A New Synthetic Route to 1,5-Benzothiazepines. Synthesis of Derivatives of Diltiazem

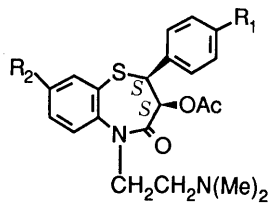
Tsunehiro HARADA, Masamichi MORIMOTO, Masaaki NAGASAWA,[1] Norio TAKAMURA,* Hirozumi INOUE, Tokuro OH-ISHI and Mikio TAKEDA

Organic Chemistry Research Laboratory, Tanabe Seiyaku Co., Ltd., 2-2-50, Kawagishi, Toda, Saitama 335, Japan. *Received November 21, 1991*

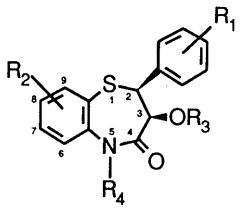
Several derivatives of diltiazem (9a—c) have been synthesized from the oxamate (6) through the carbon–carbon ring closure of the sulfur-stabilized benzylic anion and the ester carbonyl group, followed by stereoselective reduction of the C_3-carbonyl of the 1,5-benzothiazepine-dione (7).

Keywords diltiazem derivative; synthesis; ring closure; 1,5-benzothiazepine; calcium antagonist

In view of the clinical utility of diltiazem, a typical calcium channel blocker,[2] a variety of synthetic methods have been developed for the synthesis of the (2*RS*,3*RS*)-2-aryl-1,5-benzothiazepin-4(5*H*)-one (**1**). These involve the lactam formation of the carboxylic acid and the amino group (C_4–N_5 bond formation),[3] Goldberg reaction of the aromatic carbon and the amido group (C_{5a}–N_5 bond formation),[4] Michael addition of the thiol group to the cinnamamide carbon (S_1–C_2 bond formation),[5] and the ring expansion of 1,4-benzothiazine followed by C_3-carbonyl reduction.[6]



