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

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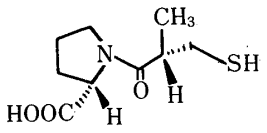
The design and synthesis of new structural types of angiotensin converting enzyme (ACE) inhibitors, (*R*)-3-amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic acids (**7**, **26**, **33** and **37**) and (*S*)-3-amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetic acids (**8** and **27**), are described. A number of compounds in these series showed potent ACE inhibitory activity *in vitro* and *in vivo*. The structure–activity relationship is also discussed.

Keywords——angiotensin converting enzyme inhibitor; ACE inhibitor; 3-amino-4-oxo-1,5-benzothiazepine-5-acetic acid derivative; 3-amino-4-oxo-1,5-benzoxazepine-5-acetic acid derivative; structure–activity relationship; conformationally restricted analog; 1,5-benzothiazepine; 1,5-benzoxazepine

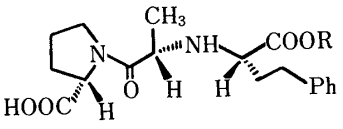
Captopril (**1**)[1a] and enalapril (**2a**)[1b] are potent and orally active angiotensin converting enzyme (ACE) inhibitors. They have been confirmed to be effective for the treatment of hypertension in man.[2] Since the discovery of these drugs, many analogues have been prepared and the structure–activity relationships of these inhibitors have also been studied.[2,3] Ondetti and Petrillo proposed the active site model of ACE interaction with inhibitors.[2b] However, the spatial orientation of binding sites of the enzyme and the conformation of inhibitors required for the binding have not been clarified. One way to approach the problem is to restrict the possible conformations of ACE inhibitors by synthesizing rigid molecules. A few examples have been reported based on such an approach,[4] and the conformationally restricted lactams **3**[3a,5a,c] and **4**[5b] have been prepared.

Recently we reported two new ACE inhibitors, CV-3317 (**5a**)[6] and the dicarboxylic acid derivative CV-3317-COOH (**5b**), which is equipotent with MK-422 (**2b**) *in vitro*. We then tried to evaluate the preferred spatial arrangement[4] of the functional groups of **5** for interaction with the enzyme. We hoped that such an approach might allow us to develop more potent inhibitors.

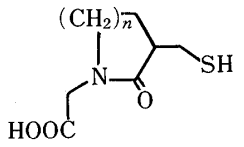
On conformational examination by using a Dreiding model, **5c**[7] in Chart 2 seemed to be stable because of low levels of nonbonded interactions. Although the tricyclic fused compound (**6**) bridged with one atom X between the methyl group of the L-alanine moiety and the methylene group of the indan portion would clearly correspond to **5c**, the structure was rather complicated to synthesize. Since the hydrophobic character of indan was shown to be important[6] for potent *in vivo* inhibitory activity, we replaced this with benzene and designed the new benzofused 7-membered heterocyclic inhibitors,[8] (*R*)-3-[(*S*)-1-carboxy-3-phenylpropyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic acid (**7a**) and (*S*)-3-[(*S*)-1-carboxy-3-phenylpropyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetic acid (**8a**). This paper describes the synthesis as well as ACE inhibitory activity of **7a**, **8a** and related compounds (**26**, **27**, **33** and **37**; Table I).



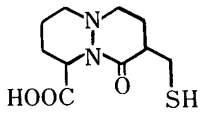
1



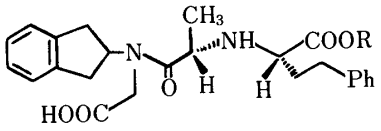
2a : R=Et
2b : R=H



3 (n=2–5)

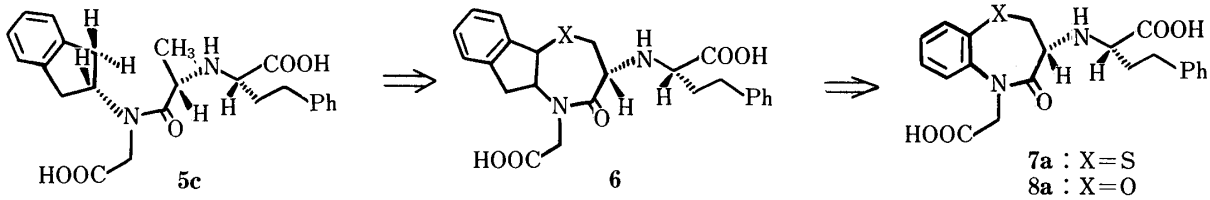


4



5a : R=Et
5b : R=H

Chart 1



5c **6** **7a** : X=S
8a : X=O

Chart 2

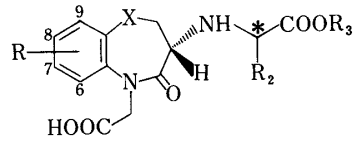
Chemistry

Our synthetic strategy involved the construction of optically active 3-amino derivative intermediates (**15** and **22**) starting from natural amino acids, followed by reductive alkylation with ethyl 2-oxo-4-phenylbutyrate (**23a**), separation of diastereomers, and removal of the protective groups on the carboxyl moieties at the final step. The key intermediates in the synthesis, the (*R*)-3-amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic acid (**15**) and (*S*)-3-amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetic acid (**22**) derivatives, were prepared as shown in Charts 3 and 4.

(*R*)-3-(2-Nitrophenyl)thio-2-aminopropionic acid (**10a**),[9] prepared from 2-nitroaniline (**9a**) and L-cysteine, was led to the *N*-protected amino acid derivative **12a** (R=H) by reaction with *N*-ethoxycarbonylphthalimide, followed by catalytic reduction over palladium carbon (Pd–C). Intramolecular condensation of **12a** was achieved with the use of diethyl phosphorocyanidate (DEPC) to afford (*R*)-3-phthalimido-2,3,-dihydro-1,5(5*H*)-benzothiazepin-4-one (**13a**), which was allowed to react with *tert*-butyl chloroacetate followed by treatment with hydrazine hydrate to give the desired intermediate **15a** (R=H).

We attempted to prepare the (*S*)-3-(2-nitrophenoxy)-2-aminopropionic acid derivative required for the synthesis of **22** from 2-halonitrobenzenes and L-serine derivatives under a variety of conditions. The preparation of the material was accomplished by the use of 2-fluoronitrobenzene (**16**) and *N*-*tert*-butoxycarbonyl (Boc)-L-serine in the presence of 2-fold molar excess of sodium hydride in *N*,*N*-dimethylformamide (DMF) to yield (*S*)-3-(2-nitrophenoxy)-2-*tert*-butoxycarbonylaminopropionic acid (**17**). Catalytic reduction of the nitro group of **17** and subsequent cyclization of the resulting 2-aminophenoxy compound (**18**) by treatment with DEPC gave (*S*)-3-*tert*-butoxycarbonylamino-2,3-dihydro-1,5(5*H*)-benzoxazepin-4-one (**19**). Then, **19** was allowed to react with benzyl chloroacetate followed by removal of the Boc group with hydrogen chloride (HCl) to give the benzyl ester **22a**.

TABLE I. 1,5-Benzothiazepine (**7**, **26**, **33** and **37**) and 1,5-Benzoxazepine (**8**, **27**) Derivatives



No.	X	R	R_2	R_3	Configuration C*	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	$[\alpha]_D$ (deg.) in MeOH	(*c*) Temp. (°C)	ACE inhibition *in vitro* (%) 10^{-8} (M)	10^{-7}	10^{-6}	10^{-5}
26a	S	H	$Ph(CH_2)_2$–	C_2H_5	*S*	92	$C_{23}H_{26}N_2O_5S \cdot HCl$	57.68 (57.48	5.68 5.86	5.85 5.76)	−117	(0.7) 22	21	53	86	97
26b	S	H	$Ph(CH_2)_2$–	C_2H_5	*R*	87	$C_{23}H_{26}N_2O_5S \cdot HCl$	57.68 (57.53	5.68 5.76	5.85 5.70)	−173	(1.0) 22	—[a]	—	40	84
26c	S	7-CH_3	$Ph(CH_2)_2$–	C_2H_5	*S*	93	$C_{24}H_{28}N_2O_5S \cdot HCl \cdot 1/2\,H_2O$	57.42 (57.67	6.02 6.16	5.58 5.36)	−107	(0.6) 29	—	46	82	95
26d	S	7-CH_3	$Ph(CH_2)_2$–	C_2H_5	*R*	98	$C_{24}H_{28}N_2O_5S \cdot HCl \cdot 1/2\,H_2O$	57.42 (57.57	6.02 6.14	5.58 5.36)	−161	(0.6) 29	—	—	13	66
26e	S	7-OCH_3	$Ph(CH_2)_2$–	C_2H_5	*S*	95	$C_{24}H_{28}N_2O_6S \cdot HCl$	56.63 (56.02	5.74 5.86	5.50 5.36)	−94	(0.5) 29	—	18	61	87
26f	S	7-OCH_3	$Ph(CH_2)_2$–	C_2H_5	*R*	89	$C_{24}H_{28}N_2O_6S \cdot HCl$	56.63 (56.06	5.74 5.89	5.50 5.38)	−138	(0.6) 29	—	—	33	75
26g	S	7-Cl	$Ph(CH_2)_2$–	C_2H_5	*S*	79	$C_{23}H_{25}ClN_2O_5S \cdot HCl$	53.80 (53.65	5.10 5.23	5.46 5.71)	−99	(0.4) 24	—	41	81	96
26h	S	7-Cl	$Ph(CH_2)_2$–	C_2H_5	*R*	73	$C_{23}H_{25}ClN_2O_5S \cdot HCl$	53.80 (53.73	5.10 5.34	5.46 5.21)	−145	(0.4) 24	—	10	31	77
26i	S	7,8-$(CH_2)_3$	$Ph(CH_2)_2$–	C_2H_5	*RS*[b]	84[c]	$C_{26}H_{30}N_2O_5S \cdot HCl$	60.16 (59.97	6.02 6.31	5.40 5.11)	—		—	58	85	96
26j	S	7-CF_3	$Ph(CH_2)_2$–	C_2H_5	*RS*	79	$C_{24}H_{25}F_3N_2O_5S \cdot HCl$	51.02 (51.24	5.00 5.01	4.96 5.55)	—		—	—	24	67

