[Chem. Pharm. Bull. 33(5)2011—2022(1985)]

Studies on Angiotensin Converting Enzyme Inhibitors. III.[1a,b] 2-Carboxyethylcarbamoyl-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid Derivatives[2]

KIMIAKI HAYASHI,*,[a] KEN-ICHI NUNAMI,[a] KAZUO SAKAI,[a] YASUHIKO OZAKI,[a] JYOJI KATO,[a] KEIZO KINASHI,[b] and NAOTO YONEDA[a]

Research Laboratory of Applied Biochemistry[a] and Safety Research Laboratory,[b] Tanabe Seiyaku Co., Ltd., 16–89 Kashima-3-chome, Yodogawa-ku, Osaka 532, Japan

(Received August 24, 1984)

(3*S*)-2-[*N*-Substituted *N*-(2-carboxyethyl)carbamoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivaties (**8a—d** and **12a—t**) and their monoester compounds (**13a—k**) were synthesized by condensation of (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylates (**6a, b**), 3-aminopropionates (**5a, b** or **10a—m**) and phosgene, followed by deprotection of ester groups. Their *in vitro* angiotensin converting enzyme (ACE) inhibitory activities and antihypertensive effects were evaluated, and the structure–activity relationship is discussed. Some of the *N*-ethylcarbamoyl analogs (**12h, 12j, 12k, 12l** and **12o**), which had hydrophobic substituents (C_8H_{17}–$C_{12}H_{25}$, CH_2CH_2Ph) at the α-position to the carboxyl group in the side chain, showed potent *in vitro* ACE inhibitory activities with IC_{50} values of $4.0—8.8 \times 10^{-9}$ M.

The monoesters **13e, 13h,** and **13i** reduced the systolic blood pressure by more than 30 mmHg in spontaneously hypertensive rats (SHR) at an oral dose of 50 mg/kg.

Keywords——ACE; ACE inhibitor; inhibitory activity; antihypertensive activity; (3*S*)-2-[*N*-substituted *N*-(2-carboxyethyl)carbamoyl]-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid; ureido carbonyl; hydrophobic substituent; structure–activity relationship

Angiotensin converting enzyme (ACE) inhibitors have been receiving much attention as a new type of antihypertensive drug since Ondetti *et al.* developed D-3-mercapto-2-methylpropionyl-L-proline (captopril).[3a,b] Among the structure–activity relationships discussed to date,[3,4a–h] the carbonyl oxygen of ω-carboxyalkanoyl-L-proline derivatives has been proposed to play an important role as a hydrogen bond acceptor from the donor site in the active site of the enzyme.[5a,b]

In the course of our studies on novel 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid derivatives, we previously reported that 2-[*N*-substituted *N*-(2-carboxyethyl)carbamoyl]-compounds **1**[1b] exhibited enhanced ACE inhibitory activities. The finding of the more fa-

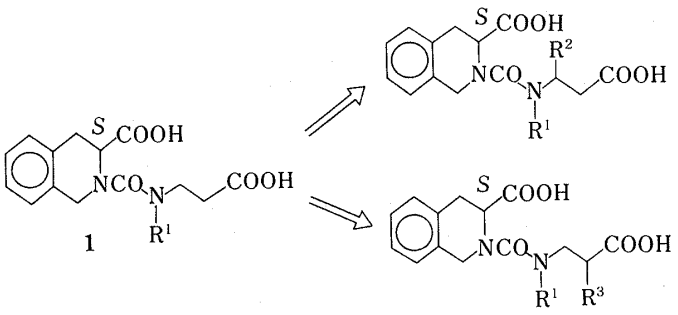


Chart 1

vorable binding character of the ureidocarbonyl group than of the amidocarbonyl group prompted us to carry out further modification of **1**.

In the present paper, we describe the syntheses and the structure–activity relationship of a series of 2-carboxyethylcarbamoyl-tetrahydroisoquinoline derivatives, in which a hydrophobic substituent was introduced at a position (R^2 or R^3) on the side chain (see Chart 1).

Chemistry

β-Substituted compounds **8** were synthesized by the route shown in Chart 2. Namely, the starting optically active 3-substituted 3-(*N*-benzyloxycarbonylamino)propionates (**3**) were obtained by carbon chain elongation of the corresponding *N*-benzyloxycarbonyl-α-amino acids (**2**) (Arndt–Eistert method). *N*-Alkylation followed by catalytic hydrogenolysis of **3** gave 3-substituted 3-alkylaminopropionates (**5**). Condensation of **5** and methyl (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**6a**) with phosgene and subsequent alkaline hydrolysis of the diesters (**7**) afforded the dicarboxylic acids (**8**).

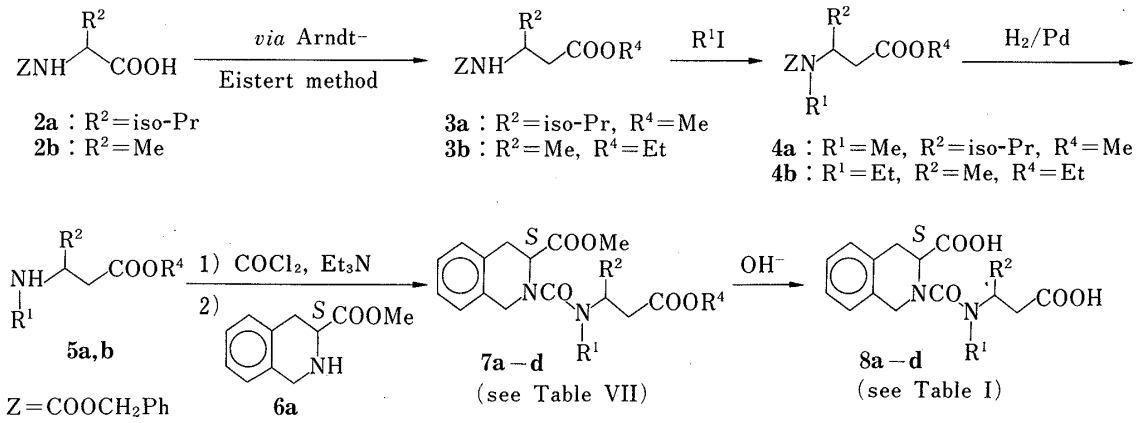


Chart 2

α-Substituted compounds **12** and **13** were prepared according to Chart 3. Condensation of 2-substituted 3-(*N*-substituted amino)propionates (**10**), which were prepared by Michael addition of primary amines to α-substituted acrylates (**9**), and benzyl (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**6b**) with phosgene was carried out to give the diesters (**11**) as a mixture of approximately equimolar amounts of diastereoisomers, which were separated by silica gel column chromatography. The absolute configuration of the side chains of the isomers was determined as follows. For example, in the cases of **11s** and **11t** (R^1=Et, R^3=CH_2CH_2Ph, R^4=Et), optically active ethyl 2-phenethyl-3-(*N*-ethylamino)propionates [(*R*)-**10k** and (*S*)-**10k**)] were obtained by the resolution of racemic **10k** as described in the next section, and each was derived to the diester in the same manner. The (*S*,*R*)-isomer **11s** was identical with the product eluted in the early fractions of silica gel column chromatography, and the (*S*,*S*)-isomer **11t** with that from the later fractions. The signal of the methine proton at the 3-position of the tetrahydroisoquinoline moiety in the nuclear magnetic resonance (NMR) spectrum of the (*S*,*R*)-isomer **11s** was observed at lower field than that of the (*S*,*S*)-isomer **11t**. This tendency was also observed in the NMR spectra of other diesters. Accordingly, the stereochemical assignment for other compounds **11c—r** and **11u—x** could be tentatively made on the basis of the NMR spectra and chromatographic characteristics. The ester residues of **11** were removed by alkaline hydrolysis to give the corresponding dicarboxylic acids (**12**).

