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Synthesis and Angiotensin Converting Enzyme-Inhibitory Activity of 1,5-Benzothiazepine and 1,5-Benzoxazepine Derivatives. III[1)]

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A series of (*R*)-3-amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic acids (**8**) and (*S*)-3-amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetic acids (**9**) having an (*S*)-1-carboxy-ω-(4-piperidyl)alkyl group on the amino group at the 3-position was prepared as part of a search for long-acting inhibitors of the angiotensin converting enzyme (ACE). The length (*n*) of the carbon chain in the piperidylalkyl moiety was varied from two to six in order to determine the optimal structure. The most prolonged activity *in vivo* was observed with (*R*)-3-[(*S*)-1-carboxy-5-(4-piperidyl)pentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic acid (**8c**: CV-5975) on i.v. and *p.o.* administrations.

Keywords——angiotensin converting enzyme inhibitor; ACE inhibitor; 1,5-benzothiazepine derivative; 1,5-benzoxazepine derivative; α-amino-ω-(4-piperidyl)alkanoic acid derivative; activity duration; CV-5975

In recent years much attention has been directed to developing orally active angiotensin coverting enzyme (ACE) inhibitors. Their therapeutic utility in treating hypertension and congestive heart failure in humans has been established with captopril (**1**)[2)] and enalapril (**2a**).[3)] Since these inhibitors involve a natural amino acid, L-proline, at the C-terminal, most attempts to find new inhibitors have been focused on derivatives of L-proline and proline analogues.[4)] We tried instead to replace the L-proline moiety with a synthetic amino acid[5)] in order to search for new inhibitors with better pharmacological properties. This led to the discovery of the 2-indanylglycine derivative (**3a**: CV-3317),[5c,d)] which is currently undergoing clinical trials. A study of the stable conformation of CV-3317–COOH (**3b**) prompted us to design conformationally restricted analogues,[6)] 1,5-benzothiazepine (**4**)[7)] and 1,5-benzoxazepine (**5**) derivatives. In previous reports,[1,8)] we described the synthesis and the potent ACE-inhibitory activities of the series of new inhibitors (**4**—**7**).

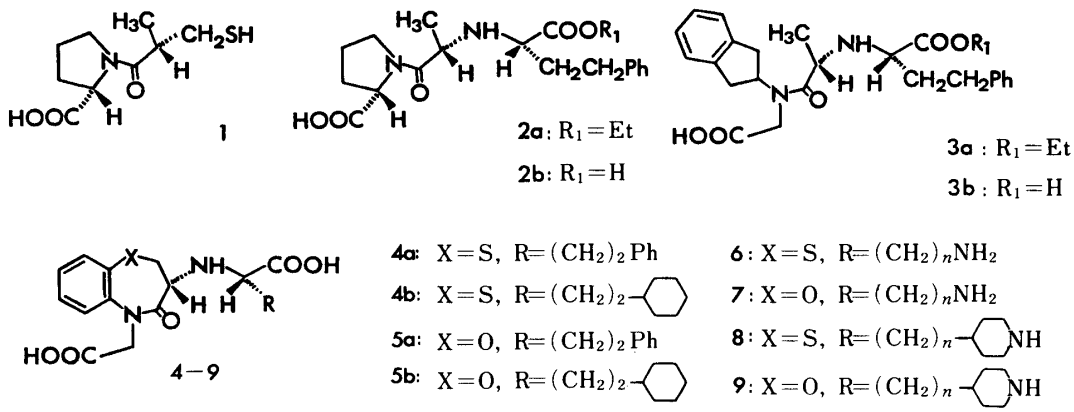
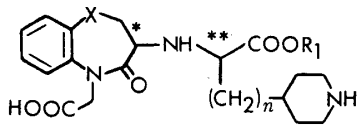


Chart 1

TABLE I. 1,5-Benzothiazepine (**8**, **16**, **20**, **30**, **31**) and 1,5-Benzoxazepine (**9**, **18**, **19**, **21**) Derivatives[a)]



No.	X	R_1	*n*	Configuration of C*	Configuration of C**	Yield (%)	Formula	*Anal.* (%) Calcd (Found) C	H	N	MS or SIMS (*m/z*)	$[\alpha]_D^{deg.}$ Temp. °C (*c*) Solvent	ACE-inhibitory activity *in vitro* (%)[b)] 10^{-8}	10^{-7}	10^{-6} (M)
16a	S	Et	2	*R*	*S*	86[c]	$C_{22}H_{31}N_3O_5S \cdot 2HBr \cdot 2H_2O$	40.81 (40.47	5.76 5.32	6.49 6.28)	449 (M^+)	−86 22 (0.6) MeOH	—	— (10^{-5}; 84)	24
17a	S	Et	2	*R*	*R*	85	$C_{22}H_{31}N_3O_5S \cdot 2HBr \cdot H_2O$	41.98 (41.43	5.60 5.39	6.68 6.30)	449 (M^+)	−106 22 (0.6) MeOH	—	—	7
8a	S	H	2	*R*	*S*	59[d)]	$C_{20}H_{27}N_3O_5S \cdot H_2O$	54.65 (54.05	6.65 6.17	9.56 9.21)	422 (MH^+)	−128 23 (0.1) MeOH	38	91	99
16b	S	Et	3	*R*	*S*	94	$C_{23}H_{33}N_3O_5S \cdot 2HBr \cdot 3/2\,H_2O$	42.34 (42.35	5.87 6.03	6.44 6.12)	463 (M^+)	−89 23 (0.4) MeOH	—	— (10^{-5}; 89)	27
17b	S	Et	3	*R*	*R*	99	$C_{23}H_{33}N_3O_5S \cdot 2HBr \cdot 2H_2O$	41.76 (42.07	5.94 6.16	6.35 6.09)	463 (M^+)	−111 23 (0.4) MeOH	—	— (10^{-5}; 8) (10^{-4}; 70)	—
8b	S	H	3	*R*	*S*	83[d)]	$C_{21}H_{29}N_3O_5S \cdot 2H_2O$	53.49 (53.77	7.05 7.11	8.91 8.96)	436 (MH^+)	−117 23 (0.3) MeOH–H_2O	38	92	—

16c	S	Et	4	*R*	*S*	81	$C_{24}H_{35}N_3O_5S \cdot 2HBr \cdot H_2O$	43.85 (43.85	5.98 6.44	6.39 5.99)	477 (M^+)	−89 24.5 (0.5) MeOH	—	— (10^{-5}; 97)	44
17c	S	Et	4	*R*	*R*	68	$C_{24}H_{35}N_3O_5S \cdot 2HBr \cdot H_2O$	43.85 (43.95	5.98 6.29	6.39 6.47)	477 (M^+)	−108 24.5 (0.4) MeOH	—	—	—
8c	S	H	4	*R*	*S*	90[d]	$C_{22}H_{31}N_3O_5S \cdot 2H_2O$	54.42 (54.84	7.27 7.38	8.66 8.61)	450 (MH^+)	−131 24.5 (0.5) MeOH–H_2O	52	98	—
20c	S	H	4	*R*	*R*	53[d]	$C_{22}H_{31}N_3O_5S \cdot 3/2\,H_2O$	55.44 (55.33	7.19 7.06	8.82 8.65)	450 (MH^+)	−149 24 (1) H_2O	20	68	94
30	S	H	4	*S*	*R*	38[e]	$C_{22}H_{31}N_3O_5S$[f]	58.78 (58.34	6.95 6.98	9.35 9.35)	450 (MH^+)	+128 24 (0.3) H_2O	—	19	90
31	S	H	4	*S*	*S*	82[e]	$C_{22}H_{31}N_3O_5S \cdot H_2O$	56.51 (56.66	7.11 7.26	8.99 9.08)	450 (MH^+)	+143 24 (0.7) H_2O	—	15	63
8d	S	H	5	*R*	*S*	65[e]	$C_{23}H_{33}N_3O_5S$	55.29 (55.75	7.47 7.48	8.41 8.35)	464 (MH^+)	−121 26 (0.5) H_2O	53	98	—
20d	S	H	5	*R*	*R*	64[e]	$C_{23}H_{33}N_3O_5S \cdot 3/2\,H_2O$	56.30 (56.66	7.40 7.33	8.57 8.40)	464 (MH^+)	−144 26 (0.5) H_2O	—	76	95
8e	S	H	6	*R*	*S*	49[e]	$C_{24}H_{35}N_3O_5S \cdot 2H_2O$	56.12 (56.28	7.65 7.82	8.18 7.88)	478 (MH^+)	−116 26.5 (0.3) H_2O	51	98	—