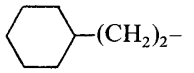
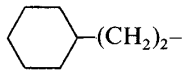
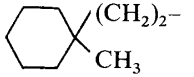
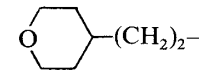
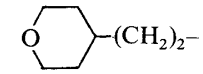
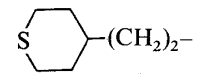
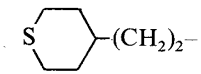
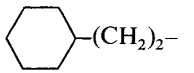
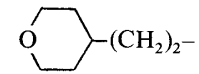
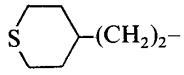
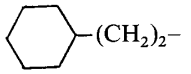
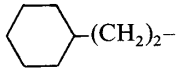
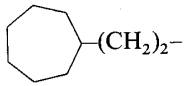
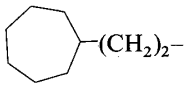
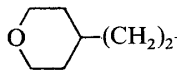
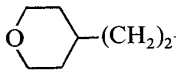
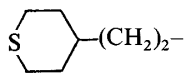
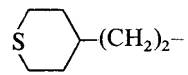
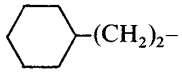
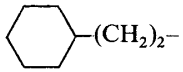
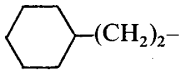
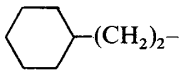
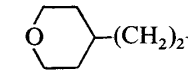
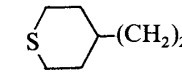
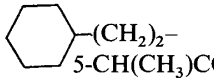
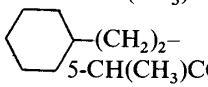
26k	S	H		C_2H_5	*S*	92	$C_{23}H_{32}N_2O_5S \cdot HCl$	56.95 (56.52	6.86 6.86	5.78 5.50)	−125	(0.7) 19	39	83	95	99
26l	S	H		C_2H_5	*R*	97	$C_{23}H_{32}N_2O_5S \cdot HCl$	56.95 (56.85	6.86 7.15	5.78 5.55)	−161	(0.9) 22	—	20	73	93
26m	S	H	$CH_3(CH_2)_7-$	C_2H_5	*RS*	66	$C_{23}H_{34}N_2O_5S \cdot HCl$	56.72 (56.18	7.24 7.31	5.75 5.57)	—		—	57	88	97
26n	S	H	$(Ph)_2CHCH_2-$	C_2H_5	*RS*	86	$C_{29}H_{30}N_2O_5S \cdot HCl$	62.75 (62.28	5.63 5.75	5.05 4.55)	—		—	23	64	89
26o	S	H	$(CH_3)_2CH(CH_2)_2-$	C_2H_5	*S*	84	$C_{20}H_{28}N_2O_5S \cdot HCl$	53.99 (53.98	6.57 6.79	6.30 6.04)	−150	(0.5) 24.5	—	48	84	96
26p	S	H	$(CH_3)_2CH(CH_2)_2-$	C_2H_5	*R*	52	$C_{20}H_{28}N_2O_5S \cdot HCl$	53.99 (53.86	6.57 6.81	6.30 5.99)	−175	(0.5) 24.5	—	16	30	69
26q	S	H		C_2H_5	*RS*	79	$C_{24}H_{34}N_2O_5S \cdot HCl$	57.76 (57.28	7.07 7.23	5.61 5.39)	−145	(1.0) 25	—	53	87	98
26r	S	H		C_2H_5	*S*	89	$C_{22}H_{30}N_2O_6S \cdot HCl \cdot$ $1/2\,H_2O$	53.26 (53.50	6.50 6.61	5.65 5.53)	−119	(0.6) 22	—	—	70	91
26s	S	H		C_2H_5	*R*	50	$C_{22}H_{30}N_2O_6S \cdot HCl$	54.26 (54.09	6.42 6.60	5.75 5.33)	−151	(0.6) 22	—	—	—	25
26t	S	H		C_2H_5	*S*	85	$C_{22}H_{30}N_2O_5S_2 \cdot HCl$	52.53 (52.20	6.21 6.32	7.57 7.31)	−108	(0.6) 22	—	—	83	95
26u	S	H		C_2H_5	*R*	74	$C_{22}H_{30}N_2O_5S_2 \cdot HCl$	52.53 (52.49	6.21 6.41	7.51 7.11)	−144	(0.6) 22	—	—	—	37
26v	S	H	$Ph(CH_2)_2-$	$PhCH_2-$	*S*	74	$C_{28}H_{28}N_2O_5S \cdot HCl$	62.16 (61.77	5.40 5.44	5.18 4.96)	−82	(0.5) 24	14	59	90	99
7a	S	H	$Ph(CH_2)_2-$	H	*S*	92	$C_{21}H_{22}N_2O_5S$	60.86 (60.53	5.35 5.36	6.76 6.79)	−119	(0.4) 25	46	91	99	—
7b	S	H	$Ph(CH_2)_2-$	H	*R*	48	$C_{21}H_{20}N_2Na_2O_5S \cdot$ $5/2\,H_2O$	50.10 (50.28	5.00 5.29	5.56 5.91)	—		—	—	50	86
7c	S	H		H	*S*	77	$C_{21}H_{28}N_2O_5S \cdot H_2O$	57.52 (57.20	6.89 6.91	6.39 6.42)	−137	(1.0) 25	77	96	100	—
7d	S	H		H	*S*	98	$C_{20}H_{26}N_2O_6S \cdot$ $1/2\,H_2O$	55.67 (55.52	6.30 5.91	6.49 6.43)	−140	(0.6) 23	50	93	—	—

TABLE I. (continued)

No.	X	R	R_2	R_3	Configuration C*	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	$[\alpha]_D$ (deg.) in MeOH	(*c*) Temp. (°C)	ACE inhibition *in vitro* (%) 10^{-8} (M)	10^{-7} (M)	10^{-6} (M)	10^{-5} (M)
7e	S	H		H	*S*	73	$C_{20}H_{26}N_2O_5S_2 \cdot H_2O$	52.61 (52.78	6.18 5.94	6.14 6.05)	−106	(0.2)[d] 23	47	90	—	—
27a	O	H	$Ph(CH_2)_2-$	C_2H_5	*S*	85	$C_{23}H_{26}N_2O_6 \cdot HCl \cdot 1/2\,H_2O$	58.54 (58.45	5.98 6.08	5.94 5.71)	−70	(0.6) 24	—	12	54	90
27b	O	H	$Ph(CH_2)_2-$	C_2H_5	*R*	87	$C_{23}H_{26}N_2O_6 \cdot HCl \cdot H_2O$	57.44 (57.39	6.08 5.97	5.83 5.74)	−99	(0.6) 24	—	—	17	70
27c	O	H		C_2H_5	*S*	99	$C_{23}H_{32}N_2O_6$	63.87 (64.07	7.46 7.64	6.48 6.45)	−166	(0.6) 25	—	47	88	98
27d	O	H		C_2H_5	*R*	46	$C_{23}H_{32}N_2O_6 \cdot HCl$	58.91 (58.89	7.09 7.23	5.97 5.82)	−134	(0.5) 25	—	—	—	53
27e	O	H		C_2H_5	*S*	95	$C_{24}H_{34}N_2O_6 \cdot HCl \cdot 1/2\,H_2O$	58.59 (58.29	7.38 7.41	5.69 5.58)	−101	(0.6) 24	—	57	93	—
27f	O	H		C_2H_5	*R*	91	$C_{24}H_{34}N_2O_6 \cdot HCl \cdot 1/2\,H_2O$	58.59 (58.43	7.38 7.40	5.69 5.60)	−125	(0.6) 24	—	—	25	—
27g	O	H	$(C_2H_5)_2CH(CH_2)_2-$	C_2H_5	*S*	87	$C_{22}H_{32}N_2O_6 \cdot HCl \cdot 1/2\,H_2O$	56.70 (56.81	7.35 7.28	6.01 6.00)	−104	(0.5) 24	12	34	80	—
27h	O	H	$(C_2H_5)_2CH(CH_2)_2-$	C_2H_5	*R*	82	$C_{22}H_{32}N_2O_6 \cdot HCl \cdot 1/2\,H_2O$	56.70 (56.64	7.35 7.34	6.01 5.97)	−123	(0.5) 24	—	—	16	—
27i	O	H	$CH_3(CH_2)_7-$	C_2H_5	*RS*	91	$C_{23}H_{34}N_2O_6 \cdot HCl \cdot 1/2\,H_2O$	57.55 (57.60	7.56 7.50	5.84 5.93)	−134	(0.5) 23	—	34	84	—
27j	O	H		C_2H_5	*S*	90	$C_{22}H_{30}N_2O_7 \cdot HCl \cdot 1/2\,H_2O$	55.06 (54.72	6.72 6.66	5.84 5.71)	−105	(0.6) 22	—	—	36	—
27k	O	H		C_2H_5	*R*	72	$C_{22}H_{30}N_2O_7 \cdot HCl \cdot 1/2\,H_2O$	55.06 (55.11	6.72 6.78	5.84 5.38)	−121	(0.5) 22	—	—	—	—
27l	O	H		C_2H_5	*S*	72	$C_{22}H_{30}N_2O_6S \cdot HCl \cdot 1/2\,H_2O$	53.27 (53.15	6.50 6.20	5.65 5.77)	−59	(0.5) 23	—	—	60	—
27m	O	H		C_2H_5	*R*	74	$C_{22}H_{30}N_2O_6S \cdot HCl \cdot 1/2\,H_2O$	53.27 (53.32	6.50 6.47	5.65 5.59)	−69	(0.4) 23	—	—	—	—

27n	O	H		$PhCH_2-$	*S*	71	$C_{28}H_{34}N_2O_6 \cdot HCl$	63.33 (63.02	6.64 6.94	5.28 5.03)	−115	(0.5) 25	—	51	88	—
27o	O	H		$CH_3(CH_2)_3-$	*S*	86	$C_{25}H_{36}N_2O_6 \cdot HCl$	60.41 (60.33	7.50 7.36	5.64 5.49)	−106	(0.4) 23	—	51	92	—
27p	O	H		$H_5C_2OCOCH_2-$	*S*	94	$C_{25}H_{34}N_2O_8 \cdot HCl \cdot 1/2\,H_2O$	56.02 (56.02	6.76 6.72	5.23 5.09)	−114	(0.6) 23	—	—	45	—
8a	O	H	$Ph(CH_2)_2$	H	*S*	72	$C_{21}H_{22}N_2O_6 \cdot H_2O$	60.57 (60.44	5.81 5.69	6.73 6.68)	−87	(0.4) 25	31	91	99	—
8b	O	H	$Ph(CH_2)_2-$	H	*R*	23	$C_{21}H_{22}N_2O_6 \cdot 3/2\,H_2O$	59.29 (59.63	5.92 5.64	6.59 6.73)	−112	(0.3) 25	—	—	76	—
8c	O	H		H	*S*	76	$C_{21}H_{28}N_2O_6 \cdot H_2O$	59.70 (59.80	7.16 7.03	6.63 6.68)	−131	(0.4) 23	—	95	100	—
8d	O	H		H	*S*	93	$C_{20}H_{26}N_2O_7 \cdot 1/2\,H_2O$	57.82 (57.41	6.55 6.01	6.74 6.36)	−128	(0.4) 23	42	93	—	—
8e	O	H		H	*S*	85	$C_{20}H_{26}N_2O_6S \cdot H_2O$	54.53 (54.12	6.41 6.32	6.36 6.30)	−68	(0.5) 23	52	93	—	—
37a	S	H		C_2H_5	*S*	67	$C_{24}H_{34}N_2O_5S \cdot HCl$	57.81 (57.76	7.30 7.07	5.14 5.61)	—		—	62	92	—
37b	S	H		C_2H_5	*R*	—	$C_{24}H_{34}N_2O_5S \cdot HCl \cdot 1/2\,H_2O$	56.74 (56.92	7.14 7.20	5.51 5.26)	—		—	—	38	—
33	S	H	$Ph(CH_2)_2$–1-oxide	C_2H_5	*S*	56	$C_{23}H_{26}N_2O_6S \cdot HCl \cdot H_2O$	53.85 (54.29	5.70 5.70	5.46 5.27)	—		—	—	21	64
2b (MK-422)													62	97	—	—
5a (CV-3317)													—	59	88	—
5b (CV-3317-COOH)													53	87	—	—

a) Not determined. *b*) Mixture of diastereomers. *c*) Based on **15e**. *d*) In MeOH–1 N HCl.

