[Chem. Pharm. Bull. 29(6)1554—1560(1981)]

Convenient Synthesis of 1,4-Thiazane-3-carboxylic Acid Derivatives[1]

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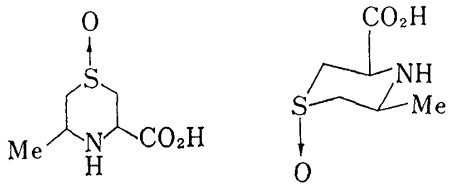
(Received December 1, 1980)

A convenient method to synthesize 1,4-thiazane-3-carboxylic acid derivatives was established. Condensation of L-cysteine methyl ester (**2a**) with monochloroacetone (**3a**) followed by reduction with sodium borohydride yielded methyl (3*R*,5*S*)-5-methyl-1,4-thiazane-3-carboxylate (**6a**) and its (5*R*)-methyl isomer (**7a**) in a ratio of 3.1 : 1. The use of cysteine isopropyl ester (**2c**) instead of methyl ester (**2a**) gave the corresponding (5*S*)-methyl isomer (**6e**) more stereoselectively. The reaction of chloromethyl ethyl ketone (**3b**) or α-bromoacetophenone (**3c**) with **2a** gave the corresponding 5-substituted-1,4-thiazane-3-carboxylates. Hydrolysis and oxidation of **6a** yielded cycloalliin (**1a**).

Keywords——1,4-thiazane-3-carboxylic acid; cycloalliin; L-cysteine; α-halogeno-ketone; chondrine; cyclization; reduction

In 1956 Virtanen and Matikkala isolated[2] cycloalliin (**1a**), a sulfur-containing amino acid, in a deoxy form from onion, and confirmed[3] the structure to be 5-methyl-1,4-thiazane-3-carboxylic acid 1-oxide. The X-ray analysis of **1a** hydrochloride hydrate proved the absolute configuration to be (1*S*, 3*R*, 5*S*)-5-methyl-1,4-thiazane-3-carboxylic acid 1-oxide, in which both carboxyl and methyl groups were equatorial and sulfoxide was axial.[4]



cycloalliin (**1a**)

Fig. 1

Two synthetic methods for **1a** have been reported. Virtanen and Matikkala found, by a paper chromatographic study, that **1a** can be synthesized by the addition of hydrogen bromide to S-allyl-L-cysteine followed by ring closure and oxidation.[3] Carson and Boggs synthesized **1a** and its diastereomer by the ring closure of *cis*-S-(1-propenyl)-L-cysteine S-oxide in dilute base.[5] However, the latter method requires a long reaction time and complicated procedure to isolate the product, resulting in a low yield, from 10% to 16%.[6] Carson *et al.* synthesized several analogs of **1a** by using similar methods,[7–10] but deoxycycloalliin and its analogs have never been synthesized directly.

Recently, the finding of a fibrinolytic activity[11] of **1a** has led to particular interest in its analogs from a pharmacological viewpoint.

In the present paper, we describe a new, simple and more stereoselective method for the synthesis of 1,4-thiazane-3-carboxylic acid derivatives.

(3*R*)-1,4-Thiazane-3-carboxylic Acid Derivatives

Methyl 5-methyl-1,4-thiazane-3-carboxylates (**6a** and **7a**) were prepared as a mixture of two diastereomers by condensation of L-cysteine methyl ester (**2a**) and monochloroacetone (**3a**) in the presence of potassium hydroxide, followed by cyclization and reduction with sodium borohydride. Its structure was determined by elemental analysis and spectral data.

The gas chromatographic analysis proved that the formation ratio of the diastereomers was 3.1 : 1. The main product (α-isomer) was isolated from the reaction mixture as the hydrochloride, mp 211—213° (dec.), in 47% yield. From the mother liquor, the minor product (β-isomer) was isolated as the oxalate, mp 150—151° (dec.), in 15% yield.

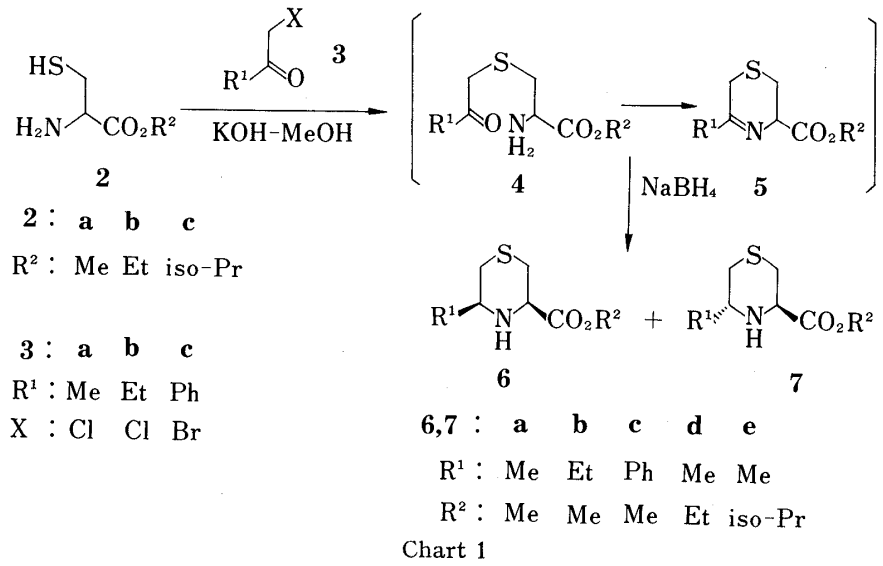


Chart 1

The configurations of α- and β-isomers were established on the basis of the reaction mechanism and nuclear magnetic resonance (NMR) spectra.