As reported in the previous paper,[1b] esterification of the side chain of **1** resulted in an improvement in the stability in acidic solution and the absorbability from the gastro-intestinal

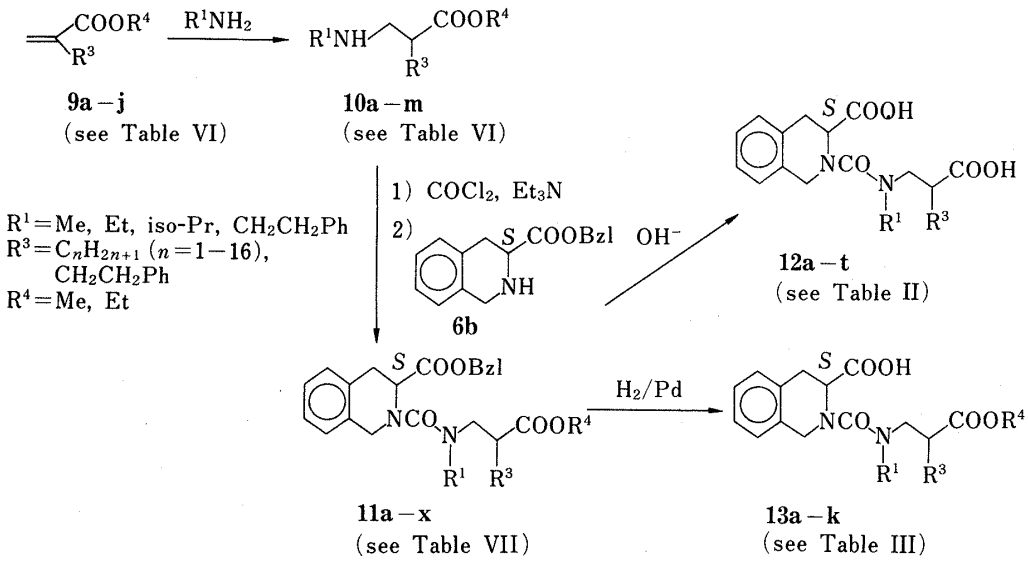


Chart 3

tract. Thus, in order to improve the acid lability and to derive effective prodrugs for oral administration, monoester derivatives **13** were prepared by catalytic debenzylation of the ester group at the 3-position of the tetrahydroisoquinoline nucleus.

Optical Resolution of Side Chain Precursor (10k)——Chart 4 shows the procedure for optical resolution of racemic **10k** using optically active *N*-benzyloxycarbonylphenylalanine (**14**) as a resolving agent. When racemic **10k** was treated with (*S*)-14 in ethyl acetate–diisopropyl ether, a crystalline salt [(*S*)-**10k**·(*S*)-**14**] was preferentially precipitated in 33.6% yield. After treatment of the mother liquor with aqueous sodium carbonate, resolution of the resultant free base with (*R*)-**14** was carried out in the same manner to afford (*R*)-**10k**·(*R*)-**14** in 37.8% yield. Subsequently, each salt was converted to (*S*)-**10k**·HCl and (*R*)-**10k**·HCl, which had the same physical constants and equal rotations of opposite sign. The absolute configuration of (*R*)-**10k** was determined by X-ray diffraction analysis of (*R*)-**10k**·HBr.

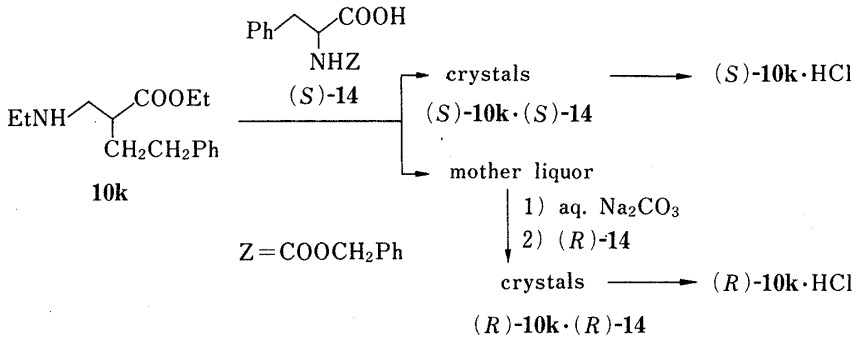
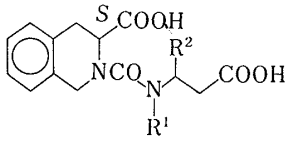


Chart 4

Biological Results and Discussion

The *in vitro* ACE inhibitory activities of the dicarboxylic acids (**1**, **8a—d**, and **12a—t**) were determined using ACE obtained from pig renal cortex and hippuryl-histidyl-leucine as a substrate according to the procedure reported previously.[1a] The results are shown in Tables I—III.

TABLE I. Physical Data and *in Vitro* ACE Inhibitory Activity of Dicarboxylic Acid Derivatives



Compd. No.	R^1	R^2 (Config.)	Yield (%)	mp (°C, dec.)	Formula	Analysis (%) Calcd (Found) C	H	N	IC_{50} (M)[a]
1a[b]	C_2H_5	H	66.4	278—280	$C_{16}H_{18}CaN_2O_5 \cdot H_2O$	51.05 (50.75	5.36 5.48	7.44 7.23)	3.0×10^{-8}
8a[c]	CH_3	iso-C_3H_7 (*R*)	92.5	233—236	$C_{18}H_{24}N_2O_5 \cdot 2C_6H_{14}N_2O_2$	56.23 (55.92	8.18 8.34	13.12 13.01)	1.7×10^{-5}
8b[c]	CH_3	iso-C_3H_7 (*S*)	93.8	230—238	$C_{18}H_{14}N_2O_5 \cdot 2C_6H_{14}N_2O_2$	56.23 (56.03	8.18 8.34	13.12 13.11)	5.6×10^{-6}
8c[c]	C_2H_5	CH_3 (*R*)	82.9	230—231	$C_{17}H_{22}N_2O_5 \cdot 2C_6H_{14}N_2O_2$	55.57 (55.39	8.04 8.24	13.41 13.39)	1.0×10^{-5}
8d[c]	C_2H_5	CH_3 (*S*)	73.2	219—220	$C_{17}H_{22}N_2O_5 \cdot 2C_6H_{14}N_2O_2$	55.57 (55.53	8.04 8.18	13.41 13.09)	4.0×10^{-5}

a) Molar concentration for 50% inhibition. *b*) Calcium salt; reference 1*b*. *c*) 2 L-Lysine salt.