diltiazem : R_1=OMe, R_2=H
clentiazem((+)-**10a**) : R_1=OMe, R_2=Cl



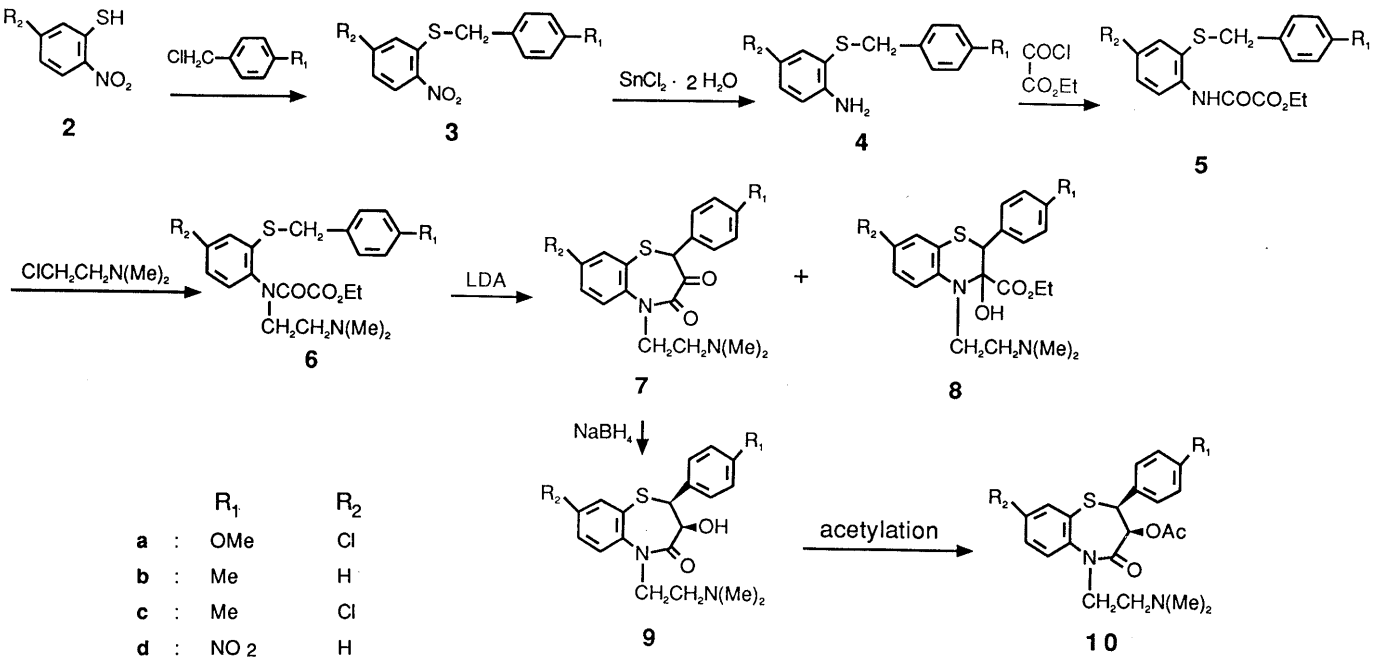
1

Chart 1

We now wish to describe a new synthetic route to **1**, involving the ring closure of the sulfur-stabilized benzylic anion and the ester carbonyl group (C_2–C_3 bond formation), as shown in Chart 2.

(2*RS*,3*RS*)-3-Acetoxy-8-chloro-5-[2-(dimethylamino)-ethyl]-2,3-dihydro-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (**10a**) was first chosen as a target compound, since the (+)-(2*S*,3*S*) isomer of **10a** was demonstrated to possess potent and long-lasting vasodilating activity[3f,7] and is now under clinical trial as a cerebral vasodilating and antihypertensive agent, clentiazem[8] (TA-3090).

The starting nitro compound (**3a**), readily prepared from 5-chloro-2-nitrothiophenol (**2a**) and 4-methoxybenzyl chloride in 83% yield, was satisfactorily reduced with stannous chloride dihydrate to give the amine (**4a**) in 88% yield. Acylation of **4a** with ethyl chloroglyoxylate (87% yield), followed by alkylation with 2-(dimethylamino)ethyl chloride afforded the *N*-(2-(dimethylamino)ethyl)oxamate (**6a**) in 90% yield. When the oxamate (**6a**) was treated with 2.3 eq of lithium diisopropylamide (LDA) in tetrahydrofuran (THF) at −60 °C, the desired 1,5-benzothiazepine-dione (**7a**) was obtained in 25% yield. Addition of



	R_1	R_2
a :	OMe	Cl
b :	Me	H
c :	Me	Cl
d :	NO_2	H

Chart 2