TABLE I. (continued)

No.	X	R_1	*n*	Configuration of C*	Configuration of C**	Yield (%)	Formula	*Anal.* (%) Calcd (Found) C	H	N	MS or SIMS (*m/z*)	$[\alpha]_D^{deg.}$ Temp. °C (*c*) Solvent	10^{-8}	(%)[b] 10^{-7}	10^{-6} (M)
18a	O	Et	2	*S*	*S*	90	$C_{22}H_{31}N_3O_6 \cdot 2HCl \cdot H_2O$	50.39 (50.36	6.73 6.68	8.01 7.56)	433 (M^+)	−93 23 (0.5) MeOH	—	10	63
9a	O	H	2	*S*	*S*	63[d]	$C_{20}H_{27}N_3O_6 \cdot 3/2\,H_2O$	55.54 (55.28	6.99 6.31	9.72 9.54)	406 (MH^+)	−132 23 (0.6) MeOH	46	95	99
18b	O	Et	3	*S*	*S*	72	$C_{23}H_{33}N_3O_6 \cdot 2HCl \cdot 2H_2O$	49.64 (49.83	7.06 7.07	7.55 7.29)	477 (M^+)	−93 23 (0.5) MeOH	—	15	74
19b	O	Et	3	*S*	*R*	22	$C_{23}H_{33}N_3O_6 \cdot 2HCl \cdot 2H_2O$	49.64 (49.17	7.06 6.99	7.55 7.52)	447 (M^+)	−121 23 (0.5) MeOH	—	—	29
9b	O	H	3	*S*	*S*	71[d]	$C_{21}H_{29}N_3O_6 \cdot 3/2\,H_2O$	56.49 (56.86	7.22 7.31	9.41 9.41)	420 (MH^+)	−133 23 (0.5) MeOH	51	95	—
9c	O	H	4	*S*	*S*	69[e]	$C_{22}H_{31}N_3O_6 \cdot 3/2\,H_2O$	57.38 (57.01	7.44 7.76	9.13 9.00)	434 (MH^+)	−118 25 (0.4) H_2O	56	99	—
21c	O	H	4	*S*	*R*	64[e]	$C_{22}H_{31}N_3O_6 \cdot 3/2\,H_2O$	57.38 (57.39	7.44 7.62	9.13 9.06)	434 (MH^+)	−149 25 (0.4) H_2O	—	—	—

9d	O	H	5	*S*	*S*	65[e]	$C_{23}H_{33}N_3O_6 \cdot 3/2\,H_2O$	58.21 (58.48	7.65 7.58	8.85 8.74)	448 (MH^+)	−133 26 (0.4) H_2O	61	99	—
21d	O	H	5	*S*	*R*	52[e]	$C_{23}H_{33}N_3O_6 \cdot 3/2\,H_2O$	58.21 (58.31	7.65 7.78	8.85 8.47)	448 (MH^+)	−139 26 (0.5) H_2O	—	—	—
9e	O	H	6	*S*	*S*	61[e]	$C_{24}H_{35}N_3O_6 \cdot 3/2\,H_2O$	59.00 (59.47	7.83 7.33	8.60 8.59)	462 (MH^+)	−108 26.5 (0.4) H_2O	58	99	—
21e	O	H	6	*S*	*R*	41[e]	$C_{24}H_{35}N_3O_6 \cdot 3/2\,H_2O$	59.00 (59.36	7.83 7.51	8.60 8.57)	462 (MH^+)	−119 26.5 (0.4) H_2O	—	—	—
Enalaprilat (**2b**)													62	97	—
CV-3317–COOH (**3b**)													53	87	—
4a													46	91	—
5a													31	91	—
4b													77	96	—
5b													58	96	—
6 ($n=7$)													79	98	—
7 ($n=7$)													84	99	—

a) Each compound was obtained as an amorphous powder. *b*) Each value is the average of the results obtained in two or more experiments. *d*) Method D. *e*) Method E. *f*) Recrystallized from water, mp indefinite (dec.).

Our extensive study on the structure–activity relationships of the series provided some information on the structural requirements of the substituent R for prolonging the *in vivo* ACE-inhibitory activity. Cyclohexylethyl derivatives (**4b**, **5b**) displayed longer-lasting activity than the corresponding phenethyl derivatives (**4a**, **5a**) upon i.v. administration. In the case of ω-aminoalkyl derivatives (**6**, **7**), the duration after i.v. administration depended on the length (*n*) of the carbon chain in the substituent R. It was particularly noted that 8-amino-1-carboxyoctylamino derivatives, **6** ($n=7$) and **7** ($n=7$), possessed long-lasting inhibitory activity in the series not only on i.v. but also oral (*p.o.*) administration to rats.[8]

On the basis of the above findings, we designed the 1-carboxy-ω-(4-piperidyl)alkyl group as a new substituent R. Since the duration of *in vivo* activity was expected to be dependent on the length of the carbon chain in the substituent, the number *n* was varied from 2 to 6 to determine the optimal structure. This report describes the synthesis and ACE-inhibitory activities of (*R*)-3-[(*S*)-1-carboxy-ω-(4-piperidyl)alkyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic acids (**8**), (*S*)-3-[(*S*)-1-carboxy-ω-(4-piperidyl)alkyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetic acids (**9**) and related derivatives.

Chemistry

As illustrated in Chart 2, (*R*)-3-amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic acid *tert*-butyl ester (**10**)[8] was alkylated using sodium cyanoborohydride ($NaBH_3CN$) with ethyl ω-(1-benzyloxycarbonyl-4-piperidyl)-2-oxoalkanoate (**23**, $n=2$—6), or by S_N2 reaction with an α-haloester (**28**) or an α-sulfonyloxy ester (**29**) to yield a diastereomeric mixture of diesters **12** and **13**. The mixture of the diastereomers could be separated by column chromatography on silica gel, giving **12** (lower *Rf*) and **13** (higher *Rf*).[9] The *tert*-butyl (^{t}Bu) and benzyloxycarbonyl (Z) moieties of each diester were simultaneously removed with hydrogen bromide–acetic acid solution (HBr–AcOH) to obtain the monoacids **16** and **17**, respectively. The absolute configuration of the asymmetric center in the ethoxycarbonyl-ω-(4-piperidyl)alkyl moiety of each diastereomer **16** and **17** could be assigned as *S* and *R*, respectively, by comparison of their *in vitro* ACE inhibitory activities (Table I).[10]

The stereochemical assignment was confirmed by X-ray crystallographic analysis (Fig. 1) of (*RS*)-3-[(*SR*)-1-ethoxycarbonyl-5-(4-piperidyl)pentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic acid (racemic **16c**).[11]

Saponification of the monoacid derivatives **16** and **17** provided the corresponding diacids **8** and **20**.[12] The oxazepine congeners **9** were prepared by the same sequence of reactions starting with (*S*)-3-amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetic acid *tert*-butyl ester (**11a**) or benzyl ester (**11b**) *via* the intermediates **14** (lower *Rf*) and **18**. In the case of the benzylester (**14**: $R_2=CH_2Ph$), deprotection was carried out by catalytic hydrogenolysis using palladium–carbon (Pd–C) as a catalyst to obtain the monoacids **18**.

