# Synthesis and Antihypertensive Activity of 3-Acetoxy-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (Diltiazem) Derivatives Having Substituents at the 8 Position

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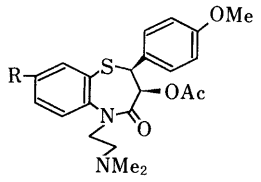
**In order to improve the potency and duration of biological actions of diltiazem, a number of 1,5-benzothiazepine derivatives having the substituents at the 8 position were prepared and evaluated for their antihypertensive activity in spontaneously hypertensive rats. The introduction of methyl, ethyl, isopropyl, benzyl, methoxy, ethoxy, phenoxy, and methylthio groups increased the antihypertensive activity and prolonged duration of action, whereas cyclohexyl, cyclopentoxy, tolyloxy, *p*-methoxyphenoxy and phenylthio derivatives were less active than diltiazem. Among them, the 8-benzyl and phenoxy derivatives showed the most potent and long-lasting antihypertensive action.**

**Keywords** calcium entry blocker; 1,5-benzothiazepine; diltiazem; antihypertensive agent; synthesis; antihypertensive activity

Calcium entry blockers have been widely used for the treatment of cardiovascular disorders such as hypertension and angina. The chemical structures of the major blockers are classified into three groups[1]: dihydropyridines, phenylalkylamines and 1,5-benzothiazepines, which are represented by nifedipine, verapamil and diltiazem (**1**), respectively. Because of their highly clinical usefulness a number of modifications have been done on dihydropyridines and phenylalkylamines for the purpose of improving their bioavailability and duration of action. However, there have been only a few reports concerning modifications of benzothiazepines.[2] Recently, the structure–activity relationship of benzothiazepines that have the halogen atom at the 6 to 9 positions have been reported,[2e] and the 8-chloro derivative (**2**) has shown the most potent efficacy with long duration.



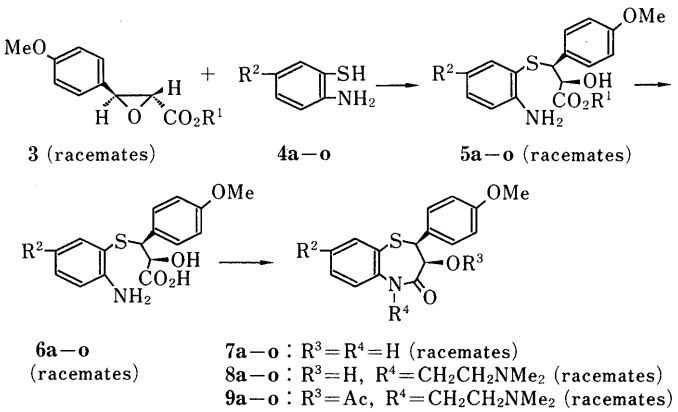
**1** : R=H, HCl salt
**2** : R=Cl, maleate

Diltiazem is usually administered twice or three times a day and its antihypertensive potency is far less than that of dihydropyridines. A potent and long-lasting diltiazem congener, therefore, would be beneficial to patients. We intended to synthesize the benzothiazepines that have the substituents at the 8 position in order to enhance antihypertensive activity and elongate its effectiveness. Such substituents were expected to enhance the affinity for the target organs and receptors and to improve potency and duration. This paper describes the synthesis of these benzothiazepines and their antihypertensive activity in spontaneously hypertensive rats (SHR).

## Synthesis

The racemic benzothiazepines (**9a—o**) were prepared as shown in Chart 1. Ring opening reaction[2e] of the *trans*-glycidate (**3**) with the *o*-aminobenzenethiols (**4a—o**)[3] in toluene at 90 °C gave the *threo*-α-hydroxyesters (**5a—o**) which were hydrolyzed with sodium hydroxide to give the amino acids (**6a—o**). Intramolecular condensations of **6a—d**, **6f—h**, **6n** and **6o** were carried out with diphenylphosphoryl azide to afford the lactams (**7a—d**, **f—h**, **n**, **o**). The other amino acids (**6e**, **i—m**) were converted to the lactams (**7e**, **i—m**) by heating in xylene. *N*-Alkylation of **7a—o** with 2-dimethylaminoethyl chloride gave **8a—o** which were acetylated with acetic anhydride to afford the desired benzothiazepines (**9a—o**).

The optically active benzothiazepines (**16a, b**) were synthesized from *l*-menthyl *trans*-3-(4-methoxyphenyl)glycidate (**11**),[4] which was the mixture of the (2*S*,3*R*) and (2*R*,3*S*)-glycidates prepared by Darzens reaction of *l*-menthyl chloroacetate with *p*-methoxybenzaldehyde in the presence of sodium hydride, as shown in Chart 2. Reaction of the thiols (**4e, i**) with **11** afforded a mixture of the (2*S*,3*S*)-esters (**12a, b**) and their diastereoisomers, (2*R*,3*R*)-esters, which were derived from the (2*R*,3*S*) and (2*S*,3*R*)-glycidates (**11**), respectively. The desired isomers (**12a, b**) were easily separated as crystals from the reaction solution by cooling. The esters (**12a, b**) were converted to the benzothiazepines (**16a, b**) *via* **13a, b**, **14a, b** and **15a, b**



**3** (racemates) **4a—o** **5a—o** (racemates)

**6a—o** (racemates)

**7a—o** : $R^3=R^4=H$ (racemates)
**8a—o** : $R^3=H$, $R^4=CH_2CH_2NMe_2$ (racemates)
**9a—o** : $R^3=Ac$, $R^4=CH_2CH_2NMe_2$ (racemates)

$R^1$=Me or Et
$R^2$ : **a**=Me, **b**=Et, **c**=isopropyl, **d**=cyclohexyl, **e**=benzyl, **f**=OMe, **g**=OEt, **h**=cyclopentoxy, **i**=phenoxy, **j**=*o*-methylphenoxy, **k**=*m*-methylphenoxy, **l**=*p*-methylphenoxy, **m**=*p*-methoxyphenoxy, **n**=SMe, **o**=phenylthio.

Chart 1

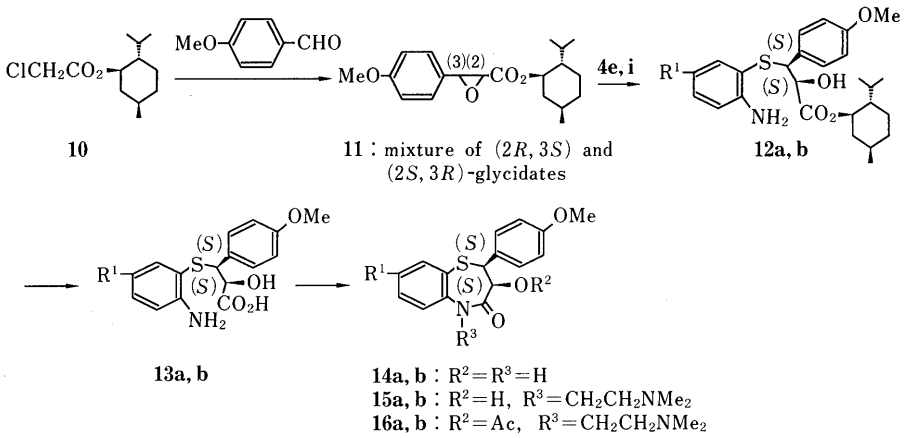



Chart 2

in the similar manners described in the preparation of **9e, i**.

The stereochemistries at the 2 and 3 positions of **16a, b** were assigned to be both *S* configurations by the large positive optical rotations of the amino acids (**13a, b**) and more potent activity[5] of **16b** than its enantiomer.[6] That is, optical rotations of **13a** and **13b**, +305° and +358°, respectively, in a 0.4% solution in ethanol are comparable with one, +348°,[4] of (2*S*,3*S*)-3-(2-aminophenylthio)-2-hydroxy-3-(4-methoxyphenyl)propionic acid. Furthermore, the stereochemistries at the 2 and 3 positions of **1** have been known to remarkably influence the pharmacological activity, *i.e.*, **1** whose configurations at the 2 and 3 positions are both *S* is more potent than its enantiomer.[7]

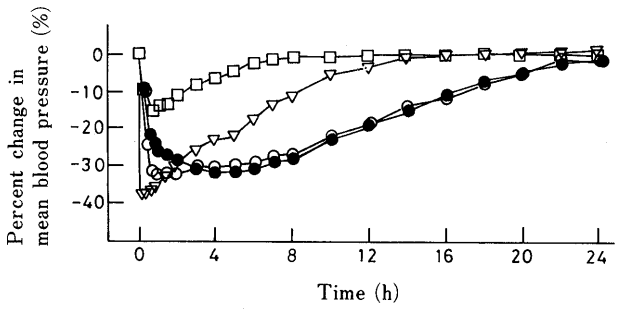



Fig. 1. Antihypertensive Effects of **1**, **2**, **16a** and **16b** in Conscious SHR

**1** (open square), **2** (open triangle), **16a** (closed circle) or **16b** (open circle) was administered by gavage at a dose of 10 mg/kg and mean blood pressure was observed for 24 h ($n$=3—6 for each compound).

## Pharmacological Results and Discussion

Antihypertensive effects of racemic benzothiazepines (**9a—o**) and optically active ones (**16a, b**) were evaluated on SHR. At first the racemates (**9a—o**) were intravenously administered at a dose of 0.1 mg/kg on SHR and their antihypertensive activities were estimated by the potency ratios to racemic diltiazem [(±)-**1**] and duration times ($T_{1/2}$) for a 50% reduction of the maximal antihypertensive effect. The results are shown in Table VI.