Dedicated to the memory of Professor Shigehiko Sugasawa.

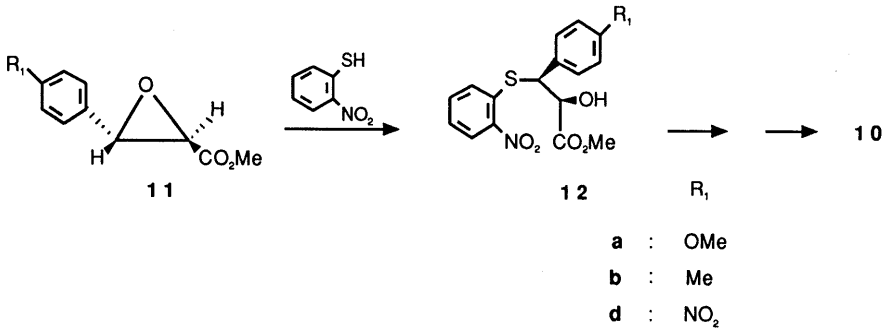


Chart 3

1.5 eq of hexamethylphosphoric triamide (HMPA) to the reaction mixture as an additive gave **7a** in much improved yield (57%) together with the 1,4-benzothiazine (**8a**) in 12% yield.[9] Reduction of the dione (**7a**) with sodium borohydride in ethanol stereoselectively afforded the *cis*-lactam (**9a**, 78% yield),[10] which was identical with an authentic sample[3f] (melting point, and infrared (IR) and nuclear magnetic resonance (NMR) spectra). Compound **9a** thus obtained was readily acetylated to give **10a** in good yield.[3f]

In a preceding paper,[11] we described the opening of the oxirane ring of the 3-phenylglycidic ester (**11**) carrying various substituents on the benzene ring with 2-nitrothiophenol by the use of appropriate catalysts to give the *threo*-nitroesters (**12**) (Chart 3). In this reaction, both the reactivity and stereoselectivity of the oxirane ring-opening of **11** were markedly influenced by the electronic nature of the substituent (R_1). The glycidate carrying an electron-donating substituent such as a methoxy group (**11a**) reacted smoothly and gave the desired *threo*-product (**12a**) selectively, while the ester with a methyl substituent (**11b**) or an electron-withdrawing substituent (**11d**) gave unsatisfactory results as regards both reactivity and stereoselectivity (*threo*/*erythro* ratio).

