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Synthesis and Antihypertensive Activity of *N*-(Mercaptoacyl)-thiazolidinecarboxylic Acids[1)]

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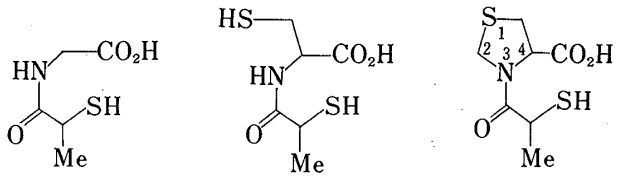
The synthesis and antihypertensive activity of a new series of *N*-(mercaptoacyl)-thiazolidinecarboxylic acids (VIIa—d) are described. Antihypertensive activity was evaluated in terms of angiotensin I-converting enzyme (ACE) inhibitory activity. The activities of these compounds were compared with that of (2*S*)-1-[(2*S*)-3-mercapto-2-methylpropanoyl]proline, SQ 14225, and many of them were found to be relatively potent inhibitors of ACE. The most potent was (4*R*)-2-(2-hydroxyphenyl)-3-(3-mercaptopropanoyl)-4-thiazolidinecarboxylic acid (**62**). Structure–activity relationships among the thiazolidines and some related compounds are discussed.

Keywords——(4*R*)-2-(2-hydroxyphenyl)-3-(3-mercaptopropanoyl)-4-thiazolidinecarboxylic acid; *S*-benzoyl-2-mercaptopropanoic acid; *S*-benzoyl-3-mercapto-2-methylpropanoic acid; *N*-(mercaptoacyl)thiazolidinecarboxylic acid; thiazolidinecarboxylic acid; thiazolidine; thiol; optical resolution; absolute configuration; angiotensin I-converting enzyme inhibitor; antihypertensive agent; structure–activity relationship

In a series of studies aimed at the development of new antihypertensive agents, we have synthesized various mercaptoacylamino acids, tiopronin (I) analogs, and screened them for inhibitory activities against angiotensin I-converting enzyme (ACE).[1b-d,2)] The inhibitory activities of I and *N*-(2-mercaptopropanoyl)-L-cysteine-a (II), a cysteine derivative, against ACE were pI_{50}: 4.70 and 5.52 (angiotensin I), respectively. The activity of II was found to be 10 times more potent than that of I.[2b)]



I II III

Chart 1

These findings prompted us to close the ring by condensation between the thiol and amino groups in the cysteine moiety of II with aldehyde to synthesize (4*R*)-3-(2-mercaptopropanoyl)-4-thiazolidinecarboxylic acid (III), a thiazolidine derivative. Further, compounds having various substituents at C_2 on the thiazolidine ring of III were synthesized. Compounds having different lengths of methylene chain between the thiol and carbonyl groups in the mercaptoacyl moiety were also synthesized. As the C_2-substituent on the thiazolidine ring, we considered the phenyl group substituted by a hydroxyl group, because the pI_{50} values of *N*-(2-mercaptopropanoyl)-L-tyrosine-b and *N*-(2-mercaptopropanoyl)-L-phenylalanine-a were 6.00 and 5.34 (angiotensin I), respectively, and the introduction of a hydroxyphenyl group in tyrosine was useful for increasing the activity.[1b)] Compounds having heterocycles as substituents were synthesized as well, because *N*-(2-mercaptopropanoyl)-L-tryptophan had pI_{50}: 5.85 (angiotensin I).[2b)] 3-Mercaptoacyl-2-thiazolidinecarboxylic acids substituted by a carboxyl

Chart 2

group in different positions from III were also synthesized. These compounds were tested for inhibitory activity against ACE.

(4*R*)-2-(2-Hydroxyphenyl)-3-(3-mercaptopropanoyl)-4-thiazolidinecarboxylic acid (**62**), SA 446, was found to be the most potent compound. The activity was pI_{50}: 7.55 (angiotensin I), that is, several times more potent than that of (2*S*)-1-[(2*S*)-3-mercapto-2-methylpropanoyl]-proline, SQ 14225.[3]

In this report the syntheses of a series of thiazolidine derivatives and the results of studies of their structure–antihypertensive activity relationships are described.

1. Syntheses

Syntheses of thiazolidine ring systems were accomplished by the condensation–ring closure of aldehydes or ketones with L-cysteine in water or aqueous alcohol, or by similar ring closure of cysteamine with glyoxylic acid, to give (4*R*)-4-thiazolidinecarboxylic acid (IVa), (±)-2-thiazolidinecarboxylic acid (IVb), 2-monosubstituted (4*R*)-4-thiazolidinecarboxylic acid (IVc), and 2,2-disubstituted (4*R*)-4-thiazolidinecarboxylic acid (IVd) as shown in Chart 2.

As illustrated in Chart 3, *S*-benzoylmercaptoalkanoic acids {*e.g.*, *S*-benzoylmercaptoacetic acid (Va: mp 106.5—107°C), (±)-*S*-benzoyl-2-mercaptopropanoic acid [(±)-Vb: mp 67.5—68°C], and *S*-benzoyl-3-mercaptopropanoic acid (Vc: mp 81—82°C)} were prepared by benzoylation of thioglycolic acid, (±)-thiolactic acid or 3-mercaptopropanoic acid, and (±)-*S*-benzoyl-3-mercapto-2-methylpropanoic acid [(±)-Vd: mp 63—64°C] was prepared by addition of thiobenzoic acid to methacrylic acid under heating. The structure of (±)-Vd was deduced from the fact that it was produced by hydrolysis and benzoylation of (±)-*S*-acetyl-3-mercapto-2-methylpropanoic acid [prepared by addition of thioacetic acid to methacrylic acid].[4] (±)-*S*-Benzoyl-3-mercaptobutanoic acid [(±)-Ve: mp 71—72°C] was prepared by heating *trans*-crotonic acid and thiobenzoic acid neat.[5] *S*-Benzoyl-4-mercaptobutanoic acid (Vf: mp 41—43.5°C) was prepared by benzoylation of 4-mercaptobutanoic acid,[6] which was obtained by refluxing γ-butyrolactone and thiourea in 47% hydrobromic acid for 6 h followed by alkaline hydrolysis.

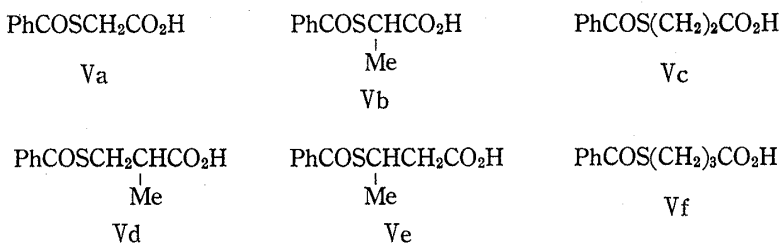
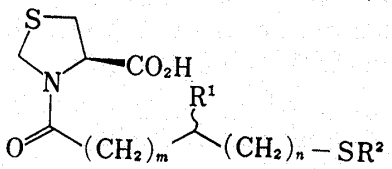


Chart 3

N-(*S*-Benzoylmercaptoacyl)thiazolidinecarboxylic acids (VIa—d) were prepared by the reaction of thiazolidinecarboxylic acids (IVa—d) with *S*-benzoylmercaptoalkanoic acids (Va—f) or their reactive derivatives according to methods A—D in Chart 2. The ammonolysis of the *S*-benzoyl derivatives gave *N*-(mercaptoacyl)thiazolidinecarboxylic acids (VIIa—d). The experimental section is limited to five brief descriptions (methods A—D and ammonolysis) of typical procedures.

(4*R*)-3-Mercaptoacyl-4-thiazolidinecarboxylic Acids (VIIa) in Table I——(4*R*)-3-(*S*-Benzoylmercaptoacetyl)-4-thiazolidinecarboxylic acid (**1**) was obtained by Schotten–Baumann reaction of IVa with the acid chloride of Va using sodium bicarbonate as a base. Compound IVa [mp 195°C (dec.); $[\alpha]_D^{25}$ −142.7° (*c*=1.0, ethanol)][7] was prepared by reaction of 37% formalin with L-cysteine. The acid chloride was prepared by treating Va with thionyl chloride. Compound **1** was also prepared by methods C and D. Ammonolysis of **1** with 28% ammonia gave (4*R*)-3-(mercaptoacetyl)-4-thiazolidinecarboxylic acid (**2**).

TABLE I. (4*R*)-3-Mercaptoacyl-4-thiazolidinecarboxylic Acids (VIIa) and Their *S*-Benzoyl Derivatives (VIa)



No. 1—12

Compd. No.	Confign. of R^1	R^1	R^2	m	n	Prepn. method of VIa[a]	Yield (%)	mp (°C)[b]	Recrystn. solvent	$[\alpha]_D^{25}$ deg. in MeOH	IR ν_{max}^{Nujol} cm^{-1}
1		H	COPh	0	0	A	65	112—113	Benzene	−103.3(1.0)	1739, 1660, 1620,
						C	69				1580, 1205, 915
						D	84				
2		H	H	0	0		72	115—122	EtOAc	−137.9(1.0)	2600, 1705, 1605,
											1285, 1250, 970
3a[c]	(*S*)	Me	COPh	0	0	A	20	174—175	EtOAc	−158.9(1.0)	1738, 1650, 1617,
						D	75				1203, 915
3a·DCHA[d]								198—199	EtOAc–EtOH	−135.8(1.0)	
3b[c]	(*R*)	Me	COPh	0	0	A	19	Oil[e]		−20.8(1.0)	
3b·DCHA[d]								157—158	EtOAc–ether	−74.1(1.0)	1655, 1615, 1575,
											1203, 905
4a[c]	(*S*)	Me	H	0	0		89	122—123	EtOAc	−110.4(1.0)	2590, 1737, 1600,
											1185, 1070
4b[c]	(*R*)	Me	H	0	0		83	161—163	EtOAc	−166.2(1.0)	2580, 1750, 1605,
											1200, 1170, 1080
5		H	COPh	0	1	A	82	107—109	Ether	−84.9(1.0)	1718, 1650, 1615,
											1207, 910
6		H	H	0	1		90	112—114	EtOAc–benzene	−126.0(1.0)	2580, 1703, 1600,
											1282, 1235
7a[c]	(*S*)	Me	COPh	0	1	A	29	137—139	Benzene	−172.4(1.0)	1740, 1700, 1648,
						D	83				1632, 1210, 908
7a·DCHA[d]								199—200	EtOAc–EtOH	−109.9(1.0)	
7b[c]	(*R*)	Me	COPh	0	1	A	24	Oil[e]		−19.5(1.0)	
7b·DCHA[d]								140—141	EtOAc	−53.2(1.0)	1655, 1640, 1625,
											1205, 921
8a[c]	(*S*)	Me	H	0	1		72	113—114	Ether	−172.0(1.0)	2600, 1720, 1610,
											1260, 1203, 1070
8a·DCHA[d]								190—191	EtOAc	−116.1(1.0)	
8b[c]	(*R*)	Me	H	0	1		58	101.5—104	Benzene	−89.6(0.9)	2560, 1720, 1595,
											1270, 1190
8b·DCHA[d]								179—180	EtOAc–EtOH	−84.5(1.0)	
9a[c]		Me	COPh	1	0	A	38	149—150	EtOH–benzene	−82.0(2.3)	1748, 1638, 1612,
						D	30				1210, 1200, 925
9a·DCHA[d]								185—186.5	EtOH	−69.6(1.9)	
9b[c]		Me	COPh	1	0	A	32	Oil[e]		−71.4(2.1)	
9b·DCHA[d]								156—158	EtOH	−84.2(2.0)	1660, 1640, 1565,
											1212, 922
10a[c]		Me	H	1	0		64	103—106	Benzene	−116.0(1.6)	2560, 1720, 1595,
											1265, 1180
10b[c]		Me	H	1	0		88	Oil[e]		−90.6(2.5)	2560, 1725, 1650,
											1410, 1230, 1190
											($CHCl_3$)
10b·DCHA[d]								192—193.5	EtOH–ether		
11		H	COPh	0	2	A	68	Amorph.[e]		−74.1(1.6)	1720, 1645, 1610,
						D	80				1235, 1200, 915
11·DCHA[d]								178.5—180	EtOH		
12		H	H	0	2		70	Oil[e]		−135.3(2.6)	
12·DCHA[d]								166—167.5	EtOH		1630, 1570, 1200,
											1150

