[Chem. Pharm. Bull. 30(2) 484—493 (1982)]

Thiol Compounds. V.[1] Absolute Configuration and Crystal Structure of (4*R*)-2-(2-Hydroxyphenyl)-3-(3-mercaptopropionyl)-4-thiazolidinecarboxylic Acid

Masayuki Oya,*,[a] Eishin Kato,[a] Jun-ichi Iwao,[a] and Noritake Yasuoka[b]

Research Laboratory, Santen Pharmaceutical Co., Ltd.,[a] 9-19, Shimoshinjo 3-chome, Higashi Yodogawa-ku, Osaka, 533, Japan and Institute for Protein Research, Osaka University,[b] 5311, Yamada Kami, Suita, 565, Japan

(Received June 6, 1981)

The absolute configuration of (4*R*)-2-(2-hydroxyphenyl)-3-(3-mercaptopropionyl)-4-thiazolidinecarboxylic acid (**11a**), SA 446, which has a potent inhibitory activity against angiotensin I-converting enzyme (ACE), was determined to be (2*R*,4*R*) by nuclear magnetic resonance (NMR) spectroscopy, specific rotation measurement and X-ray crystallography.

The structure-activity relationships of the (2*R*,4*R*)- and (2*S*,4*R*)-isomers are discussed, and stereoselective acylation of (4*R*)-2-aryl-4-thiazolidinecarboxylic acids (**1**—**3**) is also described.

Keywords——(2*R*,4*R*)-2-(2-hydroxyphenyl)-3-(3-mercaptopropionyl)-4-thiazolidinecarboxylic acid; (4*R*)-2-(2-hydroxyphenyl)-3-(3-mercaptopropionyl)-4-thiazolidinecarboxylic acid; stereoselective acylation; absolute configuration; X-ray crystallography; angiotensin I-converting enzyme inhibitor; structure-activity relationship

We recently reported structure-activity relationships of *N*-(mercaptoacyl)thiazolidinecarboxylic acids having inhibitory activity against angiotensin I-converting enzyme (ACE).[1] (4*R*)-2-Aryl-3-mercaptoacyl-4-thiazolidinecarboxylic acids showed potent activity. In particular, (4*R*)-2-(2-hydroxyphenyl)-3-(3-mercaptopropionyl)-4-thiazolidinecarboxylic acid (**11a**), SA 446, was found to be the most potent of the synthetic compounds. The absolute configuration of the 2-hydroxyphenyl group at the C_2-position on the thiazolidine ring was not clear. Thus, in the present study, the absolute configuration was determined by nuclear magnetic resonance (NMR) spectroscopy, specific rotation measurement and X-ray crystallography. Stereoselective acylation of (4*R*)-2-aryl-4-thiazolidinecarboxylic acids (**1**—**3**) with S-benzoyl-3-mercaptopropionyl chloride was also studied.

Syntheses

Diastereoisomers having an (*R*)- or (*S*)-aryl group at C_2 on the thiazolidine ring, namely (4*R*)-2-aryl-3-(*S*-benzoyl-3-mercaptopropionyl)-4-thiazolidinecarboxylic acids (**4a, 5a** and **6a**), were isolated by acylation of (4*R*)-2-aryl-4-thiazolidinecarboxylic acids (**1**—**3**)[2] [prepared from (*R*)-cysteine and aryl aldehydes] with *S*-benzoyl-3-mercaptopropionyl chloride in sodium carbonate-water (method A in Chart 1). Acylation of **1**—**3** with the acid chloride in pyridine (method B in Chart 1) gave diastereomeric mixtures having (*R*)- and (*S*)-aryl groups. The mixtures were separated by preparative-layer chromatography (PLC) to give **4a, 4b, 5a, 5b, 6a,** and **6b**. Ammonolysis of these *S*-benzoyl derivatives gave the corresponding thiols, (4*R*)-2-aryl-3-(3-mercaptopropionyl)-4-thiazolidinecarboxylic acids (**9a, 9b, 10a, 10b, 11a,** and **11b**). Their physicochemical properties and IR and NMR spectral data are listed in Tables I and II. In Tables I, II, VI, and VIII, "a" and "b" represent diastereoisomers wherein one configuration is (2*R*,4*R*) and the other (2*S*,4*R*). It seems that differences of specific rotation and NMR spectra of the diastereoisomers depend on the configuration at C_2.

NMR Analyses

Although various 2-aryl-4-thiazolidinecarboxylic acids have already been synthesized, the configuration at C_2 on the thiazolidine ring was not determined.[3] Kulkarni *et al.*[4] reported a conformational study of 4-thiazolidinecarboxylic acid by NMR spectroscopy. Recently

TABLE I. Physicochemical Properties of (4*R*)-3-Acyl-2-aryl-4-thiazolidinecarboxylic Acids