Consequently, in order to examine the effect of the substituent (R_1) on the new ring closure described above, we investigated the cyclization of various oxamates (**6b—d**). Treatment of **6b**, prepared similarly from **2b**, with 2.2 eq of LDA in THF containing 1.5 eq of HMPA at −60 °C afforded the expected 1,5-benzothiazepine-dione (**7b**) in 28% yield together with the 1,4-benzothiazine (**8b**)[9] as a major product (63% yield). Although various reaction conditions such as solvents, additives and bases were examined to improve the yield of **7b**, the major product was invariably **8b**, and **7b** was obtained in only about 20% yield. The ring closure of **6c** gave almost the same results as that of **6b**. Treatment of the nitro compound (**6d**) with various kinds of bases always gave a complex mixture and no cyclized product was obtained. Thus, the presence of the 4-methoxy substituent on the benzene ring of the benzylthio group was also found to be favorable for cyclization to form the 1,5-benzothiazepine-dione (**7**) (Table I). Scarcely any effect of chlorine substitution at the 4 position of the benzene ring of the oxamate (**6**) on the ring closure was observed (**6b** *vs.* **6c**).

An attempt to cyclize compound **5b** to the *N*-nor dione (**13b**) using LDA was unsuccessful. The only isolated product was the diisopropylamide (**14b**, 17% yield)[12] (Chart 4). Various attempts to convert the 1,4-benzothiazine (**8**)

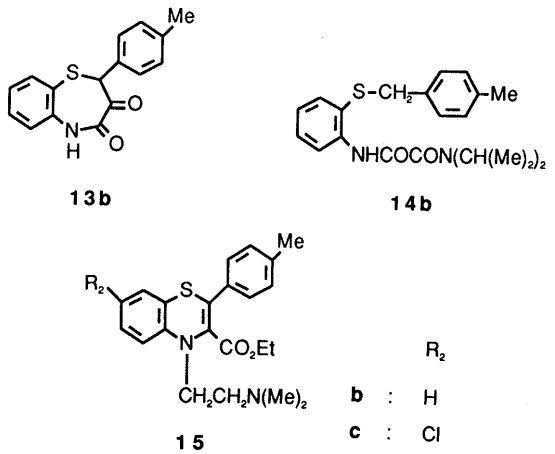


Chart 4

TABLE I. Ring Closure of the Oxamate (**6**) to the 1,5-Benzothiazepine (**7**) and the 1,4-Benzothiazine (**8**)

	Compound (**6**)		Isolated yield (%)	
	R_1	R_2	**7**	**8**
a	OMe	Cl	57	12
b	Me	H	28	63
c	Me	Cl	21	59
d	NO_2	H	0	0

to the 1,5-benzothiazepine-dione (**7**) by treatment with several acids or bases were also unsuccessful. When the 1,4-benzothiazines (**8b, c**) were treated with acetic acid at room temperature, the dehydrated compounds (**15b, c**) were obtained in good yields.

Experimental

All melting points are uncorrected. IR spectra were taken with a Hitachi IR-215 or an Analect FX-6200 FT-IR spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL PMX60 or a JEOL JNM-FX-100 spectrometer with tetramethylsilane as an internal reference. Mass spectra (MS) were obtained on a Hitachi RMU-6 mass spectrometer. Microanalyses were performed on a Perkin-Elmer 240B C, H, N analyzer and a Yokokawa IC-100 ion chromatographic analyzer.

5-Chloro-2-nitrophenyl 4-Methoxybenzyl Sulfide (3a) A solution of the thiol (**2a**, 21 g, 0.11 mol) in THF (120 ml) was added to a cooled solution of EtONa (8.9 g, 0.13 mol) in EtOH (300 ml). 4-Methoxybenzyl chloride (20.4 g, 0.13 mol) was then added dropwise under ice-cooling, and the mixture was stirred at room temperature for 3.5 h. The reaction mixture was concentrated and diluted with H_2O to give yellow crystals. Recrystallization from EtOH afforded **3a** (28.7 g, 83%) as yellow leaflets. The sulfides (**3b, c**) were similarly obtained in 79% and 57% yields, respectively. Spectroscopic data and elemental analysis data of these sulfides are given in Table II.

4-Chloro-2-[(4-methoxybenzyl)thio]aniline (4a) Stannous chloride dihydrate (18.1 g, 80 mmol) was added to a suspension of the sulfide (**3a**, 5.0 g, 16 mmol) in EtOH (300 ml), and the mixture was stirred at 70 °C for 1.5 h under an argon atmosphere. The reaction mixture was cooled, concentrated, poured into ice-water and basified with saturated $NaHCO_3$ solution. AcOEt was added to the mixture, which was filtered to remove a precipitate. The two-phase filtrate was separated, the aqueous phase was extracted with AcOEt, and the combined organic layers were washed with brine, dried over $MgSO_4$ and evaporated. Purification of the residue on a silica gel column (eluent: benzene) gave **4a** (3.98 g, 88%) as slightly yellow crystals. In a similar way, **4b** and **4c** were obtained in 87% and 79% yields, respectively. Spectroscopic data and elemental analysis data of these amines are given in Table II.