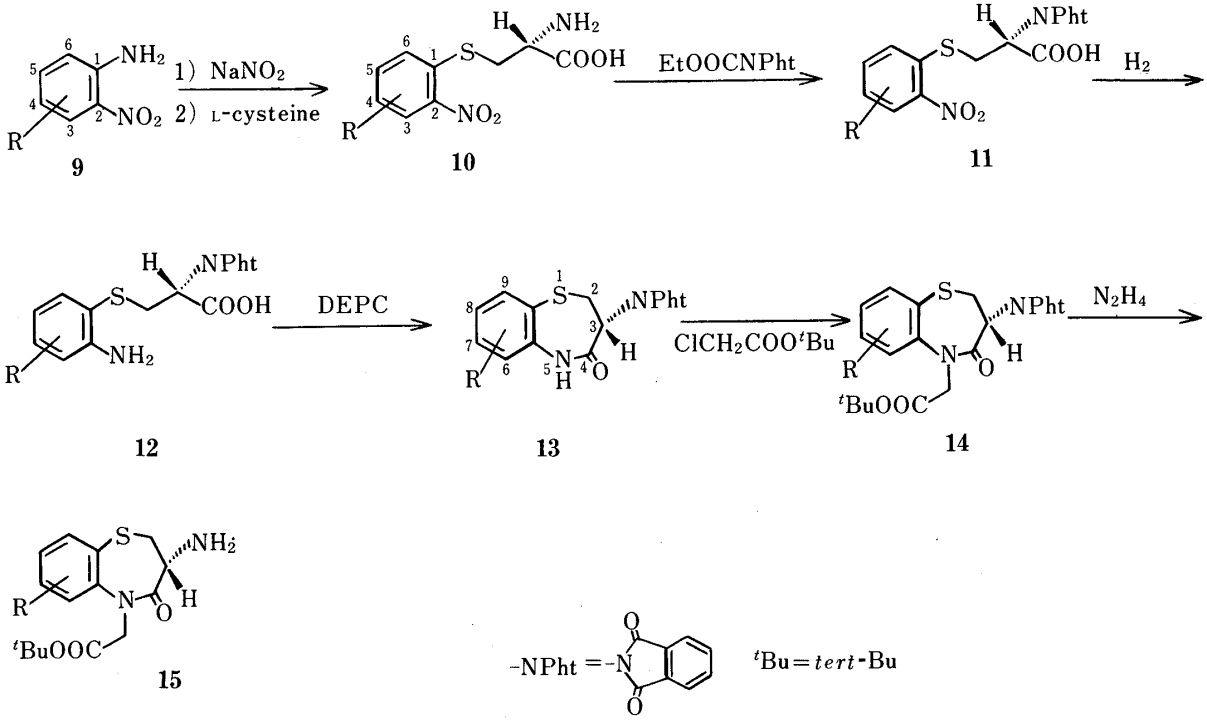


Chart 3

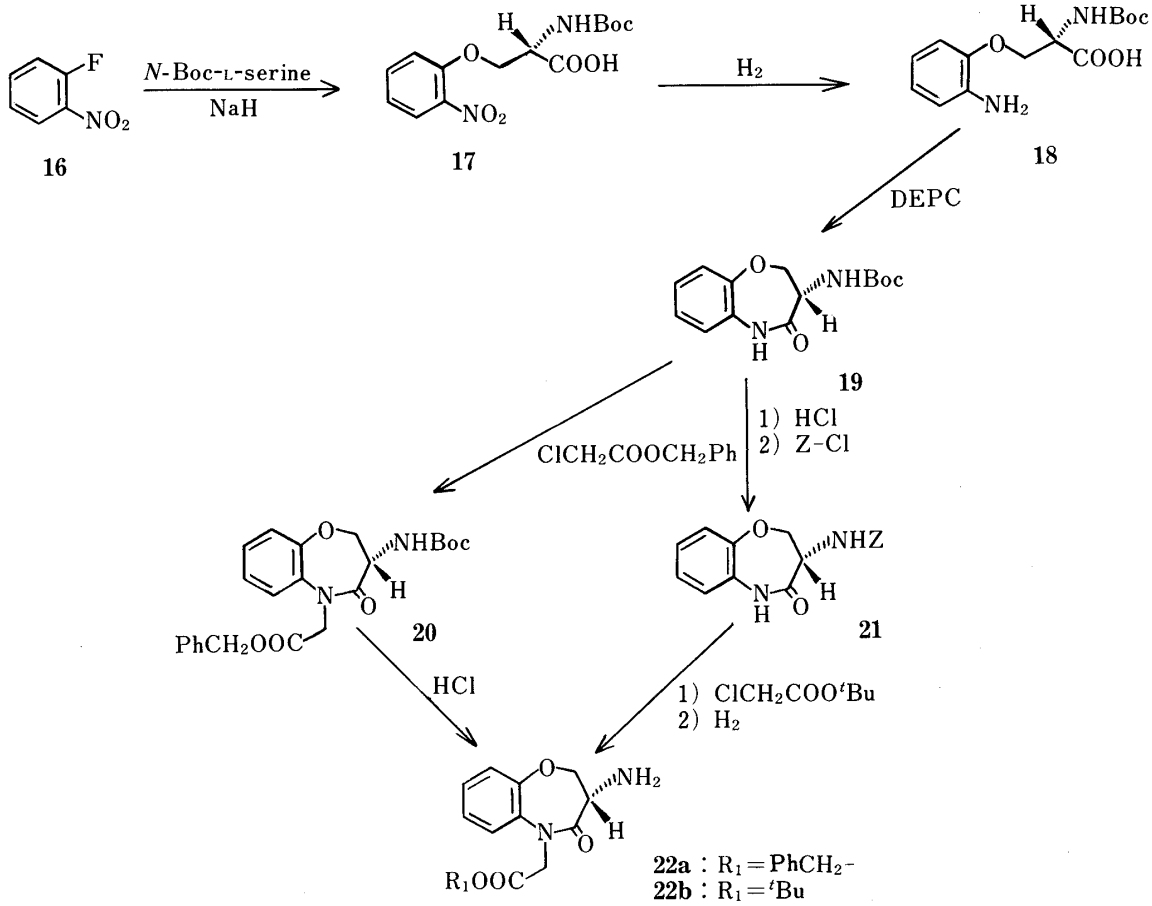


Chart 4

Furthermore the *tert*-butyl ester **22b** was prepared on account of the synthetic utility of the *tert*-butoxy moiety, which is stable under alkaline and catalytic hydrogenation conditions. Thus, the Boc group of **19** was removed with HCl and the benzyloxycarbonyl (Z) group was introduced with Z-Cl. The resulting (*S*)-3-benzyloxycarbonylamino derivative **21** was allowed to react with *tert*-butyl chloroacetate followed by catalytic hydrogenolysis to afford **22b**.

The synthetic route to **7a** and **8a** from **15a** and **22a** is illustrated in Chart 5. Reductive alkylation of the benzothiazepine derivative **15a** with **23a** in the presence of sodium cyanoborohydride ($NaBH_3CN$) afforded a mixture of two diastereomers **24a, b** (R = H, R_1 = *tert*-butyl, R_2 = phenethyl), which were separated by silica gel column chromatography to give **24a** with lower *Rf* and **24b** with higher *Rf*. The *tert*-butyl ester of each isomer **24a** and **24b** was deprotected smoothly with HCl at room temperature to yield the monoacids **26a, b** (R = H, R_2 = phenethyl) respectively.

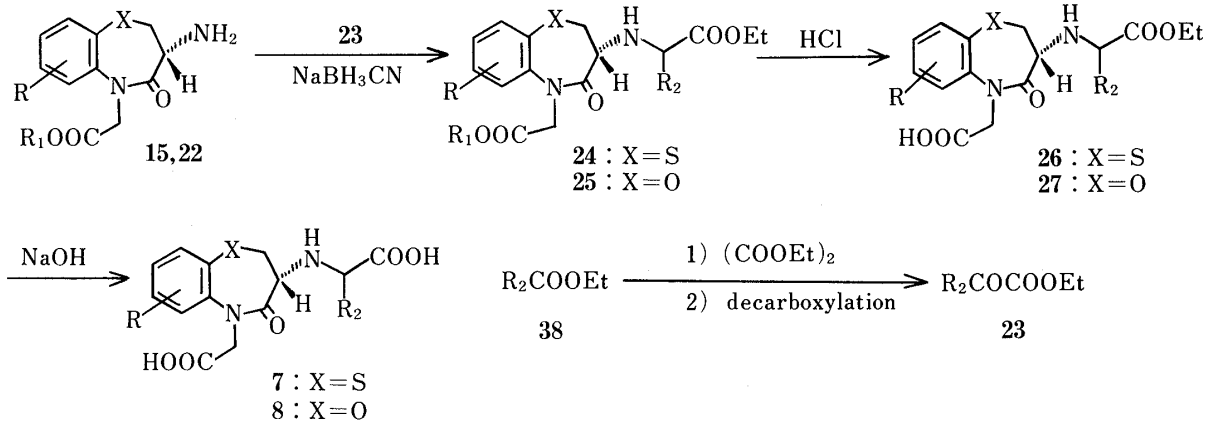


Chart 5

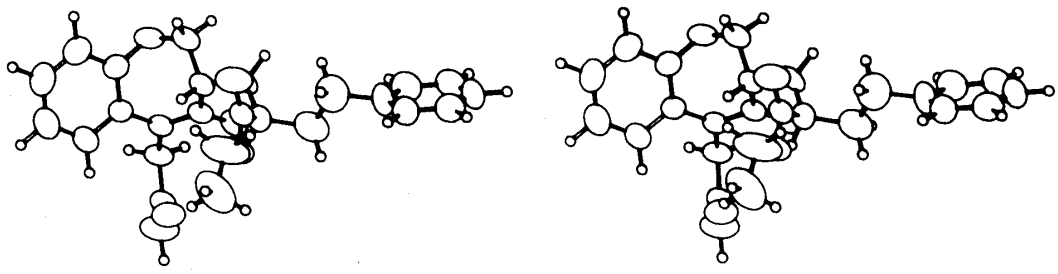


Fig. 1. Stereoscopic Drawing of **27a**

In a manner similar to that used for the preparation of **24a, b**, the oxazepine derivatives **25a** (lower *Rf*) and **25b** (higher *Rf*) were prepared by reductive alkylation of **22a** with **23a** followed by chromatographic separation of the resulting diastereomers. In this case, deprotection of the benzyl esters (**25a, b**) was carried out by catalytic hydrogenolysis using Pd–C to give **27a, b** (R = H, R_2 = phenethyl), respectively.

The monoacids (**26a, b** and **27a, b**) obtained above were tested for *in vitro* ACE inhibitory activity. The results are shown in Table I. Compounds **26a** and **27a** proved to be about ten times more active than the corresponding isomers **26b** and **27b**. It was previously observed in studies of *N*-carboxymethyldipeptide inhibitors such as **2**[1b] and **5**[6] that the isomer with (*S*)-configuration at the chiral center in the 1-ethoxycarbonyl-3-phenylpropyl moiety is more active than the corresponding (*R*)-diastereomer. Therefore, the newly formed asymmetric center of **26a** and **27a** should have (*S*)-configuration. The stereochemical assignment was

confirmed by X-ray analysis of (*RS*)-3-[(*RS*)-1-ethoxycarbonyl-3-phenylpropyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic acid (racemic **27a**),[10] shown in Fig. 1.

Our target compounds **7a** and **8a**, which were generated from the corresponding monoacids (**26a** and **27a**) by saponification, exhibited very potent ACE inhibitory activity *in vitro*, as shown in Table I.

This result led us to investigate further modification of the substituents[11] of the fused benzene and 3-amino moieties in order to find even more potent inhibitors.

First, benzothiazepine derivatives (**26c—i**, Table I) with a variety of substituents on the benzene ring were prepared starting from substituted 2-nitroanilines **9b** (R = 4-CH_3), **9c** (R = 4-CH_3), **9d** (R = 4-Cl) and **9e** (R = 4,5-$(CH_2)_3$-) as illustrated in Charts 3 and 5.[12] The 7-trifluoromethyl derivative (**26j**) was prepared *via* another route (shown in Chart 6) starting from **9f** (R = 4-CF_3).

