-cystinyl dichloride[5] formed was filtered off and washed with anhydrous ether. The acid chloride was added to a mixture of 300 m*l* of anhydrous ether and 200 m*l* of tetrahydrofuran, which was saturated with ammonia gas at 0°C, with cooling in an ice bath. The reaction mixture was stirred for 3 hr and then concentrated *in vacuo*. Crystals formed upon addition of water were filtered off. Recrystallization from ethanol gave 21.5 g (85%) of I; mp 188—190°C, $[\alpha]_D^{14}$ −177° (*c* 1.10, dimethylformamide).

Found: C, 51.85; H, 5.21; N, 10.94; S, 12.56%. Calcd for $C_{22}H_{26}O_6N_4S_2$: C, 52.16; H, 5.17; N, 11.06; S, 12.66%.

Benzyloxycarbonyl-L-cysteinamide (II). To a solution of 5.1 g (0.01 mol) of I in a mixture of 50 m*l* of

7) G. Amiard, R. Heymes and L. Velluz, *Bull. Soc. Chim. Fr.*, **1956**, 698.

8) N. Izumiya and S. Makisumi, *Nippon Kagaku Zasshi*, **78**, 662 (1957).

dimethylformamide and 6.5 m*l* of concentrated hydrochloric acid was added 3.0 g of zinc dust in small portions over a period of 15 min with vigorous stirring on cooling in an ice bath. The mixture was stirred for an additional 30 min at room temperature and then filtered. Precipitate was formed upon addition of water to the filtrate. It was filtered off and washed with water. Recrystallization from ethanol–water gave 4.1 g (80%) of II; mp 136—138°C, $[\alpha]_D^{14}$ +7.7° (*c* 2.28, dimethylformamide).

Found: C, 51.90; H, 5.55; N, 10.95; S, 12.56%. Calcd for $C_{11}H_{14}O_3N_2S$: C, 51.95; H, 5.55; N, 11.01; S, 12.61%.

L-Cysteinamide Hydrobromide (III). To a mixture of 10.0 g (0.04 mol) of II and 4.0 g of anisole was added 40 m*l* of 30% hydrogen bromide in acetic acid, and the reaction mixture was kept at room temperature for 3 hr with occasional swirling. To the reaction mixture was added 150 m*l* of anhydrous ether, and the precipitate formed was filtered off. Recrystallization from anhydrous methanol-anhydrous ether gave 6.5 g (81%) of III; mp 178—180°C (decomp.), $[\alpha]_D^{16}$ +8.2° (*c* 2.91, anhydrous methanol).

Found: C, 18.30; H, 4.59; N, 13.78%. Calcd for $C_3H_9ON_2SBr_2$: C, 17.92; H, 4.51; N, 13.93%.

2-Benzyloxycarbonylaminomethyl-R-Δ^2-thiazoline-4-carboxamide (IV). To a solution of 10.1 g (0.05 mol) of III in a mixture of 50 m*l* of anhydrous tetrahydrofuran and 10 m*l* of anhydrous methanol was added 11.8 g (0.05 mol) of benzyloxycarbonylaminoacetimino ethyl ether.[2] After the reaction mixture had been kept at room temperature for 3 hr, ammonium bromide was deposited. The reaction mixture was concentrated *in vacuo*. The residue obtained was dissolved in ethyl acetate. The solution was washed with water, dried with sodium sulfate, and then evaporated *in vacuo* to give crystals. Recrystallization from ethyl acetate–petroleum ether gave 13.0 g (89%) of IV; mp 110—112°C, $[\alpha]_D^{17}$ +46.5° (*c* 2.98, dimethylformamide), λ_{max}^{EtOH} 235 mμ (ε 2300), 252 mμ (ε 2800), $\lambda_{max}^{EtOH\text{-}HCl}$ 268 mμ (ε 5900).

Found: C, 53.15; H, 5.19; N, 14.38; S, 10.67%. Calcd for $C_{13}H_{15}O_3N_3S$: C, 53.23; H, 5.15; N, 14.32; S, 10.93%.

2-Aminomethyl-R-Δ^2-thiazoline-4-carboxamide Dihydrobromide (V). To a solution of 11.6 g (0.04 mol) of IV in 100 m*l* of acetic acid was added 40 m*l* of 30% hydrogen bromide in acetic acid. The reaction mixture was kept at room temperature for 2 hr. To the mixture was added 200 m*l* of anhydrous ether. The precipitate formed was filtered off and washed with methylene chloride and acetone; wt of V: 10.8 g (84%), mp 100—105°C (decomp.), $[\alpha]_D^{25}$ +3.3° (*c* 1.05, anhydrous methanol), $\lambda_{max}^{abs\ MeOH}$ 234 mμ (ε 2400), 250 mμ (ε 2000). $\lambda_{max}^{12N\ HCl}$ 277 mμ (ε 3400). It was reprecipitated from anhydrous methanol—anhydrous ether; mp 100—105°C (decomp., sintered at 90°C).

