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

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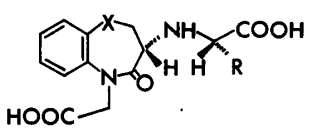
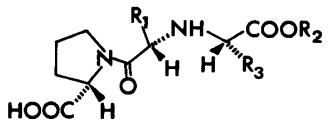
A series of (*R*)-3-amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic acids (**4** and **13**) and (*S*)-3-amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetic acids (**5** and **14**) having an (*S*)-ω-amino-1-carboxyalkylamino group at the 3-position was prepared as part of our search for long-acting angiotensin converting enzyme (ACE) inhibitors. A number of derivatives had potent *in vitro* and *in vivo* ACE inhibitory activities. The structure–activity relationship of the series indicated that the duration of *in vivo* ACE inhibitory activity depends on the length of the carbon chain in the ω-aminoalkylamino substituent at the 3-position. The most prolonged activity was observed with (*S*)-8-amino-1-carboxyoctylamino derivatives (**4d** and **5d**).

Keywords——angiotensin converting enzyme inhibitor; ACE inhibitor; 1,5-benzothiazepine derivative; 1,5-benzoxazepine derivative; α,ω-diaminoalkanoic acid derivative; structure–activity relationship

In the preceding paper,[1] we described the synthesis of new types of angiotensin converting enzyme (ACE) inhibitors, (*R*)-3-[(*S*)-1-carboxy-3-phenylpropyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic acid (**1a**) and (*S*)-3-[(*S*)-1-carboxy-3-phenylpropyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetic acid (**1b**), which were designed to incroporate conformational restriction in rigid skeletons. Based on the fact that **1a**, **b** and their derivatives showed potent ACE inhibitory activities, we speculated that functional groups on **1** such as carboxyl, amido, amino and hydrophobic moieties are located in favorable positions for binding to active sites[2a] in ACE. Further modifications of **1** were done in order to improve the duration of the *in vivo* inhibitory activity in association with the bioavailability and the tissue distribution.



1a : X=S, R=$(CH_2)_2Ph$
1b : X=O, R=$(CH_2)_2Ph$
4a : X=S, R=$(CH_2)_4NH_2$
5a : X=O, R=$(CH_2)_4NH_2$

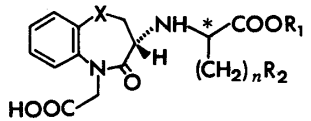


2 : $R_1=CH_3$, $R_2=H$, $R_3=(CH_2)_4NH_2$
3a(lisinopril) : $R_1=(CH_2)_4NH_2$, $R_2=H$, $R_3=(CH_2)_2Ph$
3b(enalapril) : $R_1=CH_3$, $R_2=Et$, $R_3=(CH_2)_2Ph$
3c(enalaprilat) : $R_1=CH_3$, $R_2=H$, $R_3=(CH_2)_2Ph$

Chart 1

In the series of *N*-carboxymethyldipeptide-type ACE inhibitors, such as **1** and enalapril (**3b**),[3a] the hydrophobic character of the phenethyl moiety has been considered to be important for binding to the S_1 subsite[2a] of the enzyme. However, compound **2**,[2] which has an aminobutyl residue in place of the phenethyl group of enalaprilat (**3c**),[3a] has been reported

TABLE I. 1,5-Benzothiazepine (**4**, **13**, **15**—**17**) and 1,5-Benzoxazepine (**5**, **14**) Derivatives[a]



No.	X	R_1	*n*	R_2	Config. of C*	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	MS or SIMS *m/z*	$[\alpha]_D^{deg.}$ Temp. (°C) (*c*, in MeOH)	ACE inhibitory activity (%) *in vitro*[b] 10^{-8} (M)	10^{-7} (M)
13a	S	C_2H_5	4	NH_2	*S*	94	$C_{19}H_{27}N_3O_5S \cdot 2HCl \cdot H_2O$	45.60 (45.09	6.24 5.77	8.40 8.35)	409 (M^+)	−128 22 (0.5)	—	— (10^{-5}; 36) (10^{-6}; 87)
13b	S	C_2H_5	4	NH_2	*R*	86	$C_{19}H_{27}N_3O_5S \cdot 2HCl$	47.30 (47.10	6.06 6.09	8.71 8.59)	409 (M^+)	−161 26 (0.7)	—	— (10^{-4}; 7)
13c	S	C_2H_5	2	NH_2	*S*	84	$C_{17}H_{23}N_3O_5S \cdot 2HCl$	44.50 (44.94	5.60 5.55	9.16 9.25)	382 (MH^+)	−149 26 (0.5)	—	—
13d	S	C_2H_5	5	NH_2	*S*	94	$C_{20}H_{29}N_3O_5S \cdot 2HCl \cdot H_2O$	46.49 (46.56	6.47 6.83	8.17 7.79)	423 (M^+)	−121 24 (0.5)	—	—
13e	S	C_2H_5	6	NH_2	*S*	88	$C_{21}H_{31}N_3O_5S \cdot 2HCl \cdot H_2O$	47.73 (47.74	6.67 6.19	7.95 8.00)	437 (M^+)	−122 24 (0.2)	—	— (10^{-5}; 76) (10^{-4}; 99)
13f	S	C_2H_5	7	NH_2	*S*	80	$C_{22}H_{33}N_3O_5S \cdot 2HCl \cdot 1/2\,H_2O$	49.44 (49.39	6.98 6.61	7.86 7.73)	451 (M^+)	−125 23.5 (0.4)	—	—
13g	S	C_2H_5	8	NH_2	*S*	79	$C_{23}H_{35}N_3O_5S \cdot 2HCl \cdot H_2O$	49.82 (49.64	7.14 7.06	7.26 7.55)	465 (M^+)	−110 24 (0.5)	—	—
13h	S	C_2H_5	9	NH_2	*S*	86	$C_{24}H_{37}N_3O_5S \cdot 2HCl \cdot H_2O$	50.52 (50.60	7.24 6.83	7.36 7.24)	479 (M^+)	−116 23 (0.1)	—	—
4a	S	H	4	NH_2	*S*	63	$C_{17}H_{23}N_3O_5S \cdot H_2O$	51.12 (50.87	6.31 5.83	10.52 10.34)	382 (MH^+)	−151[c] 23 (0.2)	31	82 (10^{-6}; 98)

TABLE I. (continued)

