Preparation of 5-Alkyl-3-carboxymethylrhodanines and Their Aldose Reductase Inhibitory Activity

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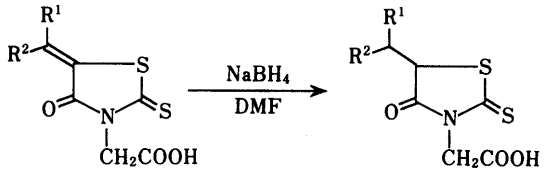
5-Alkyl-3-carboxymethylrhodanines (2) were prepared from 5-alkylmethylidene-3-carboxymethylrhodanines (1). The *exo* double bond of 1 was successfully reduced with $NaBH_4$. The 1,4-addition reaction path was confirmed on the basis of proton nuclear magnetic resonance spectrum of the product (4b) obtained from the reduction of 3 using $NaBD_4$. Optical resolution of the *tert*-butyl compound (2i) was achieved upon epimerization–crystallization method using L-3-amino-ε-caprolactam. The alkyl compounds (2) and the optical active compounds ((+)-2i, (−)-2i) were evaluated for aldose reductase inhibitory potency.

Keywords 5-alkyl-3-carboxymethylrhodanine; 5-alkylmethylidene-3-carboxymethylrhodanine; $NaBH_4$ reduction; *exo* carbon–carbon double bond; imide group; 1,4-addition; optical resolution; epimerization–crystallization method; aldose reductase inhibitory potency

Since Dvornik's proposal in 1973,[1] many kinds of compounds have been prepared and their aldose reductase (AR) inhibitory activity have been examined in the search to create drugs for treatment of diabetic complications. AR inhibitors are divided into structural types, many compounds with carboxyl group have been particularly well studied[2] and several representative compounds are now being tested in clinical stage.[3] Recently we reported synthesis and AR inhibitory activity of two kinds of novel AR inhibitors having carboxyl group: benzo[*b*]furans derivatives possessing a carboxymethylsulfamoyl group[4] and 5-alkylmethylidene-3-carboxymethylrhodanines (**1**).[5] In the course of the studies on 3-carboxymethylrhodanine derivatives, the AR inhibitory activity of 5-alkyl-3-carboxymethylrhodanines (**2**) was compared with that of 5-alkylmethylidene-3-carboxymethylrhodanines (**1**). In this paper, we describe reduction of **1** to **2** and aldose reductase inhibitory potency of **2**.



1a—o **2a—o**

	R^1	R^2	yield of 2 (%)
a	$CH(CH_3)_2$	H	59.5
b	$CH_2CH(CH_3)_2$	H	31.5
c	$CH(CH_2CH_3)_2$	H	50.6
d	$CH(CH_3)CH_2CH_3$	H	23.2
e	C_6H_{11}	H	63.6
f	$(CH_2)_3CH_3$	H	65.0
g	$(CH_2)_5CH_3$	H	41.2
h	$(CH_2)_2CH_3$	H	42.8
i	$C(CH_3)_3$	H	79.0
j	CH_3	CH_3	42.6
k	CH_2CH_3	CH_2CH_3	61.2
l [a]	$CH(CH_3)_2$	CH_3	49.7
m [a]	CH_2CH_3	CH_3	34.3
n [a]	$CH_2CH_2CH_3$	$CH_2CH_2CH_3$	81.4
o [a]	$CH_2CH_2CH_3$	CH_2CH_3	45.4

a) A mixture of the *E*- and *Z*-isomer.

Chart 1

There is appreciable interaction between *exo* carbon–carbon double bond at 5-position and functions (C=O, S) of the rhodanine ring. We expect that reduction of the *exo* double bond of **1** may alter the inhibitory potency. Selective reduction of the *exo* double bond of **1a—o** was carried out with $NaBH_4$ in *N*,*N*-dimethylformamide (DMF) without reduction of carbonyl and thiocarbonyl group of the rhodanine moiety under mild conditions to give the corresponding saturated compounds (**2a—o**) in reasonable yields (Chart 1, Table I).

The use of $NaBH_4$ for the reduction of aldehydes and ketones is now well established,[6] and a few applications to reduction of carbon–carbon double bond conjugated with nitro,[7] nitrile,[8] carbonyl[9] and ester functions[10] have been reported. To the best of our knowledge, the present successful reduction of the carbon–carbon double bond conjugated with the imide group may be the first finding in $NaBH_4$ reduction.