The compounds (**9a—c**) which have the alkyl groups at the 8 position showed more long-lasting activity than (±)-**1** and (±)-**2**. The isopropyl derivative (**9c**) showed the longest duration in **9a—o**. In contrast to the alkyl groups, the cyclohexyl derivative (**9d**) had weak activity with short duration. The benzyl derivative (**9e**) was more effective than (±)-**1** for a long period ($T_{1/2}$=8.1 min).

Similar results were obtained in the alkoxy and phenoxy series. Antihypertensive effects were prolonged by alkoxylation (**9f, g**) or phenoxylation (**9i**), while the cyclopentoxy derivative (**9h**) was as weak as **9d**. The interesting results were observed in **9j—m**, that is, antihypertensive activity of **9i** was reduced by methylation or methoxylation on the phenyl group of **9i**. Other interesting results were seen in **9n** and **9o**. The methylthio derivative (**9n**) had the same efficacy as **9a** and **9f** whereas the phenylthio one (**9o**) was less active than the structural analogues (**9e, i**). Highly effective compounds (**9c, e, f, i**) were orally administered on SHR at a dose of 30 mg/kg and their antihypertensive effects were evaluated by maximal reduction of blood pressure ($\Delta BP$) and half duration time ($T_{1/2}$). The results are shown in Table VI. The tested compounds showed potent maximal antihypertensive effects, 31—35%, which were twice as potent as (±)-**1** (16%) and the same as (±)-**2** (34%) and their effects were observed for a long period. Especially the half duration times of **9e** and **9i** were 12 and 11 h, respectively.

Next the optically active compounds (**16a, b**) of **9e** and **9i**, respectively, were evaluated for their antihypertensive efficacy. The results are shown in Table VI and Fig. 1. As expected from **9e** and **9i**, these compounds showed potent and long-acting activity. The maximal antihypertensive effects of **16a** and **16b**, 31 and 32%, respectively, on oral administration were twice as potent as **1** and slightly less potent than **2**. The half duration times of **16a, b** were both over 17 min on intravenous administration. When administered orally at a dose of 10 mg/kg, they had long half duration times, 13.1 and 12.9 h, which were twice as long as **2**.

## Conclusion

We synthesized the racemic benzothiazepines (**9a—o**) and optically active ones (**16a, b**) which have the substituents at the 8 position. From biological investigations the properly bulky and hydrophobic groups such as isopropyl, benzyl and phenoxy groups brought about potent and long-acting antihypertensive activity. Among them the benzyl and

phenoxy derivatives (**16a, b**) showed the most potent and long-lasting effect.

## Experimental

Melting points were determined on a Yanagimoto micromelting point apparatus and were uncorrected. Infrared (IR) spectra were recorded on a JASCO FT/IR-8300 IR spectrophotometer. $^1$H-Nuclear magnetic resonance ($^1$H-NMR) spectra were taken on a Varian EM390 or EM360L spectrometer. Optical rotations were measured on a Perkin-Elmer 241 polarimeter at 20°C. Extraction solvents were dried over anhydrous $MgSO_4$. Flash chromatography was done on Merck Silica gel 60 (230—400 mesh). Thin layer chromatography (TLC) was performed on precoated plates of Merck Silica gel 60 $F_{254}$ and spots were detected by UV irradiation.

**2-Amino-5-benzylbenzenethiol (4e)** General Procedure: A mixture of 2-amino-6-benzylbenzothiazole[8] (15 g, 0.062 mol) and KOH (67.5 g, 1.21 mol) in $H_2O$ (62 ml) and ethylene glycol (20 ml) was refluxed under nitrogen atmosphere for 40 h. After cooling to 30 °C, the reaction mixture was mixed with toluene (200 ml) and then neutralized with AcOH (67.5 ml). The precipitates were filtered off and the organic phase was concentrated to give **4e** (13.3 g) as an oil which was applied to the next reaction without further purification.

The other compounds (**4a—d, f—o**) were prepared in a similar manner from the 2-aminobenzothiazoles which have the substituents $R^2$ at the 6 position.

**Methyl (±)-*threo*-3-(2-Amino-5-benzylphenyl)thio-2-hydroxy-3-(4-methoxyphenyl)propionate (5e)** General Procedure: A solution of methyl *trans*-(±)-3-(4-methoxyphenyl)glycidate (**3**, 13.34 g, 0.064 mol) in toluene (150 ml) was heated at 90 °C for 16 h. After concentration of the reaction solution, the residue was chromatographed on silica gel with EtOAc–benzene (2 : 1) to give crystalline **5e** (11.1 g).

The other compounds (**5a—d, f—o**) were prepared in a similar manner using 2-aminobenzenethiols (**4a—d, f—o**), respectively. Yields, melting points, recrystallization solvents, microanalyses, IR, and $^1$H-NMR data for **5a—o** are given in Table I.

**(±)-*threo*-3-(2-Amino-5-benzylphenyl)thio-2-hydroxy-3-(4-methoxyphenyl)propionic Acid (6e)** General Procedure: A mixture of **5e** (5 g, 11.8 mmol) and NaOH (0.56 g, 14.0 mmol) in MeOH (50 ml) and $H_2O$ (10 ml) was stirred at room temperature for 3 h. The reaction mixture was neutralized with 1 N HCl (14 ml) to afford **6e** (4.6 g) as precipitates.

The other compounds (**6a—d, f—o**) were prepared in a similar procedure from **5a—d** and **5f—o**, respectively. Yields, melting points, recrystallization solvents, microanalyses, IR, and $^1$H-NMR data for **6a—o** are given in Table II.

**(±)-*cis*-2,3-Dihydro-3-hydroxy-2-(4-methoxyphenyl)-8-methyl-1,5-benzothiazepin-4(5*H*)-one (7a)** General Procedure A: To a solution of **6a** (1.55 g, 4.66 mmol) and diphenylphosphoryl azide (1.26 ml, 5.85 mmol) in *N*,*N*-dimethylformamide (DMF) (17 ml) was added *N*-methylmorpholine (1.24 ml, 11.3 mmol) dropwise and the mixture was stirred at room temperature for 16 h. The reaction mixture was partitioned between EtOAc and $H_2O$, the organic phase was separated and concentrated *in vacuo* to give crystalline **7a** (1.04 g).

Compounds (**7a—d, f—h** and **n—o**) were prepared from **6a—d, 6f—h** and **6n—o**, respectively. Yields, melting points, recrystallization solvents, microanalyses, IR, and $^1$H-NMR data for **7a—d, 7f—h** and **7n—o** are given in Table III.

**(±)-*cis*-8-Benzyl-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (7e)** General Procedure B: A suspension of **6e** (4.35 g, 10.6 mmol) in xylene (260 ml) was refluxed for 24 h. The reaction solution was cooled to room temperature to give **7e** (2.45 g) as precipitates.

Compounds (**7i—m**) were similarly prepared from **6i—m**, respectively. Yields, melting points, recrystallization solvents, microanalyses, IR, and

TABLE I. Physical and Spectral Data for α-Hydroxy Esters (**5**)