The effectiveness of substituents at the ureido nitrogen on inhibitory activity was in the order Et, iso-Pr, Me, and CH_2CH_2Ph, as had been observed in **1** previously.[1b] On the other hand, introduction of β-substituents (R^2) with respect to the ω-carboxyl group in the side chain markedly reduced the activity in compounds of both *R*- and *S*-configuration. The results suggest that the steric requirements of the enzyme region surrounding the side chain are too strict to allow the presence of any β-substituents. On the other hand, introduction of α-substituents (R^3) caused an enhancement of the activity depending on the chain length of R^3. It should be noted that the compounds having a substituent with *R*-configuration showed about ten times the activity of those with *R*-configuration. The activities of some *N*-ethyl analogs (**12h**, **12j**, **12k**, **12l** and **12o**) were nearly equal to that of the reference compound, captopril.

Further, the structure–activity relationship for *N*-ethyl-α-substituted compounds of *R*-configuration was analyzed quantitatively by the Hansch–Fujita method.[6] The activity was found to be represented by Eq. 1 based on the π values as a parameter of hydrophobicity.

$$pI_{50} = -0.040\pi^2 + 0.368\pi + 7.391 \quad (1)$$

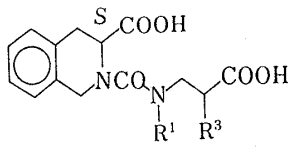
$$n = 11, \quad s = 0.161, \quad r = 0.903$$

In this equation, n is the number of compounds included in the correlation, s is the standard deviation, and r is the correlation coefficient. According to Eq. 1, the activity is related parabolically to the π values, the optimum π value being 4.62.

Table IV shows the calculated data together with the observed results; good agreement can be seen. Compound **12j** ($R^3 = C_9H_{19}$), corresponding to the maximal pI_{50}, showed the most potent activity ($IC_{50} = 4.0 \times 10^{-9}$ M). From these results it is clear that the hydrophobicity of the α-substituent is directly related to the inhibitory activity. Thus, there may be a hydrophobic pocket close to the zinc ion at the active site of ACE.

The antihypertensive activities after oral administration were compared among some

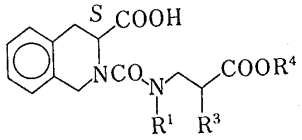
TABLE II. Physical Data and *in Vitro* ACE Inhibitory Activity of Dicarboxylic Acid Derivatives



Compd. No.	R^1	R^3 (Config.)	Yield (%)	mp (°C, dec.)	Formula	Analysis (%) Calcd (Found) C	H	N	IC_{50} (M)
12a[a]	CH_3	C_2H_4Ph (*RS*)	85.2	254—258	$C_{23}H_{24}CaN_2O_5 \cdot 2H_2O$	57.01 (57.08	5.82 5.76	5.78 5.65)	6.5×10^{-8}
12b[a]	C_2H_5	CH_3 (*RS*)	78.0	>260	$C_{17}H_{20}CaN_2O_5 \cdot H_2O$	52.29 (52.23	5.68 5.66	7.18 7.17)	5.8×10^{-8}
12c[b]	C_2H_5	iso-C_3H_7 (*R*)	40.0	208—212	$C_{19}H_{26}N_2O_5 \cdot 2C_6H_{14}N_2O_2$	56.86 (56.69	8.31 8.30	12.84 12.83)	1.4×10^{-8}
12d[b]	C_2H_5	iso-C_3H_7 (*S*)	59.0	172—175	$C_{19}H_{26}N_2O_5 \cdot 2C_6H_{14}N_2O_2$	56.86 (56.68	8.31 8.43	12.84 12.76)	1.8×10^{-7}
12e	C_2H_5	C_4H_9 (*R*)	66.0	113—115	$C_{20}H_{28}N_2O_5$	63.81 (63.81	7.50 7.47	7.44 7.29)	1.7×10^{-8}
12f[a]	C_2H_5	C_4H_9 (*S*)	26.0	187—195	$C_{20}H_{26}CaN_2O_5 \cdot 2H_2O$	53.32 (53.28	6.71 6.76	6.22 6.16)	2.4×10^{-7}
12g	C_2H_5	C_6H_{13} (*R*)	67.0	103—105	$C_{22}H_{32}N_2O_5$	65.32 (65.22	7.97 7.67	6.93 6.91)	1.5×10^{-8}
12h	C_2H_5	C_8H_{17} (*R*)	76.4	100—101	$C_{24}H_{36}N_2O_5$	66.64 (66.74	8.39 8.37	6.48 6.33)	4.2×10^{-9}
12i[a]	C_2H_5	C_8H_{17} (*S*)	95.6	208—211	$C_{24}H_{34}CaN_2O_5 \cdot H_2O$	58.99 (58.78	7.43 7.42	5.73 5.68)	4.7×10^{-8}
12j	C_2H_5	C_9H_{19} (*R*)	47.0	104—106	$C_{25}H_{38}N_2O_5$	67.23 (67.21	8.58 8.42	6.27 6.32)	4.0×10^{-9}
12k	C_2H_5	$C_{10}H_{21}$ (*R*)	63.1	103—105	$C_{26}H_{40}N_2O_5$	67.80 (68.08	8.75 8.85	6.08 6.14)	5.2×10^{-9}
12l	C_2H_5	$C_{12}H_{25}$ (*R*)	76.4	116—118	$C_{28}H_{44}N_2O_5$	68.82 (68.90	9.08 9.28	5.73 5.85)	8.8×10^{-9}
12m[b]	C_2H_5	$C_{12}H_{25}$ (*S*)	63.9	187—190	$C_{28}H_{44}N_2O_5 \cdot 2C_6H_{14}N_2O_2$	61.51 (61.53	9.29 9.22	10.76 10.68)	2.6×10^{-7}
12n	C_2H_5	$C_{16}H_{33}$ (*R*)	44.0	92—94	$C_{32}H_{52}N_2O_5$	70.55 (70.61	9.62 9.65	5.14 5.28)	2.8×10^{-8}
12o	C_2H_5	C_2H_4Ph (*R*)	53.5	118—120	$C_{24}H_{28}N_2O_5$	67.91 (67.94	6.65 6.65	6.60 6.54)	6.5×10^{-9}
12p[a]	C_2H_5	C_2H_4Ph (*S*)	67.7	235—239	$C_{24}H_{26}CaN_2O_5 \cdot 3H_2O$	55.80 (56.18	6.24 6.16	5.42 5.51)	6.9×10^{-8}
12q	iso-C_3H_7	C_2H_4Ph (*R*)	58.4	120—122	$C_{25}H_{30}N_2O_5$	68.47 (68.39	6.90 6.90	6.39 6.23)	2.3×10^{-8}
12r[a]	iso-C_3H_7	C_2H_4Ph (*S*)	62.3	238—240	$C_{25}H_{28}CaN_2O_5 \cdot 2H_2O$	58.58 (58.75	6.29 6.17	5.47 5.49)	4.2×10^{-7}
12s[b]	C_2H_4Ph	C_2H_4Ph (*R*)	74.3	*ca.* 77	$C_{30}H_{32}N_2O_5 \cdot 2C_6H_{14}N_2O_2$	63.94 (63.98	7.67 7.57	10.15 10.04)	9.1×10^{-8}
12t[a]	C_2H_4Ph	C_2H_4Ph (*S*)	69.2	212—214	$C_{30}H_{30}CaN_2O_5 \cdot H_2O$	64.73 (64.61	5.79 5.80	5.03 5.00)	1.3×10^{-6}
	Captopril[c]								6.9×10^{-9}