No.	X	R_1	*n*	R_2	Config. of C*	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	MS or SIMS *m/z*	$[\alpha]_D^{deg.}$ Temp. (°C) (c, in MeOH)	ACE inhibitory activity (%) *in vitro*[b] 10^{-8} (M)	10^{-7} (M)
4b	S	H	5	NH_2	*S*	87	$C_{18}H_{25}N_3O_5S \cdot 3/2\,H_2O$	51.17 (51.21	6.68 6.97	9.95 9.95)	396 (MH^+)	−145[c] 24 (0.5)	44	90
4c	S	H	6	NH_2	*S*	83	$C_{19}H_{27}N_3O_5S \cdot 3/2\,H_2O$	52.27 (51.79	6.93 6.91	9.63 9.56)	410 (MH^+)	−148[c] 24 (0.6)	58 (10^{-6}; 100)	96
4d	S	H	7	NH_2	*S*	85	$C_{20}H_{29}N_3O_5S \cdot 3/2\,H_2O$	53.32 (53.77	7.16 6.80	9.32 9.40)	424 (MH^+)	−141[c] 24 (0.1)	79	98
4e	S	H	8	NH_2	*S*	85	$C_{21}H_{31}N_3O_5S \cdot H_2O$	55.37 (54.94	7.08 6.91	9.23 9.11)	438 (MH^+)	−138[c] 24 (0.1)	80	99
4f	S	H	9	NH_2	*S*	52	$C_{22}H_{33}N_3O_5S$	58.52 (58.06	7.37 7.29	9.31 9.33)	452 MH^+)	−151[c] 23 (0.1)	82	98
15	S	Bu	4	NH_2	*S*	94	$C_{21}H_{31}N_3O_5S \cdot 2HCl \cdot H_2O$	47.72 (47.95	6.68 6.36	7.95 7.94)	437 (M^+)	−123 23.5 (0.4)	—	—
16a	S	C_2H_5	4	NHAc	*S*	98	$C_{21}H_{29}N_3O_6S \cdot HCl \cdot 2H_2O$	48.13 (48.63	6.54 6.07	8.01 7.73)	451 (M^+)	−121 24 (0.4)	28 (10^{-6}; 97)	81
16b	S	C_2H_5	4	NHCOPh	*S*	56	$C_{26}H_{31}N_3O_6S \cdot HCl \cdot 1/2\,H_2O$	55.86 (55.86	5.77 5.69	7.52 7.97)	514 (M^+)	−117 23.5 (0.3)	— (10^{-6}; 50) (10^{-5}; 85)	—
16c	S	C_2H_5	4	NPht	*S*	66	$C_{27}H_{29}N_3O_7S \cdot HCl \cdot 1/2\,H_2O$	55.42 (55.09	5.34 5.12	7.18 7.15)	539 (M^+)	−114 22 (0.5)	— (10^{-6}; 88) (10^{-5}; 98)	59
17a	S	H	4	$NHCH(CH_3)_2$	*S*	96	$C_{20}H_{29}N_3O_5S$	—	—	—	424 (MH^+)	−129[c] 23.5 (0.2)	31 (10^{-6}; 98)	83
17b	S	H	4	NH–⬡	*S*	80	$C_{23}H_{33}N_3O_5S \cdot H_2O$	57.36 (56.86	7.32 7.48	8.72 8.34)	464 (MH^+)	−117[c] 23.5 (0.5)	52 (10^{-6}; 100)	93

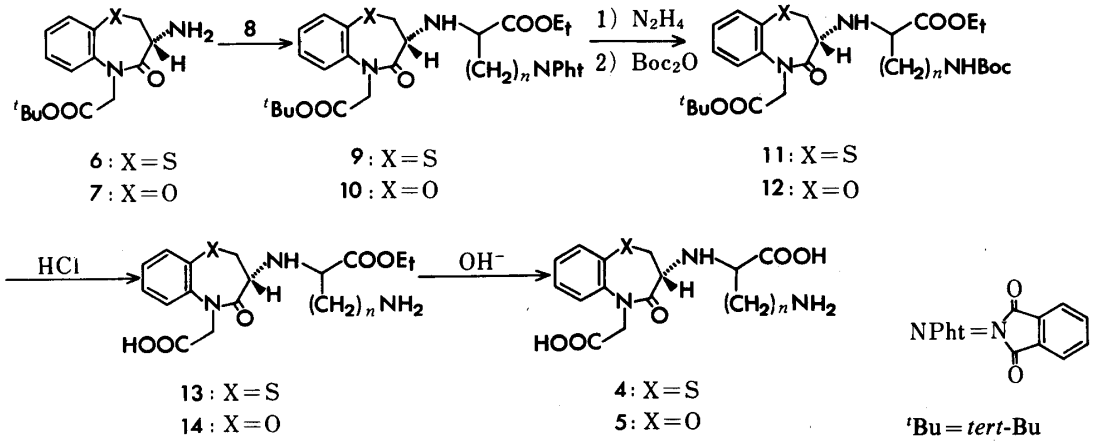
17c	S	H	4	N(/Bu \Bu)	*S*	80	$C_{25}H_{39}N_3O_5S \cdot 1/2\,H_2O$	59.73 (59.36	8.02 7.60	8.36 8.62)	494 (MH^+)	−106[c] 24 (0.3)	45 (10^{-6}; 99)	91
14a	O	C_2H_5	4	NH_2	*S*	75	$C_{19}H_{27}N_3O_6 \cdot 2HCl \cdot AcOEt$	47.32 (47.02	6.39 6.84	7.20 7.42)	393 (M^+)	−110 24.5 (0.7)	— (10^{-5}; 66) (10^{-4}; 95)	—
14b	O	C_2H_5	4	NH_2	*R*	70	$C_{19}H_{27}N_3O_6 \cdot 2HCl \cdot AcOEt$	47.32 (47.29	6.39 6.83	7.20 7.40)	393 (M^+)	−130 24.5 (0.8)	— (10^{-4}; 12)	—
14c	O	C_2H_5	5	NH_2	*S*	87	$C_{20}H_{29}N_3O_6 \cdot 2HCl \cdot H_2O$	48.47 (48.19	6.78 6.67	8.07 8.43)	407 (M^+)	−118 24 (0.35)	—	—
14d	O	C_2H_5	6	NH_2	*S*	91	$C_{21}H_{31}N_3O_6 \cdot 2HCl \cdot 3/2\,H_2O$	48.85 (48.37	7.12 6.96	7.43 8.06)	421 (M^+)	−108 24.5 (0.7)	—	—
14e	O	C_2H_5	7	NH_2	*S*	92	$C_{22}H_{33}N_3O_6 \cdot 2HCl \cdot H_2O$	50.37 (50.19	7.16 7.08	7.66 7.98)	435 (M^+)	−114 24 (0.4)	—	—
14f	O	C_2H_5	8	NH_2	*S*	85	$C_{23}H_{35}N_3O_6 \cdot 2HCl \cdot H_2O$	51.11 (51.17	7.27 7.57	7.77 7.34)	449 (M^+)	−110 25 (0.4)	—	—
5a	O	H	4	NH_2	*S*	83	$C_{17}H_{23}N_3O_6 \cdot 3/2\,H_2O$	52.03 (52.32	6.68 6.18	10.71 10.68)	366 (MH^+)	−169 25.5 (0.4)	40 (10^{-6}; 98)	87
5b	O	H	5	NH_2	*S*	65	$C_{18}H_{25}N_3O_6 \cdot H_2O$	54.40 (54.69	6.85 6.55	10.57 10.41)	380 (MH^+)	−157[c] 24 (0.3)	58	93
5c	O	H	6	NH_2	*S*	84	$C_{19}H_{27}N_3O_6 \cdot H_2O$	55.46 (55.63	7.10 6.73	10.21 10.05)	394 (MH^+)	−159[c] 24.5 (0.2)	65 (10^{-6}; 100)	98
5d	O	H	7	NH_2	*S*	83	$C_{20}H_{29}N_3O_6 \cdot H_2O$	56.46 (56.61	7.34 6.86	9.87 9.85)	408 (MH^+)	−145[c] 24 (0.16)	84	99
5e	O	H	8	NH_2	*S*	90	$C_{21}H_{31}N_3O_6$	57.39 (57.42	7.57 7.27	9.56 9.58)	422 (MH^+)	−142[c] 25 (0.2)	86	99
1a													46	91
1b													31	91
3c (Enalaprilat)													62	97