| Compd. No. | $R^1$ | $R^2$ | Yield (%) | mp (°C) (Recryst. solvent) | Formula | Analysis (%) Calcd (Found) C | H | N | S | IR (C=O) $\nu_{cm^{-1}}^{KBr}$ | $^1$H-NMR δ ($CDCl_3$) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **5a** | Et | Me | 20.7 | 113—114 (Toluene–IPE) | $C_{19}H_{23}NO_4S$ | 63.14 (63.42 | 6.41 6.46 | 3.88 3.99 | 8.87 9.12) | 1713 | 1.14 (3H, t, $J$=6.5 Hz), 2.10 (3H, s), 3.76 (3H, s), 3.80—4.30 (5H, m), 4.46 (2H, br), 6.50—7.00 (5H, m), 7.33 (2H, d, $J$=8.5 Hz) |
| **5b** | Me | Et | 53.5 | 109—111 (IPE) | $C_{19}H_{23}NO_4S$ | 63.14 (63.33 | 6.41 6.42 | 3.88 3.71 | 8.87 8.97) | 1734 | 1.06 (3H, t, $J$=7 Hz), 2.40 (2H, q, $J$=7 Hz), 3.54 (3H, s), 3.75 (3H, s), 4.20 (3H, br), 4.48 (2H, br), 6.55—7.05 (5H, m), 7.34 (2H, d, $J$=9.0 Hz) |
| **5c** | Et | Isopropyl | 35.6 | 104—105 (IPE) | $C_{21}H_{27}NO_4S$ | 64.76 (64.96 | 6.99 6.91 | 3.60 3.59 | 8.23 7.93) | 1730 | 1.06 (6H, d, $J$=7 Hz), 1.16 (3H, t, $J$=4 Hz), 2.66 (1H, quintet, $J$=4 Hz), 3.76 (3H, s), 3.85—4.30 (5H, m), 4.46 (2H, br), 6.60—7.10 (5H, m), 7.33 (2H, d, $J$=8.5 Hz) |
| **5d** | Me | Cyclohexyl | 28.2 | 129—131 (Toluene–IPE) | $C_{23}H_{29}NO_4S$ | 66.48 (66.53 | 7.03 7.17 | 3.37 3.35 | 7.72 7.89) | | 1.10—2.00 (10H, m), 2.00—2.40 (1H, m), 3.56 (3H, s), 3.77 (3H, s), 4.24 (3H, br), 4.52 (2H, br), 6.60—7.10 (5H, m), 7.35 (2H, d, $J$=8.5 Hz) |
| **5e** | Me | Benzyl | 41.0 | 97—98 (Toluene–IPE) | $C_{24}H_{25}NO_4S$ | 68.06 (68.30 | 5.95 6.16 | 3.31 3.18 | 7.57 7.82) | 1733 | 3.51 (3H, s), 3.71 (2H, s), 3.76 (3H, s), 3.80—4.55 (5H, m), 6.50—7.40 (12H, m) |
| **5f** | Me | OMe | 26.0 | 101 (Toluene–IPE) | $C_{18}H_{21}NO_5S$ | 59.49 (59.71 | 5.82 5.89 | 3.85 3.86 | 8.82 8.90) | 1735 | 3.42 (3H, s), 3.66 (3H, s), 4.25 (1H, d, $J$=6 Hz), 4.36 (1H, d, $J$=6 Hz), 5.90 (4H, br s), 6.40—6.90 (5H, m), 7.30 (2H, d, $J$=8.5 Hz) |
| **5g** | Et | OEt | 19.2 | 91—92 (IPE) | $C_{20}H_{25}NO_5S$ | 61.36 (61.42 | 6.44 6.37 | 3.58 3.57 | 8.19 8.29) | 1729 | 1.11 (3H, t, $J$=7 Hz), 1.23 (3H, t, $J$=7 Hz), 3.55—4.30 (7H, m), 3.71 (3H, s), 4.46 (2H, s), 6.60—6.90 (5H, m), 7.32 (2H, d, $J$=8.5 Hz) |
| **5h** | Et | Cyclopentoxy | 29.6 | 81—82 (IPE) | $C_{23}H_{29}NO_5S$ | 64.01 (64.32 | 6.77 6.91 | 3.25 3.19 | 7.43 7.51) | 1729 | 1.20 (3H, t, $J$=6.5 Hz), 1.40—1.95 (8H, m), 3.76 (3H, s), 3.20—4.60 (8H, m), 6.50—6.90 (5H, m), 7.18 (2H, d, $J$=9 Hz) |
| **5i** | Me | Phenoxy | 40.4 | 106—107 (Toluene) | $C_{23}H_{23}NO_5S$ | 64.92 (64.94 | 5.45 5.57 | 3.29 3.20 | 7.54 7.69) | 1744 | 3.62 (3H, s), 3.72 (3H, s), 3.90—4.30 (4H, m), 4.40—4.60 (2H, m), 6.55—7.40 (12H, m) |
| **5j** | Me | *o*-Methyl-phenoxy | 29.5 | 100—101 (IPE) | $C_{24}H_{25}NO_5S$ | 65.58 (65.36 | 5.73 5.76 | 3.19 3.00 | 7.30 7.00) | 1734 | 2.20 (3H, s), 3.67 (3H, s), 3.77 (3H, s), 4.48 (1H, d, $J$=3 Hz), 4.53 (1H, d, $J$=3 Hz), 6.59—7.31 (11H, m) |
| **5k** | Me | *m*-Methyl-phenoxy | 60.0 | 123—125 (IPE) | $C_{24}H_{25}NO_5S$ | 65.58 (65.77 | 5.73 5.74 | 3.19 3.38 | 7.30 7.47) | 1736 | 2.26 (3H, s), 3.63 (3H, s), 3.74 (3H, s), 3.90—4.30 (3H, m), 4.40—4.60 (2H, m), 6.60—7.40 (11H, m) |
| **5l** | Me | *p*-Methyl-phenoxy | 63.4 | 108—109 (IPE) | $C_{24}H_{25}NO_5S$ | 65.58 (65.78 | 5.73 5.87 | 3.19 3.17 | 7.30 7.34) | 1741 | 2.30 (3H, s), 3.66 (3H, s), 3.77 (3H, s), 3.90—4.25 (3H, m), 4.45—4.55 (2H, m), 6.67—7.33 (11H, m) |
| **5m** | Me | *p*-Methoxy-phenoxy | 26.8 | 108—109 | $C_{24}H_{25}NO_6S$ | 63.28 (63.16 | 5.53 5.38 | 3.07 3.98 | 7.04 6.75) | 1736 | 3.60 (3H, s), 3.74 (6H, s), 4.14 (3H, br), 4.48 (2H, br), 6.70—6.90 (9H, m), 7.28 (2H, d, $J$=9 Hz) |
| **5n** | Me | SMe | 30.2 | 117—119 (Toluene–IPE) | $C_{18}H_{21}NO_4S_2$ | 56.97 (57.03 | 5.58 5.64 | 3.69 3.56 | 16.90 16.64) | 1737 | 2.27 (3H, s), 3.60 (3H, s), 3.77 (3H, s), 3.90—4.60 (5H, m), 6.50—7.40 (7H, m) |
| **5o** | Me | Phenylthio | 69.2 | 103—105 (IPE) | $C_{23}H_{23}NO_4S_2$ | 62.56 (62.90 | 5.25 5.38 | 3.17 3.16 | 14.52 14.58) | 1735 | 3.61 (3H, s), 3.72 (3H, s), 4.30—4.60 (3H, m), 6.55—7.40 (12H, m) |

IPE, isopropyl ether.

TABLE II. Physical and Spectral Data for α-Hydroxycarboxy Acids (**6**)

| Compd. No. | Yield (%) | mp (°C) (Recryst. solvent) | Formula | Analysis (%) Calcd (Found) C | H | N | S | IR (C=O) $\nu_{cm^{-1}}^{KBr}$ | $^1$H-NMR δ (DMSO-$d_6$) |
|---|---|---|---|---|---|---|---|---|---|
| **6a** | 96.5 | 189—190 | $C_{17}H_{19}NO_4S$ | 61.24 | 5.74 | 4.20 | 9.62 | 1608 | 1.98 (3H, s), 3.70 (3H, s), 4.25 (1H, d, $J$=6 Hz), 4.32 (1H, d, $J$=6 Hz), 6.54—6.80 (5H, m), 7.17 (2H, d, $J$=8.5 Hz) |
| | | | | (61.16 | 5.75 | 3.96 | 9.69) | | |
| **6b** | 94.9 | 136—139 | $C_{18}H_{21}NO_4S$ | 62.23 | 6.09 | 4.03 | 9.23 | 1609 | 0.93 (3H, t, $J$=7 Hz), 2.26 (2H, q, $J$=7 Hz), 3.69 (3H, s), 4.26 (1H, d, $J$=6 Hz), 4.30 (1H, d, $J$=6 Hz) |
| | | | | (62.53 | 6.22 | 3.89 | 9.07) | | |
| **6c** | >98 | Gum | | Not analysed | | | | | Not observed |
| **6d** | 97.6 | 138—140 | $C_{22}H_{27}NO_4S$ | 65.81 | 6.78 | 3.49 | 7.99 | 1610 | 0.90—1.80 (10H, m), 2.00—2.40 (1H, m), 3.70 (3H, s), 4.36 (1H, d, $J$=6 Hz), 4.48 (1H, d, $J$=6 Hz), 6.70—7.30 (7H, m) |
| | | | | (65.59 | 6.59 | 3.46 | 7.99) | | |
| **6e** | 95.3 | 146—148 | $C_{23}H_{23}NO_4S$ | 67.46 | 5.66 | 3.42 | 7.83 | 1612 | 3.60 (2H, s), 3.72 (3H, s), 4.27 (1H, d, $J$=6 Hz), 4.37 (1H, d, $J$=6 Hz), 6.60—7.35 (12H, m) |
| | | | | (67.85 | 5.79 | 3.39 | 7.94) | | |
| **6f** | 85.5 | 220 | $C_{17}H_{19}NO_5S$ | 58.44 | 5.48 | 4.01 | 9.18 | 1609 | 3.42 (3H, s), 3.66 (3H, s), 4.25 (1H, d, $J$=6 Hz), 4.36 (1H, d, $J$=6 Hz), 6.40—7.30 (7H, m) |
| | | | | (58.43 | 5.27 | 4.01 | 9.38) | | |
| **6g** | 88.5 | 195—197 | $C_{18}H_{21}NO_5S$ | 59.49 | 5.82 | 3.85 | 8.82 | 1609 | 1.17 (3H, t, $J$=7 Hz), 3.67 (2H, q, $J$=7 Hz), 3.70 (3H, s), 4.27 (1H, d, $J$=6 Hz), 4.39 (1H, d, $J$=6 Hz), 6.40—6.85 (5H, m), 7.23 (2H, d, $J$=9 Hz) |
| | | | | (59.53 | 5.82 | 3.86 | 8.88) | | |
| **6h** | 90.5 | 167—169 | $C_{21}H_{25}NO_5S$ | 62.51 | 6.25 | 3.47 | 7.95 | 1608 | 1.30—1.70 (8H, m), 3.68 (3H, s), 4.15—4.45 (3H, m), 6.30—6.90 (5H, m), 7.18 (2H, d, $J$=9 Hz) |
| | | | | (62.51 | 6.13 | 3.53 | 8.11) | | |
| **6i** | 93.1 | 151—153 | $C_{22}H_{21}NO_5S$ | 64.22 | 5.14 | 3.40 | 7.79 | 1609 | 3.66 (3H, s), 4.27 (1H, d, $J$=5.5 Hz), 4.42 (1H, d, $J$=5.5 Hz), 6.60—7.40 (12H, m) |
| | | | | (64.24 | 5.17 | 3.40 | 7.87) | | |
| **6j** | 95.0 | 178—180 (dec.) | $C_{23}H_{23}NO_5S$ | 64.92 | 5.45 | 3.29 | 7.54 | 1598 | 2.09 (3H, s), 3.69 (3H, s), 4.26 (1H, d, $J$=6 Hz), 4.38 (1H, d, $J$=6 Hz), 6.29—7.19 (11H, m) |
| | | | | (65.06 | 5.59 | 3.12 | 7.49) | | |
| **6k** | 91.0 | 171—173 | $C_{23}H_{23}NO_5S$ | 64.92 | 5.45 | 3.29 | 7.54 | 1608 | 2.22 (3H, s), 3.77 (3H, s), 4.27 (1H, d, $J$=6 Hz), 4.43 (1H, d, $J$=6 Hz), 6.50—7.30 (11H, m) |
| | | | | (65.03 | 5.61 | 3.35 | 7.74) | | |
| **6l** | 90.2 | 164—166 (AcOEt) | $C_{23}H_{23}NO_5S$ | 64.92 | 5.45 | 3.29 | 7.54 | 1609 | 2.24 (3H, s), 3.69 (3H, s), 4.27 (1H, d, $J$=6 Hz), 4.40 (1H, d, $J$=6 Hz), 6.45—7.16 (11H, m) |
| | | | | (65.17 | 5.54 | 3.12 | 7.42) | | |
| **6m** | 88.5 | 171—172 (AcOEt) | $C_{23}H_{23}NO_6S$ | 62.57 | 5.25 | 3.17 | 7.26 | 1609 | 3.72 (6H, s), 4.26 (1H, d, $J$=6 Hz), 4.39 (1H, d, $J$=6 Hz), 6.40—7.25 (11H, m) |
| | | | | (62.30 | 5.21 | 3.15 | 7.06) | | |
| **6n** | 86.8 | 189—190 (AcOEt) | $C_{17}H_{19}NO_4S_2$ | 55.87 | 5.24 | 3.83 | 17.55 | 1607 | 2.14 (3H, s), 3.70 (3H, s), 4.25 (1H, d, $J$=6 Hz), 4.34 (1H, d, $J$=6 Hz), 6.60 (2H, d, $J$=6 Hz), 6.75—7.25 (5H, m) |
| | | | | (55.93 | 5.30 | 3.87 | 18.08) | | |
| **6o** | 96.0 | 134—137 | $C_{22}H_{21}NO_4S_2$ | 61.81 | 4.95 | 3.28 | 15.00 | 1607 | 3.73 (3H, s), 4.25 (1H, d, $J$=6 Hz), 4.38 (1H, d, $J$=6 Hz), 6.60—7.25 (12H, m) |
| | | | | (61.90 | 5.14 | 3.22 | 15.26) | | |