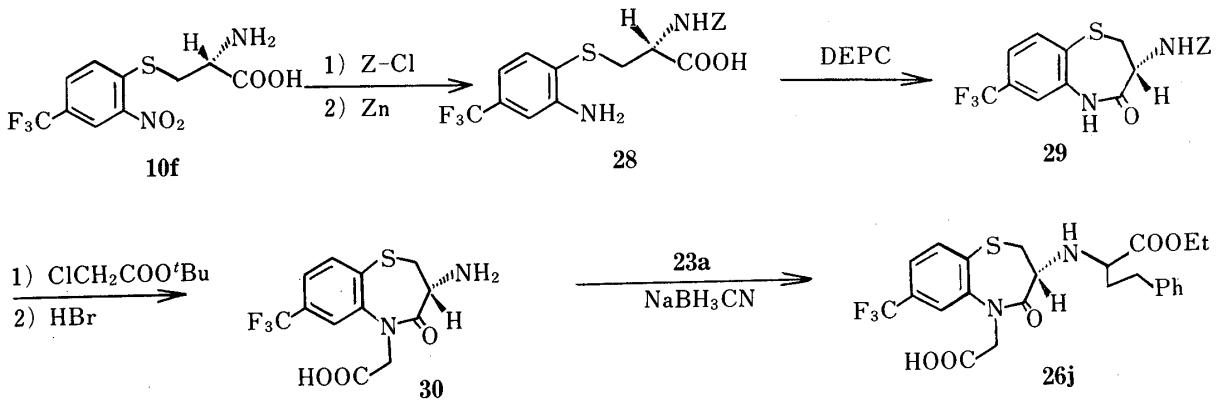


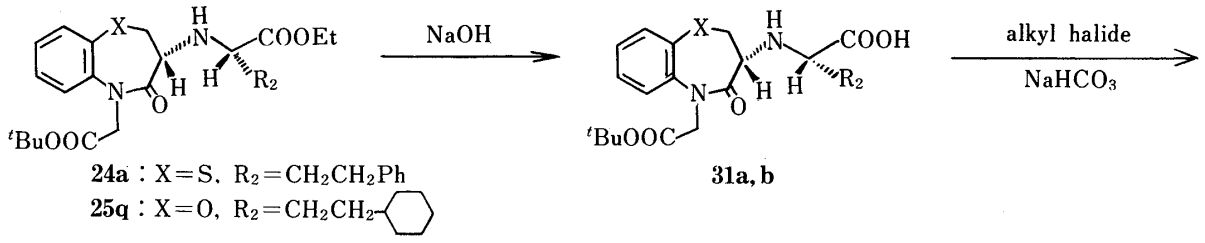
Chart 6

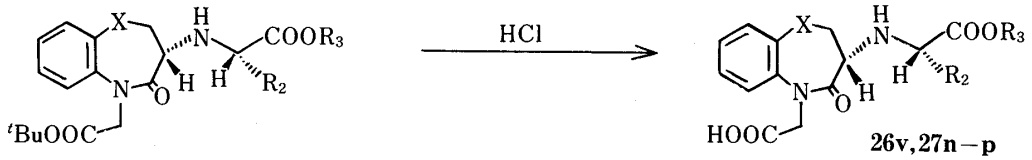
Thus, the amino acid **10f** was protected with the Z group followed by reduction of the nitro group with zinc to give **28**, which was cyclized with DEPC to give the benzothiazepin-4-one derivative (**29**). After the introduction of the *tert*-butoxycarbonylmethyl group at the 5-position, deprotection[13] was carried out with hydrogen bromide (HBr) to yield **30**, reductive alkylation of which in the presence of $NaBH_3CN$ gave **26j**.

Secondly, modification of the substituents of the 3-amino moiety was carried out. The required α-oxoesters **23b—j** (Table VI) were prepared from the corresponding esters (**38b—j**) by condensation reaction with diethyl oxalate followed by decarboxylation. These oxoesters (**23b—j**) were allowed to react with **15a** or **22a** under reductive conditions, and the resulting diesters **24** and **25** were led to the monoacids (**26k—u** and **27c—m**, Table I). Some of the monoacids (**26k**, **r**, **t** and **27c**, **j**, **l**) were converted to diacids (**7c—e** and **8c—e**, Table I) by hydrolysis. Next, modification of the ethyl ester moiety was carried out as shown in Chart 7 in order to examine the change of *in vivo* character after oral administration. Thus, the *tert*-butyl ester derivative of thiazepine (**24a**) was treated with alkali to give the monoacid derivative (**31a**), which was alkylated with benzyl bromide to give the diester (**32a**) treatment of which with HCl gave **26v**.

In the case of oxazepine, the (*S*),(*S*)-isomer of the diester intermediate (**25q** with lower *Rf*) was prepared from **22b** by reductive alkylation with **23b** (R_2 = cyclohexylethyl) using $NaBH_3CN$, followed by separation by silica gel column chromatography. The monoacid **31b** obtained from **25q** by alkaline hydrolysis was alkylated with benzyl bromide, butyl iodide and ethyl bromoacetate to give **32b**, **c**, **d**, deprotection of which gave **27n**, **o**, **p**, respectively.

Finally, synthesis of the *S*-oxide and 5-propionic acid derivatives of thiazepine was undertaken (Chart 8). Oxidation of the sulfur atom of **26a** proceeded smoothly with the use of *m*-chloroperbenzoic acid to give **33**.[14]





32a : X=S, $R_2=CH_2CH_2Ph$, $R_3=CH_2Ph$
32b : X=O, $R_2=CH_2CH_2$-cyclohexyl, $R_3=CH_2Ph$
32c : X=O, $R_2=CH_2CH_2$-cyclohexyl, $R_3=(CH_2)_3CH_3$
32d : X=O, $R_2=CH_2CH_2$-cyclohexyl, $R_3=CH_2COOEt$

Chart 7

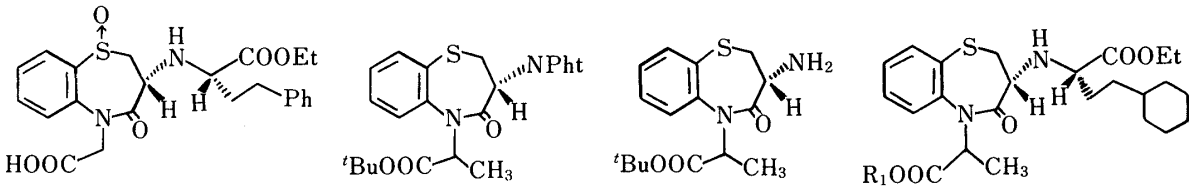


Chart 8

Thorsett *et al.* reported[5c] that the introduction of a methyl group at the α-carbon of the acetic acid moiety in the series of monolactam derivatives (**3**) enhanced the *in vitro* ACE inhibitory activity. Therefore we prepared the α-methylacetic acid derivative (**37a**)[14] by a method similar to those illustrated in Charts 3 and 5 by way of the intermediates **13a**, **34**, **35** and **36a**.

Biological Results and Discussion

The compounds (**7**, **8**, **26**, **27**, **33** and **37**) described above were evaluated for *in vitro* inhibition of rabbit lung ACE using the method reported by Cushman and Cheung[15] with a slight modification. The results are shown in Table I. The initially designed benzofused heterocyclic lactams **7a** and **8a** were highly active inhibitors and their *in vitro* potency was comparable to that of CV-3317-COOH (**5b**) or MK-422 (**2b**). In the case of substituted *N*-carboxymethyldipeptide ACE inhibitors such as **2** and **5**, it is known[1-3,5,6] that the monoacid is an orally well absorbed pro-drug for the corresponding diacids, and therefore the former is less active *in vitro* than the latter. In this series of benzothiazepine and benzoxazepine derivatives, the same feature was observed in comparing the *in vitro* activities of monoacids (**26a** and **27a**) and diacids (**7a** and **8a**). The modification of substituents on the fused benzene

TABLE II. ACE Inhibitory Activity *in Vivo*

No.	Inhibition of angiotensin I pressor response in rats 10 mg/kg *p.o.* (%)					
	1/3	1	2	3	4	5 (h)
26a	85	68	51	54	33	30
26k	92	72	68	60	45	28
26r	88	78	41	30	—[a]	—
26v	89	79	76	57	36	38
27a	95	83	46	27	23	11
27c	92	87	81	72	65	55
27e	96	76	60	37	34	19
27g	93	73	63	61	38	35
27n	87	78	82	84	84	80
27o	98	96	86	88	80	71
37a	81	55	13	22	24	26
CV-3317 (**5a**)	93	87	77	64	60	53

a) Not determined.

of benzothiazepines proved to have little effect on the potency (**26c**—**j**). Oxidation of the sulfur atom led to reduced potency (compare **33** with **26a**). As regards replacement of the phenethyl group in the side chain at the 3-position with other lipophilic substituents, slightly enhanced potency was observed in the cyclohexylethyl derivatives (**26k** and **7c**).

Selected monoacid derivatives (**26a**, **k**, **r**, **v**, **27a**, **c**, **e**, **g**, **n**, **o** and **37a**) were tested for *in vivo* ACE inhibitory activity. The activity was assessed in terms of the inhibition (percentage) by the compounds, after oral administration, of the vasopressor response induced by intravenous administration of angiotensin I in conscious normotensive rats (Table II). Most of the compounds showed potent *in vivo* inhibitory activity. A duration of activity nearly equal to that of CV-3317 (**5a**) was found in the cyclohexylethyl derivative **27c**. The modification of the ethyl ester moiety of **27c** was proved to result in an increase of duration (**27n** and **27o**). The effect of methylation of the α-carbon in the 5-acetic acid moiety was found to be insignificant *in vivo* (compare **37a** with **26k**).

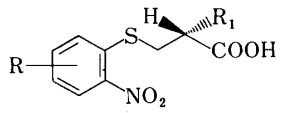
For effective interaction with ACE, the inhibitor should have the functional groups at the optimum positions in space. The high ACE inhibitory activity of the series of benzothiazepines and benzoxazepines shown in Tables I and II suggests that these conformationally restricted drivatives exist in a conformation suitable for binding to ACE. The result of X-ray analysis of racemic **27a** (Fig. 1) indicates that the arrangement of functional groups such as carboxyl, amino, amido and hydrophobic groups corresponds well to that of the initially assumed stable conformer **5c** of CV-3317. Benzothiazepine derivatives may take a conformation[7] similar to that of benzoxazepines, since the two series show little difference in *in vitro* and *in vivo* activities.

This work has provided useful information with regard to the spatial requirements of ACE inhibitors. Further work is in progress.

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 in the indicated solvents on Varian EM-360, EM-390 and XL-100A 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. $[\alpha]_D$ values were determined in

TABLE III. (*R*)-2-Amino-3-(2-nitrophenyl)thiopropionic Acid Derivatives (**10** and **11**)



No.	R	R_1	mp (dec.) °C	Yield (%)	Formula	Analysis (%) Calcd (Found) C	H	N	$[\alpha]_D$ (deg)[a]	(*c*) Temp. (°C)
10a	H	NH_2	167 169	60	$C_9H_{10}N_2O_4S$	44.63	4.16	11.57	+68	(0.6)
						(44.51	4.43	11.43)		24
10b	4-CH_3	NH_2	156—158	27	$C_{10}H_{12}N_2O_4S \cdot 1/2\,H_2O$	45.29	4.92	10.56	+44	(0.2)
						(44.90	4.60	10.86)		26.5
10c	4-OCH_3	NH_2	166—168	14	$C_{10}H_{12}N_2O_5S$	44.11	4.44	10.29	+24	(0.2)
						(43.67	4.52	9.94)		26
10d	4-Cl	NH_2	169—171	47	$C_9H_9ClN_2O_4S \cdot 1/2\,H_2O$	37.84	3.53	9.81	+46	(0.4)
						(37.58	3.26	9.65)		29
10e	4,5-$(CH_2)_3$	NH_2	157—158	6.1	$C_{12}H_{14}N_2O_4S \cdot 1/2\,H_2O$	49.47	5.19	9.62	+33	(0.2)
						(49.13	5.00	9.58)		27
10f	4-CF_3	NH_2	181—183	41	$C_{10}H_9F_3N_2O_4S$	38.71	2.92	9.03	+53	(0.1)
						(38.43	2.86	9.02)		24
11a	H	NPht[c]	220—222	81	$C_{17}H_{12}N_2O_6S$	54.84	3.25	7.53	−79	(0.9)
						(54.46	3.26	7.46)		24
11b	4-CH_3	NPht	—[b]	81	$C_{18}H_{14}N_2O_6S$	—	—	—	—	
11c	4-OCH_3	NPht	157—159	89	$C_{18}H_{14}N_2O_7S$	53.73	3.51	6.96	−120	(0.7)
						(53.82	3.50	6.65)		26
11d	4-Cl	NPht	183—185	37	$C_{17}H_{11}ClN_2O_6S$	50.19	2.73	6.89	−116	(0.6)
						(50.18	2.74	6.80)		28
11e	4,5-$(CH_2)_3$	NPht	219—222	58	$C_{20}H_{16}N_2O_6S$	58.25	3.91	6.79	−149	(0.1)
						(58.25	3.96	6.73)		26.5

a) In 1 N HCl. *b*) Used for the next step without purification. *c*) Phthalimido group.

the indicated solvents on a JASCO DIP-181 4-4822.