a) Calcium salt. *b*) 2 L-Lysine salt. *c*) This compound was prepared in our laboratory, mp 88—89 °C, $[\alpha]_D^{20}$ −131.8° ($c=1$, EtOH).

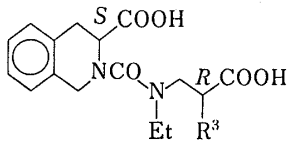
TABLE III. Physical Data and *in Vitro* ACE Inhibitory Activity of Monoester Derivatives



Compd. No.	R^1	R^3 (Config.)	R^4	Yield (%)	mp (°C, dec.)	Formula	Analysis (%) Calcd (Found) C	H	N	IC_{50} (M)
15[a,b]	C_2H_5	H	C_4H_9	66.9	135—136	$C_{40}H_{54}CaN_4O_{10}$	60.74 (60.76)	6.88 (6.98)	7.08 (7.15)	3.5×10^{-6}
13a[a]	CH_3	C_2H_4Ph (*RS*)	C_2H_5	97.0	129—131	$C_{50}H_{58}CaN_4O_{10}\cdot2H_2O$	64.36 (64.77)	6.27 (6.15)	6.00 (5.89)	2.5×10^{-4}
13b[c]	C_2H_5	CH_3 (*RS*)	CH_3	28.0	142—145	$C_{18}H_{24}N_2O_5\cdot C_6H_{13}N$	64.40 (64.41)	8.33 (8.31)	9.39 (9.30)	4.5×10^{-4}
13c[c]	C_2H_5	iso-C_3H_7(*R*)	C_2H_5	44.8	116—117	$C_{21}H_{30}N_2O_5\cdot C_6H_{13}N$	66.23 (65.88)	8.85 (8.51)	8.58 (8.35)	8.9×10^{-5}
13d[a]	C_2H_5	C_6H_{13} (*R*)	C_2H_5	68.0	102	$C_{48}H_{68}CaN_4O_{10}\cdot1/2H_2O$	63.34 (63.45)	7.64 (7.68)	6.16 (6.13)	1.4×10^{-5}
13e[a]	C_2H_5	C_8H_{17} (*R*)	C_2H_5	99.2	116—119	$C_{52}H_{78}CaN_4O_{10}\cdot1/2H_2O$	63.77 (63.90)	8.15 (8.25)	5.66 (5.73)	5.2×10^{-6}
13f[a]	C_2H_5	C_9H_{19} (*R*)	C_2H_5	57.0	82	$C_{54}H_{82}CaN_4O_{10}\cdot H_2O$	64.51 (64.09)	8.42 (8.49)	5.57 (5.32)	8.3×10^{-6}
13g[a]	C_2H_5	$C_{10}H_{21}$ (*R*)	C_2H_5	68.3	84	$C_{56}H_{86}CaN_4O_{10}\cdot3/2H_2O$	64.52 (64.59)	8.61 (8.69)	5.38 (5.28)	4.7×10^{-7}
13h[a]	C_2H_5	$C_{12}H_{25}$ (*R*)	C_2H_5	74.0	80—83	$C_{60}H_{94}CaN_4O_{10}\cdot H_2O$	66.14 (65.98)	8.88 (8.91)	5.14 (5.03)	5.4×10^{-8}
13i[a]	C_2H_5	C_2H_4Ph (*R*)	C_2H_5	91.0	147—148	$C_{52}H_{62}CaN_4O_{10}\cdot H_2O$	64.98 (64.93)	6.71 (6.71)	5.83 (5.66)	1.6×10^{-5}
13j[a]	iso-C_3H_7	C_2H_4Ph (*R*)	C_2H_5	55.0	92—95	$C_{54}H_{66}CaN_4O_{10}\cdot H_2O$	65.51 (65.09)	6.93 (6.74)	5.66 (5.57)	1.7×10^{-5}
13k[c]	C_2H_4Ph	C_2H_4Ph (*R*)	C_2H_5	71.0	102—104	$C_{32}H_{36}N_2O_5\cdot C_6H_{13}N$	72.70 (72.68)	7.87 (7.81)	6.69 (6.80)	2.2×10^{-5}

a) 1/2 Calcium salt. *b*) Reference 1*b*. *c*) Cyclohexylamine salt.

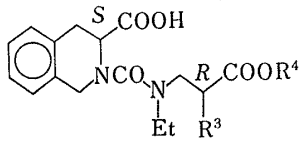
TABLE IV. *In Vitro* ACE Inhibitory Activity of *N*-Ethyl Analogs



Compd. No.	R^3	π[a]	pI_{50} Obsd.	pI_{50} Calcd[b]	Compd. No.	R^3	π	pI_{50} Obsd.	pI_{50} Calcd
1a	H	0	7.52	7.39	**12j**	C_9H_{19}	4.86	8.40	8.24
12b	CH_3	0.54	7.54[c]	7.58	**12k**	$C_{10}H_{21}$	5.40	8.28	8.22
12c	iso-C_3H_7	1.40	7.85	7.83	**12l**	$C_{12}H_{25}$	6.48	8.06	8.10
12e	C_4H_9	2.16	7.77	8.00	**12n**	$C_{16}H_{33}$	8.64	7.55	7.60
12g	C_6H_{13}	3.24	7.90	8.16	**12o**	C_2H_4Ph	2.66	8.19	8.09
12h	C_8H_{17}	4.32	8.38	8.24					

a) Calculated from π values based on log *P* for substituents by means of the additivity principle. *b*) Calculated by Eq. 1. *c*) Taken as the value of a mixture of diastereomers.