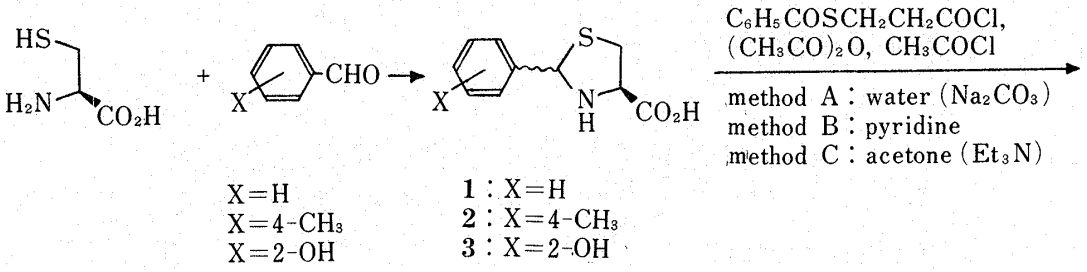
Compd. No.[a]	Confign. of aryl group	Prepn. method for 4—8[b]	Yield (%)	mp (°C)[c]	Recrystn. solvent	$[\alpha]_D$ deg. in MeOH (*c*, °C)	TLC *Rf* value	Formula	Analysis (%) Calcd (Found) C	H	N
4a	*R*	A	88	126 (dec.)	EtOAc	+110.5(1.0, 25)	0.37[j]	$C_{20}H_{19}NO_4S_2 \cdot H_2O$	57.26 (57.21	5.04 5.08	3.34 3.36)
4b	*S*	B	25	Amorph.[h]	—	−214.0(0.5, 25)	0.25[j]				
4b•DCHA[d]	*S*			195—197	EtOAc–MeOH	−150.0(0.5, 25)		$C_{20}H_{19}NO_4S_2 \cdot C_{12}H_{23}N$	65.95 (66.17	7.26 7.29	4.81 4.91)
5a	*R*	A	55	122 (dec.)	EtOAc	+131.4(1.0, 26)	0.38[j]	$C_{21}H_{21}NO_4S_2 \cdot H_2O$	58.18 (58.20	5.35 5.33	3.23 3.28)
5b	*S*	B	20	Amorph.[h]	—	−210.0(0.5, 25)	0.24[j]				
5b•DCHA[d]	*S*			194—196	EtOAc–MeOH	−162.2(0.5, 25)		$C_{21}H_{21}NO_4S_2 \cdot C_{12}H_{23}N$	66.41 (66.76	7.43 7.41	4.69 4.76)
6a	*R*	A	68	100.5—101 (dec.)	EtOAc–benzene	+130.8(1.0, 26)	0.36[j]	$C_{20}H_{19}NO_5S_2 \cdot C_6H_6$	63.01 (63.01	5.08 5.07	2.83 2.61)
6b	*S*	B	23	Amorph.[h]	—	−228.0(0.5, 25)	0.23[j]				
7a[e]	*R*	A	60	181.5—183.5	EtOH	+130.8(1.0, 25)	0.28[k]	$C_{13}H_{15}NO_3S$	58.85 (59.01	5.70 5.66	5.28 5.34)
7b[f]	*S*	B	57	204—205	EtOH	−319.4(0.5, 25)	0.14[k]	$C_{13}H_{15}NO_3S$	58.85 (58.98	5.70 5.65	5.28 5.35)
8a	*R*	C	26	171—173 (dec.)	EtOAc–MeOH	+212.2(0.5, 25)	0.26[k]	$C_{12}H_{13}NO_4S$	53.92 (54.10	4.90 5.03	5.24 5.05
8b	*S*	C	7	199—200 (dec.)	MeOH	−401.8(0.5, 25)	0.16[k]	$C_{12}H_{13}NO_4S$	53.92 (53.93	4.90 4.89	5.24 5.24)
9a	*R*		81	Amorph.[h]	—	+104.3(1.0, 25)	0.33[j]				
9b	*S*		70	Amorph.[h]	—	−255.0(0.6, 25)	0.23[j]				
10a	*R*		74	Amorph.[h]	—	+125.2(1.0, 26)	0.35[j]	$C_{14}H_{17}NO_3S_2$	54.00 (53.81	5.50 5.51	4.50 4.28)
10b	*S*		66	Amorph.[h]	—	−267.8(0.5, 25)	0.21[j]				
11a	*R*		83	146—148[i]	EtOAc	+176.8(1.0, 26)	0.27[j]	$C_{13}H_{15}NO_4S_2$	49.82 (49.74	4.82 4.88	4.47 4.32)
11a[g]	*R*			144—145	EtOAc–benzene	+109.0(1.0, 27)	0.44[k]	$C_{17}H_{19}NO_6S_2$	51.37 (51.58	4.82 4.75	3.52 3.50)
11b	*S*		76	115—117 (dec.)	EtOAc–benzene	−328.0(0.3, 25)	0.18[j]				
11b[g]	*S*			156—159	EtOAc	−237.8(0.5, 25)	0.35[k]	$C_{17}H_{19}NO_6S_2$	51.37 (51.31	4.82 4.83	3.52 3.46)

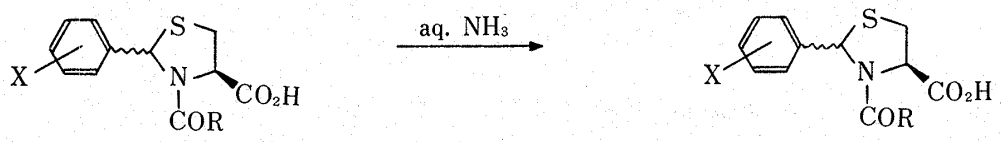
a) Compounds **4a**, **5a**, **6a**, **7a**, **8a**, **9a**, **10a**, and **11a** are diastereoisomers of compounds **4b**, **5b**, **6b**, **7b**, **8b**, **9b**, **10b**, and **11b**, respectively. *b*) Methods: see "Experimental." *c*) Melting points are uncorrected. *d*) DCHA is dicyclohexylamine. *e*) Ref. 5: mp 177—178°C, $[\alpha]_D^{22}$ +134° (*c*=1.0, MeOH); Ref. 7: mp 185—187°C, $[\alpha]_D$ +131° (MeOH). *f*) Ref. 7: mp 214—216°C, $[\alpha]_D$ −286° (MeOH). *g*) As the O,S-diacetyl derivative, which was prepared by acetylation of the corresponding thiol with acetic anhydride. *h*) Purified by chromatography. *i*) Melted with slow decomposition (confirmed by IR and NMR). *j*) SiO_2, benzene–EtOAc–HOAc=25: 25: 1. *k*) SiO_2, EtOAc–EtOH–HOAc=40: 1: 1.

TABLE II. IR and NMR Spectral Data for (4*R*)-3-Acyl-2-aryl-4-thiazolidinecarboxylic Acids