2-[(4-Nitrobenzyl)thio]aniline (4d) A solution of 2-aminothiophenol (1.25 g, 10 mmol) in EtOH (5 ml) and 4-nitrobenzyl bromide (2.37 g, 11 mmol) were successively added to a solution of EtONa (0.75 g, 11 mmol) in EtOH (20 ml) under ice-cooling. The mixture was stirred at room temperature for 30 min, concentrated, diluted with H_2O and extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$ and evaporated to give a residue, which was chromatographed over silica gel (eluent: benzene) to give **4d** (2.18 g, 84%) as yellow crystals. Spectroscopic data and elemental analysis data of **4d** are given in Table II.

Ethyl *N*-[4-Chloro-[2-(4-methoxybenzyl)thio]phenyl]oxamate (5a) A solution of $NaHCO_3$ (0.92 g, 11 mmol) in H_2O (20 ml) was added to a solution of the aniline (**4a**, 1.53 g, 5.5 mmol) in CH_2Cl_2 (25 ml) and cooled in an ice bath. A solution of ethyl oxalyl chloride (1.37 g, 11 mmol) in CH_2Cl_2 (5 ml) was then added dropwise and the two-phase mixture was stirred at 0—3 °C for 1 h. The mixture was separated, and the organic layer was washed with brine, dried over $MgSO_4$ and evaporated to give a crystalline residue, which was recrystallized from isopropyl alcohol to give **5a** (1.81 g, 87%) as colorless needles. In a similar way, **5b**, **5c** and **5d** were obtained in 71%, 76% and 95% yields, respectively. Spectroscopic data and elemental analysis data of these compounds are given in Table II.

Ethyl *N*-[4-Chloro-[2-(4-methoxybenzyl)thio]phenyl]-*N*-[2-(dimethylamino)ethyl]oxamate (6a) A mixture of **5a** (1.50 g, 3.9 mmol), 2-(dimethylamino)ethyl chloride (1.27 g, 11.8 mmol), powdered K_2CO_3 (1.64 g, 11.8 mmol) and 18-crown-6 (0.1 g) in CH_3CN (30 ml) was warmed at 50 °C for 3 h under stirring and concentrated. The residue was dissolved in AcOEt (100 ml) and H_2O (50 ml), and then separated. The aqueous layer was extracted with AcOEt and the combined extracts were washed with brine, dried over $MgSO_4$ and evaporated. Purification of the residue on a silica gel column (eluent: $CHCl_3$–EtOH) gave **6a** (1.60 g, 90%) as a pale yellow oil. The oxamates (**6b—d**) were similarly obtained in 80%, 97% and 48% yields, respectively. Spectroscopic data of these oxamates are given in Table II.

8-Chloro-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-1,5-benzothiazepine-3,4(2*H*,5*H*)-dione (7a) and Ethyl 7-Chloro-4-[2-(dimethylamino)ethyl]-3,4-dihydro-3-hydroxy-2-(4-methoxyphenyl)-2*H*-1,4-benzothiazine-3-carboxylate (8a) A solution of the oxamate (**6a**, 200 mg, 0.44 mmol) and HMPA (119 mg, 0.66 mmol) in THF (30 ml) was cooled to −65 °C under an argon atmosphere. A solution of LDA, prepared from diisopropylamine (103 mg, 1.02 mmol) and *n*-BuLi (0.64 ml, 1.6 M in hexane, 1.02 mmol) in THF (10 ml), was added dropwise to the cooled solution[13] during a period of 5 min, and then the whole mixture was stirred at −60 °C for 10 min. Saturated NH_4Cl solution was added, and the mixture was extracted with AcOEt. The organic layer was washed with brine, dried over $MgSO_4$, and evaporated. Chromatography of the residue over silica gel (eluent: $CHCl_3$–EtOH) gave **7a** (102 mg, 57%) as a pale yellow oil and **8a** (24 mg, 12%)[9] as colorless crystals. The 1,5-benzothiazepines (**7b, c**) and the 1,4-benzothiazines (**8b, c**)[9] were similarly obtained, and the yields are given in Table I. Spectroscopic data and elemental analysis data of these compounds are given in Table III.