The α-isomer was determined to be methyl (3*R*, 5*S*)-5-methyl-1,4-thiazane-3-carboxylate (**6a**),[12] in which the methyl and the ester groups are in *cis*-configuration, while the β-isomer was presumed to be the (5*R*)-methyl analog (**7a**) having *trans*-configuration. Periodical analysis of the reaction mixture by thin-layer chromatography (TLC) suggested that prior to the cyclization the sulfide (**4**) was formed between **2a** and **3a** at the first step of the reaction, followed by the formation of a cyclic imine (**5**) in an acidic reaction medium. Subsequent reduction of **5** by sodium borohydride would proceed stereoselectively from the less hindered side, so that the formation of **6a** (*cis*-configuration) would predominate over that of **7a** (*trans*-configuration).

Carson *et al.* have already established the configurations and ring conformations of the two isomers by the NMR analysis of (3*R*)-5-methyl-1,4-thiazane-3-carboxylic acid 1,1-dioxide.[9] In the NMR spectra of the α- and β-isomers of methyl (3*R*)-5-methyl-1,4-thiazane-3-carboxylate, the C-3 proton appeared as a double doublet at δ 3.68 ppm with the α-isomer whereas the C-3 proton appeared as a triplet at δ 3.89 ppm in the case of the β-isomer. This result, as compared with the result obtained by Carson *et al.*, supported the view that the α- and β-isomers correspond to **6a** and **7a**, respectively. Further evidence of the *cis*-configuration of **6a** was provided by the finding that cycloalliin (**1a**) (*cis*-configuration) was derived exclusively from **6a** as described later.

In order to obtain the *cis*-isomer (**6**) more selectively, the effect of the ester group of **2a** was examined. L-Cysteine ethyl ester (**2b**) or isopropyl ester (**2c**) was allowed to react with **3a** under the same reaction condition as in the case of **2a**. Though the use of the ethyl group

Table I. The Retention Times and Formation Ratios of Diastereomers of (3*R*)-5-Methyl-1,4-thiazane-3-carboxylates (**6a, d, e** and **7a, d, e**)

Compds.	Retention time (min)	Ratio **6**/**7**
6a	28	3.1 : 1
7a	31	
6d	29	2.9 : 1
7d	32	
6e	29	4.3 : 1
7e	32	

gave nearly the same ratio of *cis* (**6d**) to *trans* (**7d**) as in the case of the methyl group, the use of the isopropyl group markedly improved the ratio (**6e** to **7e**) to 4.3: 1, as expected, as shown in Table I. However, purification of isopropyl ester derivatives was difficult, *e.g.*, **6e** was isolated as the oxalate in 32% yield, while **7e** was not isolated in a pure form.

The synthesis of methyl (3*R*)-5-substituted-1,4-thiazane-3-carboxylates having substituents other than a methyl group at the 5-position was then attempted. Chloromethyl ethyl ketone (**3b**) or α-bromoacetophenone (**3c**) was allowed to react with **2a** to afford methyl (3*R*)-5-ethyl-1,4-thiazane-3-carboxylates (**6b** and **7b**) or the 5-phenyl analogs (**6c** and **7c**), respectively. The configuration of the products (**6b**, **c** and **7b**, **c**) was determined by NMR analysis.

Chondrine, (3*R*)-1,4-thiazane-3-carboxylic acid 1-oxide, was isolated from the red alga *Chondria crassicaulis*[13,14] and brown alga *Undaria pinnatifida*,[15] and synthesized by Carson and Wong[16] and Dabrits and Virtanen.[17]

In order to synthesize deoxychondrine using the same method as described above, **2a** was allowed to react with chloroacetoaldehyde (**8**) under the same reaction conditions. However, the yield of methyl (3*R*)-1,4-thiazane-3-carboxylate (**9**) was only 12%. In this procedure, the ring closure to form **5** (R^1=H) would be difficult and a by-product, S-(2-hydroxyethyl)-L-cysteine methyl ester (**10**), was formed simultaneously during sodium borohydride reduction.