a) Each compound was obtained as an amorphous powder. *b*) Each value is the average of results obtained in two or more experiments. *c*) The enantiomeric purity of the diacid derivatives has not been determined.

to show high inhibitory activity *in vitro*. On the other hand, replacement of the L-alanine moiety of **3c** with L-lysine led to a potent and long-acting inhibitor, lisinopril (**3a**).[3] These facts prompted us to prepare lysine derivatives of the benzo-fused seven-membered heterocyclic lactams, (*R*)-3-[(*S*)-5-amino-1-carboxypentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic acid (**4a**) and (*S*)-3-[(*S*)-5-amino-1-carboxypentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetic acid (**5a**). This paper describes the synthesis of **4a**, **5a** and related derivatives (**4b**—**f**, **5b**—**e** and **13**—**17**; Table I), as well as their ACE inhibitory activities.

Chemistry

The 3-(5-amino-1-carboxypentyl)amino derivatives (**4a**, **5a**) were prepared using the S_N2 reaction as the key step, as shown in Chart 2. Thus, *tert*-butyl (*R*)-3-amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetate (**6**)[1] was allowed to react with ethyl 2-bromo-6-phthalimidohexanoate (**8a**: $n=4$) in the presence of potassium carbonate (K_2CO_3) in *N*,*N*-dimethylformamide (DMF), or better, by using triethylamine (Et_3N) as the base instead of K_2CO_3 in acetonitrile (CH_3CN) to obtain a diastereomeric mixture of diesters, **9a**, **b** ($n=4$). They were separated by chromatography on silica gel to give **9a** with lower *Rf* and **9b** with higher *Rf*.[4] The phthalimido group of each isomer was deprotected with hydrazine hydrate ($N_2H_4 \cdot H_2O$) followed by reprotection with di-*tert*-butyl dicarbonate (Boc_2O) to afford **11a** ($n=4$) and **11b** ($n=4$), respectively. Treatment of the compounds (**11a**, **b**) with hydrogen chloride–ethyl acetate solution (HCl–AcOEt) provided the corresponding monoacids **13a** ($n=4$) and **13b** ($n=4$). The absolute configuration at the newly formed asymmetric carbon in the side chain of **13a** and **13b** was assigned as *S* and *R*, respectively, by comparison of the ACE inhibitory activities *in vitro* (Table I) based on the fact that the diastereomer with the *S*-configuration at this center is more active than the corresponding *R*-isomer. This relationship has been established for the series of *N*-carboxymethyldipeptides and analogous ACE inhibitors.[1-3] Saponification of the more active isomer, (*R*)-3-[(*S*)-5-amino-1-ethoxycarbonylpentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic acid (**13a**), afforded the desired diacid **4a**.



6: X=S
7: X=O

9: X=S
10: X=O

11: X=S
12: X=O

13: X=S
14: X=O

4: X=S
5: X=O

Chart 2

The oxazepine congener **5a** was prepared by the same sequence starting with *tert*-butyl (*S*)-3-amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetate (**7**)[1] *via* the intermediates **10a** ($n=4$: lower *Rf*), **12a** ($n=4$) and **14a** ($n=4$).

Our target compounds **4a** and **5a** showed very potent ACE inhibitory activity *in vitro*. In addition, the benzothiazepine derivative (**4a**) revealed long-lasting inhibitory activity, comparable to that of enalaprilat (**3c**), on the angiotensin I (A-I)-induced pressor response after

intravenous (i.v.) administration in rats. However, the diacid (**4a**) and even the monoacid (**13a**) proved less active than enalapril (**3b**) when they were administered orally as shown in Table II. In order to improve their bioavailabilities, we modified the benzothiazepine derivatives as shown in Chart 3, by a) increasing the lipophilicity of the ethyl ester moiety, b) N-acylating the ω-amino group and c) N-alkylating the ω-amino group.

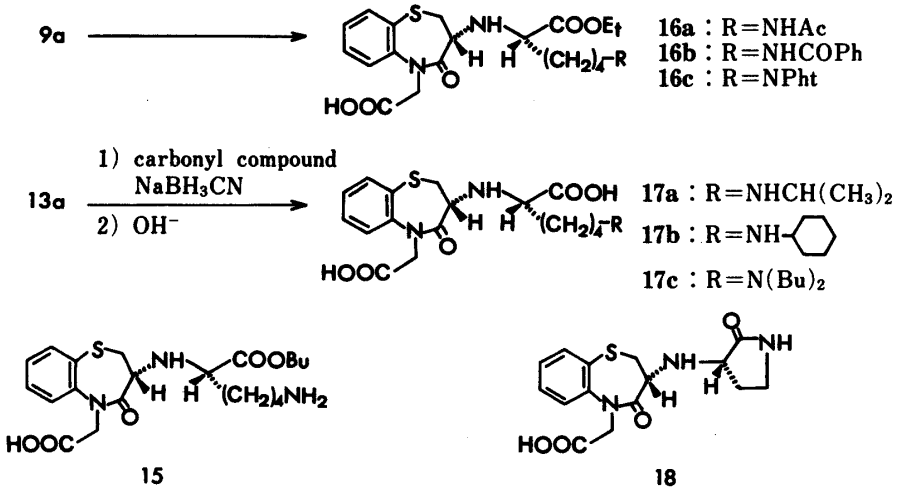


Chart 3

Thus, the butyl ester congener (**15**)[5] was prepared using butyl 2-bromo-5-phthalimidohexanoate (**8h**) as a starting material. N-Acetylation and N-benzoylation were conducted at the stage of the intermediate after deprotection of **9a** with $N_2H_4 \cdot H_2O$, and subsequent treatment with HCl–AcOEt gave the corresponding monoacids **16a** and **16b**. Treatment of **9a** with HCl–AcOEt gave the phthalimido derivative **16c**. N-Alkylation of the monoacid **13a** with carbonyl compounds (acetone, cyclohexanone and butyraldehyde) in the presence of sodium cyanoborohydride ($NaBH_3CN$) followed by saponification afforded the N-alkylated diacid derivatives, **17a**—**c**.