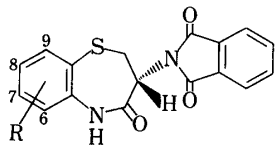
Reactions were run at room temperature unless otherwise noted, and followed by thin-layer chromatography (TLC) on Merck F-254 silica gel plates. Standard work-up procedures were as follows. The reaction mixture was partitioned between the indicated solvent and water. The organic extract was washed successively with the following aqueous solutions: water, NaOH solution (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.

(*R*)-2-Amino-3-(2-nitrophenyl)thiopropionic Acids (10, Table III)——(*R*)-2-Amino-3-(2-nitrophenyl)thiopropionic acid (**10a**) was prepared according to the reported procedure.[9] Substituted derivatives (**10b—f**) were obtained from substituted 2-nitroaniline (**9b—f**) and cysteine by a procedure similar to that used for **10a**.

(*R*)-3-(2-Nitrophenyl)thio-2-phthalimidopropionic Acids (11, Table III)——*N*-Ethoxycarbonylphthalimide (3.5 g) and **10a** (2.9 g) were added to an aqueous solution (200 ml) of Na_2CO_3 (1.4 g). After being stirred for 5 h, the mixture was filtered and filtrate was made acidic with conc. HCl. The deposited crystals were collected by filtration and recrystallized from EtOH to give **11a** (3.6 g) as pale yellow needles. Compounds **10b—e** were allowed to react with *N*-ethoxycarbonylphthalimide similarly to yield **11b—e**.

(*R*)-3-Phthalimido-2,3-dihydro-1,5-(5*H*)-benzothiazepin-4-ones (13, Table IV)——A mixture of **11a** (10 g) and MeOH (300 ml) was hydrogenated over 5% Pd–C (3.5 g) at atmospheric pressure. After absorption of the calculated amount of hydrogen, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was crystallized from Et_2O–petroleum ether to give **12a** (8.4 g, 91%) as pale yellow crystals. DEPC (5.5 g) was added dropwise to a stirred solution of **12a** (8.4 g) in DMF (50 ml) at ice bath temperature. The mixture was stirred for 5 min, then Et_3N (2.28 g) was added dropwise at ice bath temperature. The stirring was continued for 30 min at ice bath temperature and for another 1 h at room temperature, then the mixture was diluted with water (200 ml) and allowed to stand overnight. The deposited solid was collected by filtration and purified by silica gel column chromatography (CH_2Cl_2 : AcOEt = 2 : 1) to give **13a** (5.4 g) as colorless prisms. MS *m/z*: 324 (M^+). IR ν_{max}^{Nujol} cm^{-1}:

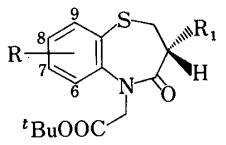
TABLE IV. (*R*)-3-Phthalimido-2,3-dihydro-1,5(5*H*)-benzothiazepin-4-one Derivatives (**13**)



13	R	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found)			$[\alpha]_D$ (deg)	(*c*) Temp. (°C)
					C	H	N		
a	H	202—205	68	$C_{17}H_{12}N_2O_3S$	62.95	3.73	8.64	−164[b]	(0.9)
					(63.15	4.02	8.49)		21
b	7-CH_3	222—225	39[a]	$C_{18}H_{14}N_2O_3S$	63.89	4.17	8.28	−180[b]	(0.5)
					(63.96	4.27	8.20)		27
c	7-OCH_3	255—258	43	$C_{18}H_{14}N_2O_4S$	61.01	3.98	7.90	−34[c]	(0.5)
					(60.96	3.92	7.64)		26
d	7-Cl	256—258	22	$C_{17}H_{11}ClN_2O_3S$	56.91	3.09	7.81	−169[b]	(0.1)
					(57.15	3.22	7.80)		25
e	7,8-$(CH_2)_3$	240—243	39	$C_{20}H_{16}N_2O_3S$	65.92	4.43	7.69	−136[b]	(0.1)
					(65.97	4.53	7.56)		27

a) Based on **10b**. *b*) In MeOH. *c*) In $CHCl_3$.

TABLE V. *tert*-Butyl (*R*)-3-Amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetate Derivatives (**14** and **15**)



No.	R	R_1	mp (°C)	Yield (%)	Formula	Analysis (%) Calcd (Found)			$[\alpha]_D$[c] (deg)	(*c*) Temp. (°C)
						C	H	N		
14a	H	NPht	181—184	74[a] 71[b]	$C_{23}H_{22}N_2O_5S$	63.01	5.06	6.39	−164	(0.4)
						(62.95	5.10	6.34)		24.5
14b	7-CH_3	NPht	140—143	75[a]	$C_{24}H_{24}N_2O_5S$	63.70	5.35	6.19	−151	(0.6)
						(63.49	5.43	6.13)		27
14c	7-OCH_3	NPht	155—157	66[a]	$C_{24}H_{24}N_2O_6S$	61.53	5.16	5.98	−139	(0.8)
						(61.57	5.20	6.00)		26
14d	7-Cl	NPht	182—184	85[a]	$C_{23}H_{21}ClN_2O_5S$	58.41	4.48	5.92	−148	(0.4)
						(58.36	4.67	5.83)		24
14e	7,8-$(CH_2)_3$	NPht	195—198	69[a]	$C_{26}H_{26}N_2O_5S$	65.26	5.48	5.85	−114	(0.6)
						(65.48	5.61	5.82)		27
15a	H	NH_2	86—89	71	$C_{15}H_{20}N_2O_3S$	58.42	6.54	9.08	−238	(1.0)
						(58.73	6.48	9.13)		20
15b	7-CH_3	NH_2	159—160[d]	96	$C_{16}H_{22}N_2O_3S \cdot C_2H_2O_4 \cdot H_2O$	50.22	6.09	6.51	−146	(0.5)
						(49.84	5.66	6.14)		27
15c	7-OCH_3	NH_2	175—178	92	$C_{16}H_{22}N_2O_4S \cdot HCl \cdot 1/2\,H_2O$	50.07	6.30	7.30	−147	(0.5)
						(49.88	6.21	7.26)		26.5
15d	7-Cl	NH_2	158—160[d]	77	$C_{15}H_{19}ClN_2O_3S \cdot C_2H_2O_4 \cdot H_2O$	45.29	5.14	6.21	−102	(0.4)
						(45.15	4.75	6.33)		24
15e	7,8-$(CH_2)_3$	NH_2	Oil	69[e]	$C_{18}H_{24}N_2O_3S$	—	—	—	—	

a) Method A. *b*) Method B. *c*) In MeOH. *d*) Oxalic acid salt. *e*) Used for the next step without purification.

1770, 1710, 1670 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 3.55 (1H, dd J=6, 12 Hz, C_2-H), 4.55 (1H, t, J=12 Hz, C_3-H), 5.05 (1H, dd J=6, 12 Hz, C_2-H). Substituted benzothiazepin-4-one derivatives (**13b—e**) were prepared similarly from **11b—e**.

***tert*-Butyl (*R*)-4-Oxo-3-phthalimido-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetate (14, Table V)**——Method A) Compound **13a** (4 g) was added to a cooled mixture of NaH (60% in oil, 0.5 g) and DMF (50 ml) in an ice bath. The mixture was stirred for 5 min, $ClCH_2COO^tBu$ (2 g) was added, and stirring was continued for 15 min. The mixture was diluted with ice-water (200 ml) and deposited crystals were collected by filtration, dried and purified by silica gel column chromatography (hexane : AcOEt = 3 : 1) to give **14a** (4 g) as colorless crystals. Recrystallization from ethyl ether gave colorless prisms.

Method B) *tert*-Butyl chloroacetate (39 g), K_2CO_3 (36 g) and KI (2 g) were added to a solution of **13a** (70 g) in DMF (300 ml). The mixture was stirred overnight and worked up (AcOEt; 0.1 N aq. HCl, water). The residue was crystallized from EtOH to give **14a** (67.4 g) as colorless crystals. IR ν_{max}^{Nujol} cm^{-1}: 1780, 1740, 1730, 1690 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.40 (9H, s, ^{t}Bu), 3.50 (1H, dd, J=6, 12 Hz, C_2-H), 4.10 (1H, d, J=17 Hz, N_5-CH), 4.65 (1H, t, J=12 Hz), 4.60 (1H, d, J=17 Hz, N_5-CH), 5.08 (1H, dd, J=6, 12 Hz, C_2-H), 7.20—7.55, 7.65—7.95 (8H, m, phenyl protons).

Substituted benzothiazepine-5-acetate derivatives (**14b—e**) were prepared from **13b—e** according to method A.

***tert*-Butyl (*R*)-3-Amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetates (15, Table V)**——A mixture of **14a** (4 g), $N_2H_4 \cdot H_2O$ (1.4 g) and EtOH (100 ml) was heated under reflux for 1 h, concentrated *in vacuo* and worked up (AcOEt; NaOH, water). The oily residue was crystallized from Et_2O–petroleum ether to give **15a** (2 g) as colorless prisms. IR ν_{max}^{Nujol} cm^{-1}: 3380, 3320 (NH), 1740, 1670 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.50 (9H, s, ^{t}Bu), 1.75 (2H, s, NH_2), 2.80 (1H, t, J=12 Hz, C_3-H), 3.45—3.75 (2H, m, 2 × C_2-H), 3.95 (1H, d, J=17 Hz, N_5-CH), 4.85 (1H, d, J=17 Hz, N_5-CH), 6.1—7.75 (4H, m, phenyl protons). Compounds **14b—e** were treated with N_2H_4 similarly to yield **15b—e**.

(*S*)-2-*tert*-Butoxycarbonylamino-3-(2-nitrophenoxy)propionic Acid (17)——A solution of Boc-L-serine (25 g) in DMF (10 ml) was added dropwise to a stirred mixture of NaH (60% in oil, 10.1 g) and DMF (200 ml) in a stream of N_2 at 0 °C. Stirring was continued until the evolution of hydrogen stopped, then **16** (19 g) was added dropwise to the mixture. After being stirred for 4 h, the mixture was poured into ice-aq. HCl and worked up (AcOEt; water). The residue was purified by silica gel column chromatography (hexane : AcOEt = 1 : 1) to give **17** (30 g, 75%) as a colorless liquid.

(*S*)-3-(2-Aminophenoxy)-2-*tert*-butoxycarbonylaminopropionic Acid (18)——A mixture of **17** (30 g) and MeOH (500 ml) was hydrogenated over 10% Pd–C (50% wet, 1 g) under ordinary pressure. The catalyst was filtered off, and the filtrate was concentrated *in vacuo*. The residue was crystallized from AcOEt to give **18** (23 g, 84%) as colorless crystals, mp 90—91 °C. *Anal.* Calcd for $C_{14}H_{20}N_2O_5$: C, 56.75; H, 6.80; N, 9.45. Found: C, 56.48; H, 6.82; N, 9.43.