Compd. No.	IR ν_{max}^{Nujol} cm^{-1}	NMR δ (ppm)[a] J=Hz			
		Solvent	C_4–H (1H)	$J_{AX}+J_{BX}$	Others
4a	1710, 1630, 1610, 1215, 1202, 920	Acetone-d_6	4.98 (dd, J=7.5, 6.5)	14.0	2.25—3.67 (6H, m, CH_2CH_2 and C_5–H), 5.83 (3H, br s, CO_2H and H_2O), 6.30 (1H, s, C_2–H), 6.95—8.02 (10H, m, aromatic H)
4b	1783, 1652, 1203, 908 (KBr)	Acetone-d_6	5.30 (dd, J=6.0, 1.5)	7.5	2.20—3.80 (6H, m, CH_2CH_2 and C_5–H), 6.28 (1H, s, C_2–H), 6.97—8.03 (10H, m, aromatic H), 9.07 (1H, br s, CO_2H)
5a	3480, 1710, 1630, 1615, 920	Acetone-d_6	4.98 (dd, J=7.5, 6.5)	14.0	2.25 (3H, s, CH_3), 2.36—3.67 (6H, m, CH_2CH_2 and C_5–H), 5.80 (3H, br s, CO_2H and H_2O), 6.27 (1H, s, C_2–H), 6.85—8.03 (9H, m, aromatic H)
5b	1753, 1653, 1619, 1205, 916	Acetone-d_6	5.30 (dd, J=6.5, 1.5)	8.0	2.18 and 2.27 (3H, each s, CH_3), 2.38—3.73 (6H, m, CH_2CH_2 and C_5–H), 6.28 (1H, s, C_2–H), 6.93—8.08 (9H, m, aromatic H), 9.23 (1H, br s, CO_2H)
6a	3460, 1760, 1663, 1580, 1205, 910	Acetone-d_6	4.90 (dd, J=8.0, 7.5)	15.5	2.23—3.80 (6H, m, CH_2CH_2 and C_5–H), 6.43 (1H, s, C_2–H), 6.55—8.17 (15H, m, aromatic H and C_6H_6)
6b	1717, 1655, 1625, 1207, 914	Acetone-d_6	5.31 (dd, J=6.0, 1.5)	7.5	2.25—3.68 (6H, m, CH_2CH_2 and C_5–H), 6.38 and 6.52 (1H, each s, C_2–H), 6.60—8.07 (11H, m, aromatic H, OH and CO_2H)
7a	1725, 1601, 1220, 1168, 890	CD_3OD	4.90 (t, J=6.2)	12.4	1.87 and 2.13 (3H, each s, $COCH_3$), 2.30 (3H, s, CH_3), 3.25 (1H, ABq(A part) d, J=11.0, 6.2, C_5–H_A), 3.42 (1H, ABq(B part) d, J=11.0, 6.2, C_5–H_B), 6.18 (1H, s, C_2–H), 6.88—7.75 (4H, m, aromatic H)
7b	1727, 1609, 1220, 895	CD_3OD	5.19 (dd, J=7.0, 2.0)	9.0	1.88 and 2.11 (3H, each s, $COCH_3$), 2.28 and 2.31 (3H, each s, CH_3), 3.19 (1H, ABq(A part) d, J=13.0, 2.0, C_5–H_A), 3.43 (1H, ABq(B part) d, J=13.0, 7.0, C_5–H_B), 6.17 (1H, s, C_2–H), 7.04 and 7.11 (4H, each s, aromatic H)
8a	3450, 1737, 1608, 1201, 860	CD_3OD	4.82 (dd, J=8.6, 6.6)	15.2	1.87 and 2.13 (3H, each s, $COCH_3$), 3.22 (1H, ABq(A part) d, J=11.0, 8.6, C_5–H_A), 3.33 (1H, ABq(B part) d, J=11.0, 6.6, C_5–H_B), 6.40 (1H, s, C_2–H), 6.58—8.10 (4H, m, aromatic H)
8b	3230, 1721, 1588, 1225, 896	CD_3OD-acetone-d_6	5.20 (dd, J=6.0, 1.5)	7.5	1.85 and 2.13 (3H, each s, $COCH_3$), 3.27 (1H, ABq(A part) d, J=12.5, 1.5, C_5–H_A), 3.45 (1H, ABq (B part) d, J=12.5, 6.0, C_5–H_B), 6.36 and 6.43 (1H, each s, C_2–H), 6.62—7.28 (4H, m, aromatic H)
9a	1725, 1650, 1400 ($CHCl_3$)	$CDCl_3$	5.00 (t, J=7.0)	14.0	1.58 (1H, t, J=7.0, SH), 2.33—3.02 (4H, m, CH_2CH_2), 3.30 (2H, d, J=7.0, C_5–H), 6.05 (1H, s, C_2–H), 7.05—7.68 (5H, m, aromatic H), 9.71 (1H, s, CO_2H)
9b	1732, 1642, 1197 (KBr)	CD_3OD	5.25 (dd, J=6.0, 1.5)	7.5	2.10—2.93 (4H, m, CH_2CH_2), 3.23 (1H, ABq(A part)d, J=11.5, 1.5, C_5–H_A), 3.42 (1H, ABq(B part) d, J=11.5, 6.0, C_5–H_B), 6.28 (1H, s, C_2–H), 7.23 and 7.28 (5H, each s, aromatic H)
10a	1730, 1610, 1165	CD_3OD	4.91 (t, J=7.0)	14.0	2.27 (3H, s, CH_3), 2.38—2.88 (4H, m, CH_2CH_2), 3.21 (1H, ABq(A part) d, J=13.0, 7.0, C_5–H_A), 3.25 (1H, ABq(Bpart) d, J=13.0, 7.0, C_5–H_B), 6.18 (1H, s, C_2–H), 7.11 and 7.50 (4H, A_2B_2 each d, J=7.5, aromatic H)
10b	1730, 1640, 1199, 1180 (KBr)	CD_3OD	5.22 (dd, J=6.5, 1.5)	8.0	2.10—2.90 (7H, m, CH_2CH_2 and CH_3), 3.23 (1H, ABq(A part) d, J=12.5, 1.5, C_5–H_A), 3.40 (1H, ABq(B part) d, J=12.5, 6.5, C_5–H_B), 6.23 (1H, s, C_2–H), 7.08 and 7.13 (4H, each s, aromatic H)
11a	3390, 1724, 1626, 1255, 1100	CD_3OD	4.83 (dd, J=9.0, 7.0)	16.0	2.08—2.90 (4H, m, CH_2CH_2), 3.19 (1H, ABq(A part) d, J=11.5, 9.0, C_5–H_A), 3.30 (1H, ABq(B part) d, J=11.5, 7.0, C_5–H_B), 6.42 (1H, s, C_2–H), 6.60—8.07 (4H, m, aromatic H)
11a[b]	1770, 1738, 1691, 1605, 1169, 905	$CDCl_3$	4.97 (t, J=9.5)	19.0	2.27 (3H, s, $SCOCH_3$), 2.37 (3H, s, $OCOCH_3$), 2.53 (2H, t, J=7.0, $COC\underline{H}_2CH_2S$), 3.08 (2H, t, J=7.0, $COCH_2C\underline{H}_2S$), 3.30 (2H, d, J=9.5, C_5–H), 6.20 (1H, s, C_2–H), 7.00—8.17 (4H, m, aromatic H), 10.13 (1H, s, CO_2H)
11b	3310, 1725, 1604, 1583, 1230, 895	CD_3OD	5.21 (dd, J=6.5, 1.5)	8.0	2.13—2.95 (4H, m, CH_2CH_2), 3.21 (1H, ABq(A part) d, J=12.0, 1.5, C_5–H_A), 3.42 (1H, ABq(B part)d, J=12.0, 6.5, C_5–H_B), 6.43 (1H, s, C_2–H), 6.63—7.20 (4H, m, aromatic H)
11b[b]	1767, 1732, 1688, 1200, 1100, 900	$CDCl_3$	5.30 (dd, J=4.5, 3.0)	7.5	2.21 (3H, s, $SCOCH_3$), 2.35 (3H, s, $OCOCH_3$), 2.45—3.12 (4H, m, CH_2CH_2), 3.28 (1H, ABq(A part) d, J=8.0, 3.0, C_5–H_A), 3.36 (1H, ABq(B part) d, J=8.0, 4.5, C_5–H_B), 6.25 and 6.47 (1H, each s, C_2–H), 6.88—7.58 (4H, m, aromatic H), 9.98 (1H, s, CO_2H)