TABLE III. Physical and Spectral Data for 1,5-Benzothiazepines (**7**)

| Compd. No. | Procedure[a] | Yield (%) | mp (°C) (Recryst. solvent) | Formula | Analysis (%) Calcd (Found) C | H | N | S | IR (C=O) $\nu_{cm^{-1}}^{KBr}$ | $^1$H-NMR δ |
|---|---|---|---|---|---|---|---|---|---|---|
| **7a** | A | 70.8 | 225—228 (AcOEt) | $C_{17}H_{17}NO_3S$ | 64.74 | 5.43 | 4.44 | 10.17 | 1683 1640 | (DMSO-$d_6$) 2.30 (3H, s), 3.76 (3H, s), 4.28 (1H, d, $J$=7 Hz), 4.58 (1H, |
| | | | | | (64.82 | 5.59 | 4.44 | 10.33) | 1609 | d, $J$=7 Hz), 5.02 (1H, d, $J$=7 Hz), 6.86—7.41 (7H, m) |
| **7b** | A | 60.2 | 229—231 (AcOEt) | $C_{18}H_{19}NO_3S$ | 65.63 | 5.81 | 4.25 | 9.73 | 1670 1607 | ($CDCl_3$) 1.23 (3H, t, $J$=7 Hz), 2.64 (2H, q, $J$=7 Hz), 3.15 (1H, br d, |
| | | | | | (65.72 | 5.92 | 4.26 | 9.69) | | $J$=8 Hz), 3.73 (3H, s), 4.48 (1H, dd, $J$=7, 8 Hz), 5.08 (1H, d, $J$=7 Hz), 6.70—7.60 (7H, m) |
| **7c** | A | 63.0 | 244—246 (AcOEt) | $C_{19}H_{21}NO_3S$ | 66.45 | 6.16 | 4.08 | 9.34 | 1666 1609 | (DMSO-$d_6$) 1.21 (6H, d, $J$=7.5 Hz), 2.89 (1H, quintet, $J$=7.5 Hz), |
| | | | | | (66.43 | 6.08 | 4.06 | 9.13) | | 3.75 (3H, s), 4.15—4.65 (2H, m), 5.03 (1H, d, $J$=7 Hz), 6.80—7.50 (7H, m) |
| **7d** | A | 66.9 | 215—218 (AcOEt) | $C_{22}H_{25}NO_3S$ | 68.90 | 6.57 | 3.65 | 8.36 | 1674 | (DMSO-$d_6$) 1.00—2.00 (10H, m), 2.30—2.60 (1H, m), 3.76 (3H, s), |
| | | | | | (69.09 | 6.70 | 3.65 | 8.34) | 1609 (sh) | 4.10—4.70 (2H, m), 5.03 (1H, d, $J$=7 Hz), 6.80—7.50 (7H, m) |
| **7e** | B | 59.0 | 175—177 (AcOEt) | $C_{23}H_{21}NO_3S$ | 70.56 | 5.41 | 3.58 | 8.19 | 1683 | ($CDCl_3$) 2.50 (1H, br), 3.76 (3H, s), 3.97 (2H, s), 4.46 (1H, d, |
| | | | | | (70.57 | 5.43 | 3.57 | 8.11) | | $J$=7 Hz), 5.05 (1H, d, $J$=7 Hz), 6.77—7.57 (12H, m) |
| **7f** | A | 76.6 | 207—208 (AcOEt) | $C_{17}H_{17}NO_4S$ | 61.62 | 5.17 | 4.23 | 9.68 | 1676 1636 | ($CDCl_3$–DMSO-$d_6$) 3.76 (6H, s), 4.03 (1H, d, $J$=8 Hz), 4.36 (1H, dd, |
| | | | | | (61.43 | 5.21 | 4.20 | 9.94) | 1612 | $J$=7, 8 Hz), 5.04 (1H, d, $J$=7 Hz), 6.80—7.50 (7H, m) |
| **7g** | A | 80.9 | 187—190 (AcOEt) | $C_{18}H_{19}NO_4S$ | 62.59 | 5.54 | 4.06 | 9.28 | 1674 | ($CDCl_3$–DMSO-$d_6$) 1.40 (3H, t, $J$=7 Hz), 3.60 (1H, d, $J$=8 Hz), 3.80 |
| | | | | | (62.69 | 5.70 | 3.82 | 9.37) | | (3H, s), 4.04 (2H, q, $J$=7 Hz), 4.37 (1H, dd, $J$=7, 8 Hz), 5.03 (1H, d, $J$=7 Hz), 6.75—7.50 (7H, m) |
| **7h** | A | 73.1 | 188—190 (AcOEt) | $C_{21}H_{23}NO_4S$ | 65.43 | 6.01 | 3.63 | 8.32 | 1683 | ($CDCl_3$–DMSO-$d_6$) 1.50—2.00 (8H, m), 3.44 (1H, d, $J$=8 Hz), 4.38 |
| | | | | | (65.47 | 6.05 | 3.60 | 8.32) | | (1H, dd, $J$=7, 8 Hz), 4.76 (1H, m), 5.02 (1H, d, $J$=7 Hz), 6.75—7.50 (7H, m) |
| **7i** | B | 75.9 | 218—220 (AcOEt) | $C_{22}H_{19}NO_4S$ | 67.16 | 4.87 | 3.56 | 8.15 | 1687 1605 | (DMSO-$d_6$) 3.79 (3H, s), 3.80 (1H, d, $J$=7 Hz), 4.41 (1H, t, $J$=7 Hz), |
| | | | | | (67.28 | 4.94 | 3.61 | 8.18) | | 5.01 (1H, d, $J$=7 Hz), 6.60—7.10 (12H, m) |
| **7j** | B | 95.1 | 251—253 (dec.) (AcOEt) | $C_{23}H_{21}NO_4S$ | 67.79 | 5.19 | 3.44 | 7.87 | 1684 1642 | (DMSO-$d_6$) 2.18 (3H, s), 3.75 (3H, s), 4.33 (1H, dd, $J$=6.5, 7.0 Hz), |
| | | | | | (67.97 | 5.37 | 3.27 | 7.57) | 1608 | 4.66 (1H, d, $J$=6.5 Hz), 5.04 (1H, d, $J$=7 Hz), 6.89—7.39 (11H, m) |
| **7k** | B | 85.7 | 208—210 (AcOEt) | $C_{23}H_{21}NO_4S$ | 67.79 | 5.19 | 3.44 | 7.87 | 1685 | (DMSO-$d_6$) 2.30 (3H, s), 3.75 (3H, s), 4.30—4.50 (2H, m), 5.04 (1H, |
| | | | | | (67.98 | 5.50 | 3.61 | 8.12) | | d, $J$=7 Hz), 6.70—7.50 (11H, m) |
| **7l** | B | 95.3 | 258—261 (dec.) (Dioxane) | $C_{23}H_{21}NO_4S$ | 67.79 | 5.19 | 3.44 | 7.87 | 1683 | (DMSO-$d_6$) 2.30 (3H, s), 3.75 (3H, s), 4.34 (1H, dd, $J$=6.5, 7 Hz), |
| | | | | | (68.07 | 5.34 | 3.25 | 7.63) | | 4.68 (1H, d, $J$=6.5 Hz), 5.04 (1H, d, $J$=7 Hz), 6.86—7.40 (11H, m) |
| **7m** | B | 89.6 | 216—219 (AcOEt) | $C_{23}H_{21}NO_5S$ | 65.23 | 5.00 | 3.31 | 7.57 | 1685 1639 | (DMSO-$d_6$) 3.76 (6H, s), 3.85 (1H, d, $J$=8 Hz), 4.37 (1H, dd, $J$=7, |
| | | | | | (65.03 | 4.84 | 3.28 | 7.68) | 1608 | 8 Hz), 5.00 (1H, d, $J$=7 Hz), 6.75—7.50 (11H, m) |
| **7n** | A | 47.3 | 188—191 (AcOEt) | $C_{17}H_{17}NO_3S_2$ | 58.77 | 4.93 | 4.03 | 18.46 | 1680 | (DMSO-$d_6$) 2.48 (3H, s), 3.76 (3H, s), 4.20—4.50 (2H, m), 5.03 (1H, |
| | | | | | (58.51 | 4.96 | 3.93 | 18.22) | | d, $J$=7 Hz), 6.86 (2H, d, $J$=8.5 Hz), 7.10—7.50 (5H, m) |
| **7o** | A | 8.8 | 199—201 (AcOEt) | $C_{22}H_{19}NO_3S_2$ | 64.52 | 4.68 | 3.42 | 15.66 | 1685 1639 | (DMSO-$d_6$) 3.79 (3H, s), 4.37 (1H, t, $J$=7 Hz), 4.77 (1H, d, $J$=7 Hz), |
| | | | | | (64.72 | 4.76 | 3.42 | 15.80) | | 5.08 (1H, d, $J$=7 Hz), 6.85—7.55 (12H, m) |