As biological evaluation *in vivo* using rats showed no significant improvements as a result of these modifications (data not shown), we tried another approach, varying the length of the carbon chain (n) in the 3-[(*S*)-ω-amino-1-carboxyalkyl]amino moiety. The first synthesized 7-amino-1-carboxyheptyl derivative (**4c**: $n=6$) showed a remarkably improved duration of activity (see Table II). Thus, other benzothiazepine (**13c**, **d**, **f**—**h** and **4b**, **d**—**f**; Table I) and benzoxazepine (**14c**—**f** and **5b**—**e**; Table I) derivatives with aminoalkyl groups of different lengths ($n=2$, 5—9) were synthesized to determine the optimal n value for *in vivo* inhibitory activities. These derivatives could be prepared by the same sequence of reactions as that for **4a** and **5a** using ethyl α-bromo-ω-phthalimidoalkanoate (**8b**—**g**: $n=2$, 5—9), but preparation of the diacid of 3-amino-1-carboxypropyl derivative ($n=2$) was troublesome due to the formation of the five-membered ring lactam (**18**) on saponification of the monoacid hydrochloride (**13c**·HCl).

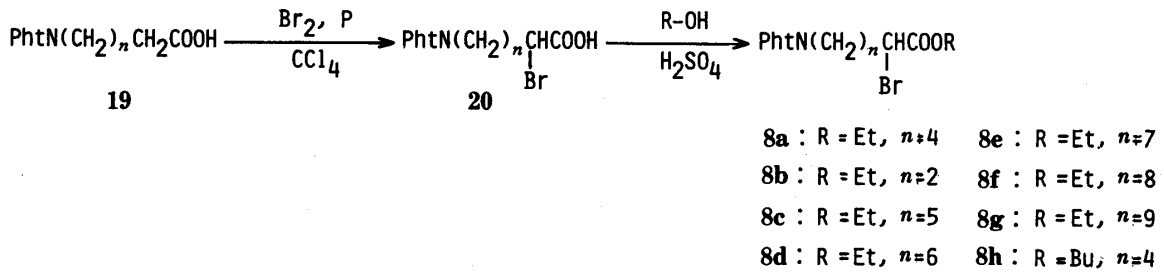


Chart 4

The required α-bromo-ω-phthalimidoalkanoic acid esters (**8a—h**) were prepared from the corresponding ω-phthalimidoalkanoic acid (**19**) by means of the Hell–Volhard–Zelinsky reaction and esterification of the resulting α-bromoacids (**20**) as shown in Chart 4.

Biological Results and Discussion

The *in vitro* ACE inhibitory activities[6] for the compounds prepared above are shown in Table I. A series of benzothiazepine (**4**) and benzoxazepine (**5**) diacid derivatives showed high *in vitro* activities comparable to that of **1** or enalaprilat (**3c**). In addition, increasing the carbon number (n) in the aminoalkyl group led to slightly enhanced inhibitory potency *in vitro* as seen in **4a—f** and **5a—e**. These high activities indicate that aminoalkyl groups of different lengths can interact with the S_1 subsite in place of the phenethyl side chain present in **1** and **3**.

Monoacids (**13a, e** and **14a**) were much less active than the corresponding diacids (**4a, c** and **5a**) *in vitro*, as in the case of enalapril (**3b**) and analogous inhibitors.[1-3]

The very potent *in vivo* ACE inhibitory activities[7] of the derivatives (**4, 5, 13** and **14**) after i.v. and oral administrations were confirmed by measuring the inhibition of A-I-induced pressor response in rats. The results are shown in Table II.

The duration of activity proved to be closely correlated to the length of the carbon chain (n) in the aminoalkyl group. Thus, 8-amino-1-carboxyoctyl derivatives ($n=7$: **4d** and **5d**) exhibited the longest duration in each series of benzothiazepines and benzoxazepines not only after i.v. but also after oral administration.

Despite the weak activities *in vitro*, the monoacids **13** and **14** showed high activities

Table II. Inhibitory Activities on Angiotensin I-Induced Pressor Response in Rats

No.	% inhibition after i.v. administration[a] (0.3 mg/kg)						% inhibition after *p.o.* administration[a] (10 mg/kg)							
	5	10	30	60	90	120 min	1/3	1	2	3	5	7	10	24 h
13a	77	88	82	41	19	17	10	59	57	53	34	26	—	—
13d	94	96	87	66	46	33	—	—	—	—	—	—	—	—
13e	100	100	99	95	81	61	79	88	85	90	81	69	64	20
13f	93	100	99	90	79	80	79	77	71	87	70	66	70	41
13g	100	100	88	44	46	21	—	—	—	—	—	—	—	—
4a	95	94	70	58	16	18	72	79	66	68	34	—	—	—
4b	100	100	94	81	45	32	71	45	—	58	48	27	22	—
4c	100	97	98	79	70	44	91	91	88	86	81	69	77	40
4d	100	100	99	97	88	77	93	95	96	95	89	84	79	49
4e	100	100	100	61	44	20	84	90	84	87	77	55	54	17
4f	100	98	83	19	10	—	93	83	—	66	39	35	14	—
14a	36	45	17	12	—	—	—	—	—	—	—	—	—	—
14d	100	100	97	93	82	65	43	83	84	87	82	70	45	20
14e	100	100	100	96	76	53	—	—	—	—	—	—	—	—
14f	100	100	100	71	14	—	—	—	—	—	—	—	—	—
5a	79	79	64	25	—	—	38	65	—	54	55	50	24	—
5b	94	91	92	56	37	18	61	75	67	63	63	32	29	11
5c	100	93	86	75	65	58	87	81	87	86	83	72	64	18
5d	100	100	100	99	86	69	100	99	91	91	91	91	82	56
5e	100	100	100	74	25	10	94	92	93	79	73	57	56	16
Enalapril (**3b**)	—	—	—	—	—	—	93	99	93	91	86	55	62	22
Enalaprilat (**3c**)	100	100	92	76	49	23	—	—	—	—	—	—	—	—

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

(nearly equal to those of the corresponding diacids, **4** and **5**) in i.v. administration tests. Presumably they are hydrolyzed immediately *in vivo* to the active diacids.