Found: C, 20.25; H, 4.14; N, 11.99%. Calcd for $C_5H_{11}ON_3SBr \cdot CH_3OH$: C, 20.41; H, 4.28; N, 11.90%.

Isolation of L-Cystine from Acid Hydrolyzate of V. A solution of 3.1 g (0.01 mol) of V in 100 ml of 6 N hydrochloric acid was refluxed for 3 hr on addition of 1.1 g of anisole. The reaction mixture was cooled and then extracted with ether. The aqueous layer was concentrated *in vacuo* to dryness. The residue obtained was dissolved in 50 ml of water, and evaporation *in vacuo* was repeated. pH of a solution of the residue in 50 ml of water was adjusted to about 8.5 with 28% aqueous ammonia. Air was bubbled through the solution until the nitroprusside reaction became negative by a spot test. After the addition of a drop of acetic acid, the reaction mixture was allowed to stand at 0°C for 2 days. The precipitate thus formed was filtered off and then dissolved in 30 m*l* of N hydrochloric acid. Undissolved substance was removed by filtration and the filtrate was adjusted to pH 5.5—6.0 by the addition of an aqueous sodium acetate solution. After standing at 0°C for 2 days, the precipitate formed was filtered off and dried at 80°C *in vacuo* for 4 hr to give 0.78 g (65%) of L-cystine; $[\alpha]_D^{19}$ −217° (*c* 1.03, N HCl).

Found: C, 29.80; H, 5.02; N, 11.77; S, 26.42%. Calcd for $C_6H_{12}O_4N_2S_2$: C, 29.99; H, 5.04; N, 11.66; S, 26.69%.

***N,N'*-Bisbenzyloxycarbonylglycyl-L-cystine Dibenzyl Ester (VI).** To a suspension of 30.7 g (0.05 mol) of dibenzyl L-cystinate dihydrochloride[6] in 300 m*l* of methylene chloride was added 10.1 g (0.1 mol) of triethylamine. After the reaction mixture had been stirred for 1 hr, 100 ml of ether was added. The precipitate formed was filtered off, and the filtrate was concentrated *in vacuo*. To the solution of the residue thus obtained in 300 m*l* of tetrahydrofuran, 20.9 g (0.1 mol) of benzyloxycarbonylglycine and 22.7 g (0.11 mol) of *N,N'*-dicyclohexylcarbodiimide were added. After the reaction mixture had been stirred for several hours, 2 m*l* of acetic acid was added to it. *N,N'*-Dicyclohexylurea formed was filtered off, and the filtrate was evaporated *in vacuo* to dryness. The residue was dissolved in ethyl acetate and the solution was washed successively with 0.5 N hydrochloric acid, water, a 5% aqueous sodium hydrogencarbonate solution, and water. Upon evaporation *in vacuo* after drying with sodium sulfate and recrystallization of the residue from methanol—water, 35.0 g (78%) of crystals of VI were obtained; mp 118—119°C, $[\alpha]_D^{24}$ −45.5° (*c* 3.49, dimethylformamide).

Found: C, 59.91; H, 5.48; N, 6.99; S, 7.88%. Calcd for $C_{40}H_{42}O_{10}N_4S_2$: C, 59.83; H, 5.27; N, 6.98; S, 7.99%.

Benzyloxycarbonylglycyl-L-cysteine Benzyl Ester (VII). To a mixture of 10.0 g (0.0125 mol) of VI and 3.5 g of zinc dust in 200 m*l* of acetone was added 8.3 m*l* of concentrated hydrochloric acid with vigorous stirring on cooling at 0°C within a period of 20 min. The mixture was stirred for an additional 10 min, and then filtered. The filtrate was concentrated *in vacuo* at 30°C. An oily product separated out on addition of water was extracted with ethyl acetate. The extract was washed with water, dried with sodium sulfate and then evaporated *in vacuo*. Recrystallization of the residual solid from ethyl acetate—petroleum ether gave 7.5 g (75%) of crystals of VII; mp 76—77.5°C, $[\alpha]_D^{25}$ −13.5° (*c* 5.30, dimethylformamide).