a) Tetramethylsilane as an internal standard. b) As the *O,S*-diacetyl derivative.





4a and **4b**: X=H, R=$CH_2CH_2SCOC_6H_5$
5a and **5b**: X=4-CH_3, R=$CH_2CH_2SCOC_6H_5$
6a and **6b**: X=2-OH, R=$CH_2CH_2SCOC_6H_5$
7a and **7b**: X=4-CH_3, R=CH_3
8a and **8b**: X=2-OH, R=CH_3

9a and **9b**: X=H, R=CH_2CH_2SH
10a and **10b**: X=4-CH_3, R=CH_2CH_2SH
11a and **11b**: X=2-OH, R=CH_2CH_2SH

Chart 1

the absolute configuration of (4*R*)-3-acetyl-2-(4-methylphenyl)-4-thiazolidinecarboxylic acid (**7a**)[5] [prepared by acetylation of (4*R*)-2-(4-methylphenyl)-4-thiazolidinecarboxylic acid (**2**) with acetic anhydride in water at 100°C] was determined to be (2*R*,4*R*) by X-ray crystallography by Parthasarathy *et al.*[6] The absolute configuration of an isomeric product (**7b**) [prepared by acetylation of **2** with acetic anhydride in pyridine at room temperature] was also determined to be (2*S*,4*R*) by specific rotation measurement and NMR spectroscopy by Szilagyi *et al.*[7] The optical rotations of **7a** and **7b** (Chart 1) were dextro- and levorotatory, respectively. In the NMR spectra, the C_2-proton signals of the thiazolidine ring in both isomers appeared in the same region. However, in the proton resonances of C_4–H and C_5–H_2, which comprise an ABX system, the C_4-proton signal in **7a** appeared at higher field than that in **7b**. Compound **7a** possessed a larger coupling constant ($J_{AX}+J_{BX}$) of its ABX system than **7b**.[7]

We aimed to apply these observations to elucidate the configurations of our compounds. (4*R*)-3-Acetyl-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid-a and -b (**8a** and **8b**) were chosen as model compounds of **6a** and **6b**, **11a** and **11b** for comparison with **7a** and **7b**, Compouns **7a** and **7b** were synthesized by the method of Parthasarathy and Szilagyi *et al.*[6,7]

(4*R*)-2-(2-Hydroxyphenyl)-4-thiazolidinecarboxylic acid (**3**)[2a,c] was acetylated with acetyl chloride in triethylamine-acetone, and the resulting diastereomeric mixture was separated by column chromatography to give isomers **8a** and **8b**. By comparison of their specific rotations and *Rf* values on thin-layer chromatography (TLC), **8a** was found to be dextrorotatory (+212.2°) with a high *Rf* value (0.26), and **8b** was levorotatory (−401.8°) with a low *Rf* value (0.16). This relation was consistent with the finding that **7a** (having a high *Rf* value) was dextrorotatory and **7b** (having a low *Rf* value) was levorotatory. In the NMR spectra, the presence of an ABX system consisting of resonances at δ 3.22 (1H, ABq(A part) d, J=11.0, 8.6 Hz), 3.33 (1H, ABq (B part) d, J=11.0, 6.6 Hz) and 4.82 (1H, dd, J=8.6, 6.6 Hz), corresponding to C_5–H_2 and C_4–H on the thiazolidine ring in **8a**, was observed, On the other hand, the above signals in **8b** appeared at δ 3.27 (1H, ABq (A part) d, J=12.5, 1.5 Hz), 3.45 (1H, ABq (B part) d, J=12.5, 6.0 Hz) and 5.20 (1H, dd, J=6.0, 1.5 Hz). The signal of the C_4-proton in **8a** appeared at higher field than that in **8b**. $J_{AX}+J_{BX}$ (15.2 Hz) from the X part, the C_4-proton, in **8a** was larger than that (7.5 Hz) in **8b**. These differences were consistent with the NMR spectral patterns of **7a** and **7b**. From these results, the absolute configurations of model compounds **8a** and **8b** were determined to be (2*R*,4*R*) and (2*S*,4*R*), respectively.

TABLE III. Atomic Coodinates and Thermal Parameters with Their Estimated Standard Deviations for Non Hydrogen Atoms