TABLE V. Hypotensive Effects of Selected Compounds in Spontaneously Hypertensive Rats



Compd. No.	R^3	R^4	Fall in blood pressure (mmHg) (Dose: 50 mg/kg, *p.o.*)
15	H	C_4H_9	−24
12o	C_2H_4Ph	H	−22
13e	C_8H_{17}	C_2H_5	−33
13h	$C_{12}H_{25}$	C_2H_5	−33
13i	C_2H_4Ph	C_2H_5	−35
	Captopril		−38

selected monoester derivatives (**15**,[1b] **13e**, **13h**, and **13i**) and the parent dicarboxylic acid **12o**, using spontaneously hypertensive rats (SHR). The results (Table V) show that monoester with an α-substituent (**13e**, **13h**, and **13i**) were much more active than dicarboxylic acid **12o**, or the monoester with no α-substituent **15**. The activity of compound **13i** was comparable to that of captopril.

Experimental

Melting points are uncorrected. Infrared (IR) spectra were obtained on a Shimadzu IR-27G spectrophotometer. ^{1}H-NMR spectra were recorded on a Hitachi R-20A instrument, using tetramethylsilane as an internal standard. Mass spectra (MS) were taken on a Hitachi M-60 spectrometer. Specific rotations were measured with a Perkin-Elmer 243 polarimeter.

Starting Materials——Methyl or benzyl (3*S*)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**6a**, **b**) was prepared from L-phenylalanine according to the general procedure.[7a,b] 3-Substituted 3-(*N*-benzyloxycarbonylamino)-propionates (**3**) were prepared from *N*-benzyloxycarbonyl L- or D-amino acids (**2**) according to the Arndt–Eistert method.[8] 3-Substituted 3-(*N*-alkyl-*N*-benzyloxycarbonylamino)propionates (**4a, b**) were obtained in quantitative yield by treatment of the corresponding alkyl iodide in the presence of Ag_2O. The physical data of compounds are as follows.

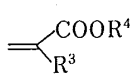
Methyl (3*S*)-3-(*N*-benzyloxycarbonyl-*N*-methylamino)-4-methylpentanoate [(*S*)-**4a**]: Colorless syrup; IR ν_{max}^{film} cm^{-1}: 1740, 1700; ^{1}H-NMR ($CDCl_3$) δ: 0.71—1.10 (6H, m, iso-Pr), 1.55—2.00 (1H, m, CH), 2.40—2.75 (2H, m, CH_2), 2.81 (3H, s, NCH_3), 3.59 (3H, s, OCH_3), 3.85—4.35 (1H, m, NCH), 5.16 (2H, s, CH_2Ph), 7.35 (5H, s, aromatic H). Ethyl (3*S*)-3-(*N*-benzyloxycarbonyl-*N*-ethylamino)butyrate [(*S*)-**4b**]: Colorless syrup; IR ν_{max}^{film} cm^{-1}: 1740, 1700; ^{1}H-NMR ($CDCl_3$) δ: 0.85—1.35 (9H, m, $CH_3 \times 3$), 2.23—2.68 (2H, m, CH_2CO), 3.06—3.40 (2H, m, NCH_2), 4.03 (2H, q, J=7 Hz, OCH_2), 3.95—4.22 (1H, m, NCH), 5.05 (2H, s, OCH_2Ph), 7.28 (5H, s, aroamtic H). (*R*)-**4a** and (*R*)-**4b**: Colorless syrup; IR and ^{1}H-NMR spectra were the same as those of (*S*)-**4a** and (*S*)-**4b**, respectively.

2-Substituted acrylates (**9a—j**) were prepared by reaction of alkyl malonic acid monoester with formaldehyde and diethylamine according to a published method.[9] Yields and boiling points of the compounds are listed in Table VI.

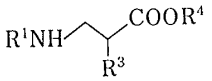
2-Substituted 3-(*N*-substituted amino)propionates (**10a—m**) were prepared by addition of primary amines to the above acrylic esters **9** according to the general procedure.[10a,b] Yields and boiling points or melting points of the compounds are listed in Table VI.

Typical Procedure for the Preparation of Diesters (7a—d). Methyl (3*S*)-2-{*N*-(2*S*)-1-Methoxycarbonyl-3-methylbut-2-yl]-*N*-methylcarbamoyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (7a)——Compound (*S*)-**4a** (8.8 g, 30 mmol) was dissolved in 25% hydrobromide–acetic acid solution (45 ml) under ice cooling and the reaction mixture was stirred at room temperature for 20 min. The solution was evaporated to dryness *in vacuo* and the resulting residue was triturated with Et_2O–*n*-hexane to give methyl (3*S*)-3-(*N*-methylamino)-4-methylpentanoate hydrobromide [(*S*)-**5a**·HBr] as a white powder.

TABLE VI. Yields and Boiling Points of Starting Materials **9** and **10**



9



10

Compd. No.	R^3	R^4	Yield (%)	bp (°C/mmHg)	Compd. No.	R^1	R^3	R^4	Yield (%)	bp (°C/mmHg)
9a	CH_3	CH_3			**10a**	CH_3	C_2H_4Ph	C_2H_5	67.0	135/3
9b	iso-C_3H_7	C_2H_5	83.0	160/3	**10b**[c]	C_2H_5	CH_3	CH_3	68.5	110—113/25
9c[a]	C_4H_9	C_2H_5	78.0	88—91/3	**10c**	C_2H_5	iso-C_3H_7	C_2H_5	42.8	115—120/25
9d[b]	C_6H_{13}	C_2H_5	76.0	99—101/15	**10d**	C_2H_5	C_4H_9	C_2H_5	78.0	135—138/35
9e	C_8H_{17}	C_2H_5	76.4	95—97/3	**10e**	C_2H_5	C_6H_{13}	C_2H_5	47.0	145/25
9f	C_9H_{19}	C_2H_5	68.5	125—127/5	**10f**	C_2H_5	C_8H_{17}	C_2H_5	74.0	146—150/7
9g	$C_{10}H_{21}$	C_2H_5	82.0	109—111/2	**10g**	C_2H_5	C_9H_{19}	C_2H_5	64.6	163—168/5
9h	$C_{12}H_{25}$	C_2H_5	48.0	134/3	**10h**	C_2H_5	$C_{10}H_{21}$	C_2H_5	82.0	142—143/2
9i	$C_{16}H_{33}$	C_2H_5	44.0	173—174/2	**10i**[d]	C_2H_5	$C_{12}H_{25}$	C_2H_5	78.5	
9j	C_2H_4Ph	C_2H_5	92.0	163—165/30	**10j**[e]	C_2H_5	$C_{16}H_{33}$	C_2H_5	45.0	
					10k	C_2H_5	C_2H_4Ph	C_2H_5	84.0	169—171/3
					10l	iso-C_3H_7	C_2H_4Ph	C_2H_5	48.0	148/4
					10m	C_2H_4Ph	C_2H_4Ph	C_2H_5	41.5	182—184/2

a) Ref. 9, bp 82—84 °C/30 mmHg. *b*) Ref. 9, bp 53—58 °C/4 mmHg. *c*) Ref. 10*b*, bp 51 °C/0.5 mmHg. *d*) Oxalate; mp 125—127 °C. *e*) Hydrochloride; mp 102—105 °C.