Found: C, 59.87; H, 5.59; N, 6.97; S, 7.79%. Calcd for $C_{20}H_{22}O_5N_2S$: C, 59.68; H, 5.51; N, 6.96; S, 7.97%.

Benzyl 2-Benzyloxycarbonylaminomethyl-R-Δ^2-thiazoline-4-carboxylate (VIII). A solution of 4.0 g (0.01 mol) of VII in 50 m*l* of chloroform was saturated with dry hydrogen chloride gas on cooling in an ice bath. The mixture was allowed to stand at room temperature overnight, and then concentrated *in vacuo*. To the residue was added 100 m*l* of ethyl acetate, and the mixture

was treated with a concentrated potassium carbonate solution. The ethyl acetate layer was washed with water, dried with sodium sulfate and then evaporated to dryness to give crystals. Recrystallization from ethyl acetate—petroleum ether gave 2.1 g of VIII; mp 86—87.5°C, $[\alpha]_D^{19}$ +84.0° (*c* 2.13, dimethylformamide), λ_{max}^{EtOH} 235 mμ (ε 2300), 252 mμ (ε 3000), $\lambda_{max}^{EtOH\text{-}HCl}$ 264 mμ (ε 5000).

Found: C, 62.43; H, 5.31; N, 7.23; S, 8.29%. Calcd for $C_{20}H_{20}O_4N_2S$: C, 62.48; H, 5.24; N, 7.29; S, 8.34%.

2-Aminomethyl-R-Δ^2-thiazoline-4-carboxylic Acid Dihydrobromide (IX). To a mixture of 1.2 g (0.003 mol) of VIII and 1.0 g of anisole was added 20 m*l* of 30% hydrogen bromide in acetic acid, and the mixture was kept at 40°C for 3 hr with occasional swirling. To the reaction mixture was added 100 m*l* of anhydrous ether. The precipitate formed was filtered off, and washed with anhydrous ether; wt of IX: 0.70 g (73%), mp 177—182°C (decomp.), $[\alpha]_D^{14}$ +30.7° (*c* 1.01, anhydrous ethanol), $\lambda_{max}^{abs\ EtOH}$ 235 mμ (ε 2900), 250 mμ (ε 2600), $\lambda_{max}^{12N\ HCl}$ 276 mμ (ε 4100).

Found: C, 18.98; H, 3.38; N, 8.50%. Calcd for $C_5H_{10}O_2N_2SBr_2$: C, 18.65; H, 3.13; N, 8.70%.

***N*-*S*-Ditrityl-L-cysteinyl-L-leucine Benzyl Ester (X).** To a solution of 13.6 g (0.02 mol) of *N*,*S*-ditrityl-L-cysteine diethylamine salt[7] and 7.9 g (0.02 mol) of benzyl L-leucinate *p*-toluenesulfonate[8] in 150 m*l* of methylenechloride was added 4.6 g (0.022 mol) of *N*,*N'*-dicyclohexylcarbodiimide. After the reaction mixture had been stirred for several hours, 1 m*l* of acetic acid was added, and the urea derivative formed was filtered off. The filtrate was washed with water and dried with sodium sulfate. Upon concentration of the solution *in vacuo* an amorphous powder was obtained.

Benzyl *S*-Trity-L-cysteinyl-L-leucinate Hydrochloride (XI). To a solution of 16.2 g (0.02 mol) of X in 100 m*l* of acetone was added 10 m*l* of 6 N hydrochloric acid. After the reaction mixture was stirred for 1 hr, the resulting clear solution was evaporated to dryness at 30°C. The residue was triturated with ether. The precipitate was filtered off, and washed with ether. Recrystallization from ethyl acetate gave 6.8 g (56%) of crystals of XI; mp 182—184°C, $[\alpha]_D^{23}$ +13.3° (*c* 5.06, ethanol).

Found: C, 69.64; H, 6.51; N, 4.64%. Calcd for $C_{35}H_{39}O_3N_2SCl$: C, 69.69; H, 6.52; N, 4.65%.

Benzyloxycarbonylglycyl-*S*-trityl-L-cysteinyl-L-leucine Benzyl Ester (XII). To a suspension of 12.1 g (0.02 mol) of XI in 50 m*l* of chloroform was added 2.0 g (0.02 mol) of triethylamine. The precipitate formed on addition of 100 m*l* of ether was filtered off, and the filtrate was evaporated *in vacuo*. To the solution of the residue obtained in 100 m*l* of tetrahydrofuran, 4.2 g (0.02 mol) of benzyloxycarbonylglycine and 4.6 g (0.022 mol) of *N*,*N'*-dicyclohexylcarbodiimide were added. The mixture was stirred for several hours, and then 1 m*l* of acetic acid was added. The urea derivative precipitated was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was dissolved in ethyl acetate, and the solution was washed as usual. Evaporation of the solvent *in vacuo* and then recrystallization of the residue from ethanol—water gave 13.2 g (87%) of XII; mp 114—116°C, $[\alpha]_D^{23}$ −11.4° (*c* 4.30, dimethylformamide).