The reduction mechanism of the double bond in 5-*tert*-butylmethylidene-3-methoxycarbonylmethylrhodanine (**3**), more suitable than the carboxyl compound (**1i**) for identification of the mechanism, was investigated using $NaBD_4$. The methylidene compound (**3**) was treated with 0.28 eq of $NaBH_4$ in DMF to afford the 5-(2,2-dimethylpropyl) compound (**4a**) in 65% yield. In the proton nuclear magnetic resonance (^{1}H-NMR) of **4a** in $CDCl_3$, methylene proton signals of 2,2-dimethylpropyl group were detected at 1.81 (1H, double doublet, J=14.5, 11.1 Hz) and 2.38 ppm (1H, double doublet, J=14.5, 2.0 Hz), and 5-H signal was observed at 4.18 ppm (1H, double doublet, J=11.1, 2.0 Hz). The same procedure was carried out except for replacement of $NaBH_4$ with $NaBD_4$ and the reduced deuterium compound (**4b**) was obtained. Two kinds of methylene proton signals in the 2,2-dimethylpropyl group were detected at 1.79 (0.5H, doublet, J=11.0 Hz) and 2.36 ppm (0.5H, doublet, J=1.5 Hz) and two kinds of 5-H signals (0.5H, doublet, J=11.0 Hz and 0.5H, doublet, J=1.5 Hz) were observed at 4.18 ppm in the ^{1}H-NMR spectrum of **4b**. In addition, **4b** contained one deuterium atom based on the mass spectra (MS) (M^+, 276). Consequently, it was confirmed that the reduced product (**4b**) was 5-(1-monodeuterio-2,2-dimethylpropyl)-3-methoxycarbonylmethylrhodanine. Since the reduction resulted in the formation of two asymmetric carbons, **4b**

TABLE I. Physical Data for the 5-Alkylmethyl-3-carboxymethylrhodanines (2)

Compd.	mp (°C)	^{1}H-NMR (ppm, in $CDCl_3$)	Formula and analysis Calcd (Found) C	H	MS (*m/z*)	IR (cm^{-1})
2a	135—138	0.98 (6H, d, J=5.2 Hz, CH_3 × 2), 1.14—2.25 (3H, m, $(CH_3)_2CHCH_2$), 4.28 (1H, dd, J=4.2, 10.0 Hz, 5-H), 4.75 (2H, s, CH_2COOH), 10.11 (1H, s, COOH)	$C_9H_{13}NO_3S_2$ 43.71 (43.87)	5.30 (5.33)	247 (M^+), 229, 191	2860, 1707
2b	115—116.5	0.93 (6H, d, J=6.0 Hz, CH_3 × 2), 1.10—2.55 (5H, m, $(CH_3)_2CHCH_2CH_2$), 4.29 (1H, dd, J=5.6, 8.0 Hz, 5-H), 4.80 (2H, s, CH_2COOH), 10.11 (1H, s, COOH)	$C_{10}H_{15}NO_3S_2$ 45.96 (46.06)	5.78 (5.75)	261 (M^+), 243, 191	2880, 1710
2c	124—126	0.88 (6H, t, J=6.0 Hz, CH_3 × 2), 1.10—1.65 (5H, m, CH_3CH_2 × 2 and $(CH_3CH_2)_2CH$), 1.72—2.30 (2H, m, $(CH_3CH_2)_2CHCH_2$), 4.33 (1H, dd, J=4.4, 10.2 Hz, 5-H), 4.72 (2H, s, CH_2COOH), 9.73 (1H, s, COOH)	$C_{11}H_{17}NO_3S_2$ 47.98 (48.18)	6.22 (6.48)	275 (M^+), 257, 191	2860, 1730
2d	120—127	0.86—1.03 (6H, m, CH_3 × 2), 1.23—2.56 (5H, m, $CH_3CH_2CH(CH_3)CH_2$), 4.21—4.48 (1H, m, 5-H), 4.82 (2H, s, CH_2COOH), 10.29 (1H, s, COOH)	$C_{10}H_{15}NO_3S_2$ 45.96 (45.85)	5.78 (6.03)	261 (M^+), 243, 191	2870, 1740
2e	149—152	0.98—2.25 (13H, m, $CH_2CHCH_2CH_2CH_2CH_2CH_2$), 4.29 (1H, dd, J=4.4, 10.2 Hz, 5-H), 4.73 (2H, s, CH_2COOH), 10.39 (1H, s, COOH)	$C_{12}H_{17}NO_3S_2$ 50.15 (49.86)	5.96 (6.05)	287 (M^+), 191	2840, 1708