Atom	x	y	z	β_{11}	β_{22}	β_{33}	β_{12}	β_{13}	β_{23}
S_1	0.52546(8)	0.1023(2)	0.6442(2)	0.00220(4)	0.0101(2)	0.0137(3)	0.0026(2)	0.0034(2)	0.0035(3)
S_{34}	0.6308 (2)	0.3773(2)	−0.0960(3)	0.0068 (1)	0.0154(3)	0.0262(5)	0.0050(3)	−0.0011(4)	0.0063(6)
O_{22}	0.3888 (2)	0.2847(4)	0.5900(5)	0.0018 (2)	0.0123(4)	0.0140(8)	0.0032(4)	0.0015(5)	−0.004 (1)
O_{31}	0.7302 (2)	0.2672(3)	0.3022(5)	0.0014 (2)	0.0086(4)	0.0206(9)	0.0006(3)	0.0012(5)	0.0020(9)
O_{41}	0.6632 (2)	0.0614(3)	0.1072(5)	0.0022 (2)	0.0090(3)	0.0100(7)	0.0036(3)	−0.0016(5)	−0.0032(8)
O_{42}	0.7590 (2)	0.0035(3)	0.2965(5)	0.0018 (2)	0.0082(3)	0.0122(7)	0.0042(3)	−0.0003(5)	−0.0008(8)
N_3	0.6142 (2)	0.2033(3)	0.3967(6)	0.0012 (2)	0.0056(3)	0.0120(8)	0.0012(3)	0.0007(5)	−0.0027(9)
C_2	0.5352 (3)	0.2205(4)	0.4805(7)	0.0012 (2)	0.0071(5)	0.012 (1)	0.0016(4)	0.0015(7)	−0.003 (1)
C_4	0.6499 (3)	0.0963(4)	0.4355(6)	0.0015 (2)	0.0062(4)	0.0100(9)	0.0011(4)	−0.0006(6)	−0.002 (1)
C_5	0.5847 (3)	0.0165(5)	0.4920(8)	0.0020 (2)	0.0066(4)	0.018 (2)	0.0009(5)	0.0023(8)	0.000 (2)
C_{21}	0.4691 (3)	0.2231(4)	0.3395(7)	0.0013 (2)	0.0068(4)	0.012 (1)	0.0009(4)	0.0006(7)	−0.001 (1)
C_{22}	0.3952 (3)	0.2558(5)	0.4036(7)	0.0018 (2)	0.0068(4)	0.011 (1)	0.0020(4)	0.0017(7)	−0.001 (2)
C_{23}	0.3317 (3)	0.2569(5)	0.2817(7)	0.0014 (2)	0.0088(5)	0.016 (2)	0.0020(5)	0.0008(7)	0.001 (2)
C_{24}	0.3411 (3)	0.2265(5)	0.0964(8)	0.0020 (2)	0.0094(5)	0.015 (2)	0.0010(5)	−0.0026(8)	0.002 (2)
C_{25}	0.4139 (3)	0.1916(5)	0.0316(8)	0.0023 (2)	0.0100(5)	0.013 (2)	0.0016(6)	−0.0004(8)	−0.001 (2)
C_{26}	0.4771 (3)	0.1907(5)	0.1539(7)	0.0018 (2)	0.0083(5)	0.012 (1)	0.0022(5)	0.0014(8)	−0.001 (2)
C_{31}	0.6601 (3)	0.2869(4)	0.3340(7)	0.0019 (2)	0.0062(4)	0.013 (1)	0.0007(4)	−0.0020(7)	−0.003 (2)
C_{32}	0.6257 (4)	0.4015(5)	0.2977(9)	0.0032 (3)	0.0059(5)	0.026 (2)	0.0026(6)	0.0015(9)	−0.001 (2)
C_{33}	0.6601 (4)	0.4521(5)	0.115 (2)	0.0041 (3)	0.0065(5)	0.042 (3)	−0.0002(6)	0.000 (2)	0.010 (2)
C_{41}	0.6981 (3)	0.0515(4)	0.2722(7)	0.0018 (2)	0.0054(4)	0.012 (1)	0.0009(4)	0.0012(7)	0.000 (1)

Compounds **4a**, **5a**, **6a**, **9a**, **10a**, and **11a**, having high *Rf* values on TLC, were all dextrorotatory, while **4b**, **5b**, **6b**, **9b**, **10b**, and **11b**, having low *Rf* values, were all levorotatory. In the NMR spectra, the signals of the C_4-proton in the former were shifted to higher field (*ca.* 0.4 ppm) than those in the latter. Furthermore, the coupling constant ($J_{AX}+J_{BX}$) of the former was almost twice that of the latter. This tendency was the same as that of **7a** and **7b**, **8a** and **8b**. Accordingly, the absolute configurations of **4a**, **5a**, **6a**, **9a**, **10a**, and **11a** were determined to be (2*R*,4*R*) and those of **4b**, **5b**, **6b**, **9b**, **10b**, and **11b** to be (2*S*,4*R*).

X-Ray Crystallography

Kamo *et al.*[8] studied the molecular structure of (4*R*)-4-thiazolidinecarboxylic acid by X-ray diffraction. We also studied the molecular structure of **11a** by X-ray crystallography in order to further confirm the absolute configuration. The result is illustrated in Fig. 1. Final atomic parameters are shown in Tables III and IV. Bond lengths and bond angles calculated from the atomic parameters in Table III are shown in Fig. 2. Lengths and angles relating to possible hydrogen bonds are listed in Table V. It was confirmed that the absolute configuration of **11a** is (2*R*,4*R*).

Table IV. Atomic Coodinates and Thermal Parameters with Their Estimated Standard Deviations for Hydrogen Atoms

Atom	*x*	*y*	*z*	*B*
H_2	0.536(3)	0.292(4)	0.552(7)	1(1)
H_4	0.680(3)	0.101(4)	0.523(7)	1(1)
H_{51}	0.607(3)	−0.057(4)	0.541(7)	1(2)
H_{52}	0.558(3)	−0.029(4)	0.393(7)	1(2)
H_{22}	0.342(5)	0.316(6)	0.62 (2)	7(3)
H_{23}	0.281(4)	0.302(5)	0.33 (1)	4(2)
H_{24}	0.290(4)	0.215(6)	0.01 (2)	6(2)
H_{25}	0.415(4)	0.139(6)	−0.08 (1)	4(2)
H_{26}	0.538(4)	0.186(5)	0.103(9)	3(2)
H_{321}	0.555(5)	0.401(7)	0.29 (2)	7(3)
H_{322}	0.638(4)	0.474(6)	0.38 (2)	6(2)
H_{331}	0.719(4)	0.459(6)	0.16 (1)	5(2)
H_{332}	0.637(4)	0.545(5)	0.106(9)	4(2)
H_{34}	0.648(4)	0.263(5)	−0.079(9)	4(2)
H_{41}	0.691(4)	0.024(5)	0.008(8)	3(2)

Table V. Hydrogen Bonding

D—H···A	D···A	D—H	H···A	D—H···A
O_{22}—H_{22}···O_{31}	2.888 Å	0.91 Å	2.23 Å	129.1°
O_{41}—H_{41}···O_{42}	2.693	0.96	1.76	162.5

Stereoselective Acylation

As mentioned above, the formation ratio of (2*R*, 4*R*)- and (2*S*, 4*R*)-3-(*S*-benzoyl-3-mercaptopropionyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acids (**6a** and **6b**) was different in acylation by methods A and B. We therefore studied the reaction products by highperformance liquid chromatography (HPLC). The results are shown in Table VI.