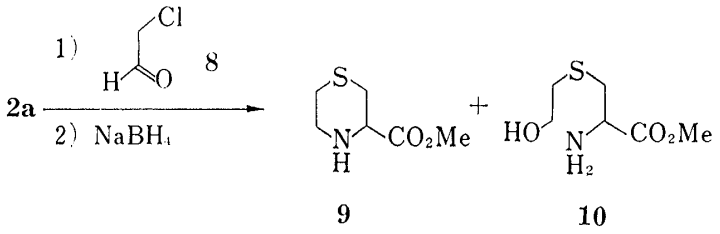


Chart 2

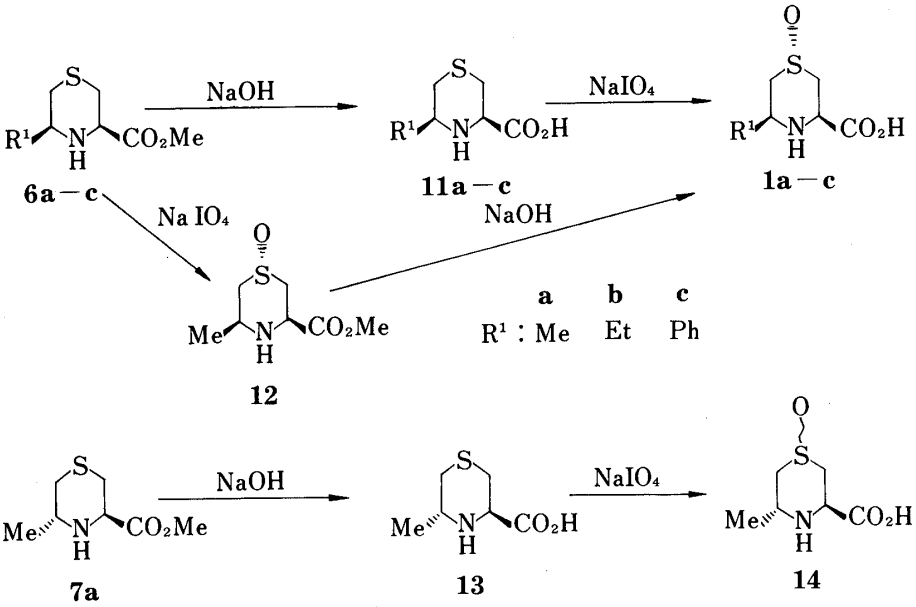


Chart 3

Cycloalliin and Its Analogs

Derivation of the above synthesized methyl (3*R*)-5-substituted-1,4-thiazane-3-carboxylates into cycloalliin (**1a**) and its analogs was attempted.

As shown in Chart 3, hydrolysis of **6a** with sodium hydroxide gave (3*R*, 5*S*)-5-methyl-1,4-thiazane-3-carboxylic acid (**11a**) in satisfactory yield. The physical constants of **11a** agreed with those of the reference compound[4] obtained by reduction of **1a** with hydriodic acid. Since Carson *et al.* reported[18] that oxidation of **11a** with sodium metaperiodate or hydrogen peroxide gave **1a** exclusively, we also performed the oxidation of **11a** by the same method to afford **1a** in good yield. On the other hand, oxidation of **6a** with sodium metaperiodate in aqueous methanol gave the corresponding S-oxide, methyl (3*R*, 5*S*)-5-methyl-1,4-thiazane-3-carboxylate 1-oxide (**12**), in high yield. The TLC results and NMR spectrum showed that this compound (**12**) was a single isomer which gave **1a** in good yield after hydrolysis. This finding proved that oxidation of **6a** took place stereoselectively to give only the (1*S*)-oxide. The structure of **1a** thus obtained from both **11a** and **12** was confirmed by comparison of the physicochemical properties with those of the reference compound.[5] Similarly, hydrolysis of **6b** and **6c** gave the corresponding carboxylic acids, (3*R*, 5*S*)-5-ethyl-1,4-thiazane-3-carboxylic acid (**11b**) and its (5*S*)-phenyl analog (**11c**), respectively. Oxidation of **11a** and **11c** with sodium metaperiodate gave (1*S*, 3*R*, 5*S*)-5-ethyl-1,4-thiazane-3-carboxylic acid 1-oxide (**1b**) and its (5*S*)-phenyl analog (**1c**), respectively, in high yields. The structures of **11b** and **1b** were elucidated by the comparison of physical constants with those of the standard substances,[7] while the structures of **11c** and **1c** were confirmed by the results of elemental and spectral analyses. Hydrolysis of the *trans*-isomer (**7a**) with sodium hydroxide gave (3*R*, 5*R*)-5-methyl-1,4-thiazane-3-carboxylic acid (**13**).[5] Oxidation of **13** with sodium metaperiodate in accordance with the method of Carson *et al.*[18] yielded the corresponding S-oxides as a mixture of two diastereomers.

Thus, we succeeded in developing a convenient synthetic method for 5-substituted-1,4-thiazane-3-carboxylic acid derivatives by condensation of a cysteine ester with an α-halogenoketone, followed by reduction with sodium borohydride. Using this method, we were able to synthesize cycloalliin and its analogs.