2f	107—109	0.89 (3H, t, J=5.0 Hz, CH_3), 1.38 (6H, m, $CH_3(CH_2)_3$), 2.07 (2H, m, $CH_3(CH_2)_3CH_2$), 4.31 (1H, dd, J=5.2, 8.0 Hz, 5-H), 4.80 (2H, s, CH_2COOH), 10.06 (1H, s, COOH)	$C_{10}H_{15}NO_3S_2$ 45.96 (46.22)	5.78 (5.76)	261 (M^+), 243, 191	3050, 1732, 1713
2g	78—79	0.87 (3H, t, J=4.2 Hz, CH_3), 1.29 (10H, m, $CH_3(CH_2)_5$), 2.05 (2H, m, $CH_3(CH_2)_5CH_2$), 4.26 (1H, dd, J=5.4, 8.2 Hz, 5-H), 4.73 (2H, s, CH_2COOH), 10.04 (1H, s, COOH)	$C_{12}H_{19}NO_3S_2$ 49.80 (49.64)	6.62 (6.48)	289 (M^+), 171	3040, 1741, 1715
2h	143—145	0.92 (3H, t, J=5.8 Hz, CH_3), 1.42 (4H, m, $CH_3(CH_2)_2$), 2.11 (2H, m, $CH_3(CH_2)_2CH_2$), 4.38 (1H, dd, J=5.2, 8.0 Hz, 5-H), 4.72 (2H, s, CH_2COOH), 8.93 (1H, s, COOH)	$C_9H_{13}NO_3S_2$ 43.71 (43.56)	5.30 (5.13)	247 (M^+), 229, 191	3030, 1732, 1713
2i	165.5—167	1.00 (9H, s, CH_3 × 3), 1.77 (1H, dd, J=11.2, 15.0 Hz, $(CH_3)_3CCH_2$), 2.40 (1H, dd, J=2.0, 15.0 Hz, $(CH_3)_3CCH_2$), 4.18 (1H, dd, J=2.0, 11.2 Hz, 5-H), 4.79 (2H, s, CH_2COOH), 7.32 (1H, s, COOH)	$C_{10}H_{15}NO_3S_2$ 45.96 (45.71)	5.78 (5.97)	261 (M^+), 243, 191	3050, 1743, 1726
2j	115—117	0.98 (3H, d, J=6.0 Hz, CH_3), 1.08 (3H, d, J=6.0 Hz, CH_3), 2.63 (1H, m, $(CH_3)_2CH$), 4.32 (1H, d, J=4.0 Hz, 5-H), 4.78 (2H, s, CH_2COOH), 10.14 (1H, s, COOH)	$C_8H_{11}NO_3S_2$ 41.19 (41.03)	4.75 (4.61)	233 (M^+), 215, 191	2870, 1720
2k	105—107	0.90 (3H, t, J=6.0 Hz, CH_3), 1.00 (3H, t, CH_3), 1.10—1.80 (4H, m, CH_3CH_2 × 2), 2.19 (1H, m, $(CH_3CH_2)_2CH$), 4.50 (1H, d, J=3.6 Hz, 5-H), 4.75 (2H, s, CH_2COOH), 10.39 (1H, s, COOH)	$C_{10}H_{15}NO_3S_2$ 45.96 (45.84)	5.78 (6.03)	261 (M^+), 191	3050, 1735
2l	143—147	0.91 (3H, d, J=6.8 Hz, CH_3), 0.98 (6H, d, J=5.6 Hz, $(CH_3)_2CH$), 1.25—2.50 (2H, m, CH × 2), 4.35—4.51 (1H, m, 5-H), 4.77 (2H, s, CH_2COOH), 10.34 (1H, s, COOH)	$C_{10}H_{15}NO_3S_2$ 45.96 (46.03)	5.78 (5.83)	261 (M^+), 191	3050, 1740
2m	112—115	0.94 (3H, d, J=7.0 Hz, $CH_3CH<$), 0.97 (3H, t, J=6.4 Hz, CH_3CH_2), 1.35 (2H, m, CH_3CH_2), 2.43 (1H, m, $CH_3CH<$), 4.36—4.47 (1H, m, 5-H), 4.78 (2H, s, CH_2COOH), 10.33 (1H, s, COOH)	$C_9H_{13}NO_3S_2$ 43.71 (43.60)	5.30 (5.02)	247 (M^+), 191, 173	3050, 1730
2n	122—124	0.92 (6H, t, CH_3 × 2), 1.10—1.80 (8H, m, $(CH_3CH_2CH_2)_2CH$), 2.35 (1H, m, $(CH_3CH_2CH_2)_2CH$), 4.49 (1H, d, J=3.6 Hz, 5-H), 4.80 (2H, s, CH_2COOH), 10.58 (1H, s, COOH)	$C_{12}H_{19}NO_3S_2$ 49.80 (49.89)	6.62 (6.71)	289 (M^+), 191, 173	3050, 1734
2o	68—101	0.92 (6H, t, CH_3 × 2), 1.10—1.70 (6H, m, $CH_3CH_2CH_2CH(CH_3CH_2)$), 2.28 (1H, m, $CH_3CH_2CH_2CH(CH_3CH_2)$), 4.50 (1H, d, J=3.6 Hz, 5-H), 4.78 (2H, s, CH_2COOH), 10.16 (1H, s, COOH)	$C_{11}H_{17}NO_3S_2$ 47.98 (47.75)	6.22 (5.92)	275 (M^+), 191	3050, 1710