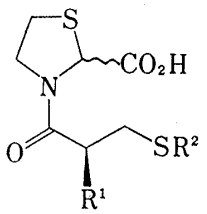
a) Methods are described in Experimental.
b) Melting points are uncorrected.
c) Compounds **3a**, **4a**, **7a**, **8a**, **9a**, and **10a** are diastereoisomers of **3b**, **4b**, **7b**, **8b**, **9b**, and **10b**, respectively.
d) DCHA is dicyclohexylamine.
e) Purified by chromatography.

The reaction of IVa with the acid chloride [prepared by treating (±)-Vb with thionyl chloride] gave a mixture of diastereoisomers, and separation of the mixture gave (4*R*)-3-[(2*S*)- and (2*R*)-*S*-benzoyl-2-mercaptopropanoyl]-4-thiazolidinecarboxylic acid (**3a** and **3b**); *Rf* values: 0.32 and 0.38, respectively.[8a] Compounds **3a** and **3b** were converted to the dicyclohexylamine (DCHA) salts and crystallized. The absolute configurations of the mercaptoacyl moieties were identified by the following procedure.

Compounds (±)-Vb was optically resolved and the absolute configurations of the isomers were identified by the method mentioned later. (2*S*)-*S*-Benzoyl-2-mercaptopropanoic acid [(*S*)-(−)-Vb] reacted with IVa (method D) to yield **3a**. The absolute configurations of the mercaptoacyl moieties of **3a** and **3b** were thus identified as (*S*) and (*R*), respectively.

Ammonolysis of **3a** and **3b** gave the corresponding thiols, (4*R*)-3-[(2*S*)- and (2*R*)-2-mercaptopropanoyl]-4-thiazolidinecarboxylic acid (**4a** and **4b**), respectively. (4*R*)-3-(*S*-Benzoyl-3-mercaptopropanoyl)-4-thiazolidinecarboxylic acid (**5**) was obtained by the reaction (method A) of IVa with the acid chloride prepared from Vc and thionyl chloride. Ammonolysis of **5** gave (4*R*)-3-(3-mercaptopropanoyl)-4-thiazolidinecarboxylic acid (**6**). In the same manner as **3a** and **3b**, IVa was reacted with the acid chloride prepared by treating (±)-Vd with thionyl chloride. The resulting mixture of diastereoisomers was chromatographed and the products were recrystallized to give (4*R*)-3-[(2*S*)- and (2*R*)-*S*-benzoyl-3-mercapto-2-methylpropanoyl]-4-thiazolidinecarboxylic acid (**7a** and **7b**); *Rf* values: 0.34 and 0.35, respectively.[8a] Both compounds were converted to DCHA salts. The absolute configurations of the mercaptoacyl moieties of these compounds were identified by the following methods, in the same manner as for **3a**.

Table II. 3-Mercaptoacyl-2-thiazolidinecarboxylic Acids (VIIb) and Their S-Benzoyl Derivatives (VIb)



No. **13**—**16**

Compd. No.	Confign. of CO_2H	R^1	R^2	Prepn. method of VIb[a]	Yield (%)	mp (°C)[b]	Recrystn. solvent	$[\alpha]_D^{25}$ deg. (c=1.0, MeOH)	IR ν_{max}^{Nujol} cm^{-1}
13	(±)	H	COPh	A	80	110—111	Benzene–hexane	—	1710, 1660, 1637, 1230, 1200, 910
14	(±)	H	H		95	Oil[e]		—	2590, 1736, 1630, 1430, 1190 (film)
14·DCHA[d]						203—204	EtOAc	—	
15a[c]		Me	COPh	D	37	105.5—106	EtOAc–hexane	−66.5	1757, 1710, 1660, 1600, 1461, 1206, 907
15b[c]		Me	COPh	D	34	140—140.5	EtOAc–hexane	−125.2	1720, 1639, 1599, 1457, 1227, 1200, 914
16a[c]		Me	H		86	Oil[e]		+16.1	2580, 1720, 1610, 1420, 1235 (film)
16b[c]		Me	H		94	93.5	EtOAc–hexane	−114.8	2600, 1705, 1633, 1457, 1410, 1185

a, *b*, *d*, *e*) See the corresponding footnotes in Table I.
c) Absolute configuration of the carboxyl group is undecided: (*R*) or (*S*).
Compounds **15a** and **16a** are diastereoisomers of **15b** and **16b**, respectively

Compound (±)-Vd was optically resolved, and the absolute configurations of the isomers were identified by the method mentioned later. (2*S*)-*S*-Benzoyl-3-mercapto-2-methylpropanoic acid [(*S*)-(−)-Vd] reacted with IVa (method D) to yield **7a**. The absolute configurations of the mercaptoacyl moieties of **7a** and **7b** were identified as (*S*) and (*R*), respectively.

Ammonolysis of **7a** and **7b** gave the corresponding thiols, (4*R*)-3-[(2*S*)- and (2*R*)-3-mercapto-2-methylpropanoyl]-4-thiazolidinecarboxylic acid (**8a** and **8b**), respectively.

In the nuclear magnetic resonance (NMR) spectra, the signals at δ 1.22 and 1.19, assigned to methyl protons in **8a** and **8b**, each appeared as a doublet (J=6.1 Hz). The signals of the C_4-proton on the thiazolidine ring appeared at δ 5.05 and 4.99 in **8a** and **8b**, respectively, as a double-doublet (J=7.0, 4.0 Hz). Both signals of **8a** were shifted to lower field than those of **8b**.

3-Mercaptoacyl-2-thiazolidinecarboxylic Acids (VIIb) in Table II——(±)-3-(*S*-Benzoyl-3-mercaptopropanoyl)-2-thiazolidinecarboxylic acid (**13**) was prepared by Schotten–Baumann reaction of (±)-IVb [mp 185°C (dec.)][9] with the acid chloride of Vc using sodium bicarbonate as a base. 3-[(2*S*)-*S*-Benzoyl-3-mercapto-2-methylpropanoyl]-2-thiazolidinecarboxylic acid-a and -b (**15a** and **15b**) were prepared from (*S*)-(−)-Vd by the mixed anhydride method (method D). The resulting mixture of diastereoisomers was separated by column chromatography. The *Rf* values of **15a** and **15b** were 0.49 and 0.42, respectively.[8b] Ammonolysis of **15a** and **15b** gave 3-[(2*S*)-3-mercapto-2-methylpropanoyl]-2-thiazolidinecarboxylic acid-a and -b (**16a** and **16b**); *Rf* values: 0.25 and 0.22, respectively.[8b]

2-Monosubstituted (4*R*)-3-Mercaptoacyl-4-thiazolidinecarboxylic Acids (VIIc) in Tables III—V——Cyclohexanecarboxaldehyde, the starting material for (4*R*)-3-[(2*S*)-*S*-benzoyl-3-mercapto-2-methylpropanoyl]-2-cyclohexyl-4-thiazolidinecarboxylic acid (**17**), was prepared by the method of Brown *et al.*[10] 2-Acetoxycyclohexanecarboxaldehyde, the starting material for (4*R*)-2-(2-hydroxycyclohexyl)-3-(3-mercaptopropanoyl)-4-thiazolidinecarboxylic acid (**20**), was prepared by acetylation of 2-(2-hydroxycyclohexyl)-1,3-dithiane prepared according to the method of Corey *et al.*[11]

The condensation reaction of aldehyde with L-cysteine was performed according to the method of Soloway *et al.*, Schmolka *et al.*, Kulkarni *et al.*, and Chodkiewicz *et al.*[12]

N-Acylation of IVc was carried out in the manner described above. In this case, it was proved that the acid chloride of (*S*)-(−)-Vd [$[\alpha]_D^{24}$ −37.6° (c=1.2, chloroform)] retained the original configuration, because the specific rotation of Vd obtained by hydrolysis of the acid chloride coincided with that of (*S*)-(−)-Vd. However, as the specific rotation of the acid chloride prepared from (*S*)-(−)-Vb was 0 and (±)-Vb was obtained by hydrolysis thereof, it was proved that (*S*)-(−)-Vb was racemized by thionyl chloride treatment.

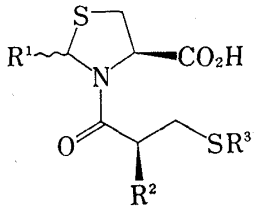
Compounds **21**, **23** and **25** could each be separated into two diastereoisomers. All these compounds have the substituent connected to C_2 on the thiazolidine ring through methylene group(s). When an aryl group was linked directly to C_2 on the thiazolidine ring, only one compound [(*R*)- or (*S*)- configuration] was isolated, but a small amount of the compound with the other configuration was detected by thin-layer chromatography (TLC) in the reaction solution.

Rf values of **21a** and **21b**, **22a** and **22b**, **23a** and **23b**, **24a** and **24b**, **25a** and **25b**, **26a** and **26b** were 0.87 and 0.87,[8a] 0.40 and 0.40,[8c] 0.55 and 0.50,[8d] 0.53 and 0.60,[8d] respectively. Moreover the *Rf* values of **29a** and **29b**, **45a** and **45b** were 0.38 and 0.27,[8e] 0.58 and 0.44,[8f] respectively.

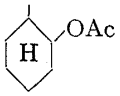
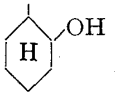
Ammonolysis of the DCHA salts of **21a**, **21b**, **23a**, **23b**, and **85** gave **22a**, **22b**, **24a**, **24b**, and **86**, respectively. The addition of potassium thiobenzoate to (4*R*)-3-chloroacetyl-2-phenyl-4-thiazolidinecarboxylic acid caused the potassium salt of **27** to precipitate (method C). The salt was collected by filtration and recrystallized from tetrahydrofuran–ether [mp 214°C (dec.); $[\alpha]_D^{25}$ +117.3° (c=1.1, dimethylformamide)].