Experimental

Melting points are uncorrected. IR spectra were recorded with a Shimadzu IR-27G infrared spectrophotometer. NMR spectra were obtained by the use of a Hitachi R-20A high resolution NMR spectrometer with tetramethylsilane or sodium 3-(trimethylsilyl)-propanesulfonate as an internal standard. Optical rotation was measured with a Perkin-Elmer 243 polarimeter. Gas-liquid chromatography was performed on a Shimadzu GC-4B gas chromatograph fitted with the SP-80 column (2m).

Starting Materials——Hydrochlorides of L-cysteine methyl ester (**2a**), ethyl ester (**2b**) and isopropyl ester (**2c**) were prepared by esterification of L-cysteine according to the method of Bergmann and Michalis[19] [**2a**·HCl: Yield 78%, mp 140—141°, $[\alpha]_D^{25}$ −2.8° (*c*=1, MeOH). **2b**·HCl: Yield 80%, mp 125—126°, $[\alpha]_D^{25}$ −11.8° (*c*=1, MeOH). **2c**·HCl: Yield 71%, mp 154—155°, $[\alpha]_D^{25}$ −18.6° (*c*=1, MeOH)]. Chloromethyl ethyl ketone (**3b**) was prepared from propionyl chloride and diazomethane according to the method of Catch *et al.*[20]

Typical Procedure for the Preparation of (3*R*)-5-Substituted-1,4-thiazane-3-carboxylic Acid Esters (6a—e and 7a—c)——L-Cysteine methyl ester (**2a**)·HCl (3.4 g, 20 mmol) was added portionwise to a stirred solution of KOH (85%, 2.7 g, 41 mmol) in MeOH (50 ml) at 0—5°. To the mixture, a solution of monochloroacetone (**3a**) (1.9 g, 20 mmol) in MeOH (10 ml) was added dropwise with stirring and the stirring was continued for 1 hr at the same temperature. Subsequently, the reaction mixture was acidified with 30% methanolic HCl (*ca.* 4 ml) at 0—5°. After additional stirring for 1 hr at the same temperature, sodium borohydride (1.5 g, 40 mmol) was added in small portions to the mixture while the temperature was kept below 5° by ice cooling. The mixture was stirred for 30 min, then excess sodium borohydride was destroyed by adding dilute HCl. The mixture was made alkaline by adding aqueous $NaHCO_3$, then extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over $MgSO_4$ and concentrated *in vacuo*, yielding an oily residue which was dissolved in dry Et_2O (50 ml). Hydrogen chloride was bubbled into the ethereal solution to afford colorless crystals which were washed with a mixture of MeOH–Et_2O (1: 10) yielding **6a**·HCl (1.6 g). The mother liquor was concentrated to remove the solvent and the resulting residue was shaken with aqueous Na_2CO_3 and $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The residual oil (a mixture

of **6a** and **7a**) was subjected to silica gel (Kieselgel 60, 0.063—0.200 mm, Merck) column chromatography using $CHCl_3$–MeOH (20: 1) as an eluent. From the first fraction an additional amount (0.3 g) of **6a** was obtained to give a total yield of 47%. From the second fraction, **7a** (0.7 g) was obtained as a colorless syrup which crystallized as an oxalate (0.8 g, 15%).

6a·HCl: Colorless needles (from MeOH–Et_2O), mp 211—213° (dec.). *Anal.* Calcd for $C_7H_{13}NO_2S$·HCl: C, 39.71; H, 6.67; N, 6.62; S, 15.15; Cl, 16.75. Found: C, 83.78; H, 6.73; N, 6.66; S, 15.00; Cl, 16.48. $[\alpha]_D^{25}$ −13.7° (c=1, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 2800—2400, 1730. **6a** free base: NMR ($CDCl_3$) δ: 1.14 (3H, d, J=6.5 Hz, 5-CH_3), 2.00 (1H, s, NH), 2.35 (2H, d, J=6.0 Hz, 6-H_2), 2.65 (1H, d, J=10.0 Hz, 2-H ax.), 2.70 (1H, d, J=4.0 Hz, 2-H eq.), 2.9—3.1 (1H, m, 5-H), 3.68 (1H, d.d, J=4.0, 10.0 Hz, 3-H), 3.72 (3H, s, CO_2CH_3).

7a·Oxalate: Colorless needles (from MeOH–Et_2O), mp 150—151° (dec.). *Anal.* Calcd for $C_7H_{13}NO_2S$·$C_2H_2O_4$: C, 40.75; H, 5.70; N, 5.28; S, 12.09. Found: C, 40.58; H, 5.67; N, 5.29; S, 12.09. $[\alpha]_D^{25}$ −36.4° (c=1, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1745. **7a** free base: NMR ($CDCl_3$) δ: 1.11 (3H, d, J=6.5 Hz, 5-CH_3), 2.23 (1H, s, NH), 2.38 (2H, d, J=6.5 Hz, 6-H_2), 2.92 (2H, d, J=4.0 Hz, 2-H_2), 3.05—3.45 (1H, m, 5-H), 3.77 (3H, s, CO_2CH_3), 3.89 (1H, t, J=4.0 Hz, 3-H).