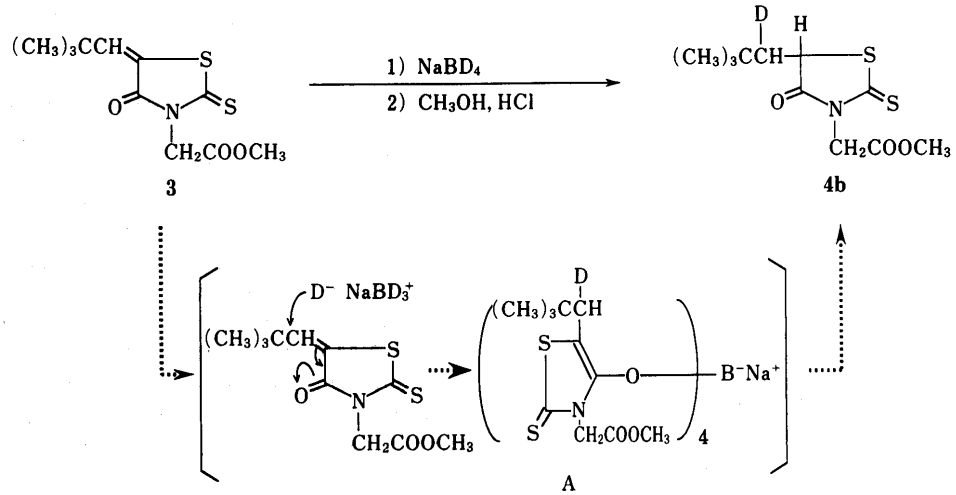


Chart 2

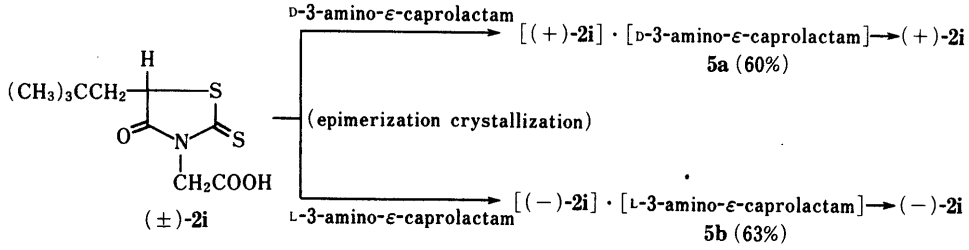


Chart 3

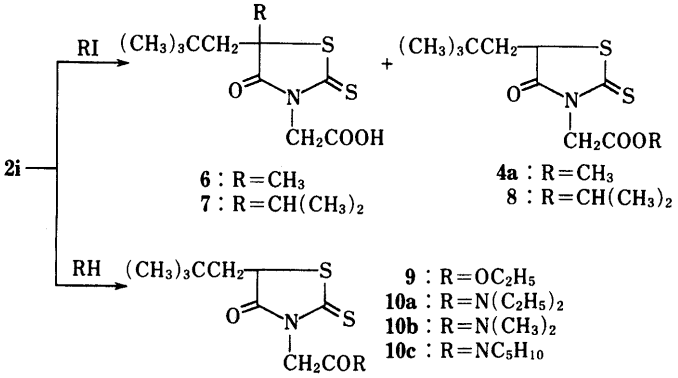


Chart 4

was obtained as a mixture of the two diastereomers in the ratio of 1 : 1. These results suggest that the reduction normally proceeds in the 1,4-addition process *via* an intermediate (A) (Chart 2).[11]

These 5-alkyl compounds (**2**) in the present report contain at least one asymmetric carbon atom. Resolution of **2** was carried out using (±)-5-(2,2-dimethylpropyl) compound (**2i**) as a typical compound. Treatment of **2i** with one equivalent of D-3-amino-ε-caprolactam resulted in the formation of a salt (**5a**) in 60% yield. On the other hand, **2i** was treated with 1 eq of L-3-amino-ε-caprolactam to give a salt (**5b**) in 64% yield. The enantiomeric acids, (+)-**2i** ($[\alpha]_D$ +69.4) and (−)-**2i** ($[\alpha]_D$ −68.7) were obtained from **5a** and **5b** respectively, in the usual manner. As **2i** has acidic methine protone at 5-position, it is presumed that (±)-**2i** can be resolved by epimerization crystallization.[12] Attempts of the resolution of the acid (**2i**) using optical active α-methylbenzylamine, 1-(1-naphthyl)ethylamine and menthol were unsuccessful (Chart 3).

In addition, alkyl group could be introduced into 5-position of **2i** to give 5-dialkylated compounds (**6, 7**) and their AR inhibition potency was checked. Alkylation of **2i** with methyl iodide and isopropyl iodide gave corresponding 5-methyl-5-(1,1-dimethylpropyl) compound (**6**) and 5-isopropyl-5-(1,1-dimethylpropyl) compound (**7**) in poor yields (5—10%). Both methyl ester (**4a**) and isopropyl ester (**8**) were obtained as main products in these alkylations. Steric hindrance among the neopentyl group, sulfur atom at 1-position and carbonyl group at 4-position of **2i** may make the replacement of 5-H by the alkyl groups difficult.[13]

Ethyl ester (**9**) and some amides (**10a—c**) of **2i** also were prepared to check their utility in *in vivo* screening (Chart 4).[14]

AR Inhibitory Activity All of the rhodanine derivatives prepared were tested for their ability to inhibit AR obtained from rat lens. The 50% inhibition of enzyme activity values are shown in Table II. All of the compounds (**2a—o**) displayed the potent inhibitory activity, with an IC_{50} of 10^{-7}—10^{-8} M. The *n*-pentyl derivative (**2f**) showed the highest activity among the compounds having five carbon chain at 5-position (**2b, d, f, i, k, l**). The branched isomers were less active than **2f**, and **2k** displayed the lowest activity (one fifth of the inhibitory activity of **2f**) in this series. The compound (**2b**) was also 3 times less active than **2f**.