In the compounds substituted with 2-hydroxyphenyl at C_2 on the thiazolidine ring, IVc

TABLE III. 2-Monosubstituted (4*R*)-3-Mercaptoacyl-4-thiazolidinecarboxylic Acids (VIIc) and Their *S*-Benzoyl Derivatives (VIc)[a]

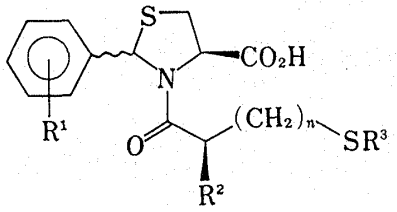


No. **17**—**26**

Compd. No.	R^1	R^2	R^3	Prepn. method of VIc[b]	Yield (%)	mp (°C)[c]	Recrystn. solvent	$[\alpha]_D$ deg. in MeOH (c, °C)	IR ν_{max}^{Nujol} cm^{-1}
17		Me	COPh	B	81	Oil[f]			1740, 1658, 1610, 1415, 1208, 914 (film)
17·DCHA[e]						128—133.5	EtOH–ether	−56.5 (1.0, 25)	
18		Me	H		76	Amorph.[f]		−72.2 (1.0, 25)	2860, 2580, 1740, 1610, 1420, 1240 (film)
19		H	COPh	B	86	Amorph.[f]		−45.7 (1.2, 25)	1737, 1650, 1615, 1408, 1235, 1207, 912
20		H	H		84	Amorph.[f]		−32.7 (1.0, 25)	3250, 1726, 1645, 1408, 1045
21a[d]	$(CH_2)_2SAc$	H	COPh	B		Oil[f]			
21a·DCHA[e]					27	186—188	EtOH	−79.1 (1.0, 25)	1675, 1650, 1630, 1570, 910
21b[d]	$(CH_2)_2SAc$	H	COPh	B		Oil[f]			
21b·DCHA[e]					23	112—114	EtOAc	−33.3 (1.0, 25)	1690, 1660, 1635, 1560, 910
22a[d]	$(CH_2)_2SH$	H	H		63	138—141.5	EtOAc	−166.3 (1.0, 25)	2600, 1735, 1600, 1207, 1186
22b[d]	$(CH_2)_2SH$	H	H		52	97.5—102.5		−52.6 (1.0, 25)	2560, 1730, 1590, 1265, 1173
23a[d]	$(CH_2)_2SAc$	Me	COPh	B		Oil[f]			
23a·DCHA[e]					21	178.5—189		−99.3 (1.0, 25)	1700, 1655, 1630, 1560, 920
23b[d]	$(CH_2)_2SAc$	Me	COPh	B		Oil[f]			
23b·DCHA[e]					25	157—158	EtOH–ether	−70.6 (1.0, 25)	1700, 1675, 1640, 1590, 920
24a[d]	$(CH_2)_2SH$	Me	H		75	141—142	EtOAc	−175.4 (1.0, 25)	2560, 1720, 1590, 1190, 1175
24b[d]	$(CH_2)_2SH$	Me	H		71	Oil[f]		−117.5 (1.0, 25)	2560, 1720, 1600, 1175, 1140 (film)
25a[d]	CH_2Ph	Me	COPh	B	38	190 (dec.)	EtOAc	−113.2 (1.3, 28)	1740, 1660, 1610, 1203, 920
25b[d]	CH_2Ph	Me	COPh	B	30	148.5—149.5	EtOAc–cyclohexane	−147.8 (1.2, 28)	1745, 1640, 1610, 1180, 920
26a[d]	CH_2Ph	Me	H		85	159—161	EtOAc	−97.6 (0.5, 25)	2650, 1730, 1610, 1285, 1220
26b[d]	CH_2Ph	Me	H		74	Amorph.[f]		−151.0 (1.0, 25)	2500, 1740, 1610, 1260, 1180

a) Absolute configuration of R^1 is undecided: (*R*) or (*S*).
b) Methods are described in Experimental.
c) Melting points are uncorrected.
d) Compounds **21a**, **22a**, **23a**, **24a**, **25a**, and **26a** are diastereoisomers of **21b**, **22b**, **23b**, **24b**, **25b**, and **26b**, respectively.
e) DCHA is dicyclohexylamine.
f) Purified by chromatography.

TABLE IV. (4*R*)-2-(Substituted Phenyl)-3-mercaptoacyl-4-thiazolidinecarboxylic Acids (VIIc) and Their *S*-Benzoyl Derivatives (VIc)



No. 27—99

Compd. No.	R^1	R^2	R^3	n	Prepn. method of VIc[a]	Yield (%)	mp (°C)[b]	Recrystn. solvent	$[\alpha]_D$ deg. (c, solv., °C)	IR ν_{max}^{Nujol} cm^{-1}
27	H	H	COPh	0	C	78	134—135.5	EtOAc–cyclohexane	+126.0 (1.0, MeOH, 25)	1745, 1655, 1580, 1430, 1210, 920
28	H	H	H	0		85	142—143.5	EtOAc	+121.0 (1.2, MeOH, 25)	2600, 1725, 1600, 1450, 1240
29a[c,g]	H	Me	COPh	0	A	33	186—186.5	EtOAc	+162.1 (1.0, DMF, 25)	1732, 1663, 1600, 1275, 1200, 1170, 910
29b[c,g]	H	Me	COPh	0	A	31	124	EtOAc–cyclohexane	+104.9 (1.0, DMF, 25)	1760, 1705, 1650, 1600, 1230, 1200, 905
30a[c,g]	H	Me	H	0		85	173—175	EtOAc	+106.8 (1.0, DMF, 25)	2560, 1740, 1623, 1180, 1075
31	H	H	COPh	1	A	88	126 (dec.)	EtOAc	+110.5 (1.0, MeOH, 25)	1710, 1630, 1610, 1215, 1202, 920
32	H	H	H	1		81	Amorph.[e]		+104.3 (1.0, MeOH, 25)	1725, 1650, 1400, ($CHCl_3$)
33	H	Me	COPh	1	B D	68 58	150—151.5	Benzene–cyclohexane	+89.1 (1.3, MeOH, 25)	1750, 1650, 1620, 1209, 920
34	H	Me	H	1		54	Oil[e]		+72.2 (0.5, MeOH, 25)	1720, 1640, 1400, ($CHCl_3$)
35	4-Me	H	COPh	1	A	55	122 (dec.)	EtOAc	+131.4 (1.0, MeOH, 26)	3480, 1710, 1630, 1615, 920
36	4-Me	H	H	1		74	Amorph.[e]		+125.2 (1.0, MeOH, 26)	1730, 1610, 1165
37	4-Me	Me	COPh	1	A	48	131—132	EtOAc–hexane	+117.6 (1.0, MeOH, 26)	1755, 1650, 1610, 1205, 1170, 915
38	4-Me	Me	H	1		83	154—156	EtOAc–cyclohexane	+112.9 (1.0, MeOH, 25)	2580, 1725, 1600, 1275, 1174
39	2-Cl	H	COPh	1	B	28	160—161	EtOAc–cyclohexane	−58.2 (1.0, MeOH, 26)	1740, 1640, 1610, 1193, 915
40	2-Cl	H	H	1		86	133—134	EtOAc	−64.6 (1.0, MeOH, 26)	2520, 1730, 1590, 1203, 1182
41	4-Cl	H	COPh	1	B	51	119 (dec.)	EtOAc	+110.0 (1.0, MeOH, 26)	3520, 1710, 1635, 1615, 1218, 920
42	4-Cl	H	H	1		90	Amorph.[e]		+77.1 (1.0, MeOH, 26)	1730, 1650, 1630, 1210

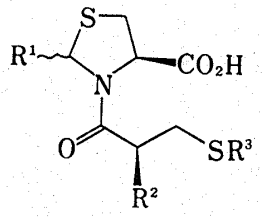
Compd. No.	R^1	R^2	R^3	n	Prepn. method of VIc[a]	Yield (%)	mp (°C)[b]	Recrystn. solvent	$[\alpha]_D$ deg. (c, solv., °C)	IR ν_{max}^{Nujol} cm^{-1}
43	2,4-Cl_2	H	COPh	0	B	16	Amorph.[e]		−187.8 (1.0, MeOH, 26)	1735, 1650, 1620, 1210, 1180
44	2,4-Cl_2	H	H	0		29	Amorph.[e]		−303.8 (0.3, MeOH, 25)	1720, 1640, 1620, 1200
45a[c,g]	4-F	Me	COPh	0	B	32	178—180	EtOAc	+155.3 (1.0, MeOH, 26)	1730, 1665, 1600, 1223, 1200
45b[c,g]	4-F	Me	COPh	0	B	18	Amorph.[e]		+98.6 (1.1, MeOH, 26)	1740, 1650, 1210, 910
46a[g]	4-F	Me	H	0		95	199—200	EtOAc	+92.2 (1.0, MeOH, 26)	2520, 1740, 1630, 1603, 1184, 1174
47	2-NO_2	Me	COPh	1	B	69	Amorph.[e]		−257.0 (0.4, MeOH, 25)	1750, 1720, 1650, 1515, 1340, 1205, 915
47·DCHA[d]							225—226	MeOH	−158.0 (1.0, MeOH, 25)	
48	2-NO_2	Me	H	1		65	118—121	EtOAc–benzene	−284.7 (0.4, MeOH, 26)	1755, 1625, 1515, 1345, 1195, 1180
49	3-NO_2	Me	COPh	1	B	43	128—130	Benzene	+34.0 (1.0, MeOH, 25)	1750, 1650, 1620, 1520, 1350, 1205, 915
50	3-NO_2	Me	H	1		55	153—154	EtOAc	+94.9 (1.0, MeOH, 25)	1745, 1600, 1520, 1350, 1223, 1210, 1160
51	4-NO_2	Me	COPh	1	B	60	Oil[d]			
51·DCHA[d]							223—228	MeOH	−234.0 (0.6, MeOH, 26)	1650, 1630, 1558, 1505, 1340, 1203, 915
52	4-NMe_2	Me	COPh	1	A	90	138—142 (dec.)			1710, 1655, 1600, 910
53	4-NMe_2	Me	H	1		65	Amorph.[e]		+4.2 (0.5, MeOH, 25)	1710, 1615, 1170
54	4-NHAc	Me	COPh	1	B	87	Oil[e]		+121.6 (0.9, MeOH, 25)	1730, 1650, 1630, 1600, 1204, 1174, 910 (film)
55	4-NHAc	Me	H	1		25	169—173	EtOAc	+126.0 (1.1, MeOH, 25)	1735, 1675, 1650, 1620, 1600, 1260, 1203
56	4-$NHCO_2$-CH_2Ph	Me	COPh	1	B	53	Oil[e]		+114.3 (0.5, MeOH, 25)	1725, 1650, 1600, 1520, 1210, 1050, 914 (film)
57	2-CO_2H	H	COPh	1	A	72	115—120	EtOAc–benzene	+171.8 (1.0, MeOH, 25)	1711, 1655, 1256, 1208, 912
58	2-CO_2H	H	H	1		81	207—208 (dec.)	EtOAc–MeOH	+236.5 (0.6, MeOH, 25)	1712, 1654, 1304, 1261, 1210
59	2-OH	H	COPh	0	B	46	Amorph.[e]		+126.9 (1.0, MeOH, 26)	3270, 1723, 1635, 1206, 915
60	2-OH	H	H	0		67	156—158 (dec.)	EtOAc–MeOH	+193.4 (1.0, MeOH, 26)	3370, 1736, 1697, 1631, 1594, 1229
61	2-OH	H	COPh	1	B	48	100.5—101 (dec.)	EtOAc–benzene	+130.8 (1.0, MeOH, 26)	3460, 1760, 1663, 1580, 1205, 910