In the same manner, other (3*R*)-1,4-thiazane-3-carboxylates (**6b—e** and **7b—d**) were obtained. Yields and physicochemical data of the products were as follows.

6b·HCl: Yield 35%. Colorless needles (from MeOH–Et_2O). mp 210—212° (dec.). *Anal.* Calcd for $C_8H_{15}NO_2S$·HCl: C, 42.56; H, 7.14; N, 6.21; S, 14.20; Cl, 15.71. Found: C, 42.51; H, 7.08; N, 6.16; S, 14.23; Cl, 15.39. $[\alpha]_D^{25}$ −22.8° (c=1, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 2800—2400, 1740. NMR (D_2O) δ: 1.01 (3H, t, J=7.5 Hz, $C\underline{H}_3CH_2$), 1.4—2.1 (2H, m, $CH_3C\underline{H}_2$), 2.5—3.5 (5H, m, 2-H_2, 5-H, 6-H_2), 3.86 (3H, s, CO_2CH_3), 4.33 (1H, d.d, J=4.0, 10.0 Hz, 3-H).

7b·Oxalate: Yield 13%. Colorless needles (from MeOH–Et_2O), mp 142—143° (dec.). *Anal.* Calcd for $C_8H_{15}NO_2S$·$C_2H_2O_4$: C, 43.00; H, 6.13; N, 5.02; S, 11.48. Found: C, 42.99; H, 6.15; N, 4.98; S, 11.33. $[\alpha]_D^{25}$ −58.9° (c=1, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1750. **7b** free base: NMR ($CDCl_3$) δ: 0.94 (3H, t, J=6.0 Hz, $C\underline{H}_3CH_2$), 1.2—1.7 (2H, m, $CH_3C\underline{H}_2$), 2.23 (1H, s, NH), 2.35 (1H, d, J=8.0 Hz, 6-H ax.), 2.42 (1H, d, J=4.0 Hz, 6-H eq.), 2.94 (2H, d, J=4.0 Hz, 2-H_2), 3.78 (3H, s, CO_2CH_3), 3.89 (1H, t, J=4.0 Hz, 3-H).

6c: Yield 29%. Colorless prisms (from Et_2O–*n*-hexane), mp 81—82.5°. *Anal.* Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90; S, 13.51. Found: C, 60.54; H, 6.32; N, 5.79; S, 13.35. $[\alpha]_D^{25}$ +27.2° (c=1, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3224, 1740. NMR ($CDCl_3$) δ: 2.32 (1H, s, NH), 2.45—3.00 (4H, m, 2-H_2, 6-H_2), 3.75 (3H, s, CO_2CH_3), 3.7—4.2 (2H, m, 3-H, 5-H), 7.35 (5H, s, arom. H).

7c: Yield 9.4%. Colorless prisms (from Et_2O–*n*-hexane), mp 102—103°. *Anal.* Calcd for $C_{12}H_{15}NO_2S$: C, 60.73; H, 6.37; N, 5.90; S, 13.51. Found: C, 60.81; H, 6.35; N, 5.99; S, 13.44. $[\alpha]_D^{25}$ −105.2° (c=1, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 3225, 1730. NMR ($CDCl_3$) δ: 2.31 (1H, s, NH), 2.4—3.2 (4H, m, 2-H_2, 6-H_2), 3.82 (3H, s, CO_2CH_3), 3.9—4.5 (2H, m, 3-H, 5-H), 7.34 (5H, s, arom. H).

6d·HCl: Yield 42%. Colorless needles (from MeOH–Et_2O), mp 221—223° (dec.). *Anal.* Calcd for $C_8H_{15}NO_2S$·HCl: C, 42.56; H, 7.14; N, 6.21; S, 14.20; Cl, 15.71. Found: C, 42.45; H, 7.20; N, 6.16; S, 14.15, Cl, 15.64. $[\alpha]_D^{25}$ −14.7° (c=1, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 2800—2400, 1750. NMR (D_2O) δ: 1.28 (3H, t, J=7.0 Hz, $C\underline{H}_3CH_2$), 1.45 (3H, d, J=6.0 Hz, 5-CH_3), 2.81 (2H, d, J=7.0 Hz, 6-H_2), 3.07 (1H, d, J=10.5 Hz, 2-H ax.), 3.12 (1H, d, J=3.5 Hz, 2-H eq.), 3.3—3.9 (1H, m, 5-H), 4.32 (2H, q, J=7.0 Hz, $CH_3C\underline{H}_2$), 4.32 (1H, d.d, J=3.5, 10.5 Hz, 3-H).