*a*) A: Diphenylphosphoryl azide was used as the condensation reagent. B: Refluxing in xylene. See Experimental section.

TABLE IV. Physical and Spectral Data for 1,5-Benzothiazepine Derivatives (**8**)

| Compd. No. | Yield (%) | mp (°C) (Recryst. solvent) | Formula | Analysis (%) Calcd (Found) C | H | N | S | IR (C=O) $\nu_{cm^{-1}}^{KBr}$ | $^1$H-NMR $\delta$ |
|---|---|---|---|---|---|---|---|---|---|
| **8a** | 96.5 | 162—164 (AcOEt) | $C_{21}H_{26}N_2O_3S$ | 65.26 (65.26 | 6.78 6.74 | 7.25 7.14 | 8.30 8.28) | 1659 1600 | ($CDCl_3$) 2.24 (6H, s), 2.35 (3H, s), 2.35—3.00 (2H, m), 3.35—3.95 (1H, m), 3.79 (3H, s), 4.20—4.80 (2H, m), 4.88 (1H, d, $J$=7.5 Hz), 6.91 (2H, d, $J$=9 Hz), 7.30—7.60 (5H, m) |
| **8b** | 97.0 | 144—146 (AcOEt) | $C_{22}H_{28}N_2O_3S$ | 65.97 (66.02 | 7.05 7.12 | 6.99 6.97 | 8.01 8.01) | 1657 1609 | ($CDCl_3$) 1.26 (3H, t, $J$=7 Hz), 2.26 (6H, s), 2.30—3.00 (2H, m), 2.68 (2H, q, $J$=7 Hz), 3.40—3.95 (1H, m), 3.80 (3H, s), 4.20—4.75 (2H, m), 4.91 (1H, d, $J$=7.5 Hz), 6.90 (2H, d, $J$=9 Hz), 7.30—7.60 (5H, m) |
| **8c** | >98 | 116—118 (AcOEt) | $C_{23}H_{30}N_2O_3S$ | 66.64 (66.49 | 7.29 7.30 | 6.76 6.74 | 7.73 7.73) | 1661 1608 | ($CDCl_3$) 1.25 (6H, d, $J$=6.5 Hz), 2.22 (6H, s), 2.05—3.10 (2H, m), 3.10 (1H, br), 3.35—3.90 (1H, m), 3.73 (3H, s), 4.26 (1H, d, $J$=7.5 Hz), 4.17—4.70 (1H, m), 4.87 (1H, m), 6.85 (2H, d, $J$=7.5 Hz), 7.30—7.60 (5H, m) |
| **8d** | >98 | 122—125 (AcOEt) | $C_{26}H_{34}N_2O_3S$ | 68.69 (68.86 | 7.54 7.54 | 6.16 6.21 | 7.05 7.16) | 1661 1600 | ($CDCl_3$) 1.10—2.10 (10H, m), 2.20 (6H, s), 2.10—2.85 (3H, m), 2.97 (1H, br), 3.40—3.90 (1H, m), 3.73 (3H, s), 4.15—4.60 (2H, m), 4.85 (1H, d, $J$=7 Hz), 6.70—7.60 (7H, m) |
| **8e** | 96.5 | 112—115 (AcOEt–IPE) | $C_{27}H_{30}N_2O_3S$ | 70.10 (70.29 | 6.54 6.61 | 6.06 5.99 | 6.93 7.05) | 1660 1607 | ($CDCl_3$) 2.24 (6H, s), 2.30—3.10 (3H, m), 3.40—4.00 (1H, m), 3.76 (3H, s), 3.95 (2H, s), 4.20—4.70 (2H, m), 4.86 (1H, d, $J$=7 Hz), 6.86 (2H, d, $J$=9 Hz), 7.20—7.60 (10H, m) |
| **8f** | >98 | 157—159 (AcOEt) | $C_{21}H_{26}N_2O_4S$ | 62.66 (62.58 | 6.51 6.55 | 6.96 6.97 | 7.97 8.04) | 1653 1608 | ($CDCl_3$–DMSO-$d_6$) 2.24 (6H, s), 2.10—2.90 (2H, m), 3.28 (1H, br), 3.40—3.90 (1H, m), 4.05—4.60 (2H, m), 4.84 (1H, d, $J$=7 Hz), 6.75—7.55 (7H, m) |
| **8g** | >98 | 130—132 (AcOEt) | $C_{22}H_{28}N_2O_4S$ | 63.44 (63.72 | 6.78 6.74 | 6.73 6.70 | 7.70 7.85) | 1656 1600 | ($CDCl_3$) 1.42 (3H, t, $J$=7 Hz), 2.25 (6H, s), 2.30—3.00 (2H, m), 3.40—3.90 (1H, m), 3.80 (3H, s), 4.06 (2H, q, $J$=7 Hz), 4.25—4.65 (2H, m), 4.90 (1H, d, $J$=7.5 Hz), 6.80—7.55 (7H, m) |
| **8h** | >98 | 101—103 (AcOEt) | $C_{25}H_{32}N_2O_4S$ | 65.76 (65.54 | 7.06 7.04 | 6.14 6.06 | 7.02 7.09) | 1666 | ($CDCl_3$) 1.50—2.10 (8H, m), 2.28 (6H, s), 2.20—2.30 (2H, m), 3.35—3.85 (1H, m), 3.79 (3H, s), 4.15—4.80 (2H, m), 4.87 (1H, d, $J$=8 Hz), 6.80—7.50 (7H, m) |
| **8i**[a] | >98 | 155—158 (EtOH) (HCl salt) | $C_{26}H_{29}ClN_2O_4S \cdot H_2O$ | 60.16 (59.88 | 6.02 5.82 | 5.40 5.23 | 6.18 6.18) | 1649 1609 (sh) | (DMSO-$d_6$) 2.82 (6H, s), 3.00—3.90 (2H, m), 3.74 (3H, s), 3.90—4.70 (2H, m), 4.32 (1H, d, $J$=8 Hz), 4.92 (1H, d, $J$=8 Hz), 6.86 (2H, d, $J$=8.5 Hz), 7.00—7.75 (10H, m) |
| **8j** | 63.8 | 117—119 (IPE) | $C_{27}H_{30}N_2O_4S$ | 67.76 (67.64 | 6.32 6.53 | 5.85 5.85 | 6.70 6.77) | 1662 | ($CDCl_3$) 2.24 (3H, s), 2.28 (6H, s), 2.43—2.53 (1H, m), 2.66—2.76 (1H, m), 2.87 (1H, d, $J$=10 Hz), 3.61—3.71 (1H, m), 3.81 (3H, s), 4.31—4.48 (2H, m), 4.88 (1H, d, $J$=7 Hz), 6.85—7.44 (11H, m) |
| **8k** | 97.0 | Oil | $C_{27}H_{30}N_2O_4S$ | Not analysed | | | | 1662[b] | ($CDCl_3$) 2.26 (6H, s), 2.33 (3H, s), 2.10—2.90 (2H, m), 2.99 (1H, s), 3.35—3.90 (1H, m), 3.77 (3H, s), 4.20—4.70 (1H, m), 4.35 (1H, d, $J$=7 Hz), 4.86 (1H, d, $J$=7 Hz), 6.80—7.50 (11H, m) |
| **8l** | 79.2 | 113—114 (IPE) | $C_{27}H_{30}N_2O_4S$ | 67.76 (67.95 | 6.32 6.41 | 5.85 5.59 | 6.70 6.44) | 1668 | ($CDCl_3$) 2.29 (6H, s), 2.37 (3H, s), 2.43—2.53 (1H, m), 2.66—2.76 (1H, m), 2.87 (1H, d, $J$=10 Hz), 3.62—3.71 (1H, m), 3.81 (3H, m), 4.31—4.49 (2H, m), 4.88 (1H, d, $J$=7.5 Hz), 6.85—7.43 (11H, m) |
| **8m** | 91.7 | Oil | $C_{27}H_{30}N_2O_5S$ | Not analysed | | | | 1663 1608[b] | ($CDCl_3$) 2.24 (6H, s), 2.10—3.00 (2H, m), 2.85 (1H, br), 3.40—3.95 (1H, m), 3.77 (3H, s), 3.79 (3H, s), 4.05—4.70 (1H, m), 4.32 (1H, d, $J$=8 Hz), 4.86 (1H, d, $J$=8 Hz), 6.80—7.55 (11H, m) |
| **8n** | 91.5 | 155—157 (AcOEt–IPE) | $C_{21}H_{26}N_2O_3S_2 \cdot 1/4AcOEt$ | 59.97 (60.16 | 6.41 6.13 | 6.36 6.67 | 14.55 14.00) | 1659 | ($CDCl_3$) 2.26 (3H, s), 2.50 (3H, s), 2.30—2.90 (2H, m), 3.45—3.90 (1H, m), 3.80 (3H, s), 4.20—4.60 (3H, m), 4.92 (1H, d, $J$=7.5 Hz), 6.91 (2H, d, $J$=8.5 Hz), 7.30—7.60 (5H, m) |
| **8o**[c] | 32.8 | 223—225 (EtOH) | $C_{26}H_{29}ClN_2O_3S_2$ | 60.39 (60.24 | 5.65 5.55 | 5.42 5.40 | 12.40 12.54) | 1663 1608 | (DMSO-$d_6$) 2.82 (6H, s), 3.00—3.60 (2H, s), 3.78 (3H, s), 3.90—4.65 (3H, m), 4.95 (1H, d, $J$=8 Hz), 6.91 (2H, d, $J$=8 Hz), 7.30—7.70 (10H, m) |