A solution of the above (*S*)-**5a**·HBr and triethylamine (10.5 ml, 75 mmol) in CH_2Cl_2 (30 ml) was added dropwise to a solution of phosgene (4.5 g, 45 mmol) in CH_2Cl_2 (30 ml) with stirring at −30 °C. After being stirred at the same temperature for 30 min, the mixture was concentrated to dryness *in vacuo*. The residue was dissolved in CH_2Cl_2 (20 ml) and a solution of **6a** (6.83 g, 30 mmol) and triethylamine (12.6 ml, 90 mmol) in CH_2Cl_2 (20 ml) was added. The mixture was stirred at room temperature overnight and concentrated *in vacuo*. The residue was diluted with AcOEt and the mixture was washed with 3% HCl, water, saturated aqueous $NaHCO_3$, and water successively. The organic layer was dried over $MgSO_4$ and the solvent was removed *in vacuo*. The residue thus obtained was purified by column chromatography on silica gel with toluene–AcOEt (4 : 1) as an eluent to give **7a** (5.2 g, 46.0%) as a colorless syrup. IR ν_{max}^{film} cm^{-1}: 1740, 1630. MS *m/e*: 376 (M^+).

Other diesters (**7b—d**) were prepared in the same manner; the yields and ^{1}H-NMR spectra are summarized in Table VII.

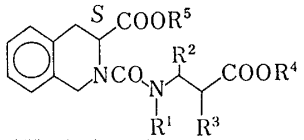
General Procedure for the Preparation of Diesters (11a—x)——Diesters (**11a—x**) were prepared by condensation of (*S*)-**6b** with the carbamoyl chloride of **10** in the same manner as described for the preparation of **7a**. The mixture of diastereomers thus obtained was separated by column chromaogoraphy on silica gel with toluene–AcOEt (20 : 1) as an eluent to give (*S,R*)-**11** from the first fraction and (*S,S*)-**11** from the second fraction, each as a colorless syrup. Yields and ^{1}H-NMR data are summarized in Table VII.

Typical Procedure for the Preparation of Dicarboxylic Acids (8a—d and 12a—t). (3*S*)-2-{*N*-[(2*R*)-2-Carboxydecyl]-*N*-ethylcarbamoyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (12h)——A solution of KOH (415 mg) in water (5 ml) was added to a solution of **11i** (1.0 g, 1.8 mmol) in EtOH (5 ml), and the mixture was stirred at room temperature for 6 h, then concentrated under reduced pressure to remove EtOH. The residue was acidified with dilute HCl and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$, and evaporated *in vacuo*. The residue thus obtained was crystallized from iso-Pr_2O and collected by filtration to give **12h** (0.6 g, 76.4%), mp 100—101 °C (dec.). IR ν_{max}^{Nujol} cm^{-1}: 1735, 1640, 1610.

Other dicarboxylic acids were prepared similarly, and their physical constants and analytical data are summarized in Tables I and II.

Typical Procedure for the Preparation of Monoesters (13a—k). (3*S*)-2-{*N*-[(2*R*)-2-Ethoxycarbonyl-4-phenylbutyl]-*N*-ethylcarbamoyl}-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (13i)——A mixture of **11s** (3.0 g, 5.5 mmol) and palladium-black (30 mg) in EtOH (30 ml) was stirred under a stream of hydrogen for 3 h at room temperature. After removal of the catalyst by fitration, $Ca(OH)_2$ (204 mg) and water (10 ml) were added to the filtrate. The mixture was stirred for 30 min at room temperature, and the insoluble materials were filtered off. The filtrate was concentrated *in vacuo*, and the resulting syrup was crystallized from water. The crystalline precipitates were collected by filtration, recrystallized from aqueous EtOH, and dried to give **13i** calcium salt as a colorless crystalline powder (2.4 g, 91.0%), mp 147—148 °C (dec.), $[\alpha]_D^{20}$ +14.6° (c=0.5, EtOH). IR ν_{max}^{Nujol} cm^{-1}: 1730, 1600,

TABLE VII. Yields and ^{1}H-NMR Data of Diesters



7a, b, 11b: $R^4 = CH_3$, other: $R^4 = C_2H_5$
7a—d: $R^5 = CH_3$, other: $R^5 = CH_2Ph$

Compd. No.	R^1	R^2 (Config.)	R^3 (Config.)	Yield (%)	^{1}H-NMR ($CDCl_3$) δ	
					Isoquinoline C_3-H (1H)	Other
7a	CH_3	iso-C_3H_7 (*S*)	H	46.0	4.69 (t, J=6.0 Hz)	0.95 (6H, d, J=7 Hz), 1.60—2.16 (1H, m), 2.48—2.75 (2H, m), 2.91 (3H, s), 3.10—3.40 (2H, m), 3.50 (3H, s), 3.67 (3H, s), 3.82—4.15 (1H, m), 4.30—4.55 (2H, m), 6.90—7.40 (4H, m)
7b	CH_3	iso-C_3H_7 (*R*)	H	61.5	4.68 (t, J=6.0 Hz)	0.93 (6H, d, J=7 Hz), 1.60—2.20 (1H, m), 2.50—2.72 (2H, m), 2.89 (3H, s), 3.10—3.38 (2H, m), 3.59 (3H, s), 3.64 (3H, s), 3.70—4.10 (1H, m), 4.39—4.55 (2H, m), 6.80—7.28 (4H, m)
7c	C_2H_5	CH_3 (*S*)	H	46.0	4.84 (t, J=6.0 Hz)	1.00—1.40 (9H, m), 2.50—2.70 (2H, m), 3.05—3.45 (4H, m), 3.67 (3H, s), 4.06 (2H, q, J=7 Hz), 3.90—4.40 (1H, m), 4.54 (2H, s), 7.00—7.30 (4H, m)
7d	C_2H_5	CH_3 (*R*)	H	50.8	4.81 (t, J=6.0 Hz)	1.00—1.40 (9H, m), 2.40—2.80 (2H, m), 3.10—3.40 (4H, m), 3.64 (3H, s), 4.06 (2H, q, J=7 Hz), 3.90—4.30 (1H, m), 4.51 (2H, s), 7.00—7.30 (4H, m)
11a	CH_3	H	C_2H_4Ph (*RS*)	85.0[a]	4.70—4.95 (m)	1.16 (3H, t, J=7 Hz), 1.50—2.20 (2H, m), 2.30—3.20 (3H, m), 2.83 (3H, s), 3.19 (2H, d, J=5.5 Hz), 3.30—4.30 (4H, m), 4.43 (2H, s), 5.03 (2H, s), 6.7—7.60 (14H, m)
11b	C_2H_5	H	CH_3 (*RS*)	84.0[a]	4.70—5.00 (m)	0.90—1.40 (6H, m), 2.40—3.80 (7H, m), 3.55 (3H, s), 4.48 (2H, s), 5.08 (2H, s), 6.90—7.50 (9H, m)
11c	C_2H_5	H	iso-C_3H_7 (*R*)	21.0	4.92 (t, J=5.5 Hz)	0.90—1.30 (6H, m), 1.60—2.10 (2H, m), 2.40—2.80 (2H, m), 2.90—3.50 (7H, m), 4.02 (2H, q, J=7 Hz), 4.48 (2H, s), 5.07 (2H, s), 6.90—7.40 (14H, m)
11d	C_2H_5	H	iso-C_3H_7 (*S*)	16.0	4.84 (t, J=5.5 Hz)	0.97—1.29 (6H, m), 1.60—2.10 (2H, m), 2.40—2.80 (2H, m), 2.95—3.60 (7H, m), 4.07 (2H, q, J=7 Hz), 4.50 (2H, s), 5.07 (2H, s), 6.90—7.40 (14H, m)
11e	C_2H_5	H	C_4H_9 (*R*)	25.0	4.93 (t, J=5.5 Hz)	0.70—1.80 (15H, m), 3.00—3.60 (7H, m), 4.02 (2H, q, J=7 Hz), 4.49 (2H, s), 5.09 (2H, s), 6.90—7.40 (9H, m)
11f	C_2H_5	H	C_4H_9 (*S*)	20.0	4.82 (t, J=5.5 Hz)	0.70—1.70 (15H, m), 3.00—3.55 (7H, m), 4.00 (2H, q, J=7 Hz), 4.51 (2H, s), 5.01 (2H, s), 6.90—7.40 (9H, m)
11g	C_2H_5	H	C_6H_{13} (*R*)	28.1	4.92 (t, J=5.5 Hz)	0.70—1.60 (19H, m), 2.50—2.90 (1H, m), 3.00—3.50 (6H, m), 4.00 (2H, q, J=7 Hz), 4.47 (2H, s), 5.06 (2H, s), 6.90—7.40 (9H, m)
11h	C_2H_5	H	C_6H_{13} (*S*)	14.8	4.82 (t, J=5.5 Hz)	0.70—1.60 (19H, m), 2.50—2.90 (1H, m), 3.00—3.50 (6H, m), 4.00 (2H, q, J=7 Hz), 4.50 (2H, s), 5.06 (2H, s), 6.90—7.40 (9H, m)
11i	C_2H_5	H	C_8H_{17} (*R*)	30.0	4.83 (t, J=5.5 Hz)	0.70—1.60 (23H, m), 2.40—2.80 (1H, m), 2.80—4.20 (8H, m), 4.38 (2H, s), 5.00 (2H, s), 6.80—7.30 (9H, m)