Found: C, 71.62; H, 6.26; N, 5.53; S, 4.16%. Calcd for $C_{45}H_{47}O_6N_3S$: C, 71.31; H, 6.25; N, 5.54; S, 4.23%.

Benzyloxycarbonylglycyl-L-cysteinyl-L-leucine Benzyl Ester (XIII). A hot solution of 1.7 g (0.01 mol) of silver nitrate and 0.95 m*l* of pyridine in 20 m*l* of ethanol was added to a warm solution of 7.6 g (0.01 mol) of XII in 40 m*l* of ethanol. After the mixture was refluxed for 30 min, the silver mercaptide of XIII was separated out; after standing for 2 hr at room temperature under nitrogen, it was filtered off and washed with ethanol and then dried; wt 5.6 g (90%).

To a suspension of 5.6 g of the mercaptide in 50 m*l* dimethylformamide, 1.3 m*l* of concentrated hydrochloric acid was added. The mixture was shaken for 2 hr at room temperature and then heated on a boiling water bath for 1 min. The precipitate of silver chloride formed was removed by filtration and washed with a small amount of dimethylformamide. After addition of chloroform to the filtrate, it was washed with water several times, dried with magnesium sulfate, and then evaporated *in vacuo*. Upon addition of water to the residue, crystals were separated out. Recrystallization from ethyl acetate—petroleum ether gave 4.0 g (78%) of XIII; mp 96—98°C, $[\alpha]_D^{26}$ −15.6° (*c* 4.24, dimethylformamide).

Found: C, 60.82; H, 6.59; N, 8.09; S, 5.95%. Calcd for $C_{26}H_{33}O_6N_3S$: C, 60.56; H, 6.45; N, 8.15; S, 6.22%.

Benzyl 2-Benzyloxycarbonylaminomethyl-R-Δ^2-thiazoline-4-carbonyl-L-leucinate (XIV). A solution of 5.2 g (0.01 mol) of XIII in 100 m*l* of chloroform was saturated with dry hydrogen chloride gas on cooling at 0°C. The mixture was allowed to stand at room temperature overnight, and then evaporated *in vacuo* to dryness. To the residue was added 100 ml of ether, and the mixture was treated with a concentrated potassium carbonate solution. The ether layer was separated, washed with water, dried with sodium sulfate and then evaporated to dryness to give a crude oil; wt 4.2 g. This was dissolved in a small amount of ether and subjected to the sillica gel column (Mallincrodt Chemical Works, 100 mesh, 50 g). Elution with petroleum ether—anhydrous ether gave 3.9 g (87%) of XIV; $[\alpha]_D^{26}$ +28.6° (*c* 2.70, ethanol), λ_{max}^{EtOH} 233 mμ (ε 2600), 252 mμ (ε 2700), $\lambda_{max}^{EtOH\text{-}HCl}$ 268 mμ (ε 4900).

Found: C, 62.26; H, 6.45; N, 8.37; S, 6.44%. Calcd for $C_{26}H_{31}O_5N_3S$: C, 62.75; H, 6.28; N, 8.44; S, 6.44%.

2-Aminomethyl-R-Δ^2-thiazoline-4-carbonyl-L-leucine Dihydrobromide (XV). To a mixture of 2.0 g (0.004 mol) of XIV and 1.0 g of anisole was added 30 m*l* of 30% hydrogen bromide in acetic acid and the reaction mixture was kept at 40°C for 3 hr with occasional swirling. To the mixture was added 100 m*l* of anhydrous ether, and the precipitate formed was filtered off and washed with anhydrous ether; wt of XV: 1.26 g (75%), mp 140—148°C (decomp.), $[\alpha]_D^{15}$ −4.1° (*c* 1.46, anhydrous ethanol), $\lambda_{max}^{abs\ EtOH}$ 230 mμ (ε 2900), 250 mμ (ε 2200), $\lambda_{max}^{12N\ HCl}$ 276 mμ (ε 3100).

Found: N, 9.56%. Calcd for $C_{11}H_{21}O_3N_3SBr_2$: N, 9.66%.