7d: Yield 16%. Colorless syrup. IR ν_{max}^{film} cm^{-1}: 3340, 1740. NMR ($CDCl_3$) δ: 1.12 (3H, d, J=7.0 Hz, 5-CH_3), 1.30 (3H, t, J=6.0 Hz, $C\underline{H}_3CH_2$), 2.32 (1H, s, NH), 2.38 (2H, d, J=7.0 Hz, 6-H_2), 2.92 (2H, d, J=3.5 Hz, 2-H_2), 3.1—3.5 (1H, m, 5-H), 3.88 (1H, t, J=3.5 Hz, 3-H), 4.24 (2H, q, J=7.0 Hz, $CH_3C\underline{H}_2$).

6e·Oxalate: Yield 32%. Colorless prisms (from MeOH–Et_2O), mp 166—167°. *Anal.* Calcd for C_9H_{17}-NO_2S·$C_2H_2O_4$: C, 45.04; H, 6.53; N, 4.78; S, 10.93. Found: C, 45.00; H, 6.48; N, 4.81; S, 10.79. $[\alpha]_D^{25}$ −10.0° (c=1, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 1740. NMR (D_2O) δ: 1.29 (6H, d, J=6.0 Hz, $CH(C\underline{H}_3)_2$), 1.44 (3H, d, J=6.0 Hz, 5-CH_3), 2.80 (2H, d, J=7.5 Hz, 6-H_2), 3.02 (1H, d, J=10.0 Hz, 2-H ax.), 3.09 (1H, d, J=4.0 Hz, 2-H eq.), 3.2—3.8 (1H, m, 5-H), 4.23 (1H, d.d, J=4.0, 10.0 Hz, 3-H), 4.85—5.30 (1H, m, $C\underline{H}(CH_3)_2$).

Methyl (3*R*)-1,4-Thiazane-3-carboxylate (9) and S-(2-Hydroxyethyl)-L-cysteine Methyl Ester (10)——An aqueous solution (50%) of chloroacetaldehyde (**8**) (4.7 g, 30 mmol) was added dropwise to a stirred solution of **2a**·HCl (3.4 g, 20 mmol) and KOH (85%, 2.7 g, 41 mmol) in MeOH (50 ml) at 0—5° and stirring was continued for 1 hr at the same temperature. Subsequently, the reaction mixture was acidified with 30% methanolic HCl (*ca.* 4 ml) at 0—5°. The mixture was stirred for 1 hr at the same temperature, then sodium borohydride (1.5 g, 40 mmol) was added portionwise to the reaction mixture while the temperature was kept below 5°. The reaction mixture was worked up in a manner similar to that described above and then chromatographed on silica gel with $CHCl_3$–MeOH (20: 1) as an eluent. From the first fraction, **9** was obtained as a colorless syrup (0.5 g) which crystallized as a hydrochloride (0.48 g, 12%). Colorless needles (from MeOH–Et_2O), mp 172—173° (dec.). *Anal.* Calcd for $C_6H_{11}NO_2S$·HCl: C, 36.45; H, 6.12; N, 7.09; S, 16.22; Cl, 17.94. Found: C, 36.50; H, 6.12; N, 7.10; S, 16.30; Cl, 17.88. $[\alpha]_D^{25}$ −20.4° (c=1, MeOH). IR ν_{max}^{Nujol} cm^{-1}: 2800—2400, 1740. NMR (D_2O) δ: 2.7—3.8 (6H, m, 2-H_2, 5-H_2, 6-H_2), 3.89 (3H, s, CO_2CH_3), 4.42 (1H, d.d, J=5.5, 8.5 Hz, 3-H).

From the second fraction, **10** (0.54 g, 15%) was obtained as a colorless syrup. IR ν_{max}^{film} cm^{-1}: 1730. NMR ($CDCl_3$) δ: 2.56 (3H, s, OH, NH_2), 2.6—3.1 (4H, m, $-CH_2-S-CH_2-$), 3.5—4.1 (3H, m, $HOC\underline{H}_2-$, $-S-$

$CH_2C\underline{H}$), 3.75 (3H, s, CO_2CH_3).

Saponification of **10** with NaOH gave S-(2-hydroxyethyl)-L-cysteine, mp 189—190°, $[\alpha]_D^{25}$ −53.3° ($c=1$, H_2O), which was identical to the reported compound[16] in terms of physicochemical properties.

General Procedure for the Preparation of (3*R*,5*S*)-5-Substituted-1,4-thiazane-3-carboxylic Acids (11a—c)——A solution of NaOH (0.4 g, 10 mmol) in H_2O (5 ml) was added to a stirred solution of a methyl (3*R*)-1,4-thiazane-3-carboxylate (**6a—c**) (5 mmol) in MeOH (20 ml) at 10°. After being stirred for 5 hr at room temperature, the reaction mixture was neutralized with 10% HCl. The resulting solution was passed through a column of cation exchanger [Dowex-50 (H^+—form)]. The ion exchanger was washed thoroughly with H_2O, and the amino acid was eluted with 2 N ammonium hydroxide. The eluate was concentrated *in vacuo* to yield a crystalline residue of (3*R*)-1,4-thiazane-3-carboxylic acids (**11a—c**). Yields and pysicochemical data of the products were as follows.