(*S*)-3-*tert*-Butoxycarbonylamino-2,3-dihydro-1,5(5*H*)-benzoxazepin-4-one (19)——A solution of **18** (21.4 g) in DMF (120 ml) was treated with DEPC (14 g) and Et_3N (7 g) as described for the preparation of **13** to give **19**, which was recrystallized from AcOEt–hexane to yield colorless plates (12.3 g, 61%), mp 202—203 °C. $[\alpha]_D^{24.5}$ −19.5° (c=0.9, MeOH). *Anal.* Calcd for $C_{14}H_{18}N_2O_4$: C, 60.42; H, 6.52; N, 10.07. Found: C, 60.69; H, 6.71; N, 9.99. IR ν_{max}^{KBr} cm^{-1}: 1720, 1680 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.4 (9H, s, ^{t}Bu), 4.2 (1H, t, J=12 Hz, CH), 4.6 (2H, q, J=6 Hz, OCH_2), 5.55 (1H, m, NHBoc), 6.9—7.3 (4H, m, phenyl protons), 8.4 (1H, br s, N_5-H).

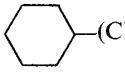
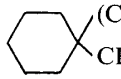
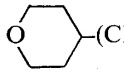
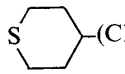
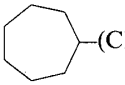
Benzyl (*S*)-3-*tert*-Butoxycarbonylamino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetate (20)——The reaction of **19** (12.3 g) with $ClCH_2COOCH_2Ph$ (8.7 g) in DMF (150 ml) in the presence of K_2CO_3 (8.7 g) and KI (1 g) was carried out according to method B. The product was recrystallized from AcOEt–hexane to give **20** (11.7 g, 62%) as colorless prisms, mp 122—124 °C. $[\alpha]_D^{24}$ −180° (c=1, MeOH). *Anal.* Calcd for $C_{23}H_{26}N_2O_6$: C, 64.78; H, 6.14; N, 6.57. Found: C, 64.65; H, 6.21; N, 6.69. IR ν_{max}^{KBr} cm^{-1}: 1730, 1710, 1690, 1680 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.4 (9H, s, ^{t}Bu), 4.3 (1H, d, J=17 Hz, N_5-CH), 4.75 (1H, d, J=17 Hz, N_5-CH), 4.1—4.8 (3H, m), 5.2 (2H, s, CH_2Ph), 5.45 (1H, m, NHBoc), 7.15 (4H, m, phenyl protons).

Benzyl (*S*)-3-Amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetate (22a)——A mixture of **20** (7.6 g) in 5 N HCl–AcOEt (30 ml) was allowed to stand for 3 h and then concentrated *in vacuo*. The residue was crystallized from AcOEt–Et_2O to give **22a** · HCl (6.2 g, 96%) as a colorless crystalline powder, mp 169—172 °C. *Anal.* Calcd for $C_{18}H_{18}N_2O_4 \cdot HCl$: C, 59.59; H, 5.28; N, 7.72. Found: C, 59.09; N, 5.12; N, 7.55. IR ν_{max}^{Nujol} cm^{-1}: 1730, 1680 (C=O). MS m/z: 326 (M^+). $[\alpha]_D^{24}$ −202° (c=0.6, MeOH). ^{1}H-NMR (DMSO-d_6 + D_2O) δ: 4.3—5.0 (5H, m), 5.33 (2H, s, CH_2Ph), 7.4—7.7 (9H, m, phenyl protons).

***tert*-Butyl (*S*)-3-Amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetate (22b)**——A mixture of **19** (5 g) and 5 N HCl–AcOEt (30 ml) was allowed to stand for 3 h. The deposited crystals were collected by filtration to give (*S*)-3-amino-2,3-dihydro-1,5(5*H*)-benzoxazepin-4-one · HCl (3.8 g, 98%) as colorless needles, mp 230—240 °C (dec.). *Anal.* Calcd for $C_9H_{10}N_2O_2 \cdot HCl$: C, 50.36; H, 5.17; N, 13.05. Found: C, 50.30; H, 5.18; N, 13.02. $[\alpha]_D^{24}$ −227° (c=0.4, MeOH). Z-Cl (1.5 ml) was added to a stirred mixture of the above 3-amino derivative (1.5 g), AcOEt (100 ml), K_2CO_3 (excess) and water (50 ml) at ice bath temperature. After being stirred for 1 h, the mixture was worked up (AcOEt; water). The reasidue was crystallized from Et_2O to give **21** (2 g, 92%), which was recrystallized from AcOEt–Et_2O to yield colorless needles, mp 157—159 °C. *Anal.* Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.54; H,

TABLE VI. α-Oxoesters (**23a—j**)

$R_2COCOOCH_2CH_3$

23	R_2	Method	Yield (%)	bp (°C) (mmHg)
a	$Ph(CH_2)_2-$	C	76	123—141 (3)
b		D	52	105—110 (1.5)
c	$CH_3(CH_2)_7-$	D	63[a]	—
d	$(Ph)_2CHCH_2-$	D	20	165—175 (1)
e	$(CH_3)_2CH(CH_2)_2-$	D	52	100—110 (26)
f		D	40[a]	—
g		E	70	115—125 (2)
h		E	72	148—151 (3)
i		D	50	118—123 (2)
j	$(C_2H_5)_2CH(CH_2)_2-$	D	65	102 (27)

a) Used for the next step without purification.

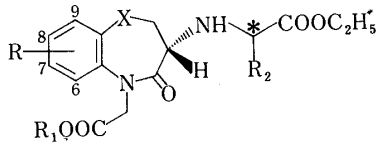
5.19; N, 8.95. $[\alpha]_D^{23}$ −175° (c=0.7, MeOH). This compound **21** (1.9 g) was allowed to react with $ClCH_2COO^tBu$ (1.1 g) as described for the preparation of **14** to give *tert*-butyl (*S*)-3-benzyloxycarbonylamino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetate (2.5 g, 96%) as a pale yellow liquid. IR ν_{max}^{neat} cm^{-1}: 3350, (NH); 1730, 1680 (C=O). MS *m/z*: 426 (M^+). Catalytic hydrogenolysis of the above 5-acetate (2.5 g) was carried out in a manner similar to that described in the preparation of **12** to give **22b** (1.2 g, 67%) as a colorless liquid. *Anal.* Calcd for $C_{15}H_{20}N_2O_4$: C, 61.63; H, 6.90; N, 9.58. Found: C, 61.75; H, 6.91; N, 9.37. MS *m/z*: 292 (M^+). $[\alpha]_D^{22}$ −253° (c=0.9, MeOH). IR ν_{max}^{neat} cm^{-1}: 3380, 3310 (NH); 1730, 1670 (C=O). ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s, ^{t}Bu), 1.7 (2H, s, NH_2), 3.6—4.8 (5H, m), 7.1 (4H, s, phenyl protons).

α-Oxoesters (23, Table VI)——Preparation of Materials (**38**): Ethyl nonanate (**38c**) was purchased from Wako Pure Chemical Ind. Ethyl 3-phenylpropionate (**38a**, bp 145—148 °C, 25 mmHg), ethyl 3,3-diphenylpropionate (**38d**) and ethyl 4-methylpentanoate (**38e**) were prepared from the corresponding acids purchased from Wako or Aldrich Chemical Co. by usual esterification using EtOH and H_2SO_4. Ethyl 3-cyclohexylpropionate (**38b**) was prepared as follows: a mixture of cyclohexanecarbaldehyde (Aldrich, 35 g), $Ph_3PCHCOOEt$ (119 g) and benzene (500 ml) was refluxed for 1 h and then concentrated *in vacuo*. The residue was triturated with petroleum ether (1 l) and the insoluble solid was removed by filtration. The filtrate was concentrated and distilled *in vacuo* to give ethyl 3-cyclohexylacrylate (51 g, 90%) as a colorless liquid, bp 86—91 °C (3 mmHg). A solution of this ester (51 g) in EtOH (300 ml) was hydrogenated under atmospheric pressure using 10% Pd–C (50% wet, 5 g) as a catalyst. After absorption of hydrogen had stopped the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was purified by vacuum distillation to yield **38b** (27 g, 91%; bp 65—70 °C, 3 mmHg) as a colorless liquid.

Ethyl 3-(1-methylcyclohexyl)propionate (**38f**), ethyl 3-(3,4,5,6-tetrahydro-2*H*-pyran-4-yl)propionate (**38g**, bp 121—123 °C, 16 mmHg), ethyl 3-(4-thianyl)propionate (**38h**, bp 155—157 °C, 15 mmHg), ethyl 3-cycloheptylpropionate (**38i**, bp 142—145 °C, 27 mmHg) and ethyl 4-ethylhexanoate (**38j**, bp 102 °C, 27 mmHg) were prepared from the corresponding aldehydes, 1-methylcyclohex-3-enecarbaldehyde,[16] 3,4,5,6-tetrahydro-2*H*-pyran-4-carbaldehyde,[17] 4-thianylcarbaldehyde,[18] cycloheptanecarbaldehyde[19] and 2-ethylbutyraldehyde (Wako), respectively in a manner similar to that described in the preparation of **38b**.

Preparation of **23**: Method C) A mixture of **38a** (14.3 g), $(COOEt)_2$ (23.4 g) and 28% NaOMe–MeOH (15.4 ml) was evaporated under reduced pressure at 60—70 °C for 1.5 h. After cooling, 15% H_2SO_4 (130 ml) was added. The mixture was stirred for 15 h under reflux and worked up (AcOEt; water) to give 2-oxo-4-phenylbutyric acid (14.4 g), which was dissolved in a mixture of H_2SO_4 (1.3 ml) and EtOH (65 ml). The resulting solution was heated under reflux for 5 h, concentrated *in vacuo* to a half the initial volume and worked up (AcOEt; water). The residue was purified by vacuum distillation to yield **23a** (11.4 g) as a pale yellow liquid.

TABLE VII. Diesters of Benzothiazepine and Benzoxazepine Derivatives (**24** and **25**)