TABLE VII. (continued)

Compd. No.	R^1	R^2 (Config.)	R^3 (Config.)	Yield (%)	^{1}H-NMR ($CDCl_3$) δ	
					Isoquinoline C_3-H (1H)	Other
11j	C_2H_5	H	C_8H_{17} (*S*)	28.1	4.69 (t, J=5.5 Hz)	0.70—1.70 (23H, m), 2.40—2.80 (1H, m), 2.90—3.40 (6H, m), 3.95 (2H, q, J=7 Hz), 4.45 (2H, s), 5.02 (2H, s), 6.90—7.30 (9H, m)
11k	C_2H_5	H	C_9H_{19} (*R*)	33.3	4.93 (t, J=5.5 Hz)	0.70—1.70 (25H, m), 2.50—2.90 (1H, m), 3.00—3.50 (6H, m), 4.00 (2H, q, J=7 Hz), 4.48 (2H, s), 5.06 (2H, s), 6.90—7.40 (9H, m)
11l	C_2H_5	H	C_9H_{19} (*S*)	15.8	4.82 (t, J=5.5 Hz)	0.70—1.70 (25H, m), 2.50—2.90 (1H, m), 3.00—3.55 (6H, m), 4.01 (2H, q, J=7 Hz), 4.51 (2H, s), 5.07 (2H, s), 6.90—7.40 (9H, m)
11m	C_2H_5	H	$C_{10}H_{21}$ (*R*)	41.0	4.92 (t, J=5.5 Hz)	0.70—1.70 (27H, m), 2.40—3.50 (7H, m), 3.95 (2H, q, J=7 Hz), 4.46 (2H, s), 5.05 (2H, s), 6.80—7.30 (9H, m)
11n	C_2H_5	H	$C_{10}H_{21}$ (*S*)	26.5	4.82 (t, J=5.5 Hz)	0.70—1.70 (27H, m), 2.40—3.50 (7H, m), 3.95 (2H, q, J=7 Hz), 4.45 (2H, s), 5.06 (2H, s), 6.80—7.30 (9H, m)
11o	C_2H_5	H	$C_{12}H_{25}$ (*R*)	31.0	4.92 (t, J=5.5 Hz)	0.50—1.80 (31H, m), 2.40—3.80 (7H, m), 4.00 (2H, q, J=7 Hz), 4.48 (2H, s), 5.06 (2H, s), 6.80—7.50 (9H, m)
11p	C_2H_5	H	$C_{12}H_{25}$ (*S*)	10.6	4.82 (t, J=5.5 Hz)	0.60—1.80 (31H, m), 2.40—3.60 (7H, m), 4.00 (2H, q, J=7 Hz), 4.50 (2H, s), 5.06 (2H, s), 6.80—7.50 (9H, m)
11q	C_2H_5	H	$C_{16}H_{33}$ (*R*)	17.9	4.92 (t, J=5.5 Hz)	0.50—1.70 (39H, m), 2.40—3.50 (7H, m), 4.00 (2H, q, J=7 Hz), 4.46 (2H, s), 5.04 (2H, s), 6.90—7.40 (9H, m)
11r	C_2H_5	H	$C_{16}H_{33}$ (*S*)	14.9	4.82 (t, J=5.5 Hz)	0.70—1.80 (39H, m), 2.40—3.60 (7H, m), 4.00 (2H, q, J=7 Hz), 4.50 (2H, s), 5.05 (2H, s), 6.90—7.40 (9H, m)
11s	C_2H_5	H	C_2H_4Ph (*R*)	29.0 (82.3[b])	4.92 (t, J=5.5 Hz)	0.97—1.29 (6H, m), 1.60—2.10 (2H, m), 2.40—2.80 (2H, m), 2.90—3.50 (7H, m), 4.02 (2H, q, J=7 Hz), 4.48 (2H, s), 5.07 (2H, s), 6.90—7.40 (14H, m)
11t	C_2H_5	H	C_2H_4Ph (*S*)	22.1 (85.0[c])	4.84 (t, J=5.5 Hz)	0.97—1.29 (6H, m), 1.60—2.10 (2H, m), 2.40—2.80 (2H, m), 2.95—3.60 (7H, m), 4.04 (2H, q, J=7 Hz), 4.50 (2H, s), 5.07 (2H, s), 6.90—7.40 (14H, m)
11u	iso-C_3H_7	H	C_2H_4Ph (*R*)	39.1	4.95 (t, J=5.0 Hz)	1.08 (6H, d, J=7 Hz), 1.19 (3H, t, J=7 Hz), 1.40—2.00 (2H, m), 2.20—3.35 (8H, m), 3.40—4.20 (2H, m), 4.40 (2H, s), 5.00 (2H, s), 6.80—7.60 (14H, m)
11v	iso-C_3H_7	H	C_2H_4Ph (*S*)	32.0	4.69 (t, J=5.0 Hz)	1.07 (6H, d, J=7 Hz), 1.18 (3H, t, J=7 Hz), 1.40—2.10 (2H, m), 2.15—3.30 (8H, m), 3.96 (2H, q, J=7 Hz), 4.45 (2H, s), 4.99 (2H, s), 6.80—7.50 (14H, m)
11w	C_2H_4Ph	H	C_2H_4Ph (*R*)	41.0	4.86 (t, J=5.5 Hz)	1.11 (3H, t, J=7 Hz), 1.45—2.00 (2H, m), 2.40—3.60 (11H, m), 4.00 (2H, q, J=7 Hz), 4.39 (2H, s), 5.03 (2H, s), 6.80—7.50 (14H, m)
11x	C_2H_4Ph	H	C_2H_4Ph (*S*)	25.9	4.73 (t, J=5.5 Hz)	1.17 (3H, t, J=7 Hz), 1.60—2.10 (2H, m), 2.40—3.60 (11H, m), 4.04 (2H, q, J=7 Hz), 4.41 (2H, s), 5.04 (2H, s), 6.80—7.30 (14H, m)

