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

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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-mercaptopropionyl-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 C₂-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 C₂ 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 C₂.

NMR Analyses

Although various 2-aryl-4-thiazolidinecarboxylic acids have already been synthesized, the configuration at C₂ 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. ^{a)} No.	Confgn. of aryl group	Prepn. method for 4-8 ^{b)}	Yield (%)	mp (°C) ^{c)}	Recrystn. solvent	[α] _D deg. in MeOH (c, °C)	TLC <i>R_f</i> 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 ₄ S ₂ ·H ₂ O	57.26 (57.21)	5.04 5.08	3.34 3.36)	
4b	S	B	25	Amorph. ^{b)}	—	—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 ₄ S ₂ ·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 ₄ S ₂ ·H ₂ O	58.18 (58.20)	5.35 5.33	3.23 3.28)	
5b	S	B	20	Amorph. ^{b)}	—	—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 ₄ S ₂ ·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 ₅ S ₂ ·C ₆ H ₆	63.01 (63.01)	5.08 5.07	2.83 2.61)	
6b	S	B	23	Amorph. ^{b)}	—	—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 ₃ S	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 ₃ S	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 ₄ S	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 ₄ S	53.92 (53.93)	4.90 4.89	5.24 5.24)	
9a	R		81	Amorph. ^{b)}	—	+104.3 (1.0, 25)	0.33 ^{j)}					
9b	S		70	Amorph. ^{b)}	—	—255.0 (0.6, 25)	0.23 ^{j)}					
10a	R		74	Amorph. ^{b)}	—	+125.2 (1.0, 26)	0.35 ^{j)}	C ₁₄ H ₁₇ NO ₃ S ₂	54.00 (53.81)	5.50 5.51	4.50 4.28)	
10b	S		66	Amorph. ^{b)}	—	—267.8 (0.5, 25)	0.21 ^{j)}					
11a	R		83	146—148 ^{b)}	EtOAc	+176.8 (1.0, 26)	0.27 ^{j)}	C ₁₃ H ₁₃ NO ₄ S 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 ₆ S 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 ₆ S 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, [α]_D²⁵ +134° (c=1.0, MeOH); Ref. 7: mp 185—187°C, [α]_D²⁵ +131° (MeOH).^{f)} Ref. 7: mp 214—216°C, [α]_D²⁵ —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)} SiO₂, benzene-EtOAc-HOAc=25: 25: 1. ^{k)} SiO₂, 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 $\nu_{\max}^{\text{NaCl}}$ cm ⁻¹	Solvent	C ₄ -H (1H)	$J_{AX} + J_{BX}$	NMR δ (ppm) ^{a)} $J = \text{Hz}$	
					Others	Others
4a	1710, 1630, 1610, 1215, 1202, 920	Acetone- <i>d</i> ₆	4.98 (dd, $J = 7.5, 6.5$)	14.0	2.25—3.67 (6H, m, CH ₂ CH ₂ and C ₅ -H), 5.83 (3H, br s, CO ₂ H and H ₂ O), 6.30 (1H, s, C ₂ -H), 6.95—8.02 (10H, m, aromatic H)	
4b	1783, 1652, 1203, 908 (KBr)	Acetone- <i>d</i> ₆	5.30 (dd, $J = 6.0, 1.5$)	7.5	2.20—3.80 (6H, m, CH ₂ CH 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 ₂ H)	