Compd. No.	R^1	R^2	R^3	n	Prepn. method of VIc[a]	Yield (%)	mp (°C)[b]	Recrystn. solvent	$[\alpha]_D$ deg. (c, solv., °C)	IR ν_{max}^{Nujol} cm^{-1}
62	2-OH	H	H	1		83	146—148[f]	EtOAc	+176.8 (1.0, MeOH, 26)	3390, 1724, 1626, 1255, 1100
63	2-OH	H	COPh	2	B	48	112—114 (dec.)	MeOH	+124.6 (1.0, MeOH, 26)	3350, 1709, 1637, 1598, 1233, 1207, 920
64	2-OH	H	H	2		62	Amorph.[e]		+138.4 (1.0, MeOH, 26)	3350, 1722, 1624, 1230, 854
65	2-OH	Me	COPh	1	B	76	Amorph.[e]		+118.1 (1.0, MeOH, 26)	3260, 1724, 1658, 1624, 1208, 912
66	2-OH	Me	H	1		84	167—168 (dec.)	EtOAc	+160.6 (1.0, MeOH, 26)	3280, 1730, 1624, 1604, 1230
67	3-OCOPh	H	COPh	1	B	52	Amorph.[e]		+85.1 (1.0, MeOH, 27)	1738, 1655, 1213, 1068, 916
68	3-OH	H	H	1		69	156—157	EtOAc–MeOH–cyclohexane	+122.4 (1.0, MeOH, 26)	3220, 1724, 1626, 1592, 1281
69	3-OCOPh	Me	COPh	1	B	66	131.5—132 (dec.)	Acetone	+86.1 (1.0, MeOH, 26)	1754, 1732, 1653, 1622, 1210, 1064, 916
70	3-OH	Me	H	1		62	Amorph.[e]		+73.2 (1.0, MeOH, 26)	3280, 1731, 1620, 1600, 1206
71	4-OCO_2-CH_2Ph	H	COPh	1	A	69	101—104	EtOAc	+98.3 (1.0, MeOH, 26)	3520, 1754, 1712, 1635, 1618, 922
72	4-OH	H	H	1		67	Amorph.[e]		+78.5 (1.0, MeOH, 26)	3310, 1733, 1612, 1171 (KBr)
73	3,4-$(OH)_2$	H	COPh	1	A	67	Amorph.[e]		+117.6 (1.0, MeOH, 27)	3330, 1729, 1636, 1515, 1205, 915
74	3,4-$(OH)_2$	H	H	1		82	Amorph.[e]		+104.5 (1.0, MeOH, 27)	3330, 1726, 1609, 1290, 1194 (KBr)
75	2-OH, 5-Cl	Me	COPh	1	B	60	Amorph.[e]		+108.2 (1.0, MeOH, 25)	3230, 1722, 1624, 1209, 913
76	2-OH, 5-Cl	Me	H	1		62	159—160 (dec.)	EtOAc–benzene	+170.7 (1.0, MeOH, 25)	3330, 1703, 1605, 1209, 1113
77	2-OH, 5-SO_2NH_2	H	COPh	1	B	95	161—164	Acetone–$CHCl_3$	+156.0 (1.0, MeOH, 26)	1733, 1650, 1623, 1595, 1155, 910
78	2-OH, 5-SO_2NH_2	H	H	1		87	Amorph.[e]		+164.4 (1.0, MeOH, 26)	1715, 1620, 1590, 1150, 925
79	2-OMe	H	COPh	1	B	63	85—89	EtOAc	+139.5 (1.1, MeOH, 25)	1710, 1670, 1650, 1598, 1233, 1195, 920
80	2-OMe	H	H	1		73	138—139	EtOAc	+186.6 (1.0, MeOH, 25)	1720, 1650, 1595, 1235, 1100, 1020
81	2-OMe	Me	COPh	1	B	72	169—170	EtOAc	+130.0 (1.1, MeOH, 25)	1755, 1735, 1670, 1595, 1157, 905
82	2-OMe	Me	H	1		41	145—146	EtOAc	+173.8 (1.1, MeOH, 25)	1710, 1645, 1600, 1235, 1104, 1030

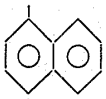
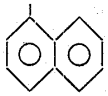
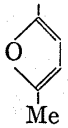
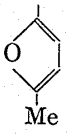
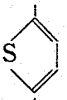
Compd. No.	R^1	R^2	R^3	n	Prepn. method of VIc[a]	Yield (%)	mp (°C)[b]	Recrystn. solvent	$[\alpha]_D$ deg. (c, solv., °C)	IR ν_{max}^{Nujol} cm^{-1}
83	4-OMe	H	COPh	1	B	88	114—116	EtOAc	+128.3 (1.0, MeOH, 26)	1710, 1635, 1620, 1238, 1210, 1175, 920
84	4-OMe	H	H	1		88	Oil[c]		+92.3 (0.9, MeOH, 25)	1735, 1640, 1595, 1240, 1172, 1027 (film)
85	4-OMe	Me	COPh	1	B	81	Oil[c]		+109.8 (0.8, MeOH, 25)	1740, 1650, 1610, 1240, 1203, 1183, 930 (film)
85·DCHA[d]							168—170	Acetone–ether	+85.6 (1.1, MeOH, 25)	
86	4-OMe	Me	H	1		85	139—140	EtOAc	+120.3 (1.0, MeOH, 25)	2580, 1720, 1610, 1238, 1204, 1170, 1023
87	3,4-$(OMe)_2$	H	COPh	1	B	55	Oil[c]		+154.0 (1.0, MeOH, 25)	1740, 1660, 1620, 1028, 915 (film)
88	3,4,5-$(OMe)_3$	Me	COPh	1	B	89	Amorph.[c]		+130.5 (1.0, MeOH, 24)	1720, 1640, 1125, 910 ($CHCl_3$)
89	3,4,5-$(OMe)_3$	Me	H	1		31	Amorph.[c]		+115.0 (1.5, MeOH, 24)	1720, 1630, 1590, 1125 ($CHCl_3$)
90	2-OH, 3-OMe	H	COPh	1	B	55	135—137	Benzene	+132.2 (1.0, MeOH, 28)	3500, 1738, 1654, 1612, 1173, 1079, 916
91	2-OH, 3-OMe	H	H	1		78	Amorph.[c]		+144.5 (1.0, MeOH, 28)	3410, 1727, 1611, 1271, 1067 (KBr)
92	2-OH, 4-OMe	H	COPh	1	B	72	Amorph.[c]		+54.6 (1.1, MeOH, 24)	3300, 1750, 1665, 1625, 1590, 1220, 925
93	2-OH, 4-OMe	H	H	1		82	134—135	Acetone–benzene	+179.0 (1.1, MeOH, 24)	3320, 1745, 1625, 1600, 1170, 1105, 1030
94	2-OH, 4-OMe	Me	COPh	1	B	82	152 (dec.)	Benzene–ether	+163.2 (0.9, MeOH, 25)	3160, 1735, 1650, 1620, 1600, 1210, 915
95	2-OH, 4-OMe	Me	H	1		84	147—148	EtOAc	+146.2 (1.0, MeOH, 24)	3300, 1745, 1620, 1600, 1235
96	4-$OCOCMe_3$, 3-OMe	Me	COPh	1	B	63	Amorph.[c]		+96.0 (1.1, MeOH, 26)	1754, 1654, 1610, 1508, 1205, 1114, 914
97	4-OH, 3-OMe	Me	H	1		62	Amorph.[c]		+104.7 (1.0, MeOH, 26)	3400, 1753, 1651, 1610, 1509, 1202 (KBr)
98	3,4-OCH_2O–	Me	COPh	1	B	98	Amorph.[c]		+98.8 (1.0, MeOH, 25)	1730, 1650, 1610, 1230, 1205, 1035, 910
99	3,4-OCH_2O–	Me	H	1		82	Amorph.[c]		+105.2 (1.0, MeOH, 25)	1720, 1610, 1030, 920

a, b, d, e) See the corresponding footnotes in Table I.
c) Compounds **29a** and **45a** are diastereoisomers of **29b** and **45b**, respectively.
f) See ref. 21.
g) Absolute ocnfiguration of R^2 is undecided : (*R*) or (*S*).

TABLE V. 2-Substituted (4*R*)-3-Mercaptoacyl-4-thiazolidinecarboxylic Acids (VIIc) and Their *S*-Benzoyl Derivatives (VIc)

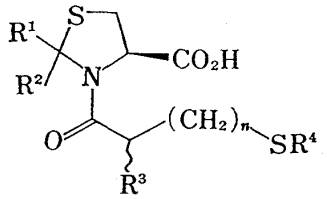


No. 100—113

Compd. No.	R^1	R^2	R^3	Prepn. method of VIc[a]	Yield (%)	mp (°C)[b]	Recrystn. solvent	$[\alpha]_D$ deg. in MeOH (c, °C)	IR ν_{max}^{Nujol} cm^{-1}
100		Me	COPh	B	75	Amorph.[c]		−101.0 (1.5, 26)	1735, 1650, 1620, 1200, 1170, 910
101		Me	H		69	Amorph.[c]		−202.0 (0.6, 26)	2520, 1735, 1650, 1190
102		Me	COPh	B	82	122—123	Benzene–hexane	+45.5 (1.0, 25)	1748, 1647, 1618, 1203, 1012, 920
103		Me	H		85	Oil[c]		+48.8 (1.0, 25)	2580, 1735, 1630, 1180, 1016 (film)
104		Me	COPh	A	81	125—126	Benzene–hexane	+79.9 (1.0, 25)	1745, 1650, 1620, 1218, 1200, 1030, 915
105		Me	H		79	Oil[c]		+78.1 (1.0, 25)	2560, 1720, 1630, 1185, 1020 (film)
106		H	COPh	C	57	141—143	Benzene	+107.7 (1.0, 25)	1745, 1645, 1610, 1210, 917
107		H	H		56	Amorph.[c]		+87.5 (1.0, 26)	2520, 1740, 1650, 1120
108		Me	COPh	D	49	136—137	Benzene	+79.6 (1.0, 25)	1750, 1650, 1620, 1205, 920
109		Me	H		42	Amorph.[c]		+55.7 (1.0, 26)	2540, 1735, 1620, 1185
110		Me	COPh	B	79	Amorph.[c]		−59.0 (1.0, 25)	1720, 1650, 1600, 1203, 910
111		Me	H		83	Amorph.[c]		−13.5 (1.0, 25)	2560, 1725, 1632, 1050
112		Me	COPh	B	60	Amorph.[c]		−4.4 (1.1, 25)	1719, 1650, 1602, 1205, 910
113		Me	H		61	Amorph.[c]		+64.0 (1.0, 23)	2550, 1720, 1640, 1200

a, *b*) See the corresponding footnotes in Table I.
c) Purified by chromatography.