α-Oxoesters **23a**—**e** required for the above synthesis were prepared from the corresponding esters **22a**—**e** by condensation reaction with diethyl oxalate followed by decarboxylation. The carboxylic acid esters **22a**—**e** with different lengths of the carbon chain were synthesized

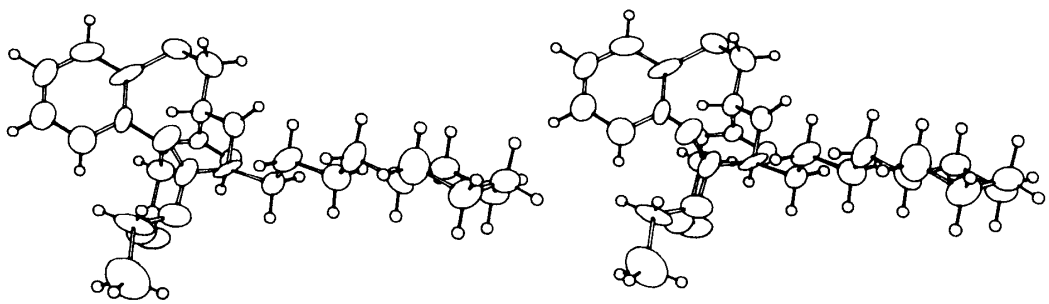


Fig. 1. Stereoscopic Drawing of **16c**

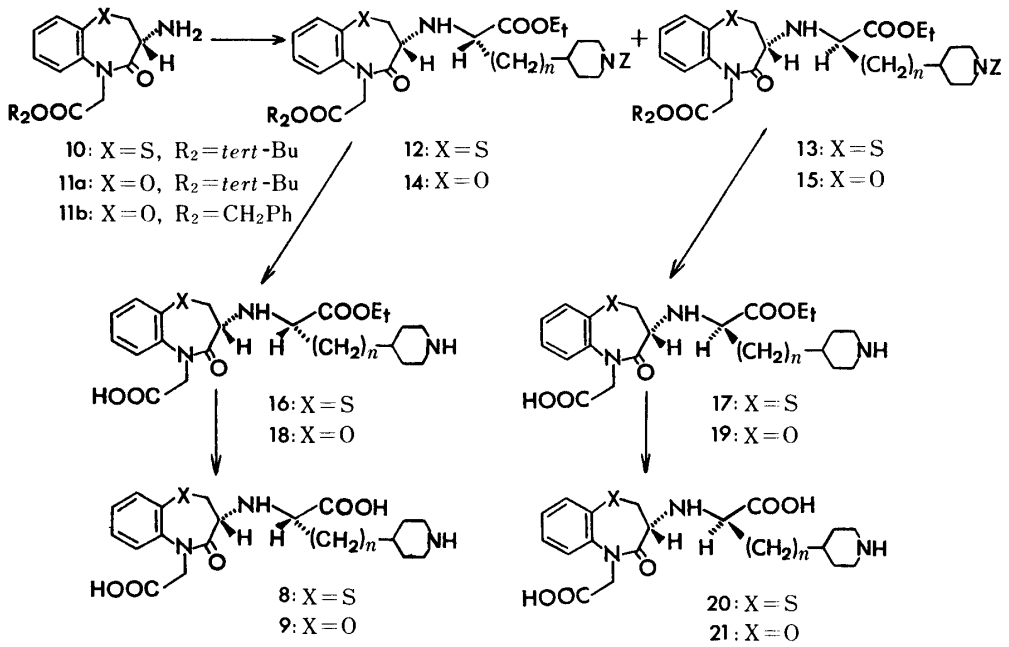


Chart 2

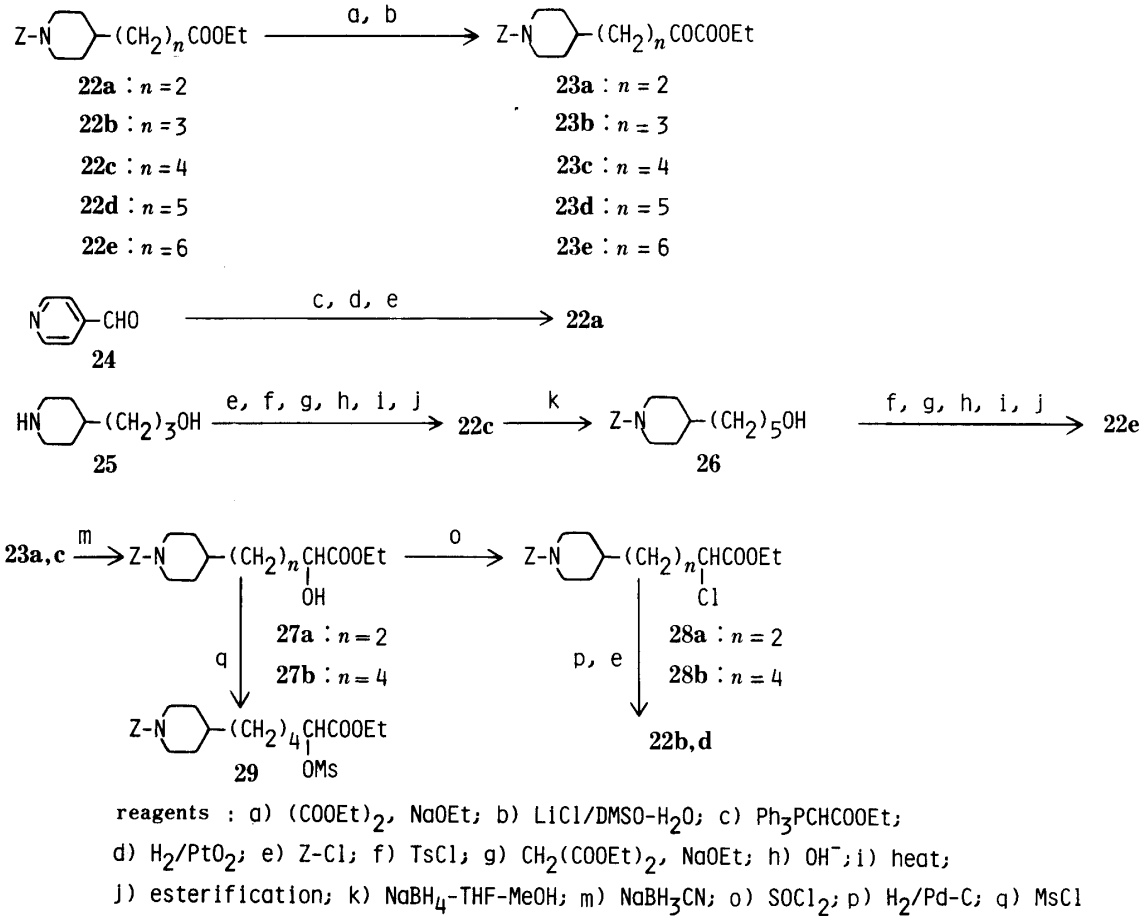


Chart 3

via the various routes shown in Chart 3. Thus, ethyl 3-(1-benzyloxycarbonyl-4-piperidyl)propionate (**22a**) was obtained from isonicotinaldehyde **24** in three steps: Wittig reaction, catalytic hydrogenation and acylation with Z–Cl. Ethyl 5-(1-benzyloxycarbonyl-4-

piperidyl)pentanoate (**22c**) was prepared *via* malonic ester synthesis starting with 3-(4-piperidyl)propanol (**25**).[13] The α-oxoesters **23a** and **23c** prepared from **22a** and **22c**, respectively, were converted to **22b** and **22d** in four steps: reduction with $NaBH_3CN$ to give **27a**, **b**, chlorination with thionyl chloride ($SOCl_2$) to give **28a**, **b**, and catalytic hydrogenolysis followed by acylation with Z–Cl. Ethyl 7-(1-benzyloxycarbonyl-4-piperidyl)heptanoate (**22e**) was obtained by the same procedure as that for **22c** starting with **26**. The α-hydroxyester **27b** was converted to the corresponding sulfonate **29** in a usual manner.

Biological Results and Discussion

The results of *in vitro* ACE-inhibitory activity assay[14] using rabbit lung ACE are listed in Table I. A series of benzothiazepine (**8**) and benzoxazepine (**9**) diacid derivatives prepared as described above showed high *in vitro* activities, comparable to those of enalaprilat (**2b**), CV-3317–COOH (**3b**) and **4**—**7**. Since all of the derivatives (**4**—**9**) including a variety of the substituent R can interact well with ACE, it seems that the S_1 subsite does not require high structural specificity for R.