5a	3480, 1710, 1630, 1615, 920	Acetone- <i>d</i> ₆	4.98 (dd, $J = 7.5, 6.5$)	14.0	2.25 (3H, s, CH ₃), 2.36—3.67 (6H, m, CH ₂ CH ₂ and C ₅ -H), 5.80 (3H, br s, CO ₂ H and H ₂ O), 6.27 (1H, s, C ₂ -H), 6.85—8.03 (9H, m, aromatic H)	
5b	1753, 1653, 1619, 1205, 916	Acetone- <i>d</i> 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 ₂ CH 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 ₂ H)	
6a	3460, 1760, 1663, 1580, 1205, 910	Acetone- <i>d</i> ₆	4.90 (dd, $J = 8.0, 7.5$)	15.5	2.23—3.80 (6H, m, CH ₂ CH ₂ and C ₅ -H), 6.43 (1H, s, C ₂ -H), 6.55—8.17 (15H, m, aromatic H and C ₆ H ₅)	
6b	1717, 1655, 1625, 1207, 914	Acetone- <i>d</i> ₆	5.31 (dd, $J = 6.0, 1.5$)	7.5	2.25—3.68 (6H, m, CH ₂ CH 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 ₂ H)	
7a	1725, 1601, 1220, 1168, 890	CD ₃ OD	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 ₃ OD	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, $J = 13.0, 2.0$, 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 ₃ OD	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, $J = 11.0, 8.6$, 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 ₃ OD-acetone- <i>d</i> 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, $J = 12.5, 1.5$, 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 ₂ CH 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 ₂ H)	
9b	1732, 1642, 1197 (KBr)	CD ₃ OD	5.25 (dd, $J = 6.0, 1.5$)	7.5	2.10—2.93 (4H, m, CH ₂ CH ₂), 3.23 (1H, ABq(A part) d, $J = 11.5, 1.5$, C ₅ -H _A), 3.42 (1H, ABq(B part) d, $J = 11.5, 1.5$, 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 ₃ OD	4.91 (t, $J = 7.0$)	14.0	2.27 (3H, s, CH ₃), 2.38—2.88 (4H, m, CH ₂ CH ₂), 3.21 (1H, ABq(A part) d, $J = 13.0, 7.0$, C ₅ -H _A), 3.25 (1H, ABq(B part) d, $J = 13.0, 7.0$, C ₅ -H _B), 6.18 (1H, s, C ₂ -H), 7.11 and 7.50 (4H, A ₂ B ₂ each d, $J = 7.5$, aromatic H)	
10b	1730, 1640, 1199, 1180 (KBr)	CD ₃ OD	5.22 (dd, $J = 6.5, 1.5$)	8.0	2.10—2.90 (7H, m, CH ₂ CH 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, $J = 12.5, 1.5$, 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 ₃ OD	4.83 (dd, $J = 9.0, 7.0$)	16.0	2.08—2.90 (4H, m, CH ₂ CH ₂), 3.19 (1H, ABq(A part) d, $J = 11.5, 9.0$, C ₅ -H _A), 3.30 (1H, ABq(B part) d, $J = 11.5, 9.0$, 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, SCOCCH ₃), 2.37 (3H, s, SCOCCH ₃), 2.53 (2H, t, $J = 7.0$, COCH ₂ CH ₂ S), 3.08 (2H, t, $J = 7.0$, COCH ₂ CH ₂ S), 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 ₂ H)	
11b	3310, 1725, 1604, 1583, 1230, 895	CD ₃ OD	5.21 (dd, $J = 6.5, 1.5$)	8.0	2.13—2.95 (4H, m, CH ₂ CH ₂), 3.21 (1H, ABq(A part) d, $J = 12.0, 1.5$, C ₅ -H _A), 3.42 (1H, ABq(B part) d, $J = 12.0, 1.5$, 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, SCOCCH ₃), 2.35 (3H, s, SCOCCH ₃), 2.45—3.12 (4H, m, CH ₂ CH ₂), 3.28 (1H, ABq(A part) d, $J = 8.0, 3.0$, C ₅ -H _A), 3.36 (1H, ABq(B part) d, $J = 8.0, 3.0$, 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 ₂ H)	