TABLE VI. 2,2-Disubstituted (4*R*)-3-Mercaptoacyl-4-thiazolidinecarboxylic Acids (VIId) and Their *S*-Benzoyl Derivatives (VId)



No. **114**—**119**

Compd. No.	Confign. of R^3	R^1	R^2	R^3	R^4	n	Prepn. method of VId[a]	Yield (%)	mp (°C)[b]	Recrystn. solvent	$[\alpha]_D^{25}$ deg. (*c*, solv.)	IR ν_{max}^{Nujol} cm^{-1}
114		Me	Me	H	COPh	1	B	84	152.5—153	Benzene	−32.3 (1.0, MeOH)	1735, 1648, 1606, 1200, 910
115		Me	Me	H	H	1		86	119—120	EtOAc–hexane	−54.2 (1.0, MeOH)	1730, 1589, 1200, 1170
116	(*S*)	Me	Me	Me	COPh	1	B	90	183—184	EtOAc–hexane	−106.3 (1.0, MeOH)	1735, 1655, 1603, 1205, 1200, 916
117	(*S*)	Me	Me	Me	H	1		88	169.5—170.5	EtOAc–hexane	−98.0 (1.0, MeOH)	2560, 1718, 1595, 1205
118a[c]	(*S*)	$-(CH_2)_5-$		Me	COPh	0	C	34	118—120	EtOAc	+4.4 (1.0, EtOH)	1710, 1645, 1635, 1195, 900
118b[c]	(*R*)	$-(CH_2)_5-$		Me	COPh	0	C	45	85—87	EtOAc	+16.2 (1.0, EtOH)	1740, 1640, 1610, 1180, 900
119a[c]	(*S*)	$-(CH_2)_5-$		Me	H	0		85	145—146.5	EtOAc–benzene	−102.4 (2.3, MeOH)	2590, 1750, 1616, 1200
119b[c]	(*R*)	$-(CH_2)_5-$		Me	H	0		87	147—148.5	EtOAc–benzene	−114.4 (2.3, MeOH)	2570, 1742, 1613, 1195

a, *b*) See the corresponding footnotes in Table I.
c) Compounds **118a** and **119a** are diastereoisomers of **118b** and **119b**, respectively.

was *N*-acylated without protection of the hydroxyl group to produce compounds **59**, **61**, **63**, **65**, **75**, **77**, **90**, **92**, and **94**. However, the 3- or 4-hydroxyl group of IVc was protected with a benzoyl, benzyloxycarbonyl, or pivaloyl group for the preparation of compounds **67**, **69**, **71**, and **96**, and then the protected compounds were *N*-acylated in order to avoid possible production of *N*,*O*-diacyl compounds due to steric hindrance. After protection of the 3,4-dihydroxyl groups of IVc by boric acid in the same manner as for dopa derivatives,[1b] the protected compound was *N*-acylated by means of the Schotten–Baumann reaction to give **73**.

The sodium salt of **104** precipitated during the Schotten–Baumann reaction and was filtered off. The crystals were dissolved in water and acidified to give compound **104**.

2,2-Disubstituted (4*R*)-3-Mercaptoacyl-4-thiazolidinecarboxylic Acids (VIId) in Table VI——(4*R*)-3-(*S*-Benzoyl-3-mercaptopropanoyl)-2,2-dimethyl-4-thiazolidinecarboxylic acid (**114**) could not be obtained by *N*-acylation of (4*R*)-2,2-dimethyl-4-thiazolidinecarboxylic acid [IVd, R=Me: mp 146—147°C; $[\alpha]_D^{25}$ −158.5° (*c*=1.1, methanol)][13] with the acid chloride of Vc by method A or D, and *N*-(*S*-benzoylmercaptoacyl)-L-cysteines were formed by thiazolidine ring cleavage. However, **114** was prepared by method B in good yield. (4*R*)-3-[(2*S*)-*S*-Benzoyl-3-mercapto-2-methylpropanoyl]-2,2-dimethyl-4-thiazolidinecarboxylic acid (**116**) was similarly prepared using the acid chloride of (*S*)-(−)-Vd. (4*R*)-2-Spirohexyl-4-thiazolidinecarboxylic acid [mp 178°C (dec.)][14] reacted with (±)-2-bromopropanoyl chloride by method C, and then it was treated with potassium thiobenzoate. The resulting mixture of diastereoisomers was separated by recrystallization and column chromatography. Ammonolysis of the *S*-benzoyl derivatives (**118a** and **118b**) gave the corresponding thiols (**119a** and **119b**, respectively).

Table VII. Elemental Analyses[a]

Compd. No.	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
1	$C_{13}H_{13}NO_4S_2$	50.15	4.21	4.50	50.34	4.26	4.46
2	$C_6H_9NO_3S_2$	34.77	4.38	6.76	34.59	4.35	6.77
3a	$C_{14}H_{15}NO_4S_2$	51.68	4.65	4.30	51.76	4.71	4.27
3a·DCHA	$C_{14}H_{15}NO_4S_2 \cdot C_{12}H_{23}N$	61.63	7.56	5.53	61.51	7.53	5.49
3b·DCHA	$C_{14}H_{15}NO_4S_2 \cdot C_{12}H_{23}N$	61.63	7.56	5.53	61.51	7.58	5.54
4a	$C_7H_{11}NO_3S_2$	37.99	5.01	6.33	38.09	4.97	6.22
4b	$C_7H_{11}NO_3S_2$	37.99	5.01	6.33	38.04	5.03	6.24
5	$C_{14}H_{15}NO_4S_2$	51.68	4.65	4.30	51.63	4.69	4.32
6	$C_7H_{11}NO_3S_2$	37.99	5.01	6.33	38.25	5.03	6.21
7a	$C_{15}H_{17}NO_4S_2$	53.08	5.05	4.13	53.21	5.00	4.19
7a·DCHA	$C_{15}H_{17}NO_4S_2 \cdot C_{12}H_{23}N$	62.28	7.74	5.38	62.32	7.73	5.40
7b·DCHA	$C_{15}H_{17}NO_4S_2 \cdot C_{12}H_{23}N$	62.28	7.74	5.38	62.27	7.70	5.36
8a	$C_8H_{13}NO_3S_2$	40.83	5.57	5.95	40.94	5.54	5.94
8a·DCHA	$C_8H_{13}NO_3S_2 \cdot C_{12}H_{23}N$	57.66	8.71	6.72	57.63	8.70	6.70
8b	$C_8H_{13}NO_3S_2$	40.83	5.57	5.95	40.97	5.53	5.97
8b·DCHA	$C_8H_{13}NO_3S_2 \cdot C_{12}H_{23}N$	57.66	8.71	6.72	57.60	8.74	6.70
9a	$C_{15}H_{17}NO_4S_2$	53.08	5.05	4.13	53.20	5.07	4.11
9b·DCHA	$C_{15}H_{17}NO_4S_2 \cdot C_{12}H_{23}N$	62.28	7.74	5.38	62.41	7.83	5.25
10a	$C_8H_{13}NO_3S_2$	40.83	5.57	5.95	41.10	5.57	5.85
10b·DCHA	$C_8H_{13}NO_3S_2 \cdot C_{12}H_{23}N$	57.66	8.71	6.72	57.71	8.72	6.66
11	$C_{15}H_{17}NO_4S_2 \cdot C_{12}H_{23}N$	62.28	7.74	5.38	62.28	7.82	5.37
12·DCHA	$C_8H_{13}NO_3S_2 \cdot C_{12}H_{23}N$	57.66	8.71	6.72	57.60	8.82	6.68
13	$C_{14}H_{15}NO_4S_2$	51.68	4.65	4.30	51.93	4.64	4.33
14·DCHA	$C_7H_{11}NO_3S_2 \cdot C_{12}H_{23}N$	56.68	8.51	6.96	57.03	8.63	6.89
15a	$C_{15}H_{17}NO_4S_2$	53.08	5.05	4.13	53.16	5.06	4.17
15b	$C_{15}H_{17}NO_4S_2$	53.08	5.05	4.13	53.36	5.08	4.11