(3*R*,5*S*)-5-Methyl-1,4-thiazane-3-carboxylic Acid (11a)——The crude product was converted to the hydrochloride, which was recrystallized from Me_2CO–H_2O. Yield 77%. Colorless needles, mp 244—245° (dec.) [lit.[5] 244°]. *Anal.* Calcd for $C_6H_{11}NO_2S\cdot HCl$: C, 36.45; H, 6.12; N, 7.09; S, 16.22; Cl, 17.94. Found: C, 36.52; H, 6.11; N, 7.13; S, 16.05; Cl, 17.94. $[\alpha]_D^{25}$ −30.0° ($c=1$, 2 N HCl) [lit[5]: −23.9° ($c=1$, 2 N HCl)]. IR ν_{max}^{Nujol} cm^{-1}: 1750. NMR (D_2O) δ: 1.64 (3H, d, $J=6.5$ Hz, 5-CH_3), 2.7—4.2 (5H, m, 2-H_2, 5-H, 6-H_2), 4.45 (1H, d.d, $J=6.0$, 8.5 Hz, 3-H).

(3*R*,5*S*)-5-Ethyl-1,4-thiazane-3-carboxylic Acid (11b)——Yield 88%. Colorless needles (from Me_2CO–H_2O), mp 275° (dec.). *Anal.* Calcd for $C_7H_{13}NO_2S\cdot H_2O$: C, 43.50; H, 7.83; N, 7.25; S, 16.59. Found: C, 43.43; H, 7.69; N, 7.17; S, 16.60. $[\alpha]_D^{25}$ −40.8° ($c=1$, 1 N HCl) [lit.[7]: −33.8° ($c=2.5$, 1 N HCl)]. IR ν_{max}^{Nujol} cm^{-1}: 1580. NMR (D_2O) δ: 1.01 (3H, t, $J=7.0$ Hz, $C\underline{H}_3CH_2$–), 1.4—2.2 (2H, m, $CH_3C\underline{H}_2$–), 2.6—3.8 (5H, m, 2-H_2, 5-H, 6-H_2), 4.23 (1H, d.d, $J=5.0$, 11.0 Hz, 3-H).

(3*R*,5*S*)-5-Phenyl-1,4-thiazane-3-carboxylic Acid (11c)——Yield 87%. Colorless needles (from H_2O), mp 269—271° (dec.). *Anal.* Calcd for $C_{11}H_{13}NO_2S$: C, 59.17; H, 5.87; N, 6.27; S, 14.36. Found: C, 59.09; H, 5.88; N, 6.33; S, 14.30. $[\alpha]_D^{25}$ −3.9° ($c=1$, 1 N HCl). IR ν_{max}^{Nujol} cm^{-1}: 3450, 1585. NMR (CF_3COOD–D_2O) δ: 2.4—3.7 (4H, m, 2-H_2, 6-H_2), 4.3—4.8 (2H, m, 3-H, 5-H), 7.50 (5H, s, arom. H).

Methyl (1*S*,3*R*,5*S*)-5-Methyl-1,4-thiazane-3-carboxylate 1-Oxide (12)——A solution of **6a**·HCl (5 g, 23.6 mmol) in H_2O (50 ml) was neutralized with $NaHCO_3$ (2 g) and then sodium metaperiodate 3 hydrate (10 g, 37.3 mmol) was added portionwise while the temperature was kept below 5°. The mixture was stirred for 2 hr, then the precipitate was filtered off and the filtrate was made alkaline with $NaHCO_3$ and extracted with $CHCl_3$. The organic layer was dried over $MgSO_4$ and concentrated to yield **12** as a syrup, which crystallized as a hydrochloride (3.9 g, 73%). Colorless needles (from MeOH–Et_2O), mp 187° (dec.). *Anal.* Calcd for $C_7H_{13}NO_3S\cdot HCl$: C, 36.92; H, 6.20; N, 6.15; S, 14.08; Cl, 15.57. Found: C, 36.88; H, 6.18; N, 6.14; S, 14.12; Cl, 15.57. $[\alpha]_D^{25}$ +6.8° ($c=1$, MeOH). IR ν_{max}^{KBr} cm^{-1}: 1750, 1015. NMR (D_2O) δ: 1.55 (3H, d, $J=7.0$ Hz, 5-CH_3), 2.6—4.5 (5H, m, 2-H_2, 5-H, 6-H_2), 3.91 (3H, s, CO_2CH_3), 4.88 (1H, d.d, $J=2.5$, 11.5 Hz, 3-H).