TABLE II. Aldose Reductase-Inhibitory Activity

Compd.	IC_{50} ($\times 10^{-7}$ M)	Compd.	IC_{50} ($\times 10^{-7}$ M)
2a	1.1	**2n**	1.2
2b	2.0	**2o**	0.84
2c	0.79	(+)-**2i**	0.85
2d	1.1	(−)-**2i**	0.85
2e	0.90	**4a**	>100
2f	0.63	**6**	>100
2g	0.81	**7**	>100
2h	1.8	**8**	>100
2i	1.1	**9**	>100
2j	1.9	**10a**	>100
2k	3.1	**10b**	>100
2l	0.76	**10c**	>100
2m	2.0	Sorbinil	2.0

Table II suggests that the activity of **2** is related to the magnitude of lipophilia of the substituted group at 5-position. It is noteworthy that the derivatives having five to seven carbon alkyl group at 5-position show the effective potency among the compounds in the present report: **2f, l** having five carbon alkyl group, **2c, o** having six carbon alkyl group and **2e, g** having seven carbon alkyl group display the potent inhibitory activity, with an IC_{50} of 10^{-8} M, but all of the compounds substituted with three or four carbon alkyl group exhibit less activity, with IC_{50} of 10^{-7} M. The five to seven carbon alkyl groups at 5-position may interact appropriately with a secondary hydrophobic site presents on the enzyme to enhance the activity.[15] The 5-dialkylated compounds (**6, 7**) show over 10^{-5} M of IC_{50}. Steric hindrance caused by the geminal dialkyl group presumably makes the interaction with the hydrophobic site difficult.

The optically active (+)-**2i** and (−)-**2i** were as active as (±)-**2i**. It is speculated that the AR is not sensitive to optical activity of the compound (**2i**) or that the AR racemizes optically active **2i**.

The rhodanine compounds (**2**) prepared by the reduction of the 5-*exo* double bond of **1** in this series had similar activity to the parent compounds (**1**).[5] Thus, it is assumed that bonding type of the 5-substitution group is independent of the affinity with the hydrophobic site.

Experimental

Melting points were determined in open capillaries with a Thomas–Hoover melting point apparatus and are uncorrected. Infrared (IR) spectra were recorded on a Shimadzu IR-17G spectrometer. ^{1}H-NMR spectra were measured on a JEOL PS-100 and a JNM-EX270 spectrometer with chemical shifts given in δ values with tetramethylsilane (TMS) as an internal standard. Low-resolution MS were obtained with a Hitachi M-52 instrument, and optical rotation was obtained with a Perkin-Elmer 241 polarimeter.

3-Carboxymethyl-5-(2,2-dimethylpropyl)rhodanine (2i) General Procedure for **2a—h** and **2j—o**: A solution of $NaBH_4$ (0.18 g, 4.62 mmol) in dry DMF (7.5 ml) was added dropwise to a solution of **1i** (1.5 g, 6.17 mmol) in dry DMF (7.5 ml) at 0 °C, and the whole was stirred for 1 h at 0 °C. The mixture was poured into ice-cold 2 N HCl and extracted with ether. The extract was washed with saturated brine, dried over Na_2SO_4 and evaporated under reduced pressure. The yellow residue was crystallized from $C_2H_4Cl_2$–C_6H_{12} (1 : 5) to give **2i** (1.2 g, 79%). Physical and spectral data are given in Table I.

3-Methoxycarbonylmethyl-5-(2,2-dimethypropyl)rhodanine (4a) A mixture of **1i** (15 g, 57.9 mmol), *p*-toluenesulfonic acid monohydrate (1.5 g), and CH_3OH (20 ml) in dry C_6H_6 (150 ml) was stirred for 5 h at 80 °C. After the usual workup, the product was recrystallized from ethyl acetate to give 5-*tert*-butylmethylidene-3-methoxycarbonylmethylrhodanine (**3**) (13.2 g, 83.5%) as colorless prisms, mp 66.0—68.0 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.24 (9H, s, $C(CH_3)_3$), 3.77 (3H, s, $COOCH_3$), 4.82 (2H, s, CH_2), 7.05 (1H, s, CH). MS *m/z*: 273 (M^+), 213.

$NaBH_4$ (78 mg, 2.0 mmol) was added to a dry DMF solution (7 ml) of **3** (2.0 g, 7.3 mmol) at 0 °C. The reaction mixture was stirred for 3 h at 0 °C and then CH_3OH (3 ml) was added. After the mixture was adjusted to pH 7.0 with 2 N HCl, the whole was concentrated under reduced pressure to give a pale yellow oil. The oil was purified by column chromatography (SiO_2, 5% ethyl acetate in C_6H_6) to give colorless prisms (**4a**, 1.3 g, 65%), mp 50.0—51.5 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (9H, s, $CH_3 \times 3$), 1.81 (1H, dd, J=14.5, 11.1 Hz, one H of $(CH_3)_3CC\underline{H}_2$), 2.37 (1H, dd, J=14.5, 2.0 Hz, one H of $(CH_3)_3CC\underline{H}_2$), 3.77 (3H, s, $COOCH_3$), 4.18 (1H, dd, J=11.1, 2.0 Hz, 5-H), 4.75 (2H, s, NCH_2). MS *m/z*: 275 (M^+), 243. *Anal.* Calcd for $C_{11}H_{17}NO_3S_2$: C, 47.98; H, 6.22. Found: C, 47.71; H, 6.35.