Reaction of **1**, **2** and **3** with *S*-benzoyl-3-mercaptopropionyl chloride under aqueous conditions by method A afforded the (2*R*,4*R*)-isomer with a selectivity of not less than 97%. The same reaction in an organic solvent such as acetone, methylene chloride or tetrahydrofuran in the presence of triethylamine as a base by method C afforded the (2*R*,4*R*)-isomer in not

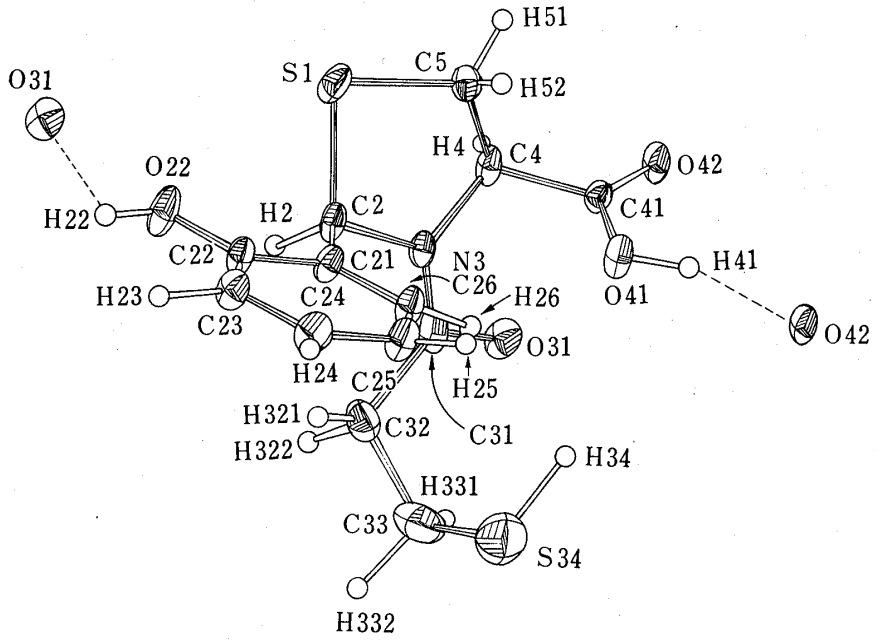


Fig. 1. Absolute Stereochemistry of **11a**

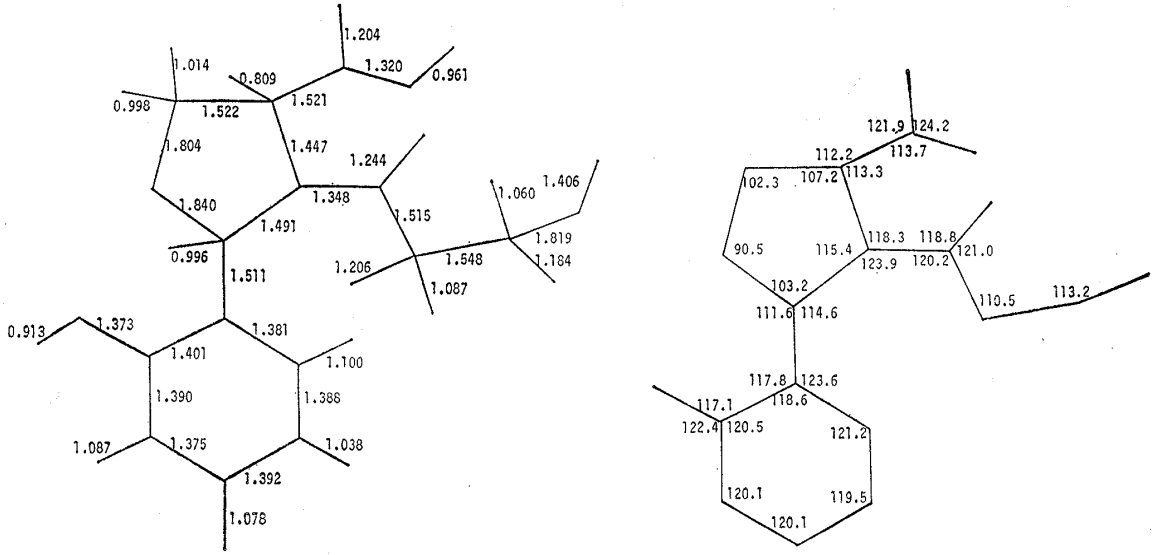


Fig. 2. Bond Lengths (Å) and Bond Angles (degree)

E.s.d. for bond lengths, 0.005—0.008 Å; for bond angles, 0.3—0.6°.

less than 90% yield. On the other hand, the formation ratio of (2*R*,4*R*)- and (2*S*,4*R*)-isomer in pyridine by method B was nearly 1: 1.

Nagasawa *et al.*[9] reported that acetylation of (4*S*)-2,5,5-trimethyl-4-thiazolidinecarboxylic acid by method A selectively afforded (2*S*,4*S*)-3-acetyl-2,5,5-trimethyl-4-thiazolidinecarboxylic acid in not more than 64% yield.

The difference of formation ratios of the isomers by methods A and B may be due to either a difference in the constituent ratio of (2*R*,4*R*)- and (2*S*,4*R*)-2-aryl-4-thiazolidinecarboxylic acid (I and II in Table VII) or a difference in the reaction rates of I and II with acid chloride. Thus, the isomer ratios were studied under three conditions by NMR spectroscopy.