The active isomers **16**, **18**, **8** and **9** with *S*-configuration of the side chain were about ten times more potent than the corresponding diastereomers **17**, **19**, **20** and **21** with the *R*-configuration. In the case of **8c**, another two stereoisomers **30** and **31** (Table I) which have the *S*-configuration at the 3-position of the benzothiazepine ring were prepared starting with D-cysteine by the same procedure as used for **8c** and **20c**, and were evaluated for *in vitro* activity. They showed only very weak activity (Table I). The importance of the chiral requirement for the activity has been established in many studies on ACE inhibitors.[2-8]

The monoacids **16** and **18** were much less active than the corresponding diacids **8** and **9** *in vitro*, as in the case of the analogous ACE inhibitors (**1**—**7**).

The potent and long-lasting *in vivo* ACE-inhibitory activities of the derivatives (**8**, **9**) in rats upon i.v. administration (0.3 mg/kg)[15] are presented in Table II. In accordance with our expectations, the duration of the activity after i.v. administration showed a clear relationship to the length of the alkylene chain (*n*) as seen in **8a**—**e** and **9a**—**e**. The maximum duration after i.v. administration was observed with 1-carboxy-5-(4-piperidyl)pentylamino derivatives (**8c**, **9c**) of each series of benzothiazepines and benzoxazepines. Especially interesting was the fact that the distance (9—10 Å[16] from a Dreiding model) between the two nitrogen atoms of the piperidylpentylamino moiety is almost equal to that of the aminooctyl moiety in **6** ($n=7$)

TABLE II. Inhibitory Activities toward Angiotensin I-Induced Pressor Response in Rats

No.	% inhibition upon i.v. administration[a] (0.3 mg/kg)									
	1/12	1/6	0.5	1	1.5	2	2.5	3	4	5 (h)
8a	97	100	94	85	74	42	22	9	—	—
8b	100	100	100	90	67	62	50	36	21	—
8c	97	96	99	93	98	90	92	81	61	52
8d	100	100	100	100	95	79	—	63	45	39
8e	100	100	91	79	51	40	37	30	11	16
9a	100	98	97	74	52	26	18	—	—	—
9b	100	100	99	92	71	54	40	26	16	—
9c	100	100	100	95	93	91	79	71	51	38
9d	100	100	100	99	96	78	—	56	38	34
9e	100	100	95	77	43	28	20	—	—	—
Enalaprilat (**2b**)	100	100	92	76	49	23	2	—	—	—

a) Each value is the average of results obtained in two or more experiments.

Table III. Inhibitory Activities of CV-5975 toward Angiotensin I-Induced Pressor Response in Rats

Compound	Dose (mg/kg)	% inhibition upon *p.o.* administration[a] 1/3	1	2	3	5	7	10	24 (h)
CV-5975 (**8c**)									
	3	70	84	90	91	88	84	78	43
	10	100	100	100	100	88	96	96	89
Enalapril (**2a**)									
	3	93	93	93	87	65	37	30	8
	10	93	99	93	91	86	55	62	22

a) Each value is the average of results obtained in two or more experiments.

and **7** ($n=7$) which displayed the greatest duration of activity among the series of aminoalkylamino derivatives (**6**, **7**). This finding indicates that a basic amino group present at the proper position is essential for long-lasting inhibitory activity *in vivo*. Although the role of the nitrogen atom in enhancing the duration is not yet clear, it might be related to the existence of an additional binding site on ACE and/or increased resistance to metabolism and excretion.

On *p.o.* administration tests,[15] (*R*)-3-[(*S*)-1-carboxy-5-(4-piperidyl)pentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic acid (**8c**: CV-5975) exhibited the longest duration not only of all the compounds in this report but also of all the inhibitors prepared by us. The results are shown in Table III and compared with those in the case of enalapril (**2a**). Furthermore, CV-5975 (**8c**) is absorbed in an active form with two free carboxyl groups. As we reported previously,[1] *N*-carboxymethyldipeptide-type ACE inhibitors are absorbed without being converted into the corresponding monoacid prodrug when they contain two basic nitrogen atoms in their molecules, as do **6** and **7**. This trend has also been reported by other research groups.[4d,e,6i,17]

The new ACE inhibitor CV-5975 (**8c**) was confirmed to show potent and long-lasting antihypertensive activities in spontaneously hypertensive rats (SHR) at a dose of 3 mg/kg *p.o.* Details of the ACE inhibitory activity and the antihypertensive activity of CV-5975 (**8c**) in experimental animals will be published elsewhere.[18]

Experimental

All melting points were determined on a Yanagimoto micro melting point apparatus (a hot stage type) and are uncorrected. The infrared (IR) spectra were recorded with Hitachi 260-10 spectrophotometer. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded in the indicated solvents on Varian EM-360, EM-390, XL-100A and JEOL JNM-GX 400FT instruments. Chemical shifts are reported as δ-values relative to tetramethylsilane (TMS) as an internal standard. Mass spectra (MS) were obtained on a JEOL JMS-01SC mass spectrometer. Secondary ion mass spectra (SIMS) were measured with Hitachi M-80A. $[\alpha]_D$ values were determined in the indicated solvents on a JASCO DIP-181 4-4822.

Reactions were run at room temperature unless otherwise noted and followed by thin-layer chromatography (TLC) on Merck Silica gel F_{254} precoated plates. Standard work-up procedures were as follows. The reaction mixture was partitioned between the indicated solvent and water. The organic extract was washed successively with the following aqueous solutions: water, $NaHCO_3$ solution (aq. $NaHCO_3$), NaOH solution (aq. NaOH) and hydrochloric acid (aq. HCl). The extract was dried over $MgSO_4$, filtered and evaporated *in vacuo*. Chromatographic separation of the residue was done on Merck Silica gel 60 with the indicated eluents.

Ethyl 3-(1-Benzyloxycarbonyl-4-piperidyl)propionate (22a)——A mixture of **24** (25 g), $Ph_3PCHCOOEt$ (82 g) and toluene (300 ml) was stirred at 100 °C for 3 h. After cooling of the mixture, the deposited crystals were removed by filtration and the filtrate was concentrated *in vacuo*. A mixture of AcOEt (200 ml) and petroleum ether (200 ml) was added to the residue, and the resulting mixture was extracted with 5% HCl (500 ml). The aqueous solution was

extracted with AcOEt (50 ml). The aqueous layer was neutralized with K_2CO_3 and cooled. The deposited crystals were collected by filtration and dried to give ethyl 3-(4-pyridyl)acrylate (34 g, 82%)[19] as colorless prisms, mp 64—66 °C.

A solution of the above ester (28 g) in AcOH (300 ml) was hydrogenated over PtO_2 (1 g) under atmospheric pressure until the absorption of hydrogen stopped. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in a mixture of $NaHCO_3$ (excess), water (500 ml) and AcOEt (300 ml). Z–Cl (25 ml) was added dropwise and the reaction mixture was worked up (AcOEt, water). The residue was purified by silica gel column chromatography (hexane : AcOEt = 2 : 1) to give **22a** (37 g, 73%) as a colorless liquid. IR ν_{max}^{neat} cm^{-1}: 1730, 1700 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.2 (3H, t, J=7 Hz, CH_3), 1.0—1.9 (7H, m), 2.2—3.1 (4H, m), 4.15 (2H, q, J=7 Hz, OCH_2), 3.9—4.4 (2H, m), 5.1 (2H, s, CH_2OCO), 7.25 (5H, s, phenyl protons).

Ethyl 4-(1-Benzyloxycarbonyl-4-piperidyl)butyrate (22b)——$NaBH_3CN$ (3 g) was added to a mixture of **23a** (17 g), AcOH (4.5 g) and EtOH (300 ml). The resulting mixture was stirred for 3 h, diluted with water (500 ml) and worked up (CH_2Cl_2). The oily residue was purified by silica gel column chromatography (hexane : AcOEt = 2 : 1—1 : 1) to yield ethyl 4-(1-benzyloxycarbonyl-4-piperidyl)-2-hydroxybutyrate (**27a**, 11.5 g, 67%) as a colorless liquid. IR ν_{max}^{neat} cm^{-1}: 3430 (OH); 1730, 1690 (C=O). ^{1}H-NMR ($CDCl_3 + D_2O$) δ: 1.0—2.0 (9H, m), 1.2 (3H, t, J=7 Hz, CH_3), 2.5—3.1 (2H, t, J=12 Hz), 3.9—4.4 (3H, m), 4.25 (2H, q, J=7 Hz, OCH_2), 5.1 (2H, s, CH_2OCO), 7.3 (5H, s, phenyl protons).