TABLE II. Spectroscopic Data and Elemental Analysis Data for the Intermediates (**3—6**)

Compd.	mp °C	IR $\nu_{max}^{(state)}$ cm^{-1}	^{1}H-NMR ($CDCl_3$) δ[a]	Formula (mp of the salt °C)	Analysis % or MS *m/z* Calcd (Found)				
					C	H	Cl	N	S
3a	122—123.5	(Nujol) 1580, 1550, 1320, 1295	3.82 (3H, s), 4.15 (2H, s), 6.70—7.60 (6H, m), 8.21 (1H, d, 8.5)	$C_{14}H_{12}ClNO_3S$	54.28 (54.56)	3.90 (3.85)	11.44 (11.55)	4.52 (4.47)	10.35 (10.51)
3b	92—94	(Nujol) 1580, 1550, 1500, 1320, 1295	2.33 (3H, s), 4.16 (2H, s), 7.00—8.40 (8H, m)	$C_{14}H_{13}NO_2S$	64.84 (64.63)	5.05 (4.94)		5.40 (5.45)	12.36 (12.12)
3c	92—93	(Nujol) 1580, 1550, 1495, 1320, 1290	2.36 (3H, s), 4.15 (2H, s), 6.95—7.50 (6H, m), 8.16 (1H, d, 9)	$C_{14}H_{12}ClNO_2S$	57.24 (57.22)	4.12 (4.10)	12.07 (12.22)	4.77 (4.73)	10.90 (10.83)
4a	84—84.5	($CHCl_3$) 3460, 3360	3.77 (3H, s), 3.86 (2H, s), 4.22 (2H, br s), 6.50—7.45 (7H, m)	$C_{14}H_{14}ClNOS$	60.10 (60.09)	5.04 (5.01)	12.67 (12.54)	5.01 (4.97)	11.46 (11.25)
4b	Oil	(Neat) 3450, 3350	2.29 (3H, s), 3.89 (2H, s), 3.60—4.50 (2H, br), 6.40—7.40 (8H, m)	$C_{14}H_{15}NS \cdot HCl$ (196—202)	63.26 (63.07)	6.07 (6.01)	13.34 (13.33)	5.27 (5.26)	12.06 (12.02)
4c·HCl	166—170	(Nujol) 3200—2400, 2000	2.26 (3H, s), 4.16 (2H, s), 6.90—7.40 (7H, m), 8.65 (3H, br s)[b]	$C_{14}H_{14}ClNS$ ·HCl	56.00 (56.29)	5.04 (4.95)	23.62 (23.44)	4.67 (4.65)	10.68 (10.50)
4d	59—59.5	($CHCl_3$) 3470, 3370, 1520, 1345	3.92 (2H, s), 4.29 (2H, br s), 6.40—6.80 (2H, m), 6.95—7.40 (6H, m), 8.05 (2H, d, 8.8)	$C_{13}H_{12}N_2O_2S$	59.98 (59.96)	4.65 (4.50)		10.76 (10.80)	12.32 (12.18)
5a	99.5—100	($CHCl_3$) 3320, 1760, 1730 (sh), 1705, 1605, 1575, 1510	1.44 (3H, t, 7), 3.74 (3H, s), 3.88 (2H, s), 4.40 (2H, q, 7), 6.55—7.60 (6H, m), 8.35 (1H, m), 9.88 (1H, br s)	$C_{18}H_{18}ClNO_4S$	56.91 (57.04)	4.78 (4.64)	9.33 (9.56)	3.69 (3.72)	8.44 (8.62)
5b	Powder	($CHCl_3$) 3300, 1760, 1730 (sh), 1705, 1580, 1520	1.44 (3H, t, 7), 2.27 (3H, s), 3.86 (2H, s), 4.41 (2H, q, 7), 6.80—7.70 (7H, m), 8.40 (1H, m), 9.95 (1H, br s)	$C_{18}H_{19}NO_3S$	329 (M^+), 256, 105 (100%)				
5c	122—124	(Nujol) 3300, 1730, 1710, 1575, 1520	1.45 (3H, t, 7), 2.28 (3H, s), 3.90 (2H, s), 4.41 (2H, q, 7), 6.75—7.60 (6H, m), 8.34 (1H, d, 9), 9.86 (1H, br s)	$C_{18}H_{18}ClNO_3S$	59.42 (59.26)	4.99 (4.90)	9.74 (9.81)	3.85 (3.78)	8.81 (8.54)
5d	100.5—101.5	($CHCl_3$) 3310, 1760, 1710, 1600, 1580, 1520	1.45 (3H, t, 7), 3.98 (2H, s), 4.43 (2H, q, 7), 6.90—7.60 (5H, m), 7.90—8.60 (3H, m), 10.02 (1H, br s)	$C_{17}H_{16}N_2O_5S$	56.66 (56.58)	4.48 (4.33)		7.81 (7.77)	8.90 (9.08)
6a	Oil	($CHCl_3$) 1740, 1670, 1610, 1580, 1510	1.04 (3H, t, 7), 2.17 (6H, s), 2.05—2.60 (2H, m), 2.90—3.50 (1H, m), 3.79 (3H, s), 4.05 (2H, q, 7), 4.11 (2H, s), 3.90—4.60 (1H, m), 6.70—7.45 (7H, m)	$C_{22}H_{27}ClN_2O_4S$	452, 450 (M^+), 379, 121 (100%)				
6b	Oil	(Neat) 1740, 1670, 1580, 1570, 1510	0.97 (3H, t, 7), 2.18 (6H, s), 2.10—2.60 (2H, m), 2.31 (3H, s), 2.90—3.55 (1H, m), 3.99 (2H, q, 7), 4.12 (2H, s), 3.90—4.60 (1H, m), 6.95—7.50 (8H, m)	$C_{22}H_{28}N_2O_3S$	400 (M^+), 329, 327, 256, 105 (100%)				
6c	Oil	(Neat) 1745, 1675, 1580, 1560, 1515	1.04 (3H, t, 7), 2.18 (6H, s), 2.05—2.60 (2H, m), 2.33 (3H, s), 2.90—3.50 (1H, m), 3.95—4.60 (1H, m), 4.03 (2H, q, 7), 4.13 (2H, s), 6.90—7.45 (7H, m)	$C_{22}H_{27}ClN_2O_3S$	436, 434 (M^+), 363, 361, 105 (100%)				
6d	Oil	($CHCl_3$) 1740, 1670	1.07 (3H, t, 7), 2.22 (6H, s), 2.10—2.65 (2H, m), 2.90—3.55 (1H, m), 3.90—4.60 (1H, m), 4.05 (2H, q, 7), 4.25 (2H, s), 7.10—7.70 (6H, m)	$C_{21}H_{25}N_3O_5S$	431 (M^+), 401, 387, 358				

a) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in Hz in parentheses. *b*) DMSO-d_6 was used as a solvent.

TABLE III. Spectroscopic Data and Elemental Analysis Data for the 1,5-Benzothiazepines (**7** and **9**) and the 1,4-Benzothiazines (**8** and **15**)

Compd.	mp °C	IR $\nu_{max}^{(state)}$ cm^{-1}	^{1}H-NMR ($CDCl_3$) δ[a]	Formula (mp of the salt °C)	Analysis % or MS *m/z* Calcd (Found)				
					C	H	Cl	N	S
7a	Oil	(Neat) 1720, 1660, 1610	2.20 (6H, s), 2.35—2.80 (2H, m), 3.75 (3H, s), 3.75—4.30 (2H, m), 5.38 (1H, br s), 6.70—7.75 (7H, m)	$C_{20}H_{21}ClN_2O_2S \cdot (CO_2H)_2$ (110—113 (dec.))	53.39 (53.31	4.68 4.95	7.16 7.06	5.66 4.95	6.48 6.36)
7b	Oil	(Neat) 1710, 1650	2.26 (6H, s), 2.33 (3H, s), 2.30—2.80 (2H, m), 3.70—4.40 (2H, m), 5.40 (1H, br s), 6.90—7.80 (8H, m)	$C_{20}H_{22}N_2O_2S \cdot (CO_2H)_2$ (178—182 (dec.))	59.45 (58.78	5.44 5.37		6.30 6.31	7.21 7.28)
7c	Oil	(Neat) 1715, 1660, 1630 (sh)	2.24 (6H, s), 2.36 (3H, s), 2.30—2.80 (2H, m), 3.75—4.30 (2H, m), 5.48 (1H, br s), 7.05—7.80 (7H, m)	$C_{20}H_{21}ClN_2O_2S$	390, 388 (M^+), 362, 360				
8a	Powder	($CHCl_3$) 3200—2300, 1735, 1610, 1580, 1510	1.18 (3H, t, 7), 2.13 (6H, s), 1.95—2.80 (2H, m), 3.71 (3H, s), 2.95—4.00 (2H, m), 4.06 (2H, q, 7), 4.43 (1H, s), 6.45—7.50 (7H, m)	$C_{22}H_{27}ClN_2O_4S$	452, 450 (M^+), 434, 432, 379, 377				
8b	147—150	(Nujol) 3100—2200, 1730, 1570	1.16 (3H, t, 7), 2.13 (6H, s), 1.90—2.70 (2H, m), 2.27 (3H, s), 3.00—4.00 (2H, m), 4.12 (2H, q, 7), 4.50 (1H, s), 6.60—7.45 (8H, m)	$C_{22}H_{28}N_2O_3S$	65.97 (65.69	7.05 7.02		6.99 6.96	8.01 8.09)
8c	139.5—140.5	(Nujol) 3200—2200, 1735, 1575	1.17 (3H, t, 7), 2.12 (6H, s), 2.00—2.80 (2H, m), 2.28 (3H, s), 2.95—4.10 (2H, m), 4.13 (2H, q, 7), 4.49 (1H, s), 6.50—7.50 (7H, m)	$C_{22}H_{27}ClN_2O_3S$	60.75 (60.70	6.26 6.23	8.15 8.01	6.44 6.35	7.37 7.19)
9a	169.5—170	($CHCl_3$) 3480, 1655, 1600, 1575, 1500	2.28 (6H, s), 2.30—3.00 (2H, m), 3.40—3.90 (1H, m), 3.83 (3H, s), 4.29 (1H, d, 7), 4.10—4.70 (1H, m), 4.91 (1H, d, 7), 6.80—7.80 (7H, m)	$C_{20}H_{23}ClN_2O_3S$	59.03 (58.76	5.70 5.69	8.71 8.80	6.88 6.92	7.88[3f] 8.05)
9b	Oil	(Neat) 3440, 1655, 1575, 1505	2.23 (6H, s), 2.31 (3H, s), 2.20—3.00 (2H, m), 3.30—3.95 (1H, m), 4.26 (1H, d, 7), 4.10—4.75 (1H, m), 4.85 (1H, d, 7), 6.95—7.80 (8H, m)	$C_{20}H_{24}N_2O_2S \cdot HCl$ (241—242.5)	61.13 (61.07	6.41 6.50	9.02 8.94	7.13 7.22	8.16[3e] 8.24)
9c	140.5—141	(Nujol) 3200—2400, 1660	2.32 (6H, s), 2.41 (3H, s), 2.30—3.00 (2H, m), 3.40—4.00 (1H, m), 4.29 (1H, d, 7), 4.10—4.70 (1H, m), 4.97 (1H, d, 7), 7.00—7.80 (7H, m)	$C_{20}H_{23}ClN_2O_2S$	61.45 (61.25	5.93 5.88	9.07 9.35	7.17 7.20	8.20[3f] 8.37)
15b	Oil	(Neat) 1715, 1610, 1575, 1510	0.95 (3H, t, 7), 2.31 (6H, s), 2.35 (3H, s), 2.40—2.85 (2H, m), 3.55—3.90 (2H, m), 4.03 (2H, q, 7), 6.70—7.40 (8H, m)	$C_{22}H_{26}N_2O_2S \cdot HCl$ (200.5—201.5 (dec.))	63.07 (63.29	6.50 6.48	8.47 8.28	6.68 6.74	7.65 7.75)
15c	84—86	(Nujol) 1710, 1615	0.95 (3H, t, 7), 2.33 (6H, s), 2.33 (3H, s), 2.40—2.80 (2H, m), 3.50—3.90 (2H, m), 4.02 (2H, q, 7), 6.70—7.40 (7H, m)	$C_{22}H_{25}ClN_2O_2S$	63.37 (63.14	6.04 6.00	8.50 8.80	6.72 6.77	7.69 7.80)

a) Chemical shifts are given with proton numbers, absorption patterns and coupling constants in Hz in parentheses.

(2*RS*,3*RS*)-8-Chloro-5-[2-(dimethylamino)ethyl]-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (9a) A solution of the dione (**7a**, 202 mg, 0.5 mmol) in 90% aqueous EtOH (10 ml) was cooled to 0 °C. $NaBH_4$ (38 mg, 1 mmol) was added to the solution, and the mixture was stirred at 0—25 °C for 30 min. Brine and AcOEt were added to the reaction mixture. The aqueous layer was extracted with AcOEt and the AcOEt layers were combined, washed with brine, dried over $MgSO_4$ and evaporated. The residue was purified on a silica gel column (eluent: $CHCl_3$–EtOH) to give the *cis*-lactam (**9a**, 158 mg, 78%) as colorless crystals. The *cis*-lactams (**9b, c**) were similarly obtained in 77% and 81% yields, respectively. Spectroscopic data and elemental analysis data of these lactams are given in Table III.