Compd. No.	Formula	Analysis (%) Calcd C	H	N	Found C	H	N
16b	$C_8H_{13}NO_3S_2$	40.83	5.57	5.95	41.03	5.67	5.99
17·DCHA	$C_{21}H_{27}NO_4S_2 \cdot C_{12}H_{23}N$	65.74	8.36	4.65	65.85	8.41	4.59
21a·DCHA	$C_{18}H_{21}NO_5S_3 \cdot C_{12}H_{23}N$	59.18	7.28	4.60	59.05	7.28	4.56
21b·DCHA	$C_{18}H_{21}NO_5S_3 \cdot C_{12}H_{23}N$	59.18	7.28	4.60	59.01	7.25	4.53
22a	$C_9H_{15}NO_3S_3$	38.41	5.37	4.98	38.57	5.32	4.92
23a·DCHA	$C_{19}H_{23}NO_5S_3 \cdot C_{12}H_{23}N$	59.78	7.44	4.50	59.72	7.43	4.45
23b·DCHA	$C_{19}H_{23}NO_5S_3 \cdot C_{12}H_{23}N$	59.78	7.44	4.50	59.66	7.45	4.43
25b	$C_{22}H_{23}NO_4S_2$	61.52	5.40	3.26	61.55	5.42	3.27
27	$C_{19}H_{17}NO_4S_2$	58.90	4.42	3.61	59.14	4.38	3.56
28	$C_{12}H_{13}NO_3S_2$	50.87	4.62	4.94	51.11	4.58	4.80
29a	$C_{20}H_{19}NO_4S_2$	59.83	4.77	3.49	59.77	4.80	3.50
29b	$C_{20}H_{19}NO_4S_2$	59.83	4.77	3.49	59.99	4.75	3.41
30a	$C_{13}H_{15}NO_3S_2$	52.51	5.08	4.71	52.77	5.03	4.65
31	$C_{20}H_{19}NO_4S_2 \cdot H_2O$	57.26	5.04	3.34	57.21	5.08	3.36
33	$C_{21}H_{21}NO_4S_2$	60.70	5.09	3.37	60.93	5.01	3.27
35	$C_{21}H_{21}NO_4S_2 \cdot H_2O$	58.18	5.35	3.23	58.20	5.33	3.28
36	$C_{14}H_{17}NO_3S_2$	54.00	5.50	4.50	53.81	5.51	4.28
37	$C_{22}H_{23}NO_4S_2$	61.52	5.40	3.26	61.60	5.42	3.26
38	$C_{15}H_{19}NO_3S_2$	55.36	5.88	4.30	55.23	5.92	4.22
41	$C_{20}H_{18}ClNO_4S_2 \cdot H_2O$	52.92	4.44	3.09	52.84	4.42	3.09
46a	$C_{13}H_{14}FNO_3S_2$	49.51	4.47	4.44	49.56	4.43	4.47
47·DCHA	$C_{21}H_{20}N_2O_6S_2 \cdot C_{12}H_{23}N$	61.75	6.75	6.55	61.42	6.69	6.41
48	$C_{14}H_{16}N_2O_5S_2 \cdot 1/2C_6H_6$	51.63	4.84	7.08	51.47	4.77	7.00
50	$C_{14}H_{16}N_2O_5S_2$	47.18	4.52	7.86	46.82	4.46	7.52
58	$C_{14}H_{15}NO_5S_2$	49.25	4.43	4.10	49.41	4.45	4.13
60	$C_{12}H_{13}NO_4S_2$	48.15	4.38	4.68	47.75	4.19	4.53
61	$C_{20}H_{19}NO_5S_2 \cdot C_6H_6$	63.01	5.08	2.83	63.01	5.07	2.61
62	$C_{13}H_{15}NO_4S_2$	49.82	4.82	4.47	49.74	4.88	4.32
63	$C_{21}H_{21}NO_5S_2 \cdot CH_4O$	57.00	5.44	3.02	56.55	5.30	2.96
68	$C_{13}H_{15}NO_4S_2$	49.82	4.82	4.47	49.66	4.72	4.35
69	$C_{27}H_{25}NO_6S_2$	61.93	4.81	2.67	62.32	4.45	2.60
77	$C_{20}H_{20}N_2O_7S_3$	48.38	4.06	5.64	48.26	4.15	5.49
79	$C_{21}H_{21}NO_5S_2$	58.45	4.90	3.25	58.24	5.21	2.96
80	$C_{14}H_{17}NO_4S_2$	51.36	5.23	4.28	51.02	5.16	4.22
81	$C_{22}H_{23}NO_5S_2$	59.31	5.20	3.14	59.26	5.18	3.16
82	$C_{15}H_{19}NO_4S_2$	52.77	5.61	4.10	52.51	5.59	4.12
83	$C_{21}H_{21}NO_5S_2 \cdot 3/2H_2O$	55.01	5.28	3.05	55.21	4.98	3.04
86	$C_{15}H_{19}NO_4S_2$	52.77	5.61	4.10	52.44	5.51	4.03
95	$C_{15}H_{19}NO_5S_2$	50.40	5.36	3.92	50.68	5.69	3.53
102	$C_{19}H_{19}NO_5S_2$	56.28	4.72	3.45	56.39	4.57	3.36
104	$C_{20}H_{21}NO_5S_2$	57.26	5.05	3.34	57.62	5.04	3.30
106	$C_{18}H_{17}NO_4S_3$	53.05	4.20	3.44	52.93	4.01	3.31
108	$C_{19}H_{19}NO_4S_3$	54.14	4.54	3.32	54.19	4.36	3.26
110	$C_{20}H_{20}N_2O_4S_2$	57.67	4.84	6.73	57.29	5.49	6.46
114	$C_{16}H_{19}NO_4S_2$	54.37	5.42	3.96	54.71	5.40	3.82
115	$C_9H_{15}NO_3S_2$	43.35	6.06	5.62	43.46	6.05	5.62
116	$C_{17}H_{21}NO_4S_2$	55.56	5.76	3.81	55.64	5.90	3.90
117	$C_{10}H_{17}NO_3S_2$	45.61	6.51	5.32	45.88	6.55	5.34
118a	$C_{19}H_{23}NO_4S_2$	57.99	5.89	3.56	58.28	5.82	3.52
118b	$C_{19}H_{23}NO_4S_2$	57.99	5.89	3.56	58.31	5.74	3.48
119a	$C_{12}H_{19}NO_3S_2$	49.80	6.62	4.84	49.89	6.61	4.85
119b	$C_{12}H_{19}NO_3S_2$	49.80	6.62	4.84	50.11	6.60	4.82

a) DCHA and $C_{12}H_{23}N$ are dicyclohexylamine.
CH_4O is methanol.

(±)-*S*-benzoyl-2-mercaptopropanoic acid ((±)-Vb)
mp 67.5—68°C 105 g

cinchonine 147 g
EtOH 600 ml, reflux

crystals 86.5 g
EtOH 200 ml, reflux
crystals 47.4 g
mp 166—167°C
$[\alpha]_D^{25}$ +123.2° (*c*=1.0, MeOH)
dil. HCl
crystals ((−)-Vb) 18.7 g
mp 63.5—64.5°C
$[\alpha]_D^{25}$ −68.7° (*c*=1.0, EtOH)
mother liquor 39.1 g

mother liquor 166.5 g
dil. HCl
oil 67.5g
$[\alpha]_D^{25}$ +15.0° (*c*=1.0, MeOH)
cinchonidine 94.5 g
acetone 970 ml, reflux
crystals 75.6 g
acetone 900 ml
reflux
crystals 52.8 g
mp 153—157°C
$[\alpha]_D^{25}$ −72.3° (*c*=2.0, MeOH)
dil. HCl
crystals ((+)-Vb) 21.2 g
mp 64—65°C
$[\alpha]_D^{25}$ +69.2° (*c*=1.0, EtOH)
mother liquor 22.8 g
mother liquor 86.4 g

Chart 4

(±)-*S*-benzoyl-3-mercapto-2-methylpropanoic acid ((±)-Vd)
mp 63—64°C 68.7 g

(*R*)-(−)-1,2-diphenylethylamine 60.4 g
acetone 400 ml, reflux

crystals 64.7 g
acetone 190 ml
reflux
crystals 38.2 g
mp 135.5—136°C
$[\alpha]_D^{25}$ −75.3° (*c*=1.6, MeOH)
dil. HCl
crystals ((−)-Vd) 21.3 g
mp 69—71.5°C
$[\alpha]_D^{25}$ −42.7° (*c*=2.0, EtOH)
mother liquor 26.5 g

mother liquor 64.4 g
dil. HCl
oil 35.2 g
$[\alpha]_D^{25}$ +20.3° (*c*=1.4, MeOH)
quinine 51.0 g
acetone 630 ml, reflux
crystals 68.9 g
acetone 580 ml
reflux
crystals 60.3 g
acetone 380 ml
reflux
crystals 52.3 g
mp 132—133°C
$[\alpha]_D^{25}$ −99.5° (*c*=1.1, MeOH)
dil. HCl
crystals ((+)-Vd) 21.0 g
mp 68—71°C
$[\alpha]_D^{25}$ +41.5° (*c*=2.0, EtOH)
mother liquor 8.0 g
mother liquor 17.3 g
mother liquor 8.6 g

Chart 5

2. Resolution of *S*-Benzoyl-2-mercaptopropanoic Acid (Vb) and *S*-Benzoyl-3-mercapto-2-methylpropanoic Acid (Vd)

Compounds (±)-Vb and (±)-Vd were optically resolved as illustrated in Chart s 4 and 5, respectively.

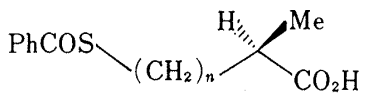
As shown in Chart 4, the diastereomeric salt of (±)-Vb was fractionally recrystallized from ethanol. By the general method, one salt was converted to (−)-Vb and the other salt in the filtrate was converted to the free acid, to which equimolar cinchonidine in acetone was added, and the diastereomeric salt was fractionally recrystallized from acetone. By the general method, the salt was converted to (+)-Vb.

As shown in Chart 5, (−)-Vd and (+)-Vd were prepared from (±)-Vd using equimolar (*R*)-(−)-1,2-diphenylethylamine[15] and quinine in acetone, respectively, in the same manner as in Chart 4.

3. Absolute Configurations of (+)- and (−)-*S*-Benzoyl-2-mercaptopropanoic Acid [(+)- and (−)-Vb] and (+)- and (−)-*S*-Benzoyl-3-mercapto-2-methylpropanoic Acid [(+)- and (−)-Vd]

The absolute configurations of (+)- and (−)-Vb, (+)- and (−)-Vd resolved as stated above were identified as follows, and are illustrated in Chart 6.

Ammonolysis of (+)- and (−)-Vb gave (+)-2-mercaptopropanoic acid [mp 36—37°C; $[\alpha]_D^{25}$ +42.6° (c=2.0, water)] and (−)-2-mercaptopropanoic acid [mp 36—37°C; $[\alpha]_D^{25}$ −41.6° (c=2.0, water)], respectively. The absolute configurations of (+)- and (−)-Vb correspond to (*R*) and (*S*), respectively, because the (+)- and (−)-acid have (*R*)- and (*S*)-configuration, respectively, according to Klyne *et al.*[16]



n=0: (*S*)-(−)-Vb
n=1: (*S*)-(−)-Vd

Chart 6

Iodine oxidation of (−)-3-mercapto-2-methylpropanoic acid [bp 91°C (3 mmHg); $[\alpha]_D^{25}$ −26.6° (c=3.0, methanol)] prepared by ammonolysis of (−)-Vd gave (−)-3,3′-dithiobis(2-methylpropanoic acid)[mp 125—126.5°C; $[\alpha]_D^{24}$ −220.0° (c= 0.5, 0.5 N ammonia)]. On the other hand, as Ställberg *et al.*[17] reported that (+)-3,3′-dithiobis-(2-methylpropanoic acid) has (*R*)-configuration, the absolute configuration of (−)-Vd was identified as (*S*). Accordingly (+)-Vd has (*R*)-configuration.

4. Structure-Activity Relationships

(4*R*)-3-[(2*S*)-2-Mercaptopropanoyl]-4-thiazolidinecarboxylic acid (**4a**) possesses a structure having the 4-thiazolidinecarboxylic acid in place of the cysteine moiety of *N*-(2-mercaptopropanoyl)-L-cysteine-a (II), a more potent diastereoisomer.[2b] Inhibitory activity of **4a** against ACE was pI_{50}: 6.43 (angiotensin I), 10 times higher than that of II. The thiazolidine ring seems to conform the amino acid moiety to a suitable position for high activity.

Effect of the Mercaptoacyl Moiety in 4-Thiazolidinecarboxylic Acids (Table I)——As regards the length of methylene chain between the thiol and carbonyl groups, $(CH_2)_2$ (compound **6**) resulted in higher activity than CH_2 (compound **2**) or $(CH_2)_3$ (compound **12**). The activities of **2** and **12** were 1/3 and 1/50 of that of **6**, respectively. On introducing a methyl group of (*S*)-configuration at the α-position in the mercaptoacyl moiety, the activity increased 15 times as compared with that of compound **2** or **6** (compound **2**→**4a**, compound **6**→**8a**). A methyl group of (*R*)-configuration (compound **8b**) reduced the activity to 1/20 of that of (*S*)-configuration (compound **8a**). Compound **8a**, having a (2*S*)-3-mercapto-2-methylpropanoyl group as the mercaptoacyl moiety, showed the highest activity among the compounds in Table I. In particular, the existence of a methyl group at the α-position in the mercaptoacyl moiety contributes greatly to the activity because it is considered that the thiol group may be sterically fixed to a certain extent by the introduction of a methyl group at the α-position.