A Diastereomeric Mixture of 5-(1-Monodeuterio-2,2-dimethylpropyl)-3-methoxycarbonylmethylrhodanine (4b) $NaBD_4$ (84 mg, 2.0 mmol) was added to a dry DMF solution (7 ml) of **3** (2.0 g, 7.3 mmol) at 0 °C. The reaction mixture was treated in a similar manner as preparation of **4a**. The deuterium compound (**4b**) was obtained as colorless prisms (1.2 g, 60%), mp 49—54 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (9H, s, $CH_3 \times 3$), 1.79 (0.5H, d, J=11.0 Hz, $(CH_3)_3CCHD$), 2.36 (0.5H, d, J=1.5 Hz, $(CH_3)_3CCDH$), 3.76 (3H, s, $COOCH_3$), 4.18 (0.5H, d, J=11.0 Hz, 5-H), 4.18 (0.5H, d, J=1.5 Hz, 5-H), 4.75 (2H, s, NCH_2). MS (*m/z*): 276 (M^+), 244.

Optical Resolution of 2i 1) An aqueous solution (25 ml) of D-3-amino-ε-caprolactam (2.5 g, 191 mmol) was added slowly to a solution of **2i** (5.0 g, 191 mmol) in EtOH (5 ml) at room temperature. The mixture was allowed to stand for 5 h. The crystals were filtered and recrystallized from $C_2H_4Cl_2$–C_6H_{12} (1 : 1) to give **5a** (4.5 g, 60%): mp 148.0—152.0 °C, $[\alpha]_D$ −8.1° (c=1.00, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.00 (9H, s, $CH_3 \times 3$), 1.40—2.45 (6H, m, $NH_2CHC\underline{H}_2C\underline{H}_2C\underline{H}_2$), 1.77 (1H, dd, J=14, 10 Hz, one H of $(CH_3)_3CC\underline{H}_2$), 2.42 (1H, dd, J=14, 2 Hz, one H of $(CH_3)_3CC\underline{H}_2$), 3.07—3.45 (2H, m, $CONHC\underline{H}_2$), 3.85—4.20 (1H, m, $NH_2C\underline{H}$), 4.25 (1H, dd, J=10, 2 Hz, SCHCO), 4.49 (2H, br s, $NC\underline{H}_2COOH$), 7.56 (4H, br s, NH, NH_2, COOH).

2) **5b** was prepared with L-3-amino-ε-caprolactam by the same procedure as above, yield 63%: mp 152.0—156.0 °C, $[\alpha]_D$ +7.3° (c=1.00, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 1.00 (9H, s, $CH_3 \times 3$), 1.35—2.40 (6H, m, $NH_2CHC\underline{H}_2C\underline{H}_2C\underline{H}_2$), 1.70 (1H, dd, J=14, 10 Hz, one H of $(CH_3)_3CC\underline{H}_2$), 2.34 (1H, dd, J=14, 2 Hz, one H of $(CH_3)_3CC\underline{H}_2$), 3.05—3.40 (2H, m, $CONHC\underline{H}_2$), 3.88—4.15 (1H, m, $NH_2C\underline{H}$), 4.22 (1H, dd, J=10, 2 Hz, SCHCO), 4.50 (2H, br s, $NC\underline{H}_2COOH$), 7.72 (4H, br s, NH, NH_2, COOH).

3) 0.1 N HCl (25.7 ml) was added dropwise to an aqueous solution (200 ml) of **5a** (1.0 g, 2.57 mmol) at 0 °C. The solution was extracted with ether, and the extract washed with saturated brine, dried over Na_2SO_4 and evaporated under reduced pressure. The residue was recrystallized from $C_2H_4Cl_2$–C_6H_{12} (1 : 1) to give (+)-**2i** (0.52 g, 77%): mp 159.0—162.0 °C, $[\alpha]_D$ +69.4° (c=1.00, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.99 (9H, s, $CH_3 \times 3$), 1.78 (1H, dd, J=10.2, 14.6 Hz, one H of $(CH_3)_3CC\underline{H}_2$), 2.41 (1H, dd, J=2.0, 14.6 Hz, one H of $(CH_3)_3CC\underline{H}_2$), 4.19 (1H, dd, J=2.0, 10.2 Hz, 5-H), 4.78 (2H, s, $C\underline{H}_2COOH$), 9.56 (1H, s, COOH). MS *m/z*: 261 (M^+), 243, 191. *Anal.* Calcd for $C_{10}H_{15}NO_3S_2$: C, 45.95; H, 5.78. Found: C, 46.20; H, 5.83.

4) (−)-**2i** was prepared from **5b** using the same procedure as above: yield 84%, mp 157.0—159.0 °C, $[\alpha]_D$ −68.7 (c=1.00, $CHCl_3$). ^{1}H-NMR ($CDCl_3$) δ: 0.99 (9H, s, $CH_3 \times 3$), 1.78 (1H, dd, J=10.2, 14.6 Hz, one H of $(CH_3)_3CC\underline{H}_2$), 2.41 (1H, dd, J=2.0, 14.6 Hz, one H of $(CH_3)_3CC\underline{H}_2$), 4.19 (1H, dd, J=2.0, 10.2 Hz, 5-H), 4.78 (2H, s, $C\underline{H}_2COOH$), 9.01 (1H, s, COOH). MS *m/z*: 261 (M^+), 243, 191. *Anal.* Calcd for $C_{10}H_{15}NO_3S_2$: C, 45.95; H, 5.78. Found: C, 45.94; H, 5.73.