IPE, isopropyl ether. *a*) Analytical sample was obtained as the hydrochloride salt: Cl; Calcd 6.83% (Found 6.83%). *b*) Liq. film. *c*) Oil. The analytical sample was obtained as the hydrochloride salt: Cl; Calcd 6.82% (Found 6.92%).

$^1$H-NMR data for **7e** and **7i—m** are given in Table III.

**(±)-*cis*-8-Benzyl-2,3-dihydro-5-[2-(dimethylamino)ethyl]-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (8e)** General Procedure: A mixture of **7e** (0.80 g, 2.04 mmol), $Me_2NCH_2CH_2Cl \cdot HCl$ (0.59 g, 4.10 mmol) and $K_2CO_3$ (0.85 g, 6.15 mmol) in acetone (45 ml) and $H_2O$ (0.45 ml) was stirred under reflux for 16 h. After removal of the solvent by evaporation, the residue was partitioned between EtOAc and $H_2O$, the organic phase was separated and concentrated *in vacuo*. The residue was subjected to flash chromatography with MeOH–$CH_2Cl_2$ (1 : 9) to afford crystalline **8e** (0.91 g).

The other compounds (**8a—d** and **8f—o**) were prepared in the similar procedure from **7a—d** and **7f—o**, respectively. Yields, melting points, recrystallization solvents, microanalyses, IR, and $^1$H-NMR data for **8a—o** are given in Table IV.

**(±)-*cis*-3-Acetoxy-8-benzyl-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (9e)** General Procedure: A solution of **8e** (0.578 g, 1.25 mmol) in $Ac_2O$ (5 ml) and pyridine (7 ml) was kept at room temperature for 16 h. The reaction solution was concentrated and the residual solvent was removed by co-distillation with toluene *in vacuo*. The residue was chromatographed on silica gel with MeOH–$CH_2Cl_2$ (1 : 9) to give **9e** (0.60 g) as a syrup. To a solution of **9e** (0.60 g, 1.19 mmol) in EtOAc (6 ml) was added 4 N HCl in EtOAc (0.6 ml). The solvent was distilled off *in vacuo* and the viscous residue was triturated in EtOAc to give the HCl salt of **9e** (0.60 g).

The other compounds (**9a—d, f—o**) were similarly prepared from **8a—d** and **8f—o**, respectively. Yields, melting points, recrystallization solvents, microanalyses, IR, and $^1$H-NMR data for the HCl salts of **9a—o** are given in Table V.

**Mixture of *l*-Menthyl (2*R*,3*S*) and (2*S*,3*R*)-3-(4-Methoxyphenyl)glycidates (11)**[4] To a slurry of 55% NaH in mineral oil (14.5 g, 0.332 mol) in tetrahydrofuran (500 ml) was added *l*-menthyl chloroacetate (51.9 g, 0.223 mol) and the mixture was stirred at room temperature for 15 min and then *p*-anisaldehyde (29.8 ml, 0.245 mol) was added. After stirring at 30 °C for 5 h, aqueous $(NH_4)_2SO_4$ (200 ml) was added under 10 °C and the precipitates were filtered off. The organic phase was separated and concentrated *in vacuo* to give **11** (79.6 g, quantitative) as a syrup which was subjected to the next step without further purification. NMR spectrum showed that **11** was the mixture of the diastereoisomers, (2*S*,3*R*) and (2*R*,3*S*)-glycidates. IR (film): 1730 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 0.75, 0.77 (6H, d, $J$=6 Hz), 0.80—2.20 (9H, m), 0.93, 0.95 (3H, d, $J$=6 Hz), 3.46 (1H, d, $J$=2 Hz), 3.79 (3H, s), 4.00 (1H, d, $J$=2 Hz), 4.60—5.05 (1H, m), 6.88 (2H, d, $J$=8.5 Hz), 7.23 (2H, d, $J$=8.5 Hz).

***l*-Menthyl (2*S*,3*S*)-3-(2-Amino-5-benzylphenyl)thio-2-hydroxy-3-(4-methoxyphenyl)propionate (12a)** A solution of **4e** (21.1 g, 0.098 mol) and **11** (32.5 g, 0.098 mol) in toluene (320 ml) was heated at 90 °C for 16 h and then cooled in an ice bath to afford **12a** (15.9 g, 30.0%) as crystals which were collected by filtration. The filtrate was concentrated and the residue was chromatographed on silica gel with $CH_2Cl_2$–hexane–EtOAc (12 : 7 : 1)

TABLE V. Physical and Spectral Data for HCl Salts of 1,5-Benzothiazepines (**9**)