$SOCl_2$ (5 ml) was added to a solution of **27a** (11.5 g) and pyridine (12 g) in AcOEt (200 ml). The mixture was heated under reflux for 1 h, cooled, diluted with water and worked up (AcOEt, aq. HCl, water) to give ethyl 4-(1-benzyloxycarbonyl-4-piperidyl)-2-chlorobutyrate (**28a**, 10.5 g, 87%) as a pale yellow oil. IR ν_{max}^{neat} cm^{-1}: 1740, 1690 (C=O). A solution of **28a** (10.5 g) in EtOH (20 ml) was hydrogenated over 10% Pd–C (50% wet, 5 g) under atmospheric pressure. After absorption of hydrogen stopped, the catalyst was removed by filtration, and the filtrate was concentrated *in vacuo* to give an oily residue, which was dissolved in a mixture of AcOEt (200 ml), water (100 ml) and $NaHCO_3$ (6 g). Z–Cl (6 ml) was added dropwise to the solution. After the addition was complete, the mixture was stirred for 1.5 h. Work-up (AcOEt) and purification by silica gel column chromatography (hexane : AcOEt = 3 : 1) gave **22b** (5.3 g, 56%) as a colorless liquid. IR ν_{max}^{neat} cm^{-1}: 1730, 1700 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (3H, t, J=7 Hz, CH_3), 1.0—1.9 (9H, m), 2.1—3.1 (4H, m), 4.15 (2H, q, J=7 Hz, OCH_2), 3.9—4.4 (2H, m), 5.1 (2H, s, CH_2OCO), 7.3 (5H, s, phenyl protons).

Ethyl 5-(1-Benzyloxycarbonyl-4-piperidyl)pentanoate (22c)——Z–Cl (100 g) and a solution of **25** (84 g)[13] in CH_2Cl_2 (100 ml) containing Et_3N (65 g) were added dropwise to a mixture of CH_2Cl_2 (400 ml) and water (40 ml) with stirring over a period of 45 min. After the addition was complete, the mixture was stirred for 1 h and worked up (CH_2Cl_2, water). The low-boiling material (bp 50—60 °C/5 mmHg) was removed by distillation *in vacuo*. 3-(1-Benzyloxycarbonyl-4-piperidyl)propanol (110 g, 68%) was obtained as an oily residue. IR ν_{max}^{neat} cm^{-1}: 3400 (OH), 1680 (C=O). TsCl (100 g) was added to a stirred mixture of this alcohol (110 g) and pyridine (500 ml) at ice-bath temperature over a period of 2 h. After the addition was complete, the resulting mixture was stirred for a further 1 h. Ice water (1000 ml) was added dropwise and then conc. HCl (500 ml) was added dropwise to the mixture at ice-bath temperature. Work-up (AcOEt, aq. HCl, water) and crystallization of the residue from EtOH gave 3-(1-benzyloxycarbonyl-4-piperidyl)propyl tosylate (99 g, 58%) as colorless crystals, mp 59—60 °C. *Anal.* Calcd for $C_{23}H_{29}NO_5S$: C, 64.01; H, 6.77; N, 3.25. Found: C, 64.25; H, 6.78; N, 3.26.

The above tosylate (90.5 g) was added to a stirred mixture of NaOEt solution (prepared from 5.8 g of Na and 300 ml of EtOH) and diethyl malonate (40 g). The resulting mixture was heated under reflux for 2 h, cooled, diluted with water (1 l) and worked up (AcOEt). The oily residue was dissolved in EtOH (200 ml) and a solution of NaOH (34 g) in water (200 ml) was added dropwise with stirring. After the addition was complete, water (300 ml) was added and the mixture was extracted with ether–petroleum ether (1 : 1, 300 ml). The aqueous layer was made acidic with conc. HCl and worked up (AcOEt, water). The oily residue was stirred at 160—170 °C for 45 min to give 5-(1-benzyloxycarbonyl-4-piperidyl)pentanoic acid (50 g, 75%) as an oil. IR ν_{max}^{neat} cm^{-1}: 1730, 1700 (C=O).

A mixture of the above acid (54.8 g), $NaHCO_3$ (29 g), EtI (21 ml) and dimethylformamide (DMF) (150 ml) was heated at 70—80 °C with stirring for 3 h. After the further addition of EtI (10 ml), the mixture was stirred at 90—100 °C for 3 h, cooled, diluted with water (1 l) and worked up (AcOEt, water, aq. HCl, aq. $NaHCO_3$) to give **22c** (58 g, 97%) as a pale yellow oil. IR ν_{max}^{neat} cm^{-1}: 1730, 1700 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.9 (14H, m), 2.1—3.1 (4H, m), 3.9—4.4 (2H, m), 4.15 (2H, q, J=7 Hz, OCH_2), 5.1 (2H, s, CH_2OCO), 7.3 (5H, s, phenyl protons).

Ethyl 6-(1-Benzyloxycarbonyl-4-piperidyl)hexanoate (22d)——The α-oxoester **23c** was converted to **22d** by way of the intermediates **27b** and **28b** in a manner similar to that described for the preparation of **22b**. **27b**: Yield 61%. IR ν_{max}^{neat} cm^{-1}: 3450 (OH); 1730, 1690 (C=O). **28b**: Yield 74%. IR ν_{max}^{neat} cm^{-1}: 1740, 1690 (C=O). **22d**: Yield 84%. IR ν_{max}^{neat} cm^{-1}: 1730, 1690 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 0.9—2.0 (12H, m), 2.1—3.1 (4H, m), 3.9—4.4 (2H, m), 4.1 (2H, q, J=7 Hz, OCH_2), 5.1 (2H, s, CH_2OCO), 7.3 (5H, s, phenyl protons).

5-(1-Benzyloxycarbonyl-4-piperidyl)pentanol (26)——$NaBH_4$ (13.4 g) was added to a solution of **22c** (26.8 g) in tetrahydrofuran (THF) (200 ml), and then MeOH (40 ml) was added dropwise to the stirred solution at 70—80 °C over a period of 1.5 h.[20] After the addition was complete, the mixture was heated under reflux for another 2 h, concentrated *in vacuo*, diluted with water (300 ml) and worked up (AcOEt, aq. HCl, water) to yield **26** (23 g, 98%) as a

colorless liquid. IR ν_{max}^{neat} cm^{-1}: 3400 (OH), 1690 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.9 (13H, m), 2.4—3.0 (3H, m), 3.5—3.8 (2H, CH_2O), 3.9—4.4 (2H, m), 5.1 (2H, s, CH_2OCO), 7.3 (5H, s, phenyl protons).

Ethyl 7-(1-Benzyloxycarbonyl-4-piperidyl)heptanoate (22e)——The alcohol **26** was converted to **22e** (overall yield 34%) in a manner similar to that described for the preparation of **22c** *via* the following intermediates: 5-(1-benzyloxy-4-piperidyl)pentyl tosylate, yield 66%, IR ν_{max}^{neat} cm^{-1}: 1700 (C=O); 7-(1-benzyloxycarbonyl-4-piperidyl)heptanoic acid, yield 72%, IR ν_{max}^{neat} cm^{-1}: 1730, 1710 (C=O). **22e**: IR ν_{max}^{neat} cm^{-1}: 1730, 1700 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.0—1.9 (15H, m), 1.25 (3H, t, J=7 Hz, CH_3), 2.3 (2H, t, J=7 Hz, CH_2), 2.5—3.0 (2H, t, J=13 Hz), 4.1 (2H, q, J=7 Hz, CH_2O), 4.0—4.3 (2H, m), 5.1 (2H, s, CH_2OCO), 7.3 (5H, s, phenyl protons).