3-Carboxymethyl-5-methyl-5-(2,2-dimethylpropyl)rhodanine (6) Methyl iodide (7.0 g, 49.3 mmol) was added to a mixture of **2i** (7.5 g, 29 mmol), acetic acid (2.6 g, 43.5 mmol) and sodium acetate (3.6 g, 43.5 mmol) in DMF (150 ml) at 30 °C. The mixture was stirred at 50 °C for 10 h, then the solvent was evaporated off under reduced pressure, and the residue was extracted with ether. The ether layer was washed with 0.5 N HCl followed by brine, and dried over Na_2SO_4. Removal of the ether gave a pale yellow oil. The oil was purified by column chromatography on silica gel (8% ethyl acetate in hexane) to give **6** as pale yellow prisms (0.8 g, 10%) and **4a** (3.9 g, 49%). **6**: mp 85.5—88.0 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.88 (9H, s, $CH_3 \times 3$), 2.28 (1H, d, J=15 Hz, one H of $(CH_3)_3CC\underline{H}_2$), 2.49 (1H, d, J=15 Hz, one H of $(CH_3)_3CC\underline{H}_2$, 3.38 (3H, s, 5-$CH_3$), 4.23 (2H, s, NCH_2), 7.81 (1H, br s, COOH). MS *m/z*: 275 (M^+), 243. *Anal.* Calcd for $C_{11}H_{17}NO_3S_2$: C, 47.98; H, 6.22. Found: C, 47.70; H, 6.13.

3-Carboxymethyl-5-(2,2-dimethylpropyl)-5-isopropylrhodanine (7) Isopropyl iodide (7.0 g, 41.5 mmol) was added to a mixture of **2i** (5.0 g, 19.2 mmol), acetic acid (1.7 g, 28.8 mmol) and sodium acetate (2.4 g, 28.8 mmol) in DMF (120 ml) at 30 °C. The mixture was stirred at 80 °C for 15 h. After workup in a similar manner as for **6**, the residue was purified by column chromatography on silica gel (8% ethyl acetate in hexane) to give **7** (0.3 g, 5%) and 5-(2,2-dimethylpropyl)-3-isopropyloxycarbonylmethylrhodanine (**8**) (2.5 g, 43%) as yellow prisms. **7**: mp 96.0—98.0 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.98 (9H, s, $(CH_3)_3C$), 1.13 (6H, d, J=6.0 Hz, $(C\underline{H}_3)_2CH$), 1.72 (1H, d, J=15.0 Hz, one H of CCH_2), 2.16 (1H, d, J=15.0 Hz, one H of CCH_2), 4.20 (2H, s, NCH_2), 4.53 (1H, m, CH), 8.01 (1H, br s, COOH). MS *m/z*: 303 (M^+), 286, 260. *Anal.* Calcd for $C_{13}H_{21}NO_3S_2$: C, 51.46; H, 6.98. Found: C, 51.60; H, 6.93. **8**: mp 72.5—75.0 °C. ^{1}H-NMR ($CDCl_3$) δ: 0.90 (9H, s, $(CH_3)_3C$), 1.14 (6H, d, J=7.0 Hz, $CH(C\underline{H}_3)_2$), 1.50 (1H, dd, J=14.5, 11.1 Hz, one H of CCH_2), 2.17 (1H, dd, J=14.5, 2.0 Hz, one H of CCH_2), 3.76 (1H, dd, J=11.1, 2.0 Hz, 5-H), 4.24 (2H, s, CH_2N), 4.58 (1H, m, $C\underline{H}(CH_3)_2$), 8.00 (1H, br s, COOH). MS *m/z*: 303 (M^+), 261. *Anal.* Calcd for $C_{13}H_{21}NO_3S_2$: C, 51.46; H, 6.98. Found: C, 51.37; H, 6.99.

3-Ethoxycarbonylmethyl-5-(2,2-dimethylpropyl)rhodanine (9) A mixture of **2i** (20.0 g, 76.5 mmol), absolute EtOH (20 ml) and *p*-toluenesulfonic acid (1.0 g) was refluxed for 8 h with azeotropic removal of water. The reaction mixture was washed successively with 2 N HCl, saturated aqueous $NaHCO_3$ and saturated brine. The solution was dried over Na_2SO_4 and evaporated off under reduced pressure. The residue was recrystallized from EtOH–H_2O (5 : 1) to give **9** (18.0 g, 62%), mp 51.0—52.0 °C. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (9H, s, $(CH_3)_3C$), 1.27 (3H, t, J=7.0 Hz, $C\underline{H}_3CH_2$), 1.77 (1H, dd, J=10.4, 14.4 Hz, one H of $(CH_3)_3CC\underline{H}_2$), 2.40 (1H, dd, J=2.0, 14.4 Hz, one H of $(CH_3)_3CC\underline{H}_2$), 4.17 (1H, dd, J=2.0, 10.4 Hz, 5-H), 4.21 (2H, q, J=7.0 Hz, $CH_3C\underline{H}_2$), 4.71 (2H, s, CH_2COO). MS *m/z*: 289 (M^+). *Anal.* Calcd for $C_{12}H_{19}NO_3S_2$: C, 49.80; H, 6.62. Found: C, 49.66; H, 6.65.