In the case of **3b** (enalapril) and analogous ACE inhibitors[1-3] which have one basic nitrogen atom in the molecule, the monoacid is known to be an orally absorbed prodrug. In contrast to such inhibitors, the derivatives (**4** and **5**) having two basic nitrogens with two free carboxyl groups are better absorbed than the corresponding monoacid derivatives (**13** and **14**). This result suggests that a form which has a suitable isoelectric point is essential for high bioavailability.

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 a Hitachi 260-10 spectrophotometer. The proton nuclear magnetic resonance (^{1}H-NMR) spectra were recorded on Varian EM-360, EM-390 and XL-100A instruments in the indicated solvent. 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 a Hitachi M-80A. $[\alpha]_D$ values were determined with a JASCO DIP-181 4-4822 in the indicated solvent.

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

***tert*-Butyl (*R*)-3-[(*S*)- and (*R*)-1-Ethoxycarbonyl-ω-phthalimidoalkyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetate (9, Table III) and *tert*-Butyl (*S*)-3-[(*S*)- and (*R*)-1-Ethoxycarbonyl-ω-phthalimidoalkyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetate (10, Table III)**——Method A: A mixture of **6** (3.08 g), **8a** (7.36 g), K_2CO_3 (2.76 g), KI (1.66 g) and DMF (20 ml) was stirred overnight. After addition of **8a** (3.68 g) and K_2CO_3 (1.38 g), stirring was continued for a further 3 d. The mixture was worked up (AcOEt–water). The residue was dissolved in a mixture of $(COOH)_2$ (5 g) and AcOEt (30 ml), and the solution was diluted with petroleum ether (120 ml). After standing, the supernatant layer was removed by decantation. This treatment with $(COOH)_2$ followed by dilution with petroleum ether was repeated 4 times. The precipitate was neutralized with aqueous $NaHCO_3$ and worked up (AcOEt). The oily residue was subjected to silica gel column chromatography (hexane : acetone = 4 : 1) to give firstly the (*R*),(*R*)-isomer **9b** (1.75 g) as an oil. IR ν_{max}^{neat} cm^{-1}: 3330 (NH); 1780, 1740, 1720, 1680 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.2 (3H, t, J=7 Hz, CH_3), 1.2—1.8 (6H, m, $CH_2 \times 3$), 1.5 (9H, s, *tert*-Bu), 2.5—3.8 (7H, m), 4.0 (1H, d, J=16 Hz, N_5-CH), 4.15 (2H, q, J=7 Hz, OCH_2), 4.8 (1H, d, J=16 Hz, N_5-CH), 7.0—7.9 (8H, m, phenyl protons). From the second fraction, the (*R*),(*S*)-isomer **9a** (2.5 g) was obtained as a colorless oil. IR ν_{max}^{neat} cm^{-1}: 3330 (NH); 1770, 1740, 1720, 1680 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.1 (3H, t, J=7 Hz, CH_3), 1.2—1.9 (6H, m, $CH_2 \times 3$), 1.5 (9H, s, *tert*-Bu), 2.3—4.3 (10H, m), 4.8 (1H, d, J=16 Hz, N_5-CH), 7.0—7.9 (8H, m, phenyl protons).

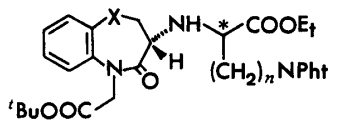
Method B: A mixture of **6** (5 g), **8a** (17.9 g), Et_3N (2.46 g) and CH_3CN (200 ml) was heated under reflux for 45 h. After evaporation of the CH_3CN, the residue was worked up (AcOEt–water) to yield an oily residue, which was subjected to column chromatography on silica gel (hexane : acetone = 4 : 1) to separate **9b** (3.9 g) and **9a** (4.1 g) as colorless oils.

Compund **6** was allowed to react with **8b—g** in a manner similar to that described in method B to give the derivatives (**9c—n**) of benzothiazepine listed in Table III.

In the case of oxazepine derivatives (**10a—j**), the reaction and work-up were carried out according to Method B using **7** and **8a, c—g** as starting materials.

***tert*-Butyl (*R*)-3-[(*S*)- and (*R*)-ω-*tert*-Butoxycarbonylamino-1-ethoxycarbonylalkyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetate (11, Table IV) and *tert*-Butyl (*S*)-3-[(*S*)- and (*R*)-ω-*tert*-Butoxycarbonylamino-1-ethoxycarbonylalkyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetate (12, Table IV)**——A mixture of **9a** (2.6 g), EtOH (30 ml) and $N_2H_4 \cdot H_2O$ (1.3 g) was allowed to stand overnight, then diluted with water (200 ml) and extracted with AcOEt (200 ml). The extract was washed successively with 0.1 N aq. NaOH and water. A solution of $NaHCO_3$ (2.6 g) in water (100 ml) was added to the AcOEt solution, then a solution of Boc_2O (1.5 g) in AcOEt (10 ml) was added dropwise with stirring. After being stirred for 30 min, the mixture was worked up (AcOEt) to yield an oily residue, which was purified by silica gel column chromatography (hexane : acetone = 3 : 1) to give **11a** (1.9 g) as a colorless oil. IR ν_{max}^{neat} cm^{-1}: 3350 (NH), 1740, 1710, 1670, (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.1. (3H, t, J=7 Hz, CH_3), 1.45 (9H, s, *tert*-Bu), 1.5 (9H, s, *tert*-Bu), 1.2—1.8 (6H, m, $CH_2 \times 3$), 2.2—3.7 (7H, m), 3.9 (1H, d, J=16 Hz, , N_5-CH), 4.05 (2H, q, J=7 Hz, OCH_2), 4.7 (1H, s, NH), 4.85 (1H, d, J=16 Hz, N_5-CH) 7.0—7.7 (4H, m, phenyl protons).