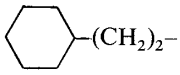
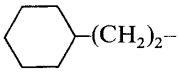
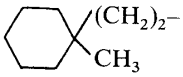
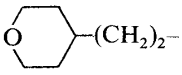
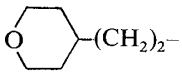
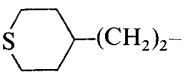
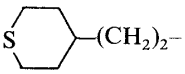
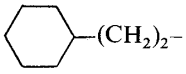
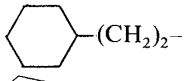
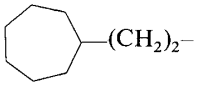
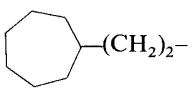
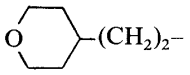
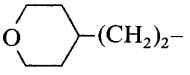
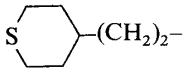
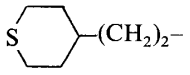
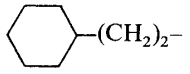
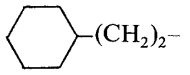
No.	X	R	R_1	R_2	Configuration C*	Yield (%)	IR ν_{max}^{neat} cm^{-1} NH	IR C=O	MS (*m/z*) M^+
24a	S	H	^{t}Bu	$Ph(CH_2)_2-$	*S*	31	3320	1740, 1670	498
24b	S	H	^{t}Bu	$Ph(CH_2)_2-$	*R*	23	3320	1730, 1670	498
24c	S	7-CH_3	^{t}Bu	$Ph(CH_2)_2-$	*S*	43	3330	1740, 1675	512
24d	S	7-CH_3	^{t}Bu	$Ph(CH_2)_2-$	*R*	22	3330	1740, 1675	512
24e	S	7-OCH_3	^{t}Bu	$Ph(CH_2)_2-$	*S*	30	3320	1730, 1660	528
24f	S	7-OCH_3	^{t}Bu	$Ph(CH_2)_2-$	*R*	17	3320	1720, 1660	528
24g	S	7-Cl	^{t}Bu	$Ph(CH_2)_2-$	*S*	36	3330	1740, 1680	532
24h	S	7-Cl	^{t}Bu	$Ph(CH_2)_2-$	*R*	26	3330	1740, 1680	532
24i	S	7,8-$(CH_2)_3$	^{t}Bu	$Ph(CH_2)_2-$	*RS*	—[a]	—	— —	538
24k	S	H	^{t}Bu		*S*	18	3320	1730, 1670	504
24l	S	H	^{t}Bu		*R*	12	3320	1730, 1670	504
24m	S	H	^{t}Bu	$CH_3(CH_2)_7-$	*RS*	7.7	3325	1730, 1690	506
24n	S	H	^{t}Bu	$(Ph)_2CHCH_2-$	*RS*	21	3325	1740, 1680	574
24o	S	H	^{t}Bu	$(CH_3)_2CH(CH_2)_2-$	*S*	22	3330	1730, 1670	464
24p	S	H	^{t}Bu	$(CH_3)_2CH(CH_2)_2-$	*R*	13	3330	1740, 1680	464
24q	S	H	^{t}Bu		*RS*	28	3335	1740, 1680	518
24r	S	H	^{t}Bu		*S*	35	3330	1745, 1680	506
24s	S	H	^{t}Bu		*R*	35	3320	1740, 1680	506
24t	S	H	^{t}Bu		*S*	36	3320	1740, 1675	522
24u	S	H	^{t}Bu		*R*	23	3320	1740, 1680	522
25a	O	H	$PhCH_2-$	$Ph(CH_2)_2-$	*S*	40	—	— —	516
25b	O	H	$PhCH_2-$	$Ph(CH_2)_2-$	*R*	30	—	— —	516
25c	O	H	$PhCH_2-$		*S*	19	3330	1740, 1680	522
25d	O	H	$PhCH_2-$		*R*	19	3330	1740, 1680	522
25e	O	H	$PhCH_2-$		*S*	14	3330	1740, 1670	536
25f	O	H	$PhCH_2-$		*R*	9	3330	1730, 1680	536
25g	O	H	$PhCH_2-$	$(C_2H_5)_2CH(CH_2)_2-$	*S*	14	3330	1740, 1670	510
25h	O	H	$PhCH_2-$	$(C_2H_5)_2CH(CH_2)_2-$	*R*	9.5	3330	1730, 1680	510
25i	O	H	$PhCH_2-$	$CH_3(CH_2)_7-$	*RS*	11	3330	1740, 1680	524

TABLE VII. (continued)

No.	X	R	R_1	R_2	Configuration C*	Yield (%)	IR ν_{max}^{neat} cm^{-1} NH	IR C=O	MS (*m/z*) M^+
25j	O	H	$PhCH_2$–	 –$(CH_2)_2$–	*S*	34	3330	1740, 1680	524
25k	O	H	$PhCH_2$–	 –$(CH_2)_2$–	*R*	26	3330	1740, 1680	524
25l	O	H	$PhCH_2$–	 –$(CH_2)_2$–	*S*	35	3330	1740, 1680	540
25m	O	H	$PhCH_2$–	 –$(CH_2)_2$–	*R*	19	3330	1740, 1680	540
25q	O	H	^{t}Bu	 –$(CH_2)_2$–	*S*	20	3330	1740, 1680	488
25r	O	H	^{t}Bu	 –$(CH_2)_2$–	*R*	15	3325	1740, 1680	488

a) Used for the next step without purification.

Method D) A mixture of **38b** (30 g), NaOEt solution (prepared from 4.5 g of Na and 100 ml of EtOH) and $(COOEt)_2$ (29 g) was heated at 70 °C for 30 min, evaporated *in vacuo* at 70 °C for 30 min, and then allowed to cool. Water (500 ml), Et_2O (200 ml) and petroleum ether (100 ml) were added, and the mixture was thoroughly shaken. The aqueous layer was separated, acidified with H_2SO_4 and worked up (AcOEt; water). The residue was dissolved in a mixture of aqueous dimethyl sulfoxide (DMSO) (water : DMSO = 1 : 9, 110 ml) and NaCl (10 g), then the whole was heated at 140 °C for 2.5 h, allowed to cool, and worked up (AcOEt; water) to yield **23b** (18 g) as a pale yellow liquid.

Ethyl 2-oxooctanoate (**23c**), ethyl 2-oxo-4,4-diphenylbutyrate (**23d**), ethyl 2-oxo-5-methylhexanoate (**23e**), ethyl 4-(1-methylcyclohexyl)-2-oxobutyrate (**23f**), ethyl 4-cycloheptyl-2-oxobutyrate (**23i**) and ethyl 2-oxo-5-ethylheptanoate (**23j**) were prepared similarly from the corresponding esters, **38c**—**f**, **i** and **j**.

Method E) Ethyl 2-oxo-4-(3,4,5,6-tetrahydro-2*H*-pyran-4-yl)butyrate (**23g**) and ethyl 2-oxo-4-(4-thianyl)-butyrate (**23h**) were prepared in a manner similar to that described in method D using LiCl instead of NaCl.

Diesters of Benzothiazepines and Benzoxazepines (24 and 25, Table VII)——A mixture of 3-amino compound (**15a**, 1.5 g), AcOH (0.3 g), α-oxoester (**23a**, 4.2 g), EtOH (50 ml) and molecular sieves 4A (8 g) was stirred for 30 min. A solution of $NaBH_3CN$ (0.6 g) in EtOH (40 ml) was added dropwise to the stirred mixture over a period of 2 h. After stirring of the mixture overnight, α-oxoester (2.1 g) was added, then a solution of $NaBH_3CN$ (1.3 g) in EtOH (40 ml) was added dropwise over a period of 2 h. After removal of the insoluble material by filtration, the solution was concentrated *in vacuo* and worked up (AcOEt). After addition of Et_2O (50 ml) and $(COOH)_2$ (2 g) to the residue, the mixture was shaken thoroughly, diluted with petroleum ether (300 ml) and allowed to stand overnight. The supernatant layer was removed by decantation. Water (50 ml), AcOEt (300 ml) and $NaHCO_3$ (excess) were added to the precipitate. The AcOEt layer was separated, dried ($MgSO_4$) and concentrated *in vacuo* to give an oily residue, which was subjected to silica gel column chromatography (hexane : AcOEt = 5 : 1—10 : 3) to yield firstly **24b** (0.55 g) as a colorless liquid. *Anal.* Calcd for $C_{27}H_{34}N_2O_5S$: C, 65.04; H, 6.87; N, 5.62. Found: C, 65.36; H, 6.91; N, 5.61. From the second fraction, **24a** (0.75 g) was obtained as a colorless liquid. *Anal.* Calcd for $C_{27}H_{34}N_2O_5S$: C, 65.04; H, 6.87; N, 5.62. Found: C, 64.90; H, 6.63; N, 5.66. ^{1}H-NMR ($CDCl_3$) δ: 1.10 (3H, t, J = 7 Hz, CH_3), 1.50 (9H, s, ^{t}Bu), 1.7—4.2 (12H, m), 4.8 (1H, d, J = 16 Hz, N_5-CH), 6.9—7.7 (9H, m, phenyl protons).

Other diesters in Table VII were prepared similarly. In the cases of **24m**, **n**, **q** and **25i**, the diesters were isolated as mixtures of diastereomers.

(*R*)-3-(1-Ethoxycarbonyl-3-phenylpropyl)amino-4-oxo-7-trifluoromethyl-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic Acid (26j, Table I)——Z-Cl (2.7 ml) and 1 N NaOH (19 ml) were simultaneously added to a stirred mixture of **10f** (5.3 g) and 2.5 N NaOH (67 ml) at ice bath temperature over a period of 30 min. The resulting mixture was stirred for a further 2.5 h and extracted with Et_2O (50 ml). The aqueous layer was acidified with 1 N aq. HCl and worked up (AcOEt) to give (*R*)-2-benzyloxycarbonylamino-3-(2-nitro-4-trifluoromethylphenyl)thiopropionic acid (5.5 g, 72%) as pale yellow crystals, mp 150—153 °C. *Anal.* Calcd for $C_{18}H_{15}F_3N_2O_6S$: C, 48.65; H, 3.40; N, 6.30. Found: C, 48.68; H, 3.41; N, 6.27. Powdered Zn (4 g) was added to a mixture of the above acid (4.3 g), AcOH (50 ml) and water (50 ml). The resulting mixture was stirred for 50 min, diluted with water (150 ml) and worked up (AcOEt; water). The residue was dissolved in Et_2O (50 ml) and treated with HCl to deposit **28**·HCl (3.4 g) as a pale yellow powder. The

ring closure reaction of **28**·HCl (3.4 g) was carried out using DEPC (1.83 g) in the presence of Et_3N (1.56 g) in a manner similar to that used in the preparation of **13a** to give **29** (1.3 g, 42%) as colorless crystals, mp 120—123 °C. $[\alpha]_D^{23}$ −161° (c=0.4, MeOH). *Anal.* Calcd for $C_{18}H_{15}F_3N_2O_3S$: C, 54.54; H, 3.81; N, 7.07. Found: C, 54.79; H, 3.90; N, 7.09. Compound **29** (1.1 g) was allowed to react with $ClCH_2COO^tBu$ (0.46 g) according to method B for the preparation of **14** to yield *tert*-butyl (*R*)-3-benzyloxycarbonylamino-4-oxo-7-trifluoromethyl-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetate (1.4 g, 98%) as a colorless viscous liquid. A solution of HBr in AcOH (30%, 10 ml) was added to a solution of the above acetate (1.4 g) in AcOH (5 ml). The resulting solution was allowed to stand for 4 h and diluted with petroleum ether (100 ml) to yield **30**·HBr (0.75 g, 60%) as colorless crystals, mp 176—180 °C. *Anal.* Calcd for $C_{12}H_{11}F_3N_2O_3S \cdot HBr \cdot H_2O$: C, 34.38; H, 3.37; N, 6.68. Found: C, 34.40; H, 3.60; N, 6.66. A mixture of **30**·HBr (0.65 g), EtOH (50 ml), NaOAc (0.2 g), AcOH (0.19 g), **23a** (1.67 g) and molecular sieves 4A (5 g) was treated with a solution of $NaBH_3CN$ (0.56 g) in EtOH (40 ml) as described for **24**. After evaporation of the solvent, the residue was worked up (AcOEt) to yield **26j** (0.7 g), which was isolated as the hydrochloride; colorless powder. MS m/z: 510 (M^+).

***tert*-Butyl (*R*)-3-[(*S*)-1-Carboxy-3-phenylpropyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetate (31a) and *tert*-Butyl (*S*)-3-[(*S*)-1-Carboxy-3-cyclohexylpropyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetate (31b)**——A mixture of **24a** (0.8 g) and 1 N NaOH (3 ml) was stirred for 2 h, diluted with water (200 ml) and extracted with Et_2O (100 ml). The aqueous layer was acidified with aq. HCl to deposit **31a** (0.5 g, 66%) as colorless crystals, mp 165—167 °C. $[\alpha]_D^{24}$ −101° (c=0.5, MeOH). *Anal.* Calcd for $C_{25}H_{30}N_2O_5S$: C, 63.81; H, 6.43; N, 5.95. Found: C, 63.69; H, 6.38; N, 5.87. IR ν_{max}^{Nujol} cm^{-1}: 1740, 1680 (C=O). ^{1}H-NMR (DMSO-d_6+D_2O) δ: 1.6 (9H, s, ^{t}Bu), 1.8—2.15 (2H, m), 2.7—3.8 (6H, m), 4.35 (1H, d, J=17 Hz, N_5-CH), 4.8 (1H, d, J=17 Hz, N_5-CH), 7.2—7.9 (9H, m, phenyl protons).