The isomer ratio of I and II was calculated from the signal intensities of C_2- and C_4-protons on the assumption that I has a larger coupling constant ($J_{AX}+J_{BX}$) for the C_4-proton. The ratio was approximately 1: 1 in DMSO-d_6 and pyridine-d_5, but the equilibrium moved towards

Table VI. Formation Ratio of (2*R*,4*R*)- and (2*S*,4*R*)-2-Aryl-3-(*S*-benzoyl-3-mercaptopropionyl)-4-thiazolidinecarboxylic Acids under Various *N*-Acylation Conditions as Determined by HPLC

Compd. No.	*N*-Acylation conditions				Formation ratio (%)	
	Base	Solvent	Temp. (°C)	Time (h)	**a**: (2*R*,4*R*)	**b**: (2*S*,4*R*)
4a and **4b**[a]	Na_2CO_3	H_2O	3—5	1	97	3
	Et_3N	Acetone	3—20	2	92	8
	Et_3N	—	3—5	2	83	17
	Pyridine	—	3—5	1	58	42
5a and **5b**[b]	Na_2CO_3	H_2O	3—5	1	98	2
	Et_3N	Acetone	3—20	2	96	4
	Et_3N	CH_2Cl_2	3—20	2	94	6
	Et_3N	THF	3—20	2	90	10
	Et_3N	—	3—5	2	89	11
	Pyridine	Acetone	3—20	2	40	60
	Pyridine	—	3—5	1	61	39
6a and **6b**[c]	Na_2CO_3	H_2O	3—5	1	98	2
	Et_3N	Acetone	3—20	2	96	4
	Et_3N	CH_2Cl_2	3—20	2	96	4
	Et_3N	THF	3—20	2	96	4
	Et_3N	—	3—5	2	95	5
	Pyridine	Acetone	3—20	3	43	57
	Pyridine	—	3—5	1	49	51

a) Conditions of HPLC: column (stainless steel, 250×4 mm i.d.), Nucleosil® $7C_{18}$ (M. Nagel); flow rate, 1 ml/min; mobile phase, 0.01 M citric acid-MeOH (32/68, V/V %). Observed retention times: **4a**, 12.1 min; **4b**, 10.6 min.

b) Conditions of HPLC: the same conditions as above except for the mobile phase, 0.01 M citric acid–MeOH (30/70, V/V %). Observed retention times: **5a**, 14.2 min; **5b**, 12.7 min.

c) Conditions of HPLC: column (stainless steel, 250×4 mm i.d.), Nucleosil® $10C_{18}$ (M. Nagel); flow rate, 1.5 ml/min; mobile phase, 0.01 M citric acid–MeOH (44/56, V/V %). Observed retention times: **6a**, 11.6 min; **6b**, 13.8 min.

Table VII. Isomerization of (2*R*,4*R*)- and (2*S*,4*R*)-2-Aryl-4-thiazolidinecarboxylic Acids Through Schiff Base Intermediates, and Isomer Ratios under Three Conditions

I : (2*R*, 4*R*) II : (2*S*, 4*R*)

Ratio of I and II (I/II)

Compd. No.	Solvent	Ratio I/II	C_2–H, δ I/II	C_4–H, δ ($J_{AX}+J_{BX}$, Hz) I/II
1	DMSO-d_6	45/55	5.45/5.65	3.87(17)/4.19(12)
	C_5D_5N	56/44	5.76/6.18	4.26(16)/4.50(12)
	Na_2CO_3–D_2O	67/33	5.46/5.76	3.88(16)/4.13(13)
2	DMSO-d_6	46/54	5.43/5.62	3.87(15)/4.21(11.5)
	C_5D_5N	58/42	5.71/6.13	4.23(16)/4.52(12)
	Na_2CO_3–D_2O	74/26	5.43/5.70	3.93(16)/—[a]
3	DMSO-d_6	48/52	5.63/5.83	3.83(15)/4.20(12)
	C_5D_5N	50/50	6.23/6.48	4.25(16)/4.53(12)
	Na_2CO_3–D_2O	94/6	5.84/6.29	3.94(16)/—[a]

a) Assignment was difficult because the signals were small and broad.

Table VIII. Inhibitory Activities of (2*R*,4*R*)- and (2*S*,4*R*)-2-Aryl-3-(3-mercaptopropionyl)-4-thiazolidinecarboxylic Acids against ACE[a]

Compd. No.	AI pI_{50}	ACE pI_{50}	BK pA_{50}
9a	6.72	6.35	8.59
9b	4.68	—	5.92
10a	5.82	5.85	7.59
10b	4.28	—	5.16
11a	7.55	7.15	9.15
11b	4.55	<5	5.16

a) Inhibitory activities of the compounds against ACE were determined according to the method described in the previous report[1] (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.

I in the presence of a base such as sodium carbonate. These isomer ratios correlated well to the formation ratios of **4a** and **4b**, **5a** and **5b**, **6a** and **6b** by methods A, B and C. Although it is not certain whether crystals of (4*R*)-2-aryl-4-thiazolidinecarboxylic acid [prepared from (*R*)-cysteine and aldehyde] (**1**—**3**) consist of I, II or their mixture, it is clear that **1**—**3** are equilibrium mixtures in solution, as shown in Table VII.[10,11]

Inhibitory Activities of Thiols against Angiotensin I-Converting Enzyme (ACE)

The inhibitory activity of (2*R*,4*R*)-isomers (**9a**, **10a** and **11a**) was 35 to 1000 times higher than that of (2*S*,4*R*)-isomers (**9b**, **10b** and **11b**) (angiotensin I), as shown in Table VIII. The difference of activity of the isomers may be due to the fixed stereostructure in these compounds (particularly **11a** and **11b**) where the aryl group is linked directly to C_2 on the thiazolidine ring.

On the other hand, despite the above difference between (2*R*,4*R*)- and (2*S*,4*R*)-isomers, the compounds in which the substituent was linked through a methylene group to C_2 showed almost the same activity in both isomers.[1] The C_2-substituents of these compounds can rotate comparatively freely, and may permit nearly the same conformation for both isomers in the neighborhood of the active site in ACE.

A compound with a rigid conformation might exert either extremely high or low activity, and thus a compound maintaining the optimum rigid conformation would be expected to have the highest activity, as appears to be the case for compound **11a**.

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 spectrometer. NMR spectra were measured with JEOL PMX-60 spectrometer.

Syntheses

Method A. (2*R*,4*R*)-3-(*S*-Benzoyl-3-mercaptopropionyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic Acid (6a)——*S*-Benzoyl-3-mercaptopropionyl chloride (4.6 g, 0.02 mol) was added dropwise to a solution of (4*R*)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (4.5 g, 0.02 mol) and sodium carbonate (3.0 g, 0.028 mol) in water (50 ml) with ice-cooling and stirring. After the addition, the mixture was stirred for 2 h, and acidified with 6 N hydrochloric acid. The separated oil was extracted with ethyl acetate (100 ml). The extract was washed with saturated sodium chloride solution, dried over Na_2SO_4, and concentrated *in vacuo*. The residual oil was crystallized from benzene–ethyl acetate. The crystals were recrystallized from benzene–ethyl acetate to give **6a** (6.7 g, 68%).