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

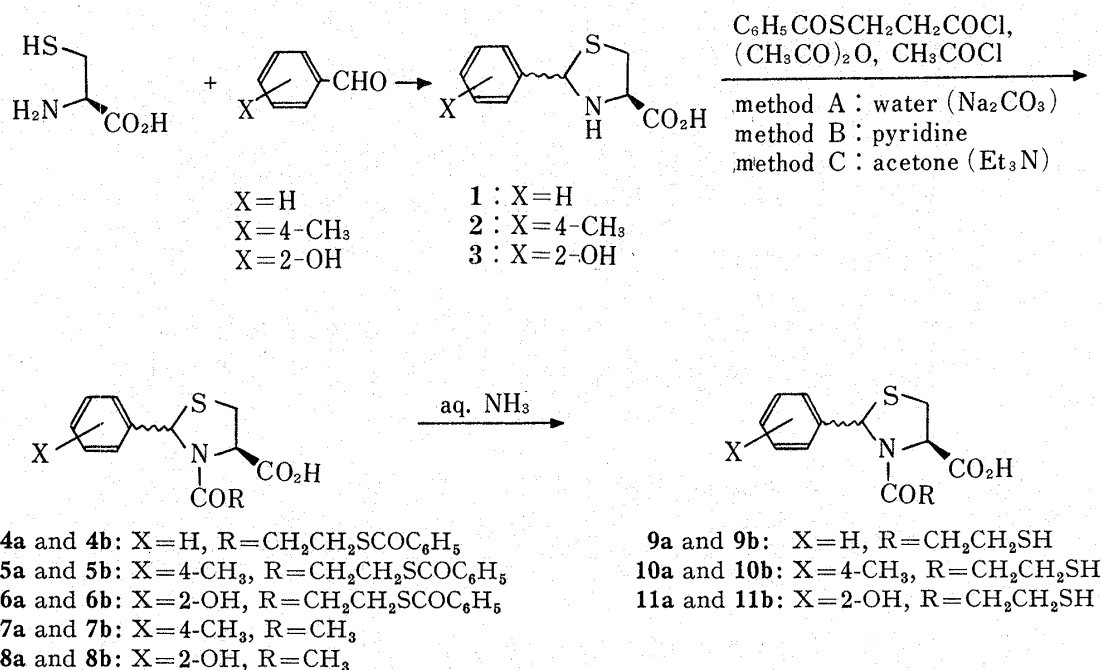


Chart 1

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 C₂-proton signals of the thiazolidine ring in both isomers appeared in the same region. However, in the proton resonances of C₄-H and C₅-H₂, which comprise an ABX system, the C₄-proton signal in **7a** appeared at higher field than that in **7b**. Compound **7a** possessed a larger coupling constant ($J_{\text{AX}}+J_{\text{BX}}$) 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**. Compounds **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 *R_f* values on thin-layer chromatography (TLC), **8a** was found to be dextrorotatory (+212.2°) with a high *R_f* value (0.26), and **8b** was levorotatory (−401.8°) with a low *R_f* value (0.16). This relation was consistent with the finding that **7a** (having a high *R_f* value) was dextrorotatory and **7b** (having a low *R_f* 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 C₅-H₂ and C₄-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 C₄-proton in **8a** appeared at higher field than that in **8b**. $J_{\text{AX}}+J_{\text{BX}}$ (15.2 Hz) from the X part, the C₄-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 Coordinates 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 ₈₄	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 *R_f* values on TLC, were all dextrorotatory, while **4b**, **5b**, **6b**, **9b**, **10b**, and **11b**, having low *R_f* values, were all levorotatory. In the NMR spectra, the signals of the C₄-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 Coordinates and Thermal Parameters with Their Estimated Standard Deviations for Hydrogen Atoms

Atom	<i>x</i>	<i>y</i>	<i>z</i>	<i>B</i>
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