Ethyl ω-(1-Benzyloxycarbonyl-4-piperidyl)-2-oxoalkanoate (23a—e)——General Procedure: A mixture of NaOEt solution (prepared from 0.43 g of Na and 10 ml of EtOH), **22** (5 g) and $(COOEt)_2$ (2.75 g) was evaporated at 60—70 °C for 45 min *in vacuo*. After cooling, the resulting viscous material was dissolved in water (200 ml), neutralized with conc. HCl and worked up (AcOEt). The residue was dissolved in a mixture of water (5 ml), dimethylsulfoxide (DMSO) (45 ml) and LiCl (0.73 g). The resulting solution was heated at 140—150 °C for 45 min. After cooling, the solution was worked up (AcOEt, water) to yield **23** as a pale brown liquid.

23a: 83% yield. IR ν_{max}^{neat} cm^{-1}: 1730, 1700 (C=O). MS *m/z*: 347 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.3 (3H, t, J=7 Hz, CH_3), 1:1—1.9 (7H, m), 2.0—3.2 (4H, m), 3.9—4.5 (2H, m), 4.3 (2H, q, J=7 Hz, CH_2O), 5.1 (2H, s, CH_2OCO), 7.25 (5H, s, phenyl protons).

23b: 87% yield. IR ν_{max}^{neat} cm^{-1}: 1730, 1700 (C=O). MS *m/z*: 361 (M^+).

23c: 75% yield. IR ν_{max}^{neat} cm^{-1}: 1730, 1690 (C=O). MS *m/z*: 375 (M^+).

23d: 83% yield. IR ν_{max}^{neat} cm^{-1}: 1720, 1690 (C=O). MS *m/z*: 389 (M^+).

23e: 86% yield. IR ν_{max}^{neat} cm^{-1}: 1730, 1700 (C=O). MS *m/z*: 403 (M^+).

Ethyl 6-(1-Benzyloxycarbonyl-4-piperidyl)-2-mesyloxyhexanoate (29)——Mesyl chloride (0.92 g) was added dropwise to a stirred solution of **27b** (1 g) in pyridine (10 ml) at ice-bath temperature. After being stirred for 1 h, the mixture was further stirred for 30 min at room temperature, and cooled again to ice-bath temperature. After addition of water (1 ml), the mixture was stirred for 30 min, then was stirred at room temperature for 30 min, and worked up (AcOEt, aq. HCl, water, aq. NaOH, water) to give **29** (1.1 g, 91%) as a colorless oil. IR ν_{max}^{neat} cm^{-1}: 1750, 1690 (C=O); 1360 (SO_2). ^{1}H-NMR ($CDCl_3$) δ: 1.3 (3H, t, J=7 Hz, CH_3), 1.0—2.1 (13H, m), 2.4—3.1 (2H, m), 3.15 (3H, s, CH_3SO_2), 4.25 (2H, q, J=7 Hz, OCH_2), 3.9—4.4 (2H, m), 5.0 (1H, t, J=6 Hz, CHOMs), 5.1 (2H, s, CH_2COO), 7.3 (5H, s, phenyl protons).

***tert*-Butyl 3-[ω-(1-Benzyloxycarbonyl-4-piperidyl)-1-ethoxycarbonylalkyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetates (12, 13: Table IV) and Benzyl or *tert*-Butyl 3-[ω-(1-Benzyloxycarbonyl-4-piperidyl)-1-ethoxycarbonylalkyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetates (14, 15: Table IV)**——Method A. General Procedure: A mixture of **10** (6.5 mmol), AcOH (0.43 g), **23** (13 mmol), molecular sieves 3A (10 g) and EtOH (50 ml) was stirred for 1 h, and then a solution of $NaBH_3CN$ (0.9 g) in EtOH (50 ml) was added dropwise to the mixture over a period of 5.5 h. The mixture was allowed to stand overnight, concentrated *in vacuo* and worked up (AcOEt). The residue was dissolved in Et_2O (50 ml) and a solution of $(COOH)_2$ (1 g) in Et_2O (50 ml) was added. The resulting mixture was diluted with petroleum ether (200 ml) and shaken thoroughly. The supernatant layer was removed by decantation and AcOEt (200 ml), water (50 ml) and $NaHCO_3$ (excess) were added to the residue. Work-up (AcOEt) gave an oily residue, which was purified by column chromatography on silica gel (hexane : AcOEt = 2 : 1—4 : 3) to give the (*R*),(*R*)-diastereomer **13** as a colorless oil from the first fraction. From the subsequent fraction, the (*R*),(*S*)-diastereomer **12** was obtained as a colorless oil.

^{1}H-NMR of **13a** ($CDCl_3$) δ: 1.2 (3H, t, J=7 Hz, CH_3), 1.45 (9H, s, ^{t}Bu), 0.9—1.9 (9H, m), 2.4—4.3 (12H, m), 4.8 (1H, d, J=16 Hz, N_5-CHCOO), 5.05 (2H, s, CH_2OCO), 6.7—7.7 (9H, m, phenyl protons).

^{1}H-NMR of **12a** ($CDCl_3$) δ: 1.1 (3H, t, J=7 Hz, CH_3), 1.9 (9H, s, ^{t}Bu), 0.8—1.9 (9H, m), 2.2—4.4 (12H, m), 4.8 (1H, d, J=16 Hz, N_5-CHCOO), 5.05 (2H, s, CH_2OCO), 6.9—7.7 (9H, m, phenyl protons).

In the case of the oxazepines (**14**, **15**), the reaction and purification were carried out similarly, and the (*S*),(*S*)-diastereomer **14** was eluted in the second fraction from silica gel column chromatography.

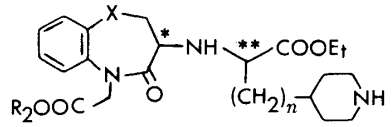
Method B: A mixture of **10** (0.4 g), **28a** (1 g), Et_3N (0.2 g), KI (0.9 g) and CH_3CN (50 ml) was heated under reflux for 3 d. The mixture was evaporated *in vacuo* and the residue was chromatographed on silica gel (hexane : AcOEt = 2 : 1) to provide **13a** (0.15 g) from the first fraction and **12a** (0.25 g) from the second fraction.

Compound **28b** (4 g) was allowed to react with **10** (3 g) similarly to yield **13c** (3.1 g) and **12c** (2.1 g) as colorless oils.

Method C: A mixture of **10** (2.05 g) and **29** (1.5 g) was heated at 90 °C for 24 h. The resulting viscous oil was worked up (AcOEt, water, 5% aq. H_2PO_4, water) to yield a pale yellow oil, which was subjected to silica gel column chromatography (hexane : AcOEt = 2 : 1), giving **13c** (0.7 g) from the first fraction. The (*R*),(*S*)-isomer **12c** (0.55 g) was obtained from the second fraction.

3-[1-Ethoxycarbonyl-ω-(4-piperidyl)alkyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic Acid (16a, b, c and 17a, b, c: Table I)——General Procedure: A 30% HBr–AcOH solution (2 ml) was added to a solution of **12** or **13** (0.6 mmol) in AcOH (2 ml). The resulting mixture was allowed to stand for 1 h and diluted with Et_2O (150 ml). The deposited precipitate was washed with Et_2O and dried to give the corresponding monoacid, **16a**—

TABLE IV. Diester Derivatives (**12**—**15**) of Benzothiazepines and Benzoxazepines