Table VIII. Inhibitory Activities of *N*-(Mercaptoacyl)-thiazolidinecarboxylic Acids against ACE[a]

Compd. No.	AI pI_{50}(M)	ACE pI_{50}(M)	BK pA_{50}(M)	Compd. No.	AI pI_{50}(M)	ACE pI_{50}(M)	BK pA_{50}(M)
2	5.15	4.92	7.01	**55**	5.59	6.04	7.14
4a	6.43	6.34	7.72	**58**	5.89	<5	—
4b	5.15	4.57	6.47	**60**	6.25	5.66	8.30
6	5.62	5.00	7.43	**62**	7.55	7.15	9.15
8a	6.80	6.59	8.46	**64**	5.77	5.17	7.77
8b	5.32	5.89	7.46	**66**	7.25	6.66	8.92
10a	5.10	5.07	6.66	**68**	7.15	6.68	8.82
10b	4.10	4.04	6.17	**70**	6.82	6.64	8.77
12	3.89	3.22	5.28	**72**	6.34	5.92	8.26
14	4.70	4.92	6.82	**74**	6.28	5.59	8.24
16a	5.21	5.49	7.36	**76**	7.04	7.12	8.70
16b	6.08	5.89	8.33	**80**	5.80	5.43	7.04
18	7.30	6.92	8.70	**82**	6.30	6.38	8.10
20	6.29	5.39	8.08	**84**	5.85	5.96	7.77
22a	6.39	6.19	7.82	**86**	7.06	6.12	8.68
22b	6.52	6.43	8.43	**89**	6.39	6.41	8.03
24a	7.07	6.60	8.85	**91**	7.44	7.03	8.96
24b	6.85	6.54	8.96	**93**	6.85	6.70	8.51
26a	6.09	5.55	7.89	**95**	6.92	6.72	8.89
26b	6.24	6.51	8.00	**97**	6.68	5.89	8.49
28	6.05	4.89	7.72	**99**	6.85	6.62	8.03
30a	5.96	5.60	7.59	**101**	6.44	5.89	7.89
32	6.72	6.35	8.59	**103**	6.62	6.47	8.43
34	6.72	7.22	8.51	**105**	6.34	6.14	8.59
36	5.82	5.85	7.59	**107**	5.89	6.06	7.32
38	6.77	6.27	8.41	**109**	6.15	6.43	8.00
40	6.15	5.44	7.80	**111**	6.85	6.08	8.54
42	5.89	6.08	7.70	**113**	7.08	6.96	8.51
44	4.10	<4	5.21	**115**	5.46	5.40	7.59
46a	<4	<4	4.64	**117**	5.92	5.60	7.49
48	5.27	4.37	7.18	**119a**	—	<4	—
50	6.74	6.40	8.60	**119b**	—	<4	—
53	4.70	4.52	6.92	SQ 14225[b]	6.68	7.09	8.44

a) Inhibitory activities of the compounds against ACE were determined according to the procedures in ref. 3 (AI, angiotensin I; BK, bradykinin). pI_{50}; $-\log$ of the molar concentration of compound which gives 50% inhibition of the enzyme activity or agonist effect. pA_{50}; $-\log$ of the molar concentration of compound which gives 50% enhancement of the agonist effect.

b) Physical constants were as follows: mp 104—106 °C, $[\alpha]_D^{25}$ −131.0° (c=2.0, EtOH). The compound was synthesized by Santen Pharmaceutical Co., Ltd.

Effect of Position of Carboxyl Group Substitution on the Thiazolidine Ring (Table II)——The 4-thiazolidinecarboxylic acid (**8a**) showed 5 times higher activity than the 2-thiazolidinecarboxylic acid (**16b**). This difference of activity seemed to be due to the slight steric difference.

Substituent Effect at C_2 on 4-Thiazolidinecarboxylic Acids (Table III—VI)——The compounds having disubstituents such as dimethyl (compounds **115** and **117**) and spirohexyl (compound **119**) at C_2 on the thiazolidine ring showed almost no activity. A compound having a monosubstituent such as benzyl (compound **26**) showed 1/5—1/3 of the activity of the non-substituted compound (compound **8a**), but cyclohexyl (compound **18**) and 2-mercaptoethyl (compound **24a**) substituents doubled the activity. The activities of separated isomers, compounds **22a** and **22b**, **24a** and **24b**, **26a** and **26b**, hardly differ. It appears that at least one hydrogen atom at C_2 on the thiazolidine ring is required for the appearance of activity.

In the case of heterocycles at C_2, the activity was higher than that of **8a** with pyridyl (compounds **111** and **113**), but lower with furyl (compounds **103** and **105**) and thienyl (compounds **107** and **109**).

The activities of **32** and **34** substituted by phenyl at C_2 were nearly the same as that of **8a**, and it is suggested that a bulky substituent does not hinder the appearance of activity. On the other hand, interestingly, the activity was the same irrespective of the presence or absence of a methyl group at the α-position in the mercaptoacyl moiety. When various substituents were introduced into the phenyl group at C_2 on the thiazolidine ring, halogen (compounds **40**, **42**, **44**, and **46**), dimethylamino (compound **53**), acetamino (compound **55**) and 2-nitro (compound **48**) reduced the activity, while 3-nitro (compound **50**) resulted in the same activity as **8a**. A methoxy substituent (compounds **80**, **82**, **84**, **86**, and **89**) did not make the compound more potent. Hydroxyphenyl compounds substituted by 2-hydroxyl (compound **62**) or 3-hydroxyl (compounds **68** and **70**) were more potent than **32** as regards inhibitory activity against ACE. In particular, compound **62** was found to be the most potent of all the synthetic compounds, that is, twice as potent as compound **66**, and 5 to 6 times more potent than compounds **8a** and **32**. This result is in agreement with the above-mentioned result that the activity becomes 5 to 6 times stronger upon replacement of phenylalanine as the amino acid moiety with tyrosine, which has a phenolic hydroxyl group. This suggests that the hydroxyl group of tyrosine derivatives and of thiazolidine derivatives may combine with the same active site of ACE.

Although the existence of a methyl group at the α-position in the mercaptoacyl moiety has been considered to be important for augmenting the activity, a new consideration was required to account for the activity of **62**. It is presumed that a hydroxyl group on a benzene ring can act as a proton donor.

The activity of **20**, having a cyclohexyl group substituted by an alcoholic hydroxyl group instead of the phenolic hydroxyl group of **62**, was decreased. Compound **58** with a carboxyl group in place of the hydroxyl group of **62**, showed low activity.

The activity depended on the position of the hydroxyl group on the phenyl nucleus, and decreased in order of *ortho* (compound **62**), *meta* (compound **68**) and *para* (compound **72**).

These results suggest that another active center exists in inhibitors in addition to the thiol group, amide bond, and carboxyl group. *S*-Methyl derivatives of **8a** and **62** were synthesized,[19] and tested for activity. As they showed little activity, a thiol group was confirmed to be required.

Experimental

Melting points were determined in open capillary tubes with a Yamato melting point apparatus and are uncorrected. Specific rotations were measured with a JASCO DIP-4 polarimeter. IR spectra were recorded on JASCO A-302 and IR-E spectrometers. NMR spectra were measured with JEOL PS-100 and PMX-60 spectrometers.[20]

Syntheses

Method A. 3-[(2*S*)- and (2*R*)-*S*-Benzoyl-3-mercapto-2-methylpropanoyl]-4-thiazolidinecarboxylic Acid (7a and 7b)——(4*R*)-4-Thiazolidinecarboxylic acid (6.7 g, 0.05 mol) and sodium bicarbonate (12.6 g, 0.15 mol) were dissolved in water (150 ml). (±)-*S*-Benzoyl-3-mercapto-2-methylpropanoyl chloride (12.1 g, 0.05 mol) was added dropwise to this solution with ice-cooling and stirring. After the addition, the mixture was stirred for 1 h, then acidified with dilute hydrochloric acid. The separated oil was extracted into ethyl acetate. The extract was washed with water, dried over Na_2SO_4, and concentrated *in vacuo*. Ether (100 ml) was added to the residue to crystallize it. The product was recrystallized from benzene to give 5.0 g (29%) of **7a**: mp 137—139°C. NMR ($CDCl_3$) δ: 1.31 (3H, d, J=6.1 Hz, $-CH_3$), 3.26 (2H, d, J=5.1 Hz, C_5–H), 2.70—3.50 (3H, m, $-C\underline{H}(CH_3)C\underline{H}_2-$), 4.50 and 4.76 (2H, ABq, J=7.9 Hz, C_2–H), 5.11 (1H, t, J=5.1 Hz, C_4–H), 7.30—8.10 (5H, m, aromatic H), 9.86 (1H, s, –COOH). Dicyclohexylamine salt of **7a**: mp 199—200°C.

The combined filtrate was concentrated *in vacuo*. The residue was placed on an SiO_2 column, and eluted with benzene–ethyl acetate (5: 1). The eluate was concentrated *in vacuo* to give 4.0 g (24%) of oily **7b**. NMR ($CDCl_3$) δ: 1.26 (3H, d, J=6.0 Hz, $-CH_3$), 3.26 (2H, d, J=5.1 Hz, C_5–H), 2.70—3.60 (3H, m, $-C\underline{H}(CH_3)C\underline{H}_2-$), 4.64 and 4.79 (2H, ABq, J=8.0 Hz, C_2–H), 5.09 (1H, t, J=5.1 Hz, C_4–H), 7.30—8.10 (5H, m, aromatic H), 8.38 (1H, s, –COOH). Dicyclohexylamine salt of **7b**: mp 140—141°C.

Method B. (4*R*)-3-(*S*-Benzoyl-3-mercaptopropanoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic Acid (61)——(4*R*)-2-(2-Hydroxyphenyl)-4-thiazolidinecarboxylic acid (6.8 g, 0.03 mol) and triethylamine (7.9 g,

0.078 mol) were dissolved in anhyd. acetone (120 ml) and *S*-benzoyl-3-mercaptopropanoyl chloride (7.1 g, 0.031 mol) was added dropwise with ice-cooling and stirring. After the addition, the solution was stirred for 1 h, then 4 N hydrochloric acid in isopropyl ether was added and the precipitate was removed by filtration. The filtrate was concentrated *in vacuo*, and the residue was dissolved in ethyl acetate. The solution was washed with 2 N hydrochloric acid and saturated sodium chloride solution, dried over Na_2SO_4, and concentrated *in vacuo* to give a solid, which was recrystallized from benzene–ethyl acetate to give 7.2 g (48%) of **61**: mp 100.5—101°C (dec.). NMR (acetone-d_6) δ: 2.23—3.80 (6H, m, $-CH_2CH_2-$ and C_5–H), 4.90 (1H, dd, J=8.0, 7.5 Hz, C_4–H), 6.43 (1H, s, C_2–H), 7.29 (6H, s, C_6H_6), 6.55—8.17 (9H, m, aromatic H).