Method B. (2*S*,4*R*)-3-(*S*-Benzoyl-3-mercaptopropionyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic Acid (6b)——*S*-Benzoyl-3-mercaptopropionyl chloride (2.5 g, 0.011 mol) was added dropwise to a solution of (4*R*)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (2.3 g, 0.01 mol) in pyridine (25 ml) with ice-cooling and stirring. After the addition, the mixture was stirred for 0.5 h with ice-cooling, and then for

1 h at room temperature. The resulting mixture was poured into 4 N sulfuric acid (90 ml)-ice mixture, and extracted with ethyl acetate (80 ml). The extract was washed with water, then saturated sodium chloride solution, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The residual oil was chromatographed on SiO_2 with a benzene–ethyl acetate solvent system, and purified by PLC [SiO_2, benzene–EtOAc–HOAc (25 : 25 : 1)] to give **6b** (1.0 g, 23%).

Method C. (2*R*,4*R*)- and (2*S*,4*R*)-3-Acetyl-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic Acid (8a and 8b) ——Acetyl chloride (7.9 g, 0.10 mol) was added dropwise to a solution of (4*R*)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (18.0 g, 0.08 mol) and triethylamine (29 ml, 0.21 mol) in anhydrous acetone (220 ml) with ice-cooling and stirring. After the addition the mixture was stirred for 1 h. The resulting mixture was acidified with 4 N hydrochloric acid in ether and the precipitate was removed by filtration. The filtrate was evaporated to dryness *in vacuo*, and water (400 ml) and ethyl acetate (200 ml) were added to the residue. The organic layer was washed with saturated sodium chloride solution, dried over Na_2SO_4, and evaporated to dryness *in vacuo*. The residue was chromatographed on SiO_2 with a benzene–ethyl acetate solvent system to give **8a** (5.5 g, 26%) and **8b** (1.5 g, 7%).

Ammonolysis. (2*R*,4*R*)-2-(2-Hydroxyphenyl)-3-(3-mercaptopropionyl)-4-thiazolidinecarboxylic Acid (11a) Aqueous ammonia (28%, 90 ml) was added to (2*R*,4*R*)-3-(*S*-benzoyl-3-mercaptopropionyl)-2-(2-hydroxyphenyl)-4-thiazolidinecarboxylic acid (**6a**) (9.9 g, 0.02 mol), and this solution 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 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 5.2 g (83%) of **11a**.

X-Ray Crystal Structure Analysis of 11a

Crystal Data——$C_{13}H_{15}NO_4S_2$, MW=313.4, orthorhombic, $P2_12_12_1$, a=17.114(5), b=11.976(5), c=7.106(4) Å, D_c=1.429 g·cm^{-3}, Z=4.

Integrated intensities of 2132 non-zero reflections in two quadrants of the reciprocal lattice (*hkl* and $\bar{h}kl$) were collected with a Rigaku rotating anode diffractometer operated at 40 kV and 200 mA, using nickel-filtered Cu $K\alpha$ radiation (θ-2θ scan mode). The structure was solved with the MULTAN78 system.[12] All the hydrogen atoms could be located on the difference map calculated after several cycles of anisotropic refinement (HBLS V program).[13] Three cycles of refinement taking account of the anomalous dispersion effects converged at R=0.0510, whereas those for a mirror image converged at R=0.0615. Thus, the absolute configuration has been established. The unit weight was applied.

Acknowledgement The authors are most grateful to Professor Makoto Suzuki of Meijo University for valuable suggestions and to Professor Masao Kakudo of the Institute for Protein Research, Osaka University, for X-ray analysis.

References and Notes

1) Thiol Compounds. IV. Synthesis and Antihypertensive Activity of *N*-(Mercaptoacyl)thiazolidinecarboxylic Acids: M. Oya, T. Baba, E. Kato, Y. Kawashima, and T. Watanabe, *Chem. Pharm. Bull.*, **30**, 440 (1982). A part of this work was presented at the 100th Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1980.
2) *a*) H. Soloway, F. Kipnis, J. Ornfelt, and P.E. Spoerri, *J. Am. Chem. Soc.*, **70**, 1667 (1948); *b*) I.R. Schmolka and P.E. Spoerri, *J. Org. Chem.*, **22**, 943 (1957); *c*) V.M. Kulkarni and H.P. Tipnis, *Curr. Sci.*, **41**, 637 (1972).
3) P.N. Confalone, G. Pizzolato, E.G. Baggiolini, D. Lollar, and M.R. Uskokovic, *J. Am. Chem. Soc.*, **97**, 5936 (1975); *Idem*, *ibid.*, **99**, 7020 (1977).
4) V.M. Kulkarni and G. Govil, *J. Pharm. Sci.*, **66**, 483 (1977).
5) B. Paul and W. Korytnyk, *J. Med. Chem.*, **19**, 1002 (1976).
6) R. Parthasarathy, B. Paul, and W. Korytnyk, *J. Am. Chem. Soc.*, **98**, 6634 (1976).
7) L. Szilagyi and Z. Györgydeak, *J. Am. Chem. Soc.*, **101**, 427 (1979).
8) J. Kamo, N. Tanaka, Y. Matsuura, T. Ashida, and M. Kakudo, *Bull. Chem. Soc. Jpn.*, **52**, 706 (1979).
9) H.T. Nagasawa, D.J.W. Goon, and E.G. DeMaster, *J. Med. Chem.*, **21**, 1274 (1978).
10) R. Bognar, Z. Györgydeak, and L. Szilagyi, *Ann. Chem.*, **1979**, 701.
11) R. Luhowy and F. Meneghini, *J. Am. Chem. Soc.*, **101**, 420 (1979); E. Öhler and U. Schmidt, *Chem. Ber.*, **112**, 107 (1979).
12) P. Main, S.E. Hull, L. Lessinger, G. Germain, J-P. Declercq, and M.M. Woolfson, MULTAN78, University of York, 1978.
13) T. Ashida, HBLS V. UNICS-Osaka, p. 53. Computation Center, Osaka University, 1979.