TABLE III. Diester Derivatives of 1,5-Benzothiazepine (**9**) and 1,5-Benzoxazepine (**10**)



No.	X	*n*	Config. C*	Yield (%)	$[\alpha]_D$ deg.	Temp. °C	(*c*) in MeOH	MS *m/z* M^+
9a	S	4	*S*	42,[a] 42[b]	−119	23	(0.3)	595
9b	S	4	*R*	29,[a] 40[b]	−110	23.5	(0.4)	595
9c	S	2	*S*	49	−134	24	(0.4)	—
9d	S	2	*R*	43	−142	24	(0.4)	—
9e	S	5	*S*	29	−125	24	(0.6)	609
9f	S	5	*R*	25	−95	24	(1.3)	609
9g	S	6	*S*	40	—	—		—
9h	S	6	*R*	35	−113	24	(0.4)	—
9i	S	7	*S*	27	−117	22	(0.4)	637
9j	S	7	*R*	22	−111	22	(0.3)	637
9k	S	8	*S*	26	−117	24	(0.4)	651
9l	S	8	*R*	25	−102	24	(0.4)	651
9m	S	9	*S*	28	−112	24	(0.5)	665
9n	S	9	*R*	28	−104	24	(0.5)	665
10a	O	4	*S*	41	−105	23	(1.0)	579
10b	O	4	*R*	32	−106	23	(0.9)	579
10c	O	5	*S*	18	−123	24	(0.3)	593
10d	O	5	*R*	16	−110	24	(0.3)	593
10e	O	6	*S*	32	−115	24.5	(0.3)	607
10f	O	6	*R*	26	−104	24.5	(0.5)	607
10g	O	7	*S*	15	−110	24	(0.2)	621
10h	O	7	*R*	13	−106	24	(0.3)	621
10i	O	8	*S*	15	−98	24	(0.2)	635
10j	O	8	*R*	12.5	−100	24	(0.3)	635

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

Compounds (**9b, c, e, g, i, k, m** and **10a—c, e, g, i**) were similarly allowed to react with $N_2H_4 \cdot H_2O$ followed by treatment with Boc_2O to yield **11b—h and 12a—f**, respectively.

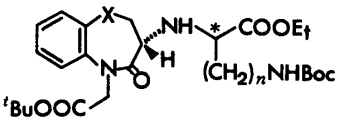
(*R*)-3-[(*S*)-1-Ethoxycarbonyl-5-phthalimidopentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic Acid (16c, Table I)——A mixture of **9a** (0.2 g) and 5 N HCl–AcOEt (5 ml) was allowed to stand for 3 h then diluted with Et_2O (50 ml) to deposit **16c**·HCl (0.13 g) as a colorless powder. ^{1}H-NMR (d_6-DMSO + D_2O) δ:1.05 (3H, 5, J=7 Hz, CH_3), 1.1—2.0 (6H, m, $CH_2 \times 3$), 3.1—3.9 (6H, m), 4.6 (2H, q, J=7 Hz, OCH_2), 4.3 (1H, d, J=16 Hz, N_5-CH), 4.7 (1H, d, J=16 Hz, N_5-CH), 7.3—7.8 (8H, m, phenyl protons). MS *m/z*: 539 (M^+).

(*R*)-3-[(*S*)- and (*R*)-ω-Amino-1-ethoxycarbonylalkyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic Acid (13, Table I) and (*S*)-3-[(*S*)- and (*R*)-ω-Amino-1-ethoxycarbonylalkyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetic Acid (14, Table I)——Compounds **11a—h** and **12a—f** were treated with 5 N HCl–AcOEt in a manner similar to that used for the preparation of **16c** to give **13a—h**·2HCl and **14a—f**·2HCl, each as a colorless powder. **13a**: ^{1}H-NMR (d_6-DMSO + D_2O) δ: 1.1 (3H, t, J=7 Hz, CH_3), 1.3—2.0 (6H, m, $CH_2 \times 3$), 2.6—4.0 (6H, m), 4.1 (2H, q, J=7 Hz, , OCH_2), 4.3 (1H, d, J=16 Hz, N_5-CH), 4.75 (1H, d, J=16 Hz, N_5-CH), 7.3—7.8 (4H, m, phenyl protons).

(*R*)-3-[(*S*)-ω-Amino-1-carboxyalkyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic Acid (4, Table I) and (*S*)-3-[(*S*)-ω-Amino-1-carboxyalkyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetic Acid (5, Table I)——A mixture of **13a**·2HCl (0.2 g) and 1 N aq. NaOH (4 ml) was stirred for 1.5 h. After acidification with AcOH (1 ml), the mixture was subjected to Amberlite XAD-2 column chromatography (MeOH : water = 3 : 7). The eluate was concentrated *in vacuo* and lyophilized to give **4a** (0.1 g) as a colorless powder. ^{1}H-NMR (d_6-DMSO + D_2O) δ: 1.2—1.8 (6H, m, $CH_2 \times 3$), 2.6—3.6 (7H, m), 4.65 (1H, d, J=16 Hz, N_5-CH), 7.1—7.7 (4H, m, phenyl protons). Compounds **13d—h** and **14a, c—f** were hydrolyzed and purified similarly to afford **4b—f** and **5a—e**, each as a colorless powder.

(*R*)-3-[(*S*)-5-Acylamino-1-ethoxycarbonylpentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic

TABLE IV. Diester Derivatives of 1,5-Benzothiazepine (**11**) and 1,5-Benzoxazepine (**12**)



No.	X	*n*	Config. C*	Yield (%)	$[\alpha]_D$ deg.	Temp. °C	(*c*) in MeOH	MS *m/z* M^+
11a	S	4	*S*	76	−136	23	(0.8)	565
11b	S	4	*R*	92	—	—		565
11c	S	2	*S*	69	−121	26	(0.2)	537
11d	S	5	*S*	95	−118	24	(0.9)	579
11e	S	6	*S*	75	−129	24	(0.45)	593
11f	S	7	*S*	92	−133	23.5	(0.4)	607
11g	S	8	*S*	94	−125	24	(0.4)	621
11h	S	9	*S*	73	−127	23	(0.7)	635
12a	O	4	*S*	81	−123	24.5	(0.7)	549
12b	O	4	*R*	79	−108	24.5	(0.7)	549
12c	O	5	*S*	87	−128	23	(0.3)	563
12d	O	6	*S*	77	−122	24.5	(0.3)	577
12e	O	7	*S*	91	−102	23	(0.4)	591
12f	O	8	*S*	80	−116	25	(0.2)	605

Acid (16a,b, Table I)——Compound **9a** (0.5 g) was treated with $N_2H_4 \cdot H_2O$ and subsequently with AcCl (0.13 g) in a manner similar to that used for the preparation of **11a** to give the *N*-acetyldiester (0.25 g, 60%) as an oil. IR ν_{max}^{neat} cm^{-1}: 3320 (Nh), 1730, 1660 (C=O). This ester was treated with 5 N HCl–AcOEt in a manner similar to that described for the preparation of **16c** to yield **16a**·HCl (0.25 g) as a colorless powder. The *N*-benzoyl derivative (**16b**) was prepared in the same manner using PhCOCl instead of AcCl.