Method C. (4*R*)-3-(*S*-Benzoyl-2-mercaptopropanoyl)-2-spirohexyl-4-thiazolidinecarboxylic Acid-a and -b (118a and 118b)——(4*R*)-2-Spirohexyl-4-thiazolidinecarboxylic acid [mp 178°C (dec.)] (6.0 g, 0.03 mol) and sodium bicarbonate (5.0 g, 0.06 mol) were dissolved in water (50 ml) and (±)-2-bromopropanoyl chloride (5.1 g, 0.03 mol) was added dropwise with ice-cooling and stirring. After the addition, the mixture was stirred for 1 h at room temperature. Potassium thiobenzoate (5.3 g, 0.03 mol) was added to this solution with ice-cooling, and the whole was stirred for 1 h at room temperature. The solution was acidified with dilute hydrochloric acid, and extracted with ethyl acetate. The extract was washed with water, dried over Na_2SO_4, and concentrated *in vacuo* to give a solid, which was recrystallized from ethyl acetate to give 4.0 g (34%) of **118a**: mp 118—120°C. NMR ($CDCl_3$) δ: 0.93—2.13 (10H, m, $-(CH_2)_5-$), 1.59 (3H, d, J=7.0 Hz, $-CH_3$), 3.10—3.43 (2H, m, C_5–H), 4.35 (1H, q, J=7.0 Hz, $-C\underline{H}(CH_3)-$), 5.42—5.72 (1H, m, C_4–H), 7.32—8.07 (5H, m, aromatic H), 9.87 (1H, s, –COOH).

The filtrate was further concentrated *in vacuo*. The residue was placed on an SiO_2 column, and eluted with benzene–ethyl acetate (10: 1). The eluate was concentrated *in vacuo* to give a solid, which was recrystallized from ethyl acetate to give 5.3 g (45%) of **118b**: mp 85—87°C. NMR ($CDCl_3$) δ: 0.73—2.23 (10H, m, $-(CH_2)_5-$), 1.51 (3H, d, J=7.0 Hz, $-CH_3$), 2.73—3.40 (2H, m, C_5–H), 4.35 (1H, q, J=7.0 Hz, $-C\underline{H}(CH_3)-$), 4.83—5.23 (1H, m, C_4–H), 5.58 (1H, s, –COOH), 7.23—8.00 (5H, m, aromatic H).

Method D. 3-[(2*S*)-*S*-Benzoyl-3-mercapto-2-methylpropanoyl]-2-thiazolidinecarboxylic Acid-a and -b (15a and 15b)——(2*S*)-*S*-Benzoyl-3-mercapto-2-methylpropanoic acid (4.5 g, 0.02 mol) and triethylamine (2.8 ml, 0.02 mol) were dissolved in anhyd. tetrahydrofuran (35 ml). Isobutyl chloroformate (2.6 ml, 0.02 mol) was added dropwise to this solution with stirring at a constant temperature of −5°C. After the addition, the mixture was stirred for 10 min at room temperature. (±)-2-Thiazolidinecarboxylic acid (2.7 g, 0.02 mol) and triethylamine (2.8 ml, 0.02 mol) in water (10 ml) were added successively to this solution. The mixture was stirred for 30 min at room temperature. Water (35 ml) was added to the reaction mixture, and the whole was washed with ethyl acetate. The aqueous layer was acidified with dilute hydrochloric acid, and the separated oil was extracted with ethyl acetate. The extract was washed with saturated sodium chloride solution, dried over Na_2SO_4, and concentrated *in vacuo*. The residue was placed on an SiO_2 column, and eluted with benzene–ethyl acetate (10: 1). The eluate was concentrated and the residue was recrystallized from ethyl acetate–hexane to give 2.5 g (37%) of **15a** and 2.3 g (34%) of **15b**. **15a**: mp 105.5—106°C. NMR (acetone-d_6) δ: 1.26 (3H, d, J=6.0 Hz, $-CH_3$), 2.90—3.50 (5H, m, C_5–H and $-C\underline{H}(CH_3)C\underline{H}_2-$), 3.98 (1H, ABq(A part)dd, J=11.0, 7.0, 6.0 Hz, C_4–H_A), 4.20 (1H, ABq(B part)dd, J=11.0, 7.0, 4.0 Hz, C_4–H_B), 4.58 (1H, s, –COOH), 5.37 (1H, s, C_2–H), 7.40—8.00 (5H, m, aromatic H). **15b**: mp 140—140.5°C. NMR (acetone-d_6) δ: 1.28 (3H, d, J=6.0 Hz, $-CH_3$), 2.90—3.40 (5H, m, C_5–H and $-C\underline{H}(CH_3)C\underline{H}_2-$), 4.03 (2H, t, J=6.0 Hz, C_4–H), 4.44 (1H, s, –COOH), 5.42 (1H, s, C_2–H), 7.30—8.00 (5H, m, aromatic H).

Ammonolysis. (4*R*)-2-(2-Hydroxyphenyl)-3-(3-mercaptopropanoyl)-4-thiazolidinecarboxylic Acid (62)——(4*R*)-3-(*S*-Benzoyl-3-mercaptopropanoyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (**61**) (9.9 g, 0.02 mol) was treated with 28% aqueous ammonia (90 ml), and the mixture was stirred for 1 h at room temperature. The excess ammonia was removed *in vacuo* and the by-product, benzamide, was extracted with ethyl acetate. The aqueous layer was acidified with dilute hydrochloric acid and the separated oil was extracted into ethyl acetate. The extract was washed with water, dried over Na_2SO_4, and concentrated *in vacuo* to give a solid, which was recrystallized from ethyl acetate to give 5.2 g (83%) of **62**: mp 146—148°C.[21] NMR (acetone-d_6) δ: 1.82 (1H, t, J=8.0 Hz, –SH), 2.17—2.95 (4H, m, $-CH_2CH_2-$), 3.22 (1H, ABq(A part)d, J=12.0, 9.0 Hz, C_5–H_A), 3.44 (1H, ABq(B part)d, J=12.0, 7.5 Hz, C_5–H_B), 4.91 (1H, dd, J=9.0, 7.5 Hz, C_4–H), 6.49 (1H, s, C_2–H), 6.63—8.25 (4H, m, aromatic H), 8.37—10.50 (2H, br s, –OH and –COOH).

Optical Resolution

Resolution of (±)-S-Benzoyl-2-mercaptopropanoic Acid [(±)-Vb]——(±)-*S*-Benzoyl-2-mercaptopropanoic acid (0.5 mol) was dissolved in ethanol and the solution was heated to reflux. To this solution, cinchonine (0.5 mol) was added and allowed to dissolve thoroughly, then the solution was cooled overnight. The crystals were collected and recrystallized from ethanol to give cinchonine (*S*)-(−)-*S*-benzoyl-2-mercaptopropanoate: mp 166—167°C. By the general method, the above salt was converted to (*S*)-(−)-*S*-benzoyl-2-mercaptopropanoic acid [(−)-Vb], optical yield 18.7 g (36%): mp 63.5—64.5°C (benzene). IR ν_{max}^{Nujol} cm^{-1}: 1708 (COOH), 1660 (COSC). NMR ($CDCl_3$) δ: 1.64 (3H, d, J=7.4 Hz, $-CH_3$), 4.44 (1H, q, J=7.4 Hz, $-C\underline{H}-(CH_3)-$), 7.10—8.06 (5H, m, aromatic H), 11.27 (1H, s, –COOH).

The salt in the filtrate was converted to the free acid by the general method, and the acid was dissolved in acetone. The solution was heated to reflux. To this solution, cinchonidine (0.32 mol) was added and

allowed to dissolve thoroughly, then the solution was left to stand overnight at room temperature. The crystals were collected and recrystallized from acetone to give cinchonidine (*R*)-(+)-*S*-benzoyl-2-mercaptopropanoate: mp 153—157°C (acetone). By the general method, the above salt was converted to (*R*)-(+)-*S*-benzoyl-2-mercaptopropanoic acid [(+)-Vb], optical yield 21.2 g (40%): mp 64—65°C (benzene). IR ν_{max}^{Nujol} cm^{-1}: 1708 (COOH), 1660 (COSC). NMR ($CDCl_3$) δ: 1.64 (3H, d, J=7.4 Hz, $-CH_3$), 4.44 (1H, q, J=7.4 Hz, $-C\underline{H}(CH_3)-$), 7.10—8.06 (5H, m, aromatic H), 11.65 (1H, s, -COOH).

Resolution of (±)-*S*-Benzoyl-3-mercapto-2-methylpropanoic Acid [(±)-Vd]——(±)-*S*-Benzoyl-3-mercapto-2-methylpropanoic acid (0.31 mol) was dissolved in acetone and the solution was heated to reflux. Then (*R*)-(−)-1,2-diphenylethylamine (0.31 mol) was added and the solution was cooled overnight. The crystals were collected and recrystallized from acetone to give (*R*)-(−)-1,2-diphenylethylamine (*S*)-(−)-*S*-benzoyl-3-mercapto-2-methylpropanoate: mp 135.5—136°C (acetone). The above salt was converted to (*S*)-(−)-*S*-benzoyl-3-mercapto-2-methylpropanoic acid [(−)-Vd], optical yield 21.3 g (62%): mp 69—71.5°C (benzene). IR ν_{max}^{KBr} cm^{-1}: 1688 (COOH), 1668, 1660 (COSC). NMR ($CDCl_3$) δ: 1.35 (3H, d, J=7.0 Hz, $-CH_3$), 2.42—3.24 (1H, m, $-C\underline{H}(CH_3)-$), 3.33 (1H, ABq(A part)d, J=8.0, 6.0 Hz, $-C\underline{H}_AH_B-$), 3.43 (1H, ABq(B part)d, J=8.0, 8.0 Hz, $-CH_A\underline{H}_B-$), 7.17—8.12 (5H, m, aromatic H), 11.47 (1H, s, -COOH).

The salt in the filtrate was converted to the free acid, which was dissolved in acetone (630 ml) and the solution was heated to reflux. Then quinine (0.157 mol) was added and allowed to dissolve thoroughly, and the solution was cooled overnight. The crystals were collected and recrystallized twice from acetone to give quinine (*R*)-(+)-*S*-benzoyl-3-mercapto-2-methylpropanoate: mp 132—133°C (acetone). The above salt was converted to (*R*)-(+)-*S*-benzoyl-3-mercapto-2-methylpropanoic acid [(+)-Vd], optical yield 21.0 g (61%): mp 68—71°C (benzene). IR ν_{max}^{KBr} cm^{-1}: 1688 (COOH), 1668, 1660 (COSC). NMR ($CDCl_3$) δ: 1.35 (3H, d, J=7.0 Hz, $-CH_3$), 2.42—3.24 (1H, m, $-C\underline{H}(CH_3)-$), 3.33 (1H, ABq(A part)d, J=8.0, 6.0 Hz, $-C\underline{H}_AH_B-$), 3.43 (1H, ABq(B part)d, J=8.0, 8.0 Hz, $-CH_A\underline{H}_B-$), 7.17—8.12 (5H, m, aromatic H), 11.17 (1H, s, -COOH).

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References and Notes

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20) With tetramethylsilane as an internal standard.
21) Melted with slow decomposition (confirmed by IR and NMR).