| Compd. No. | Yield (%) | mp (°C) (Recryst. solvent) | Formula | Analysis (%) Calcd (Found) C | H | N | S | Cl | IR (C=O) $\nu_{cm^{-1}}^{KBr}$ | $^1$H-NMR $\delta$ (DMSO-$d_6$) |
|---|---|---|---|---|---|---|---|---|---|---|
| **9a** | >98 | 184—187 (EtOH) | $C_{23}H_{29}ClN_2O_4S \cdot 1/2H_2O$ | 58.27 (58.15 | 6.38 6.29 | 5.91 5.83 | 6.76 6.65 | 7.48 7.49) | 1739 1680 | 1.86 (3H, s), 2.40 (3H, s), 2.81 (6H, s), 2.90—3.80 (2H, m), 3.81 (3H, s), 3.90—4.65 (2H, m), 5.04 (1H, d, $J$=7 Hz), 5.17 (1H, d, $J$=7 Hz), 6.95 (2H, d, $J$=9 Hz), 7.35—7.70 (5H, m) |
| **9b** | >98 | 202—205 (EtOH) | $C_{24}H_{31}ClN_2O_4S \cdot 1/2H_2O$ | 59.06 (59.29 | 6.61 6.48 | 5.74 5.72 | 6.57 6.73 | 7.27 7.17) | 1741 1682 | 1.26 (3H, t, $J$=7 Hz), 1.84 (3H, s), 2.69 (2H, q, $J$=7 Hz), 2.80 (6H, s), 2.90—3.70 (2H, m), 3.80 (3H, s), 3.90—4.70 (2H, m), 5.02 (1H, d, $J$=7.5 Hz), 5.17 (1H, d, $J$=7.5 Hz), 6.95 (2H, d, $J$=9 Hz), 7.35—7.70 (5H, m) |
| **9c** | >98 | 195—196 (EtOH) | $C_{25}H_{33}ClN_2O_5S$ | 60.90 (60.60 | 6.75 6.81 | 5.68 5.69 | 6.50 6.38 | 7.19 7.10) | 1740 1683 | 1.28 (6H, d, $J$=7 Hz), 1.84 (3H, s), 2.82 (6H, s), 2.70—3.70 (3H, m), 3.80 (3H, s), 3.90—4.70 (2H, m), 5.02 (1H, d, $J$=7 Hz), 5.18 (1H, d, $J$=7 Hz), 6.95 (2H, d, $J$=9 Hz), 7.35—7.75 (5H, m) |
| **9d** | >98 | 234—236 (EtOH) | $C_{28}H_{37}ClN_2O_4S \cdot 1/2H_2O$ | 62.03 (62.53 | 7.06 6.76 | 5.17 5.14 | 5.92 5.64 | 6.54 6.57) | 1747 1671 | 1.10—2.00 (10H, m), 1.83 (3H, s), 2.40—2.80 (1H, m), 2.80 (6H, s), 2.90—3.70 (2H, m), 3.80 (3H, s), 3.90—4.60 (2H, m), 4.99 (1H, d, $J$=7.5 Hz), 5.17 (1H, d, $J$=7.5 Hz), 6.95 (2H, d, $J$=9 Hz), 7.35—7.70 (5H, m) |
| **9e** | 95.1 | 201—204 (EtOH) | $C_{29}H_{33}ClN_2O_4S$ | 64.37 (64.29 | 6.15 6.19 | 5.18 5.11 | 5.92 5.79 | 6.55 6.48) | 1739 1681 | 1.84 (3H, s), 2.80 (6H, s), 3.00—3.65 (2H, m), 3.79 (3H, s), 3.90—4.65 (2H, m), 4.03 (2H, s), 5.00 (1H, d, $J$=7 Hz), 5.17 (1H, d, $J$=7 Hz), 6.93 (2H, d, $J$=9 Hz), 7.25—7.75 (10H, m) |
| **9f** | 80.6 | 194—197 (EtOH) | $C_{23}H_{29}ClN_2O_5S$ | 56.37 (56.32 | 6.17 6.31 | 5.72 5.42 | 6.54 6.27 | 7.24 6.81) | 1738 1679 | 1.86 (3H, s), 2.81 (6H, s), 2.90—3.65 (2H, m), 3.80 (3H, s), 3.88 (3H, s), 3.80—4.70 (2H, m), 5.05 (1H, d, $J$=8 Hz), 5.18 (1H, d, $J$=8 Hz), 6.95 (2H, d, $J$=9 Hz), 7.15—7.75 (5H, m) |
| **9g** | >98 | 189—191 (AcOEt–EtOH) | $C_{24}H_{31}ClN_2O_5S$ | 58.32 (57.95 | 6.31 6.51 | 5.66 5.49 | 6.48 6.46 | 7.16 7.46) | 1740 1682 | 1.38 (3H, t, $J$=6.5 Hz), 1.84 (3H, s), 2.80 (6H, s), 2.90—3.70 (2H, m), 3.81 (3H, s), 4.13 (2H, q, $J$=6.5 Hz), 3.90—4.70 (2H, m), 5.04 (1H, d, $J$=7.5 Hz), 5.17 (1H, d, $J$=7.5 Hz), 6.96 (2H, d, $J$=9 Hz), 7.10—7.70 (5H, m) |
| **9h** | 96.7 | 216—218 (EtOH) | $C_{27}H_{35}ClN_2O_5S$ | 60.60 (60.09 | 6.59 6.62 | 5.24 5.07 | 5.99 5.69 | 6.63 6.48) | 1746 1672 | 1.50—2.20 (8H, m), 1.85 (3H, s), 2.80 (6H, s), 2.80—3.70 (2H, m), 3.80 (3H, s), 3.80—4.70 (2H, m), 4.80—5.05 (1H, m), 5.04 (1H, d, $J$=7.5 Hz), 5.18 (1H, d, $J$=7.5 Hz), 6.95 (2H, d, $J$=9 Hz), 7.10—7.70 (5H, m) |
| **9i** | >98 | 212—214 (EtOH) | $C_{28}H_{31}ClN_2O_5S$ | 61.93 (61.57 | 5.75 5.76 | 5.16 5.06 | 5.90 5.83 | 6.53 6.57) | 1748 1671 | 1.87 (3H, s), 2.84 (6H, s), 2.65—3.70 (2H, m), 3.82 (3H, s), 3.90—4.70 (2H, m), 5.10 (1H, d, $J$=7 Hz), 5.23 (1H, d, $J$=7 Hz), 6.90—7.78 (12H, m) |
| **9j**[a] | 96.2 | 161—162 (AcOEt–EtOH) | $C_{33}H_{36}N_2O_9S$ | 62.25 (62.23 | 5.70 5.77 | 4.40 4.36 | 5.04 5.16) | | 1744 1675 | 1.84 (3H, s), 2.20 (3H, s), 2.80 (3H, s), 3.06—3.42 (2H, m), 3.77 (3H, s), 3.91—4.01 (1H, m), 4.33—4.41 (1H, m), 5.05 (1H, d, $J$=7.5 Hz), 5.17 (1H, d, $J$=7.5 Hz), 6.03 (2H, s), 6.81—7.69 (11H, m) |
| **9k** | >98 | 197—200 (AcOEt) | $C_{29}H_{33}ClN_2O_5S \cdot 1/2H_2O$ | 61.52 (61.72 | 6.05 6.03 | 4.95 4.96 | 5.66 5.43 | 6.26 6.31) | 1747 1669 | 1.84 (3H, s), 2.34 (3H, s), 2.82 (6H, s), 3.00—3.80 (3H, m), 4.00—4.60 (1H, m), 5.06 (1H, d, $J$=7.5 Hz), 5.18 (1H, d, $J$=7.5 Hz), 6.90—7.80 (11H, m) |
| **9l**[a] | 94.6 | 178—179 (AcOEt–EtOH) | $C_{33}H_{36}N_2O_9S$ | 62.25 (62.34 | 5.70 5.87 | 4.40 4.36 | 5.04 5.04) | | 1737 1678 | 1.84 (3H, s), 2.33 (3H, s), 2.81 (6H, s), 3.07—3.44 (2H, m), 3.77 (3H, s), 3.92—4.03 (1H, m), 4.34—4.43 (1H, m), 5.06 (1H, d, $J$=8 Hz), 5.17 (1H, d, $J$=8 Hz), 6.03 (2H, s), 6.87—7.69 (11H, m) |
| **9m** | >98 | 187—189 (AcOEt) | $C_{29}H_{33}ClN_2O_6S \cdot 1/2H_2O$ | 59.83 (60.04 | 5.71 5.80 | 4.81 4.73 | 5.51 5.53 | 6.09 6.23) | 1746 1678 | 1.85 (3H, s), 2.80 (6H, s), 2.70—3.65 (2H, m), 3.80 (3H, s), 3.70—4.70 (2H, m), 5.05 (1H, d, $J$=8 Hz), 5.18 (1H, d, $J$=8 Hz), 6.90—7.80 (11H, m) |
| **9n** | 98.6 | 185—187 (EtOH) | $C_{23}H_{29}ClN_2O_4S_2 \cdot H_2O$ | 53.63 (53.76 | 6.07 6.07 | 5.44 5.33 | 12.45 12.62 | 6.88 6.87) | 1735 1680 | 1.84 (3H, s), 2.56 (3H, s), 2.80 (6H, s), 3.00—3.50 (2H, m), 3.78 (3H, s), 3.80—4.70 (2H, m), 5.03 (1H, d, $J$=7.5 Hz), 5.16 (1H, d, $J$=7.5 Hz), 6.96 (2H, d, $J$=9 Hz), 7.33—7.72 (5H, m) |
| **9o** | >98 | 113—116 (IPE) | $C_{28}H_{31}ClN_2O_4S_2 \cdot 1/2H_2O$ | 59.19 (59.19 | 5.68 5.86 | 4.93 4.87 | 11.29 11.00 | 6.25 6.22) | 1745 1681 | 1.84 (3H, s), 2.80 (6H, s), 3.00—3.60 (2H, m), 3.79 (3H, s), 3.90—4.70 (2H, m), 5.04 (1H, d, $J$=7 Hz), 5.20 (1H, d, $J$=7 Hz), 6.96 (2H, d, $J$=8.5 Hz), 7.28—7.70 (10H, m) |

*a*) Maleate. IPE, isopropyl ether.

to give further **12a** (2.9 g, 5.4%). mp 157—159 °C (toluene), $[\alpha]_D$ +179° ($c$=1, DMF). IR (KBr): 1718 (C=O) cm$^{-1}$. $^1$H-NMR [$CDCl_3$–$D_2O$ (trace)] $\delta$: 0.60—2.10 (18H, m), 3.67 (2H, s), 3.78 (3H, s), 4.34 (1H, d, $J$=5 Hz), 4.50—5.00 (1H, m), 4.51 (1H, d, $J$=5 Hz), 6.63—7.40 (12H, m). *Anal.* Calcd for $C_{33}H_{41}NO_4S$: C, 72.36; H, 7.54; N, 2.56; S, 5.85. Found: C, 72.25; H, 7.47; N, 2.74; S, 5.91.

Compound **12b** was prepared in a similar manner. Yield 35.0%. mp 144—146 °C (toluene). $[\alpha]_D$ +212.3° ($c$=1, DMF). IR (KBr): 1718 (C=O) cm$^{-1}$. $^1$H-NMR [$CDCl_3$–$D_2O$ (trace)] $\delta$: 0.5—2.2 (18H, m), 3.72 (3H, s), 4.38 (1H, d, $J$=5 Hz), 4.50—5.00 (1H, m), 4.52 (1H, d, $J$=5 Hz), 6.52—7.41 (12H, m). *Anal.* Calcd for $C_{32}H_{39}NO_5S$: C, 69.92; H, 7.15; N, 2.55; S, 5.83. Found: C, 70.19; H, 7.32; N, 2.55; S, 6.09.

**(2*S*,3*S*)-3-(2-Amino-5-benzylphenyl)thio-2-hydroxy-3-(4-methoxyphenyl)propionic Acid (13a)** A mixture of **12a** (17.2 g, 31.3 mmol) and 85% KOH (6.21 g, 94.1 mmol) in EtOH (65 ml) and $H_2O$ (20 ml) was stirred at 60 °C for 2 h and then EtOH was evaporated *in vacuo*. The residue was dissolved in water and the aqueous phase was washed with $Et_2O$. The aqueous phase was mixed with EtOAc and adjusted to pH 3 with 3 N HCl. The EtOAc phase was separated and concentrated *in vacuo* to give a viscous syrup which was crystallized in $Et_2O$ by standing overnight. Filtration gave **13a** (8.96 g, 69.7%). mp 155—158 °C (EtOAc). $[\alpha]_D$ +305° ($c$=0.4, EtOH). IR (KBr): 1609 (C=O) cm$^{-1}$. $^1$H-NMR was same as one of **6e**. *Anal.* Calcd for $C_{23}H_{23}NO_4S$: C, 67.46; H, 5.66; N, 3.42; S, 7.83. Found: C, 67.53; H, 5.82; N, 3.43; S, 7.87.