Compounds **9** thus obtained were readily acetylated to give **10** in good yield.[3c,3f]

Ethyl 7-Chloro-4-[2-(dimethylamino)ethyl]-2-(4-methylphenyl)-4*H*-1,4-benzothiazine-3-carboxylate (15c) A solution of **8c** (100 mg, 0.23 mmol) in AcOH (3 ml) was stirred at room temperature for 7 d and concentrated. The residue was dissolved in AcOEt, then the solution was washed with saturated $NaHCO_3$ solution and brine, dried over $MgSO_4$, and evaporated. The residue was purified on a silica gel column (eluent: $CHCl_3$–EtOH) to give **15c** (70 mg, 73%) as yellow crystals. The benzothiazine (**15b**) was similarly obtained in 68% yield. Spectroscopic data and elemental analysis data of these benzothiazines are given in Table III.

Acknowledgement The authors are grateful to the members of Analytical Department for elemental analyses and spectral measurements.

References and Notes

1) Left Tanabe Seiyaku Co., Ltd., in April, 1989.
2) For a review, see: K. Abe, H. Inoue and T. Nagao, *Yakugaku Zasshi*, **108**, 716 (1988).
3) *a*) H. Kugita, H. Inoue, M. Ikezaki and S. Takeo, *Chem. Pharm. Bull.*, **18**, 2028 (1970); *b*) H. Kugita, H. Inoue, M. Ikezaki, M. Konda and S. Takeo, *ibid.*, **18**, 2284 (1970); *c*) *Idem*, *ibid.*, **19**, 595 (1971); *d*) H. Inoue, S. Takeo, M. Kawazu and H. Kugita, *Yakugaku Zasshi*, **93**, 729 (1973); *e*) M. Miyazaki, T. Iwakuma and T. Tanaka, *Chem. Pharm. Bull.*, **26**, 2889 (1978); *f*) H. Inoue, M. Konda, T. Hashiyama, H. Otsuka, K. Takahashi, M. Gaino, T. Date, K. Aoe, M. Takeda, S. Murata, H. Narita and T. Nagao, *J. Med. Chem.*, **34**, 675 (1991).
4) Y. Kanei, T. Tamura, S. Sato and H. Fujiwara, Japan.Patent Kokai 58-183680 (1983) [*Chem. Abstr.*, **100**, 139161*e* (1984)].
5) H. Fujita, Japan.Patent Kokai 60-116677 (1985) [*Chem. Abstr.*, **104**, 34112*u* (1986)].
6) Y. Maki, M. Sako, N. Mitsumori, S. Maeda and M. Takaya, *J. Chem. Soc., Chem. Commun.*, **1983**, 450.
7) *a*) H. Narita, S. Murata, H. Yabana, K. Kikkawa, Y. Sugawara, Y. Akimoto and T. Nagao, *Arzneim.-Forsch./Drug Res.*, **38**, 515 (1988); *b*) S. Murata, K. Kikkawa, H. Yabana and T. Nagao, *ibid.*, **38**, 521 (1988); *c*) K. Kikkawa, S. Murata and T. Nagao, *ibid.*, **38**, 526 (1988).
8) International Nonproprietary Name.
9) Such an intramolecular attack of a sulfur-stabilized carbanion to an amide carbonyl group has already been reported: *a*) Y. Ohtsuka and T. Oishi, *Chem. Pharm. Bull.*, **31**, 454 (1983); *b*) Y. Ishikawa, Y. Kurebayashi, K. Suzuki, Y. Terao and M. Sekiya, *ibid.*, **29**, 2496 (1981). The 1,4-benzothiazine (**8**) obtained here was a single stereoisomer. The stereochemistry of **8** has not yet been determined.
10) M. Morimoto, H. Kohno, K. Yasuda, T. Date, N. Takamura and S. Sugasawa, *Heterocycles*, **30**, 471 (1990).
11) T. Hashiyama, H. Inoue, M. Konda and M. Takeda, *J. Chem. Soc., Perkin Trans. 1*, **1984**, 1725.
12) **14b**: an oil. IR ν_{max}^{neat} cm^{-1}: 3280, 1685, 1630, 1570, 1510. ^{1}H-NMR ($CDCl_3$) δ: 1.29 (6H, d, J=6.6 Hz), 1.48 (6H, d, J=6.6 Hz), 2.29 (3H, s), 3.30—3.90 (1H, m), 3.93 (2H, s), 4.50—5.10 (1H, m), 6.90—7.60 (7H, m), 8.35 (1H, m), 9.90 (1H, br s). MS *m/z*: 384 (M^+), 341, 311, 297, 105 (100%).
13) Reverse addition of a solution of **6a** and HMPA in THF to a LDA solution gave almost the same result.