3-Diethylaminocarbonylmethyl-5-(2,2-dimethylpropyl)rhodanine (10a) Isobutyl chloroformate (1.0 g, 7.61 mmol) was added slowly to a mixture of **2i** (2.0 g, 7.56 mmol), triethylamine (0.8 g, 7.71 mmol) and dry THF (14 ml) at −13 °C, and the mixture was stirred for 15 min at −13 °C. A solution of diethylamine (0.6 g, 7.66 mmol) in $CHCl_3$ (14 ml) was added dropwise and the resulting mixture was stirred for 1 h at 0 °C and then 1 h at room temperature. The reaction mixture was poured into cold water and extracted with ethyl acetate. The extract was washed successively with 2 N HCl, saturated aqueous $NaHCO_3$ and saturated brine. The solution was dried over Na_2SO_4 and evaporated off under reduced pressure. The residual oil was distillated under reduced pressure to give **10a** (1.4 g, 58%), bp 260 °C/0.1 mmHg, ^{1}H-NMR ($CDCl_3$) δ: 1.00 (9H, s, $(CH_3)_3C$), 1.12 (3H, t, J=7.6 Hz, $C\underline{H}_3CH_2$), 1.31 (3H, t, J=7.6 Hz, $C\underline{H}_3CH_2$), 1.82 (1H, dd, J=10.0, 14.8 Hz, one H of $(CH_3)_3CC\underline{H}_2$), 2.41 (1H, dd, J=2.0, 14.8 Hz, one H of $(CH_3)_3CC\underline{H}_2$), 3.40 (4H, q, J=7.6 Hz, $CH_3C\underline{H}_2 \times 2$), 4.22 (1H, dd, J=2.0, 10.0 Hz, 5-H), 4.81 (2H, s, CH_2CO). MS *m/z*: 316 (M^+), 301, 283. *Anal.* Calcd for $C_{14}H_{24}N_2O_2S_2$: C, 53.13; H, 7.64. Found: C, 52.86; H, 7.55.

3-Dimethylaminocarbonylmethyl-5-(2,2-dimethylpropyl)rhodanine (10b)

The amide (**10b**) was prepared with dimethylamine using a procedure similar to that above, mp 104.0—105.5 °C from ($C_2H_4Cl_2$–C_6H_{12} (1 : 1)), yield 82%. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (9H, s, $(CH_3)_3C$), 1.81 (1H, dd, J=10.0, 14.8 Hz, one H of $(CH_3)_3CC\underline{H}_2$), 2.41 (1H, dd, J=2.0, 14.8 Hz, one H of $(CH_3)_3CC\underline{H}_2$), 2.98 (3H, s, NCH_3), 3.10 (3H, s, NCH_3), 4.20 (1H, dd, J=2.0, 10.0 Hz, 5-H), 4.81 (2H, s, CH_2CO). MS m/z: 288 (M^+). *Anal.* Calcd for $C_{12}H_{20}N_2O_2S_2$: C, 49.97; H, 6.99. Found: C, 50.23; H, 6.73.

5-(2,2-Dimethylpropyl)-3-piperidylcarbonylmethylrhodanine (10c) The amide (**10c**) was prepared with piperidine by use of a similar procedure as above, mp 142.0—144.0 °C from ($C_2H_4Cl_2$–C_6H_{12} (1 : 1)), yield 72%. ^{1}H-NMR ($CDCl_3$) δ: 1.00 (9H, s, $(CH_3)_3C$), 1.65—2.02 (7H, m, $NCH_2C\underline{H}_2C\underline{H}_2C\underline{H}_2CH_2$ and one H of $(CH_3)_3CC\underline{H}_2$), 2.39 (1H, dd, J=2.0, 14.4 Hz, one H of $(CH_3)_3CC\underline{H}_2$), 3.48 (4H, br s, $NC\underline{H}_2CH_2CH_2CH_2C\underline{H}_2$), 4.17 (1H, dd, J=2.0, 10.0 Hz, 5-H), 4.79 (2H, s, CH_2CO). MS m/z: 328 (M^+), 313, 295. *Anal.* Calcd for $C_{15}H_{24}N_2O_2S_2$: C, 54.85; H, 7.36. Found: C, 55.13; H, 7.18.

Enzyme Inhibitory Activity Aldose reductase activity was measured by the method of Hoyman and Kinoshita.[16] Assays were performed at 30 °C in 0.1 M sodium phosphate buffer (pH 6.2) containing 1.5 mM DL-glyceraldehyde, 0.25 mM reduced nicotinamide adenine diphosphate (NADPH) and an appropriate amount of enzyme (supernatant of homogenates of rat lens) in a total volume of 1.5 ml. The effect of an inhibitor on the enzyme activity was determined by adding 15 μl of dimethylsulfoxide solution of a test compound to the reaction mixture. The concentration of the inhibitor giving IC_{50} was estimated from the least-squares regression line in the plot of the logarithm of inhibition concentration *versus* remaining activity.

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