(*R*)-3-[(*S*)-1-Carboxy-5-substituted aminopentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic Acid (17a—c, Table I)——A mixture of **13a**·2HCl (0.2 g), EtOH (10 ml), cyclohexanone (2 g) and $NaBH_3CN$ (0.3 g) was allowed to stand overnight. After evaporation of the EtOH, 1 N aq. NaOH (4 ml) was added to the residue, and the resulting mixture was stirred for 1 h. The mixture was diluted with water (20 ml) and extracted with AcOEt. The aqueous layer was acidified with AcOH (1 ml) and subjected to XAD-2 column chromatography (MeOH : water = 1 : 1). The eluate was concentrated *in vacuo* and lyophilized to give **17b** (0.12 g) as a colorless powder. Compound **13a**·2HCl was allowed to react with acetone and butyraldehyde, and subsequently hydrolyzed in a manner similar to that described above to give the corresponding alkylated derivatives **17a** and **17c**, each as a colorless powder.

(*R*)-3-[(*S*)-2-Oxopyrrolidin-3-yl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic Acid (18)——Saponification of **13c** (0.1 g) was carried out in a manner similar to that used for the preparation of **4a**. The reaction mixture was neutralized with AcOH, purified by XAD-2 column chromatography and lyophilized to yield **18** (0.06 g, 77%) as a colorless powder. *Anal.* Calcd for $C_{15}H_{17}N_3O_4S \cdot 1/2H_2O$: C, 52.32; H, 5.27; N, 12.20. Found: C, 52.27; H, 5.08; N, 12.40. $[\alpha]_D^{26}$ −256° (*c* = 0.3, MeOH). SIMS *m/z*: 335 (MH^+). IR ν_{max}^{KBr} cm^{-1}: 1710, 1690, 1670 (C=O).

ω-Phthalimidoalkanoic Acid (19, Table V)——Method C: A mixture of *N*-ethoxycarbonylphthalimide (25 g), 6-aminohexanoic acid (25 g), Na_2CO_3 (22 g) and water (500 ml) was stirred for 30 min. After further addition of *N*-ethoxycarbonylphthalimide (25 g), stirring was continued for 5.5 h. The mixture was acidified with conc. HCl, and the resulting precipitate was collected by filtration and recrystallized from EtOH–water (1 : 1, 400 ml) to give 6-phthalimidohexanoic acid (**19a**, 34 g) as colorless needles. 3-AAminopropionic acid, 7-aminoheptanoic acid,[8] 8-aminooctanoic acid and 11-aminoundecanoic acid were converted to the corresponding ω-phthalimidoalkanoic acids (**19b, c, d, g**) in a manner similar to that described above.

Method D: A mixture of diethyl 2-(7-bromoheptyl)malonate[9] (10.2 g), potassium phthalimide (10 g) and DMF (100 ml) was stirred overnight and worked up (AcOEt; 0.1 N aq. HCl, 0.1 N aq. NaOH, 0.1 N aq. HCl). The residue was purified by silica gel column chromatography (hexane : AcOEt = 3 : 1) to give diethyl 2-(7-phthalimidoheptyl)malonate (8 g, 66%) as a colorless oil. IR ν_{max}^{neat} cm^{-1}: 1770, 1740, 1710 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.25 (6H, t, J = 7 Hz, $CH_3 \times 2$), 1.2—2.2 (12H, m, $CH_2 \times 6$), 3.3 (1H, t, J = 7 Hz, CH), 3.7 (2H, t, J = 7 Hz, NCH_2), 4.2 (4H, q, J = 7 Hz, $OCH_2 \times 2$), 7.5—7.9 (4H, m, phenyl protons).

A mixture of this ester (8 g), 1 N aq. HCl (150 ml) and AcOH (100 ml) was heated under reflux for 2 h. After evaporation of the solvent, the residue was crystallized from water (100 ml) and collected by filtration. The crystals

TABLE V. ω-Phthalimidoalkanoic Acid Derivatives (**19** and **20**)

PhtN–$(CH_2)_n$–$\underset{R}{\underset{|}{C}}$HCOOH

No.	n	R	Yield (%)	mp (°C)	Formula	Analysis (%) Calcd (Found)		
						C	H	N
19a	4	H	68[a]	113—114	$C_{14}H_{15}NO_4$	64.36 (64.35	5.79 5.73	5.36 5.30)
19b	2	H	36[a]	119—121	$C_{11}H_{11}NO_4$	61.80 (61.90	4.75 4.77	6.01 5.96)
19c	5	H	83[a]	115—118	$C_{15}H_{17}NO_4$	—	—	—
19d	6	H	66[a]	94—95	$C_{16}H_{19}NO_4$	66.42 (66.47	6.62 6.48	4.84 4.95)
19e	7	H	90[b]	89—91	$C_{17}H_{21}NO_4$	—	—	—
19f	8	H	39[b]	82—83	$C_{18}H_{23}NO_4$	68.12 (68.42	7.30 7.30	4.41 4.39)
19g	9	H	95[a]	86—88	$C_{19}H_{25}NO_4$	—	—	—
20a	4	Br	77	157—158	$C_{14}H_{14}BrNO_4$	49.43 (49.46	4.15 4.05	4.12 4.09)
20b	2	Br	80	159—161	$C_{12}H_{10}BrNO_4$	46.18 (46.42	3.23 3.18	4.49 4.38)
20c	5	Br	67	106—107	$C_{15}H_{16}BrNO_4$	50.87 (50.64	4.55 4.57	3.95 3.98)
20d	6	Br	96	116—118	$C_{16}H_{18}BrNO_4$	52.19 (51.97	4.93 4.95	3.80 3.73)
20e	7	Br	99	97—98	$C_{17}H_{20}BrNO_4$	53.42 (53.42	5.27 5.35	3.66 3.63)
20f	8	Br	97	102—104	$C_{18}H_{22}BrNO_4$	54.56 (54.68	5.60 5.56	3.53 3.58)
20g	9	Br	97	Oil	$C_{19}H_{24}BrNO_4$	—	—	—

a) Method C. *b*) Method D.

were heated at 150—160 °C for 1 h. After cooling, the residue was crystallized from EtOH–water to give **19e** (5.4 g) as colorless crystals.

Diethyl 2-(8-bromooctyl)malonate (15.5 g, 48%) was prepared from dibromooctane (25 g) in a manner similar to that used for the preparation of the bromoheptyl derivative.[9] This malonate (15.5 g) was converted to **19f** (4.5 g) by a method similar to that described for the preparation of **19e**.