Compound **13b** was prepared in a similar manner. Yield 49.3%. mp 159—161 °C (EtOAc). $[\alpha]_D$ +358° ($c$=0.4, EtOH). IR (KBr): 1610 (C=O) cm$^{-1}$. $^1$H-NMR was the same as that of **6i**. *Anal.* Calcd for $C_{22}H_{21}NO_5S$: C, 64.22; H, 5.14; N, 3.40; S, 7.79. Found: C, 64.22; H, 5.29; N, 3.41; S, 7.92.

**(2*S*,3*S*)-8-Benzyl-2,3-dihydro-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (14a)** In a similar manner as described in the preparation of **7e**, **13a** was converted to **14a**. Yield 90.3%. mp 200—202 °C (dec.) (EtOAc). $[\alpha]_D$ +110.0° ($c$=1, DMF). IR (KBr): 1682 (C=O) cm$^{-1}$. $^1$H-NMR was the same as that of **7e**. *Anal.* Calcd for $C_{23}H_{21}NO_5S$: C, 70.56; H, 5.41; N, 3.58; S, 8.19. Found: C, 70.67; H, 5.35; N, 3.69; S, 7.99.

Compound **14b** was prepared in a similar manner. Yield 93.1%. mp 189—190 °C (EtOAc). $[\alpha]_D$ +99.0° ($c$=1, DMF). IR (KBr): 1680 (C=O) cm$^{-1}$. $^1$H-NMR was the same as that of **7i**. *Anal.* Calcd for $C_{22}H_{19}NO_4S$:

TABLE VI. Antihypertensive Activity on SHR

| Compd. | i.v. Administration[a] | | *p.o.* Administration | | |
|---|---|---|---|---|---|
| | Potency ratio[b] | Half duration time $T_{1/2}$ (min) | Dose (mg/kg) | $\Delta BP_{max}$ (%) | Half duration time $T_{1/2}$ (h) |
| (±)-**1** | 1.0 | 0.9 | 30 | 16 | 3.9 |
| (±)-**2**[c] | 1.0 | 1.7 | 30 | 34 | 6.3 |
| **9a** | 0.7 | 3.0 | | | |
| **9b** | 0.8 | 2.2 | | | |
| **9c** | 0.7 | >11 | 30 | 31 | 8.6 |
| **9d** | 0.4 | 0.4 | | | |
| **9e** | 1.4 | 8.1 | 30 | 34 | 12.0 |
| **9f** | 0.8 | 5.2 | 30 | 35 | 5.8 |
| **9g** | 0.8 | 1.7 | | | |
| **9h** | 0.4 | 0.4 | | | |
| **9i** | 1.0 | 8.8 | 30 | 33 | 11.0 |
| **9j** | 0.6 | 0.4 | | | |
| **9k** | 0.5 | 1.2 | | | |
| **9l** | 0.8 | 0.8 | | | |
| **9m** | 0.4 | 0.8 | | | |
| **9n** | 0.8 | 3.4 | | | |
| **9o** | 0.4 | 0.3 | | | |
| **1** | 1.1 | 1.2 | 10 | 14 | 0.8 |
| **2**[c] | 1.3 | 4.1 | 10 | 37 | 5.6 |
| **16a** | 1.5 | >17 | 10 | 31 | 13.1 |
| **16b** | 0.9 | >17 | 10 | 32 | 12.9 |

*a*) 0.1 mg/kg dose. *b*) (±)-**1** = 1.0. *c*) Ref. 2*e*.

C, 67.16; H, 4.87; N, 3.56; S, 8.15. Found: C, 66.95; H, 5.10; N, 3.57; S, 8.26.

**(2*S*,3*S*)-8-Benzyl-2,3-dihydro-5-[2-(dimethylamino)ethyl]-3-hydroxy-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (15a)** In a similar manner as described in the preparation of **8e**, **14a** was treated with $Me_2NCH_2CH_2Cl \cdot HCl$ to give **15a** as an amorphous powder. Yield 95.0%. $[\alpha]_D$ +109.5° ($c$ = 1, DMF). IR (KBr): 1662, 1610 (C=O) $cm^{-1}$. $^1$H-NMR was same as one of **8e**. *Anal.* Calcd for $C_{27}H_{30}N_2O_3S$: C, 70.10; H, 6.54; N, 6.06; S, 6.93. Found: C, 69.76; H, 6.62; N, 5.98; S, 6.94.

Compound **15b** was prepared in a similar manner. Yield 90.6%. Amorphous powder. $[\alpha]_D$ +105.5° ($c$ = 1, DMF). IR (KBr): 1662, 1608 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 2.30 (6H, s), 2.40—2.90 (3H, m), 3.53—3.85 (1H, m), 3.82 (3H, s), 4.28—4.62 (2H, m), 4.88 (1H, d, $J$ = 7.5 Hz), 6.83—7.52 (12H, m). *Anal.* Calcd for $C_{26}H_{28}N_2O_4S$: C, 67.22; H, 6.08; N, 6.03; S, 6.90. Found: C, 66.98; H, 6.39; N, 5.85; S, 6.73.

**(2*S*,3*S*)-3-Acetoxy-8-benzyl-2,3-dihydro-5-[2-(dimethylamino)ethyl]-2-(4-methoxyphenyl)-1,5-benzothiazepin-4(5*H*)-one (16a)** In a similar manner as described in the preparation of **9e**, **15a** was acetylated with acetic anhydride to give **16a**. Yield 97.3%. mp 113—114 °C (hexane). $[\alpha]_D$ +84.0° ($c$ = 1, DMF). IR (KBr): 1742, 1675 (C=O) $cm^{-1}$. $^1$H-NMR ($CDCl_3$) $\delta$: 1.88 (3H, s), 2.26 (6H, s), 2.30—3.10 (2H, m), 3.40—4.00 (1H, m), 3.80 (3H, s), 3.98 (2H, s), 4.05—4.75 (1H, m), 4.97 (1H, d, $J$ = 8 Hz), 5.18 (1H, d, $J$ = 8 Hz), 6.90 (2H, d, $J$ = 7 Hz), 7.30 (5H, s), 7.46 (2H, d, $J$ = 7 Hz). *Anal.* Calcd for $C_{29}H_{32}N_2O_4S$: C, 69.02; H, 6.39; N, 5.55; S, 6.35. Found: C, 69.14; H, 6.56; N, 5.53; S, 6.48.

The HCl salt of **16a**: Yield 97.5%. mp 132—134 °C (EtOH). $[\alpha]_D$ +81.0° ($c$ = 1, DMF). IR (KBr): 1747, 1680 (C=O) $cm^{-1}$. $^1$H-NMR was same as one of **9e**. *Anal.* Calcd for $C_{29}H_{33}ClN_2O_4S \cdot 1/2H_2O$: C, 63.32; H, 6.23, Cl, 6.44; N, 5.09; S, 5.83. Found: C, 63.13; H, 6.59; Cl, 6.45; N, 4.72; S, 5.93.

Compound **16b** was prepared in a similar manner. The analytical sample was obtained as the L-tartarate. Yield 96.4%. mp 152—155 °C. $[\alpha]_D$ +64.8° ($c$ = 1, DMF). IR (KBr): 1742, 1680 (C=O) $cm^{-1}$. $^1$H-NMR (DMSO-$d_6$) $\delta$: 1.84 (3H, s), 2.20—3.00 (2H, m), 2.36 (6H, s), 3.50—4.00 (1H, m), 3.79 (3H, s), 4.05—4.55 (1H, m), 4.20 (2H, s), 5.06 (1H, d, $J$ = 8 Hz), 5.18 (1H, d, $J$ = 8 Hz), 6.85—7.77 (12H, m). *Anal.* Calcd for $C_{32}H_{36}N_2O_{11}S$: C, 58.52; H, 5.53; N, 4.27; S, 4.88. Found; C, 58.36; H, 5.56; N, 4.19; S, 4.90.

**Antihypertensive Activity** SHR of 23 weeks-old were anesthetized with sodium pentobarbital (30 mg/kg i.p.) and two polyethylene cannulae were inserted: one in the abdominal aorta through the left femoral artery for measuring arterial pressure and the other in the right femoral vein for intravenous injection of the tested compounds. The other ends of the cannulae were led under the skin and exteriorized at the back of the neck. Two days after the surgery, SHR with the indwelling cannulae were connected to a blood pressure measuring system. The system, consisting of a pressure transducer and a computerized recording system, allowed us to measure the mean blood pressure of 10 rats for more than 24 h. After the mean blood pressure (MBP) and heart rate (HR) were monitered for 1.5 h of a run-in period, a test compound was administered intravenously *via* the venous cannula or orally by gavage. MBP and HR were measured for another 24 h following intravenous or oral administration of the compound. The test drugs were dissolved in a 50% aqueous dimethyl sulfoxide solution and administered at a dose shown in Table VI.

## References and Notes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3) Compounds (**4a—o**) were prepared by alkaline hydrolysis of 2-aminobenzothiazoles which have the substituents $R^2$ at the 6 position. See Experimental Section.
4) Fuji Electrochemical Co., Japan. Patent 268663 (1986) [*Chem. Abstr.*, **108**, 131290*r* (1988)].
5) Antihypertensive activity of **16b** was 4.5 times as potent as its enantiomer when intravenously administered on SHR.
6) The enantiomer of **16b** was prepared from the enantiomer of **11**, *d*-menthyl *trans*-3-(4-methoxyphenyl)glycidate by the same procedure as the preparation of **16b**.
7) *a*) T. Nagao, M. Sato, H. Nakajima and A. Kiyomoto, *Jpn., J. Pharmacol.*, **22**, 1 (1972); *b*) M. Sato, T. Nagao, I. Yamaguchi, H. Nakajima and A. Kiyomoto, *Arzneim.-Forsch.*, **21**, 1337 (1971).
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