No.	X	R_2	n	Configuration of C*	Configuration of C**	Yield (%)	MS M^+ (m/z)	IR ν_{max}^{neat} cm^{-1} NH	IR ν_{max}^{neat} cm^{-1} C=O
12a	S	^{t}Bu	2	*R*	*S*	31,[a] 30[b]	639	3320	1740, 1700, 1690, 1670
13a	S	^{t}Bu	2	*R*	*R*	14,[a] 18[b]	639	3320	1740, 1700, 1680
12b	S	^{t}Bu	3	*R*	*S*	18[a]	653	3320	1730, 1690
13b	S	^{t}Bu	3	*R*	*R*	9[a]	653	3310	1730, 1680
12c	S	^{t}Bu	4	*R*	*S*	12,[a] 32,[b] 25[c]	667	3320	1740, 1690
13c	S	^{t}Bu	4	*R*	*R*	7,[a] 47,[b] 32[c]	667	3330	1740, 1700
12d	S	^{t}Bu	5	*R*	*S*	16[a]	681	3330	1730, 1690
13d	S	^{t}Bu	5	*R*	*R*	9[a]	681	3320	1730, 1680
12e	S	^{t}Bu	6	*R*	*S*	6.6[a]	695	3320	1730, 1690
14a	O	CH_2Ph	2	*S*	*S*	17[a]	657	3330	1740, 1690, 1680
15a	O	CH_2Ph	2	*S*	*R*	28[a]	657	3330	1740, 1690, 1680
14b	O	CH_2Ph	3	*S*	*S*	16[a]	671	3320	1740, 1690, 1680
15b	O	CH_2Ph	3	*S*	*R*	14[a]	671	3320	1740, 1690, 1680
14c	O	^{t}Bu	4	*S*	*S*	14[a]	651	3330	1740, 1690, 1680
15c	O	^{t}Bu	4	*S*	*R*	22[a]	—	—	— — —
14d	O	^{t}Bu	5	*S*	*S*	9[a]	665	3320	1730, 1680
15d	O	^{t}Bu	5	*S*	*R*	6.4[a]	665	3320	1730, 1680
14e	O	^{t}Bu	6	*S*	*S*	7.5[a]	679	3320	1740, 1690, 1680
15e	O	^{t}Bu	6	*S*	*R*	7.5[a]	679	3320	1740, 1700, 1690

a) Method A. *b*) Method B. *c*) Method C.

c·2HBr or **17a**—**c**·2HBr, as a colorless powder.

^{1}H-NMR of **16a** (DMSO-d_6 + D_2O) δ: 1.15 (3H, t, J=7 Hz, CH_3), 1.0—2.0 (9H, m), 2.6—4.0 (8H, m), 4.15 (2H, q, J=7 Hz, CH_2O), 4.3 (1H, d, 16 Hz, N_5-CHCOO), 4.8 (1H, d, J=16 Hz, N_5-CHCOO), 7.3—7.8 (4H, m, phenyl protons).

3-[1-Ethoxycarbonyl-ω-(4-piperidyl)alkyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetic Acid (18a, b and 19b: Table I)——A solution of **14a**—**b** or **15b** (0.9 mmol) in EtOH (30 ml) was hydrogenated over 10% Pd–C (50% wet, 0.2 g) under atmospheric pressure until the absorption of hydrogen stopped. The catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in Et_2O and treated with 5 N HCl–AcOEt (0.3 ml) to give the corresponding monoacid, **18a**—**b**·2HCl or **19b**·HCl as a colorless powder.

3-[1-Carboxy-ω-(4-piperidyl)alkyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic Acid (8, 20: Table I)——Method D. General Procedures: A mixture of a monoacid **16**·HBr or **17**·HBr (0.7 mmol) and 1 N NaOH (10 ml) was allowed to stand for 30 min, neutralized with AcOH (2 ml) and purified by XAD-2 column chromatography (water : MeOH = 1 : 1). The eluent was concentrated *in vacuo* and lyophilized to yield the corresponding diacid derivative, **8** or **20**, as a colorless powder. In the case of **8c**, crystallization was carried out from water to yield colorless needles, mp indefinite (dec.). IR ν_{max}^{KBr} cm^{-1}: 1670 (C=O); 1635, 1610 (carboxylate). $[\alpha]_D^{24}$ −130° (c=0.5, water). *Anal.* Calcd for $C_{22}H_{31}N_3O_5S$: C, 58.78; H, 6.95; N, 9.35. Found: C, 58.59; H, 6.99; N, 9.37. SIMS m/z: 450 (M^+). ^{1}H-NMR (DMSO-d_6 + DCl + D_2O) δ: 1.16—1.34 (7H, m), 1.39—1.54 (2H, m), 1.74—1.86 (4H, m), 2.81 (2H, t, J=12 Hz), 3.23 (2H, d, J=13 Hz), 3.73 (1H, t, J=6 Hz, C_3-NCHCOO), 3.36 (1H, d, J=12 Hz), 3.85 (1H, dd, J=12, 7 Hz, C_2-H), 4.04 (1H, dd, J=12, 7 Hz, C_3-H), 4.36 (1H, d, J=18 Hz, N_5-CHCOO), 4.74 (1H, d, J=18 Hz, N_5-CHCOO), 7.38 (1H, d, J=8 Hz, phenyl proton), 7.39 (1H, t, J=8 Hz, phenyl proton), 7.61 (1H, t, J=8 Hz, phenyl proton), 7.73 (1H, d, J=8 Hz, phenyl proton).

Method E: A 30% HBr–AcOH solution (2 ml) was added to a solution of a diester, **12** or **13** (1.3 mmol), in AcOH (1 ml). The resulting mixture was allowed to stand for 1.5 h and diluted with Et_2O (200 ml). The supernatant layer was removed by decantation, then the residue was rinsed with Et_2O and dissolved in 1 N NaOH (30 ml). The solution was allowed to stand for 45 min, neutralized with AcOH and subjected to XAD-2 column chromatography (water : MeOH = 1 : 1). The eluate was concentrated *in vacuo* and lyophilized to give the corresponding diacid, **8** or **20**, as a colorless powder.

3-[1-Carboxy-ω-(4-piperidyl)alkyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetic Acid (9, 21: Table I)——Saponification of a monoacid (**18a, b**) and purification of the product were carried out according to method D to yield the corresponding diacid (**9a, b**) as a colorless powder. In the case of **14c—e** and **15c—e**, deprotection was carried out by method E to give **9c—e** and **21c—e**, respectively.

(*S*)-3-[(*R*)-1-Carboxy-5-(4-piperidyl)pentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic Acid (30; Table I) and (*S*)-3-[(*S*)-1-Carboxy-5-(4-piperidyl)pentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic Acid (31; Table I)——D-Cysteine·HCl·H_2O (15 g) was converted to *N*-acetyl-D-cysteine by the method reported by Martin *et al.*[21] *N*-Acetyl-D-cysteine was allowed to react with 2-fluoronitrobenzene (14.5 g) by the procedure of Stanton *et al.*[7a] (*S*)-2-Acetylamino-3-(2-nitrophenyl)thiopropionic acid (18 g, 74% based on D-cysteine) was obtained as yellow crystals. *Anal.* Calcd for $C_{11}H_{12}N_2O_5S$: C, 46.47; H, 4.25; N, 9.85. Found: C, 46.25; H, 4.23; N, 9.67. mp 158—161 °C. $[\alpha]_D^{25.5}$ −84.5° (*c*=0.5, EtOH). A mixture of this acid (18 g), water (250 ml) and conc. HCl (65 ml) was refluxed for 50 min and cooled. After neutralization with NH_4OH under cooling, the mixture was made weakly acidic with AcOH. The precipitate was collected by filtration and recrystallized from water to yield (*S*)-2-amino-3-(2-nitrophenyl)thiopropionic acid (14.3 g, 93%) as yellow crystals, mp 169—170.5 °C. $[\alpha]_D^{22}$ −62.5° (*c*=0.5, 1 N HCl). *Anal.* Calcd for $C_9H_{10}N_2O_4S$: C, 44.62; H, 4.16; N, 11.56. Found: C, 44.49; H, 4.14; N, 11.55. This acid was converted to *tert*-butyl (*S*)-3-amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetate (overall yield, 47%) by the method described in our previous report.[8] mp 81—83 °C. $[\alpha]_D^{24}$ +213.4° (*c*=0.9, MeOH). *Anal.* Calcd for $C_{15}H_{20}N_2O_3S$: C, 58.42; H, 6.54; N, 9.08. Found: C, 58.40; H, 6.39; N, 8.89. IR ν_{max}^{KBr} cm^{-1}: 3370 (NH); 1740, 1660 (C=O). This aminoester (3.5 g) was allowed to react with **29** according to method C to yield the diastereomeric mixture of diesters. After separation by silica gel column chromatography, each diastereomer was deblocked by method E to give the corresponding diacid **30** or **31**. The analytical data for intermediates in the synthesis are follows.