α-Bromo-ω-phthalimidoalkanoic Acid (20, Table V)——Br_2 (9 ml) was added to a mixture of **19a** (15 g), red P (3.6 g) and CCl_4 (50 ml) for 10 min with stirring. After further addition of a solution of Br_2 (3 ml) in CCl_4 (10 ml) over a period of 5 min, the mixture was heated at 80 °C for 30 min, and then under reflux for 8 h. After cooling, the mixture was diluted with water (500 ml) and Et_2O (500 ml), and neutralized with $NaHCO_3$. Excess Br_2 was decomposed by the addition of $NaHSO_3$. The Et_2O layer was extracted with aq. $NaHCO_3$. The aqueous layers were combined and acidified with conc. HCl. The deposited crystals were collected by filtration to give **20a**, which was recrystallized from EtOH–water to yield colorless needles (17 g). IR ν_{max}^{Nujol} cm^{-1}: 1770, 1720, 1690 (C=O). ^{1}H-NMR ($CDCl_3+D_2O+d_6$-DMSO) δ: 1.3—2.3 (6H, m, $CH_2\times3$), 3.65 (2H, t, J=6 Hz, CH_2N), 4.2 (1H, t, J=7 Hz, CH-Br), 7.8 (4H, s, phenyl protons).

Compounds **19b—g** were converted to the corresponding α-bromoacids **20b—g** in a manner similar to that used for the preparation of **20a**.

Alkyl α-Bromo-ω-phthalimidoalkanoate (8)——A mixture of **20a** (15 g), H_2SO_4 (40 ml) and EtOH (300 ml) was allowed to stand overnight, concentrated *in vacuo* to half the initial volume and worked up (AcOEt; aq. $NaHCO_3$, water). The residue was crystallized from petroleum ether to give ethyl 2-bromo-6-phthalimidohexanoate (**8a**, 15.5 g,

95%) as colorless crystals, mp 47—49 °C. IR ν_{max}^{Nujol} cm^{-1}: 1770, 1720 (C=O). *Anal.* Calcd for $C_{16}H_{18}BrNO_4$: C, 52.19; H, 4.93; N, 3.80. Found: C, 52.42; H, 4.79; N, 3.91. ^{1}H-NMR ($CDCl_3$) δ: 1.3 (3H, t, J=7 Hz, CH_3), 1.2—2.4 (6H, m, $CH_2 \times 3$), 3.7 (2H, t, J=6 Hz, CH_2N), 4.2 (1H, t, J=7 Hz, CHBr), 4.25 (2H, q, J=7 Hz, OCH_2), 7.5—7.9 (4H, m, phenylprotons).

Esterfication of **20b—g** was carried out similarly to give the corresponding ethyl esters **8b—g**. Ethyl 2-bromo-4-phthalimidobutyrate (**8b**, 86% yield): mp 77—78 °C. *Anal.* Calcd for $C_{14}H_{14}BrNO_4$: C, 49.43; H, 4.15; N, 4.12. Found: C, 49.51; H, 4.18; N, 4.11. Ethyl 2-bromo-7-phthalimidoheptanoate (**8c**, oil, 98% yield). Ethyl 2-bromo-8-phthalimidooctanoate (**8d**, oil, 98% yield). Ethyl 2-bromo-9-phthalimidononanoate (**8e**, oil, 86% yield). Ethyl 2-bromo-10-phthalimidodecanoate (**8f**, oil, 83% yield). Ethyl 2-bromo-11-phthalimidoundecanoate (**8g**, oil, 77% yield).

A mixture of **20a** (10 g), BuOH (200 ml) and H_2SO_4 (25 ml) was allowed to stand overnight and worked up (AcOEt; aq. $NaHCO_3$, water) to give butyl 2-bromo-6-phthalimidohexanoate (**8h**, 10.5 g, 90%) as a colorless oil.

(*R*)-3-[(*S*)-5-Amino-1-butoxycarbonylpentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic Acid (15, Table I)——Compound **6** (2.6 g) was allowed to react with **8h** (10 g) in a manner similar to that described in Method B for the preparation of **9**. Chromatographic separation of the product on silica gel (hexane : AcOEt = 2 : 1) gave *tert*-butyl (*R*)-3-[(*R*)-1-butoxycarbonyl-5-phthalimidopentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetate (1.75 g, 33%) as a first fraction. IR ν_{max}^{neat} cm^{-1}: 3330 (NH), 1770, 1740, 1710, 1675 (C=O). MS *m/z*: 623 (M^+). From the second fraction, the (*R*),(*S*)-isomer (2.3 g, 44%) was obtained as a colorless oil. IR ν_{max}^{neat} cm^{-1}: 3320 (NH); 1770, 1740, 1710, 1670 (C=O). MS *m/z*: 623 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 0.6—2.3 (14H, m), 1.45 (9H, s, *tert*-Bu), 2.8 (1H, t, J=7 Hz, SCH), 3.0—4.4 (7H, m), 4.8 (1H, d, J=18 Hz, N_5-CH), 7.0—8.1 (8H, m, phenyl protons).

The ester of the (*R*),(*S*)-isomer (1.7 g) was treated with $N_2H_4 \cdot H_2O$ and subsequently with Boc_2O in a manner similar to that used for the preparation of **11a** to give *tert*-butyl (*R*)-3-[(*S*)-1-butoxycarbonyl-5-*tert*-butoxycarbonylaminopentyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetate (1.2 g, 74%) as a colorless oil. IR ν_{max}^{neat} cm^{-1}: 3350 (NH); 1730, 1710, 1670 (C=O). MS *m/z*: 593 (M^+). ^{1}H-NMR ($CDCl_3$)δ: 0.85 (3H, t, J=7 Hz, CH_3), 1.45 (9H, s, *tert*-Bu), 1.5 (9H, s, *tert*-Bu), 1.2—1.8 (10H, m, $CH_2 \times 5$), 2.0—4.1 (10H, m), 4.7 (1H, s, NH), 4.85 (1H, d, J=16 Hz, N_5-CH), 7.0—7.7 (4H, m, phenyl protons).

This ester (1.2 g) was deprotected with HCl in a manner similar to that used for the preparation of **16c** to yield **15** (1 g) as a colorless powder. ^{1}H-NMR (d_6-DMSO+D_2O) δ: 1.0 (3H, t, J=6 Hz, CH_3), 1.1—2.3 (10H, m, $CH_2 \times 5$), 2.7—4.3 (8H, m), 4.5 (1H, d, J=17 Hz, N_5-CH), 4.95 (1H, d, J=17 Hz, N_5-CH), 7.4—8.1 (4H, m, phenyl protons).

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References and Notes

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5) We observed that the replacement of the ethyl ester with the butyl ester in **1** derivatives led to a slight increase of the bioavailability.[1]
6) The ACE inhibitory activity *in vitro* was measured using rabbit lung ACE by the method reported by Cushman *et al.* with a slight modification.[1] D. W. Cushman and H. S. Cheung, *Biochem. Pharmacol.*, **20**, 1637 (1971).
7) The ACE inhibitory activity *in vivo* was assessed in terms of inhibition (percentage) of the vasopressor response induced by i.v. administration of A-I in conscious normotensive rats. Test compounds were administered i.v. or orally. The method was described in our previous report.[1]
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