Hydrolysis of **25q** (1.5 g) was carried out similarly to yield **31b** (1.2 g, 85%) as colorless needles, mp 180—183 °C. $[\alpha]_D^{25}$ −122° (c=0.5, MeOH). MS m/z: 460 (M^+). IR ν_{max}^{KBr} cm^{-1}: 1740, 1700, 1625 (C=O). *Anal.* Calcd for $C_{25}H_{36}N_2O_6$: C, 65.20; H, 7.88; N, 6.08. Found: C, 65.18; H, 7.83; N, 6.14. ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s, ^{t}Bu), 0.7—2.0 (15H, m), 3.1 (1H, t, J=5 Hz, C_3-N-CHCOO), 3.55 (1H, dd, J=7, 12 Hz, C_2-H), 4.15 (1H, d, J=17 Hz, N_5-CH), 4.1—4.3 (1H, m, C_3-H), 4.45 (1H, dd, J=7, 12 Hz, C_2-H), 4.6 (1H, d, J=17 Hz, N_5-CH), 7.0—7.3 (4H, m, phenyl protons).

***tert*-Butyl (*R*)-3-[(*S*)-1-Benzyloxycarbonyl-3-phenylpropyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetate (32a) and *tert*-Butyl (*S*)-3-[(*S*)-Alkoxycarbonyl-3-phenylpropyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzoxazepine-5-acetate (32b—d)**——A mixture of **31a** (0.3 g), $NaHCO_3$ (0.5 g), $PhCH_2Br$ (0.15 g) and DMF (10 ml) was stirred overnight, diluted with water (100 ml) and worked up (AcOEt; 0.1 N aq. HCl, water) to give **32a** (0.35 g, 98%) as a colorless liquid. IR ν_{max}^{neat} cm^{-1}: 3330 (NH), 1740, 1680 (C=O). MS m/z: 560 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.45 (9H, s, ^{t}Bu), 1.9—3.7 (10H, m), 3.95 (1H, d, J=17 Hz, N_5-CH), 4.75 (1H, d, J=17 Hz, N_5-CH), 5.20 (2H, s, CH_2-Ph), 6.9—7.6 (14H, m, phenyl protons).

Compound **31b** (0.25 g) was allowed to react with $PhCH_2Br$, $CH_3(CH_2)_3I$ and $BrCH_2COOEt$ as described in the case of **32a** to yield **32b** (0.25 g, 84%), **32c** (0.26 g, 91%) and **32d** (0.26 g, 88%) as colorless liquids, respectively. **32b**: ^{1}H-NMR ($CDCl_3$) δ: 1.4 (9H, s, ^{t}Bu), 0.5—2.7 (15H, m), 3.2 (1H, t, J=6 Hz, C_3-N-CHCOO), 3.6 (1H, dd, J=9, 12 Hz, C_2-H), 4.2 (1H, d, J=18 Hz, N_5-CH), 3.9—4.2 (1H, m, C_3-H), 4.4 (1H, dd, J=9, 12 Hz, C_2-H), 4.6 (1H, d, J=18 Hz, N_5-CH), 5.65 (2H, s, CH_2Ph), 6.8—7.6 (9H, m, phenyl protons). $[\alpha]_D^{25}$ −155° (c=0.6, MeOH), MS m/z: 550 (M^+). **32c**: ^{1}H-NMR ($CDCl_3$) δ: 0.85 (3H, t, CH_3), 1.4 (9H, s, ^{t}Bu), 0.7—2.3 (15H, m), 3.15 (1H, t, J=6 Hz, C_3-H), 3.6 (1H, dd, J=8, 11 Hz, C_2-H), 3.9—4.2 (3H, m), 4.15 (1H, d, J=17 Hz, N_5-CH), 4.5 (1H, dd, J=8, 11 Hz, C_2-H), 4.6 (1H, d, J=17 Hz, N_5-CH), 7.0—7.4 (4H, m, phenyl protons). $[\alpha]_D^{25}$ −145° (c=0.7, MeOH). MS m/z: 516 (M^+). **32d**: ^{1}H-NMR ($CDCl_3$) δ: 1.2 (3H, t, J=6 Hz, CH_3), 1.4 (9H, s, ^{t}Bu), 0.6—2.7 (15H, m), 3.3 (1H, t, C_3-N-CHCOO), 3.7 (1H, dd, J=7, 11 Hz, C_2-H), 4.05 (2H, q, $COOCH_2$), 4.2 (1H, d, J=18 Hz, N_5-CH), 3.9—4.2 (1H, m, C_3-H), 4.3 (1H, d, J=7, 11 Hz, C_2-H), 4.5 (2H, s, $COOCH_2CO$), 4.6 (1H, d, J=18 Hz, N_5-CH), 7.0—7.3 (4H, m, phenyl protons). $[\alpha]_D^{23}$ −200° (c=0.5, MeOH). MS m/z: 546 (M^+).

General Procedures for Deprotection of Esters (7, 8, 26, 27 and 37; Table I)——Method F) A mixture of *tert*-butyl ester (**24a—u**, **32a—d** and **36a**, **b**; 0.5 g) and 5 N HCl–AcOEt (5 ml) was allowed to stand overnight. Et_2O (20 ml) and petroleum ether (100 ml) were added to the mixture to deposit a colorless powder, which was collected by filtration to give the corresponding 5-acetic acid derivative (**26a—i**, **k—v**, **27n—p** and **37a**, **b**).

Method G) A mixture of benzyl ester (**25a—m**, 0.5 g) and EtOH (50 ml) was hydrogenated over 10% Pd–C (50% wet, 0.5 g) under atmospheric pressure. After the absorption of hydrogen had stopped, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was dissolved in Et_2O and treated with HCl to yield the hydrochloride of the corresponding 5-acetic acid derivative (**27a**, **b**, **d—p**) as a colorless powder. In the case of **27c**, colorless crystals of free base were obtained from AcOEt–Et_2O, mp 146—148 °C.

Method H) A mixture of EtOH (1 ml), 1 N NaOH (3 ml) and a monoacid derivative (**26a**, **b**, **k**, **r**, **u** and **27a**, **b**, **c**, **j**, **m**; 0.1 g) was allowed to stand for 30—120 min. In the case of **7b**, the disodium salt crystallized from the reaction mixture. In other cases, free acids **7a**, **7c** and **8a—c** were deposited as colorless crystals after concentration of the reaction mixture followed by neutralization with aq. HCl. In the cases of **7d**, **e** and **8d**, **e**, the mixture was neutralized and subjected to XAD-2 column chromatography (acetone : water = 1 : 1). The eluate was lyophilized to give the

corresponding diacid derivative as a colorless powder.

(*R*)-3-[(*S*)-1-Ethoxycarbonyl-3-phenylpropyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-acetic Acid *S*-Oxide (33, Table I)——*m*-Chloroperbenzoic acid (0.5 g) was added to a stirred solution of **26a** (0.5 g) in CH_2Cl_2 (50 ml) over a period of 2.5 h. The resulting mixture was stirred for an additional 1 h, diluted with water (200 ml) and worked up (CH_2Cl_2; water). The residue was dissolved in Et_2O and treated with HCl to yield **33**·HCl (0.3 g) as a colorless powder. MS *m/z*: 458 (M^+).

***tert*-Butyl (*R*)-3-[(*S*)-1-Ethoxycarbonyl-3-cyclohexylpropyl]amino-4-oxo-2,3,4,5-tetrahydro-1,5-benzothiazepine-5-α-methylacetate (36a, b)**——The reaction of **13a** (6.48 g) with *tert*-butyl 2-bromopropionate (6.27 g) was carried out according to method B. The product was purified by silica gel column chromatography (hexane: AcOEt = 3 : 1—2 : 1) to give **34** (7.8 g) as a colorless powder. IR ν_{max}^{neat} cm^{-1}: 1770, 1730, 1720, 1680 (C=O). *Anal.* Calcd for $C_{24}H_{24}N_2O_5S \cdot 1/2H_2O$: C, 62.46; H, 5.46; N, 6.07. Found: C, 62.62; H, 5.14; N, 6.13. ^{1}H-NMR ($CDCl_3$) δ: 1.1—1.7 (12H, m, ^{t}Bu and CH_3), 3.25—3.6 (1H, m), 4.0—5.6 (4H, m), 6.9—7.9 (8H, m, phenyl protons). A solution of **34** (7.6 g) in EtOH (250 ml) was treated with $N_2H_4 \cdot H_2O$ (2.5 g) as described for the preparation of **15a** to yield **35** (5.4 g, 99%) as a pale yellow liquid. IR ν_{max}^{neat} cm^{-1}: 1735, 1670 (C=O). MS *m/e*: 322 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.15, 1.6 (3H, d, J=7.5 Hz, CH_3), 1.4—1.5 (9H, s, ^{t}Bu), 1.8 (2H, br s, NH_2), 2.7 (1H, m), 3.2—3.7 (2H, m), 4.4—5.3 (1H, q, J=7.5 Hz), 7.0—7.7 (4H, m, phenyl protons). Reductive alkylation of **35** (2.5 g) with **23b** (6.6 g) in the presence of $NaBH_3CN$ (0.59 g) was carried out in a manner similar to that used for the preparation of **24**. The product was purified by silica gel column chromatography (hexane : AcOEt = 4 : 1) to give **36b** (0.74 g) firstly as a colorless liquid. MS *m/z*: 518 (M^+). Compound **36a** (0.28 g, 7%) was obtained from the second fraction. IR ν_{max}^{neat} cm^{-1}: 1740, 1670 (C=O). $[\alpha]_D^{23}$ −223° (c=0.4, MeOH). MS *m/z*: 518 (M^+).

ACE Inhibitory Activity *in Vitro*——The supernatant (20000 ***g***, 25 min) of albino rabbit lung homogenates in 4 volumes of 100 mM borate-HCl buffer containing 300 mM NaCl (pH 8.3) was prepared as a source of crude ACE according to a slight modification of the method of Wallace *et al.*[20] The ACE inhibitory activity was determined in terms of percent inhibition based on the amount of hippuric acid produced from the synthetic substrate hippuryl-L-histidyl-L-leucine (HHL) by ACE. Each assay mixture contained the following components: borate-HCl buffer (100 mM), NaCl (300 mM), HHL (5 mM), test compound (0.01 to 10 μM) and crude ACE (0.1 ml) in a volume of 0.25 ml. The reaction tubes were incubated at 37 °C for 1 h. After termination of the reaction by the addition of 1 N aq. HCl (0.15 ml), hippuric acid was extracted with AcOEt and the hippuric acid concentration was determined from the absorbance at 288 nm.

ACE Inhibitory Activity *in Vivo*——On the day before the experiments, 8- to 10-week-old male Sprague Dawley rats were anesthetized with sodium pentobarbital (50 mg/kg) by *i.p.* injection. The animals were surgically prepared with an aortic catheter inserted *via* the left femoral artery and a caval catheter inserted *via* the right femoral vein. Both catheters were passed subcutaneously to the neck and exposed there. The rats were placed in individual plastic cages after the surgery. At the first stage of the experiment, the aortic cannula was connected with a pressure transducer and the mean blood pressure was recorded on the polygraph. Next, angiotensin I (A-I, 300 ng) and angiotensin II (A-II, 100 ng) were injected into the femoral vein in order to measure their hypertensive activities. The A-I and A-II challenges were repeated 1/3, 1, 2, 3, 4 and 5 h after the oral administration of the test compound (10 mg/kg). The result of A-II challenge was used for correcting the percent inhibition value based on the change of vascular responsiveness during the course of the experiment.

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11) It has been known that the modification of substituents of ACE inhibitors often results in considerable change of the inhibitory activity.[1-6] A. Miyake, K. Itoh, T. Aono, S. Kishimoto, Y. Matsushita, Y. Inada, K. Nishikawa and Y. Oka, *J. Takeda Res. Lab.*, **43**, 53 (1984).

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