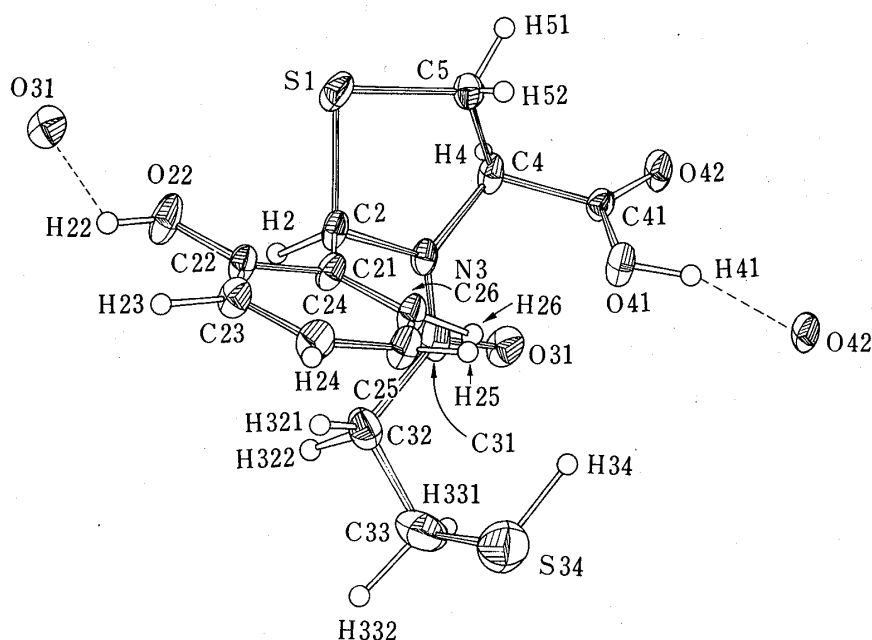


Fig. 1. Absolute Stereochemistry of 11a

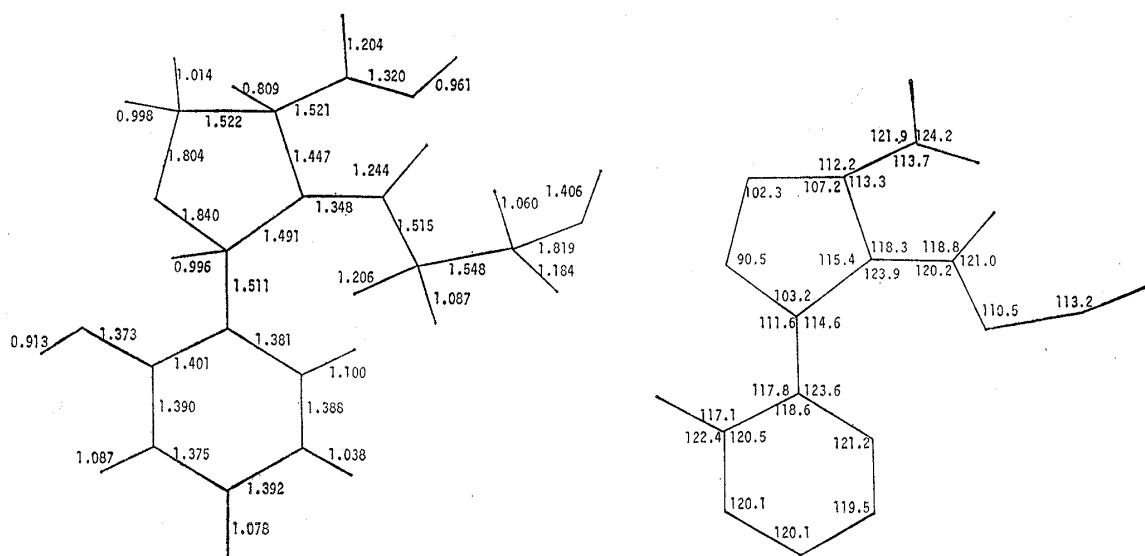


Fig. 2. Bond Lengths (Å) and Bond Angles (degree)

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 C₂- and C₄-protons on the assumption that I has a larger coupling constant ($J_{AX} + J_{BX}$) for the C₄-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.	<i>N</i> -Acylation conditions				Formation ratio (%)	
	Base	Solvent	Temp. (°C)	Time (h)	a: (2 <i>R</i> ,4 <i>R</i>)	b: (2 <i>S</i> ,4 <i>R</i>)
4a and 4b ^{a)}	Na ₂ CO ₃	H ₂ O	3—5	1	97	3
	Et ₃ N	Acetone	3—20	2	92	8
	Et ₃ N	—	3—5	2	83	17
	Pyridine	—	3—5	1	58	42
5a and 5b ^{b)}	Na ₂ CO ₃	H ₂ O	3—5	1	98	2
	Et ₃ N	Acetone	3—20	2	96	4
	Et ₃ N	CH ₂ Cl ₂	3—20	2	94	6
	Et ₃ N	THF	3—20	2	90	10
	Et ₃ N	—	3—5	2	89	11
	Pyridine	Acetone	3—20	2	40	60
	Pyridine	—	3—5	1	61	39
6a and 6b ^{c)}	Na ₂ CO ₃	H ₂ O	3—5	1	98	2
	Et ₃ N	Acetone	3—20	2	96	4
	Et ₃ N	CH ₂ Cl ₂	3—20	2	96	4
	Et ₃ N	THF	3—20	2	96	4
	Et ₃ N	—	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® 7C₁₈ (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® 10C₁₈ (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 <i>R</i> , 4 <i>R</i>)		II : (2 <i>S</i> , 4 <i>R</i>)		
Ratio of I and II (I/II)				
Compd. No.	Solvent	Ratio I/II	C ₂ -H, δ I/II	C ₄ -H, δ (<i>J</i> _{AX} + <i>J</i> _{BX} , Hz) I/II
1	DMSO- <i>d</i> ₆	45/55	5.45/5.65	3.87(17)/4.19(12)
	C ₆ D ₅ N	56/44	5.76/6.18	4.26(16)/4.50(12)
	Na ₂ CO ₃ -D ₂ O	67/33	5.46/5.76	3.88(16)/4.13(13)
2	DMSO- <i>d</i> ₆	46/54	5.43/5.62	3.87(15)/4.21(11.5)
	C ₆ D ₅ N	58/42	5.71/6.13	4.23(16)/4.52(12)
	Na ₂ CO ₃ -D ₂ O	74/26	5.43/5.70	3.93(16)/— ^{a)}
3	DMSO- <i>d</i> ₆	48/52	5.63/5.83	3.83(15)/4.20(12)
	C ₆ D ₅ N	50/50	6.23/6.48	4.25(16)/4.53(12)
	Na ₂ CO ₃ -D ₂ O	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 report¹⁾ (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 C₂ 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 C₂ showed almost the same activity in both isomers.¹⁾ The C₂-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 Na₂SO₄, 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— $\text{C}_{13}\text{H}_{15}\text{NO}_4\text{S}_2$, 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 $\bar{h}k\bar{l}$) 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 (HBL5 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.

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