(1*S*,3*R*,5*S*)-5-Methyl-1,4-thiazane-3-carboxylic Acid 1-Oxide: Cycloalliin (1a)——a) From **11a**: A solution of **11a**·HCl (3.6 g, 18 mmol) in H_2O (50 ml) was oxidized with sodium metaperiodate 3 hydrate (5.9 g, 22 mmol) according to the procedure of Carson *et al.*[18] After recrystallization from EtOH–H_2O, **1a** hydrochloride hydrate (3.1 g, 74%) was obtained as colorless needles, mp 204—206° (dec.). *Anal.* Calcd for $C_6H_{11}NO_3S\cdot HCl\cdot H_2O$: C, 31.10; H, 6.09; N, 6.05; S, 13.84; Cl, 15.30. Found: C, 31.29; H, 6.06; N, 6.01; S, 13.60; Cl, 15.40. $[\alpha]_D^{25}$ −11.4° ($c=1$, 1 N HCl) [lit.[5] −11.7° ($c=2.5$, 1 N HCl)]. IR ν_{max}^{Nujol} cm^{-1}: 3350, 1730, 1030. NMR (CF_3COOD) δ: 1.74 (3H, d, $J=7.0$ Hz, 5-CH_3), 2.8—5.0 (5H, m, 2-H_2, 5-H, 6-H_2), 5.22 (1H, d.d, $J=2.5$, 11.5 Hz, 3-H).

b) From **12**: A solution of **12**·HCl (2.3 g, 10 mmol) in H_2O (20 ml) was hydrolyzed with NaOH (1.2 g, 30 mmol) by the procedure described for the preparation of **11a—c** to yield **1a** hydrochloride hydrate (2.2 g, 94%), which was identical with the specimen obtained above.

(1*S*,3*R*,5*S*)-5-Ethyl-1,4-thiazane-3-carboxylic acid 1-oxide (**1b**) and the (5*S*)-phenyl analog (**1c**) were prepared from **11b** and **11c**, respectively. The yields and physicochemical data were as follows.

1b·HCl: Yield 82%. Colorless needles (from EtOH–H_2O), mp 223—225° [lit.[7] 230—238° (dec.)]. *Anal.* Calcd for $C_7H_{13}NO_3S\cdot HCl$: C, 36.56; H, 6.28; N, 6.15; S, 14.08; Cl, 15.57. Found: C, 36.56; H, 6.28; N, 6.10; S, 13.95; Cl, 15.85. $[\alpha]_D^{25}$ −23.0 ($c=1$, 3 N HCl) [lit.[7] −22.7° ($c=2.5$, 3 N HCl)]. IR ν_{max}^{Nujol} cm^{-1}: 2800—2400, 1735, 1030, 1020, 1003.

1c: Yield 83%. Colorless needles (from H_2O), mp 200°. *Anal.* Calcd for $C_{11}H_{13}NO_3S$: C, 55.21; H, 5.48; N, 5.85; S, 13.40. Found: C, 55.11; H, 5.44; N, 5.90; S, 13.29. $[\alpha]_D^{25}$ −59.5° ($c=1$, 2 N HCl). IR ν_{max}^{Nujol} cm^{-1}: 1625, 1035, 1015. NMR (CF_3COOD) δ: 3.4—4.2 (4H, m, 2-H_2, 6-H_2), 5.1—5.7 (2H, m, 3-H, 5-H), 7.52 (5H, s, arom. H).

(3*R*,5*R*)-5-Methyl-1,4-thiazane-3-carboxylic Acid 1-Oxide (14)——Hydrolysis of **7a** (1.0 g, 5.7 mmol) with NaOH (0.3 g, 7.5 mmol) was carried out in the same manner as for **6a** to yield (3*R*,5*R*)-5-methyl-1,4-thiazane-3-carboxylic acid (**13**). Recrystallization from Me_2CO–H_2O gave colorless needles (0.75 g, 82%), mp 293—300° (dec.). [lit.[5] 287—288°]. *Anal.* Calcd for $C_6H_{11}NO_2S$: C, 44.70; H, 6.88; N, 8.69; S, 19.89. Found: C, 44.90; H, 6.81; N, 8.55; S, 19.77. $[\alpha]_D^{25}$ −84.9° ($c=1$, 3 N HCl) [lit.[5] −70.0° (3 N HCl)]. IR ν_{max}^{Nujol} cm^{-1}: 1580. NMR (CF_3COOD–D_2O) δ: 1.45 (3H, d, $J=6.0$ Hz, 5-CH_3), 2.7—3.0 (2H, m, 6-H_2), 3.28 (2H, d, $J=4.0$ Hz, 2-H_2), 3.5—4.3 (1H, m, 5-H), 4.61 (1H, t, $J=4.0$ Hz, 3-H).

Oxidation of **13** (1.5 g, 9.3 mmol) with sodium metaperiodate 3 hydrate (4.2 g, 16 mmol) was carried out in the manner described for **11a—c** to give **14** (0.9 g, 55%), mp>280°, as a mixture of two diastereomers at the S-oxide. *Anal.* Calcd for $C_6H_{11}NO_3S$: C, 40.66; H, 6.26; N, 7.90; S, 18.09. Found: C, 44.47; H, 6.26; N, 7.85; S, 17.83. IR ν_{max}^{Nujol} cm^{-1}: 1580, 1055, 1030.

Acknowledgement The authors thank Dr. I. Chibata and M. Miyoshi for their encouragement throughout the present study.

References and Notes

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