(*S*)-3-(2-Nitrophenyl)thio-2-phthalimidopropionic Acid: Yield 87%, mp 217—221 °C, $[\alpha]_D^{23}$ +84.3° (*c*=0.5, MeOH). *Anal.* Calcd for $C_{17}H_{12}N_2O_6S$: C, 54.84; H, 3.25; N, 7.52. Found: C, 54.83; H, 3.28; N, 7.64. IR ν_{max}^{KBr} cm^{-1}: 1770, 1755, 1700 (C=O).

(*S*)-3-Phthalimido-2,3-dihydro-1,5(5*H*)-benzothiazepin-4-one: Yield 61%, mp 209—213 °C, $[\alpha]_D^{25}$ +178.9° (*c*=0.5, MeOH). *Anal.* Calcd for $C_{17}H_{12}N_2O_3S$: C, 62.95; H, 3.73; N, 8.64. Found: C, 62.99; H, 3.64; H, 8.61. IR ν_{max}^{KBr} cm^{-1}: 1770, 1710, 1670 (C=O).

tert-Butyl (*S*)-Phthalimido-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetate: Yield 93%, mp 179—181 °C, $[\alpha]_D^{24}$ +150.3° (*c*=0.9, MeOH). *Anal.* Calcd for $C_{23}H_{22}N_2O_5S$: C, 63.00; H, 5.06; N, 6.39. Found: C, 62.89; H, 4.95; N, 6.38. IR ν_{max}^{KBr} cm^{-1}: 1775, 1740, 1720, 1685 (C=O).

tert-Butyl (*S*)-3-[(*R*)-5-(1-Benzyloxycarbonyl-4-piperidyl)-1-ethoxycarbonylpentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetate: Lower *Rf*, yield 30% (colorless oil). IR ν_{max}^{neat} cm^{-1}: 3325 (NH); 1740, 1690, 1670 (C=O). MS *m/z*: 667 (M^+). $[\alpha]_D^{24}$ +95.9° (*c*=0.5, MeOH).

tert-Butyl (*S*)-3-[(*S*)-5-(1-Benzyloxycarbonyl-4-piperidyl)-1-ethoxycarbonylpentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetate: Higher *Rf*, yield 28% (colorless oil). IR ν_{max}^{neat} cm^{-1}: 3320 (NH); 1740, 1700, 1690 (C=O). MS *m/z*: 667 (M^+). $[\alpha]_D^{24}$ +94.1° (*c*=0.4, MeOH).

(*R*)-3-[(*S*)-1-Ethoxycarbonyl-5-(4-piperidyl)pentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic Acid (16c)——The monoacid **16c**·HBr, prepared from **12c** (0.9 g) by the method described above, was dissolved in water (100 ml), neutralized with excess $NaHCO_3$ and acidified with AcOH. The mixture was subjected to MCI gel column chromatography (water : MeOH = 2 : 1—1 : 2). The eluate was concentrated *in vacuo* and lyophilized to give a colorless powder. Recrystallization from THF gave colorless crystals. mp 117—119 °C. IR ν_{max}^{Nujol} cm^{-1}: 1720, 1650, 1620, 1590 (C=O and carboxylate). $[\alpha]_D^{21}$ −164° (*c*=0.7, MeOH). *Anal.* Calcd for $C_{24}H_{35}N_3O_5S \cdot 3/2H_2O$: C, 57.12; H, 7.59; N, 8.33. Found: C, 56.96; H, 7.46; N, 8.22.

(*RS*)-3-[(*SR*)-1-Ethoxycarbonyl-5-(4-piperidyl)pentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic Acid (Racemic 16c)——*tert*-Butyl (*S*)-3-[(*R*)-5-(1-benzyloxycarbonyl-4-piperidyl)pentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetate (0.8 g), prepared in the synthesis of **30**, was deblocked with HBr–AcOH and purified similarly to the case of **16c**. Lyophilization of the eluate gave (*S*)-3-[(*R*)-1-ethoxycarbonyl-5-(4-piperidyl)-pentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic acid (0.45 g, 76%) as an amorphous powder. $[\alpha]_D^{20.5}$ +146° (*c*=1, water). IR ν_{max}^{KBr} cm^{-1}: 1720, 1655, 1620, 1590 (C=O and carboxylate). *Anal.* Calcd for $C_{24}H_{35}N_3O_5S \cdot H_2O$: C, 58.16; H, 7.52; N, 8.48. Found: C, 57.80; H, 7.41; N, 8.28. This (*S*),(*R*)-isomer (0.15 g) and **16c** (0.15 g) were dissolved in EtOH (30 ml). The solution was allowed to stand overnight and the resulting crystals were collected by filtration to give racemic **16c** (0.186 g, 62%) as colorless needles, mp 204—211 °C (dec.). $[\alpha]_D$ 0° (*c*=0.5, EtOH). *Anal.* Calcd for $C_{24}H_{35}N_3O_5S \cdot 1/2H_2O$: C, 59.24; H, 7.46; N, 8.63. Found: C, 59.47; H, 7.39; N, 8.57. ^{1}H-NMR (DMSO-d_6 + DCl + D_2O) δ: 1.1 (3H, t, *J*=7 Hz, CH_3), 0.8—2.2 (13H, m), 2.65—3.05 (2H, m), 3.05—4.1 (3H, m), 4.3 (1H, d, *J*=17 Hz, N_5-CHCOO), 4.8 (1H, d, *J*=17 Hz, N_5-CHCOO), 7.2—7.9 (4H, m, phenyl protons).

(*RS*)-3-[(*SR*)-1-Carboxy-5-(4-piperidyl)pentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic Acid (Racemic 8c) ——A solution of **8c** (0.1 g) and **30** (0.1 g) in AcOH (1 ml) was diluted with MeOH to give racemic **8c** (0.1 g, 50%) as colorless crystals. mp indefinite (dec.). $[\alpha]_D$ 0° (*c*=0.9, AcOH). *Anal.* Calcd for $C_{22}H_{31}N_3O_5S \cdot 1/2H_2O$: C, 57.61; H, 7.03; N, 9.16. Found: C, 57.75; H, 7.06; N, 9.12.

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9) The configuration of the newly formed asymmetric carbon of each diastereomer was predictable from the *Rf* on a silica gel TLC plate (hexane : AcOEt = 2 : 1) on the basis of our observation[1,8] in previous studies on **4**—**7** that the diester derivative of the more active diastereomer with (*S*)-configuration at this center showed the lower *Rf* without exception.
10) The relationship that the diastereomer with (*S*)-configuration at this asymmetric carbon is more active than the corresponding (*R*)-isomer has been established for the series of *N*-carboxymethyldipeptide ACE inhibitors.[3,4,5d]
11) We searched for crystals suitable for X-ray crystallographic analysis of CV-5975 (**8c**) derivatives, and found that the **16c**-racemate formed suitable crystals for analysis. In view of the (*RS*),(*SR*)-relative configuration determined by the X-ray analysis, the configuration of the side chain was unambigously assigned as *S*. The X-ray structure in Fig. 1 shows the (*R*),(*S*)-enantiomer. The arrangement of the functional groups in this conformation corresponded well to that in the X-ray result for the **5a** derivative reported by us previously.[8] Recently, Thorsett *et al.* investigated the relation of ψ angles in a dipeptide-backbone of ACE inhibitors to the inhibitory activity by means of molecular mechanics and X-ray analysis, and defined a window of ψ angle from 130—170°: E. D. Thorsett, E. E. Harris, S. D. Aster, E. R. Peterson, J. P. Snyder, J. P. Springer, J. Hirshfield, E. W. Tristram, A. A. Patchett, E. H. Ulm and T. C. Vassil, *J. Med. Chem.*, **29**, 251 (1986). In the case of CV-5975, the ψ angle was determined to be 151° in the above crystal structure, which is close to the average value of

Thorsett *et al.* Details of the X-ray analysis will be published elsewhere.
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