a) Percent yield of a mixture of diastereomers. *b*) Yield shown in parentheses is that when (*R*)-**10k** was used as the starting material. *c*) Yield shown in parentheses is that when (*S*)-**10k** was used as the starting material.

1580.

Other monoester derivatives were obtained similarly, and their physical constants and analytical data are summarized in Table III.

Optical Resolution of Ethyl 2-Phenethyl-3-(*N*-ethylamino)propionate (10k)——Racemic amine **10k** (10.0 g, 0.04 mol) and *N*-benzyloxycarbonyl-L-phenylalanine [(*S*)-**14**, 12.0 g, 0.04 mol] were dissolved in AcOEt (45 ml) by heating on a water bath. Diisopropyl ether (60 ml) was added to the above solution and the mixture was allowed to stand at room temperature overnight. The crystalline precipitates were collected by filtration, washed with AcOEt–iso-Pr_2O (1 : 1) (15 ml), and recrystallized from AcOEt–iso-Pr_2O (1 : 1) (34 ml) to afford (*S*)-**10k**·(*S*)-**14** salt (7.4 g, 33.6%) as colorless prisms, mp 92—95 °C, $[\alpha]_D^{21}$ +16.6° (*c*=1, EtOH). *Anal.* Calcd for $C_{15}H_{23}NO_2 \cdot C_{17}H_{17}NO_4$: C, 70.05; H, 7.35; N, 5.11. Found: C, 70.11; H, 7.37; N, 5.09.

The salt (6.0 g) was suspended in Et_2O, and the mixture was shaken with aqueous Na_2CO_3. The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated to dryness. The resultant syrup was treated with ethanolic hydrochloride and triturated with Et_2O to give (*S*)-**10k**·HCl (2.8 g, 89.6%) as colorless plates, mp 113—116 °C, $[\alpha]_D^{24}$ −18.7° (*c*=1, EtOH).

The original mother liquor from (*S*)-**10k**·(*S*)-**14** salt was treated with aqueous Na_2CO_3. The organic layer was separated, washed with brine, dried over $MgSO_4$, and evaporated *in vacuo* to dryness. The resultant syrup and (*R*)-**14** (7.48 g, 0.025 mol) was dissolved in AcOEt (25 ml) by heating. The solution was diluted with iso-Pr_2O (35 ml) and cooled overnight. The crystals were collected by filtration, and washed with AcOEt–iso-Pr_2O (1 : 1) to afford (*R*)-**10k**·(*R*)-**14** salt (8.3 g, 37.8%) as colorlss prisms, mp 93—95 °C, $[\alpha]_D^{21}$ −16.9° (*c*=1, EtOH). *Anal.* Calcd for $C_{15}H_{23}NO_2 \cdot C_{17}H_{17}NO_4$: C, 70.05; H, 7.35; N, 5.11. Found: C, 70.16; H, 7.42; N, 5.07. The salt (8 g) was treated in the same manner as described for (*S*)-**10k** to give (*R*)-**10k**·HCl (4.17 g, 92.5%) as colorless plates, mp 114—116 °C, $[\alpha]_D^{24}$ +18.6° (*c*=1, EtOH).

X-Ray Crystallographic Analysis of (*R*)-10k·HBr——By the general method, the above (*R*)-**10k**·HCl was converted to the HBr salt as colorless crystals, mp 108—109 °C, $[\alpha]_D^{24}$ +16.5° (*c*=1, EtOH).

Crystal data: orthorhombic, space group $p2_12_12_1$ with a=11.045 (2), b=30.217 (5), c=10.291 (3) A; Z=8. A four-circle diffractometer (Rigaku) with Ni-filtered CuK_α radiation was used for all measurements. Of 3650 independent reflections ($2\theta \leqq 130°$), 2705 with $|F| \geqq 2.5\,\sigma(F)$ were subjected to the analysis. The structure was solved by the heavy-atom method and refined to an *R*-value of 0.095. The absolute configuration was determined by the Bijvoet difference method. Of the total of 27 Friedel pairs measured with great care, 24 pairs clearly showed the absolute configuration.

Pharmacological Methods——The *in vitro* ACE inhibitory activity was determined according to the procedure reported previously.[1a)]

The antihypertensive effect was examined in male spontaneously hypertensive rats (SHR, Charles River Japan Inc.) weighing 300 to 350 g. Groups of 6 to 8 SHR were used. The test compounds were suspended in 0.5% sodium carboxymethyl cellulose (CMC) solution and orally administered to rats which had been fasted overnight. The systolic blood pressure was measured by a tail cuff method.[11)]

Acknowledgement We wisht to express our thanks to Dr. I. Chibata, Research and Development Executive, Dr. M. Kisumi, Director of this research laboratory, and Dr. M. Miyoshi, former Vice Director of the Division of Research Administration of this company, for their encouragement and interest throughout this work. Thanks are also due to Dr. T. Date, the Organic Chemistry Research Laboratory of this company, for X-ray analysis.

References and Notes

1) *a*) Part I of this series: K. Hayashi, Y. Ozaki, K. Nunami, T. Uchida, J. Kato, K. Kinashi, and N. Yoneda, *Chem. Pharm. Bull.*, **31**, 570 (1983); *b*) Part II of this series: K. Hayashi, K. Nunami, K. Sakai, Y. Ozaki, J. Kato, K. Kinashi, and N. Yoneda, *ibid.*, **31**, 3553 (1983).

2) A part of this work was presented at the 103rd Annual Meeting of the Pharmaceutical Society of Japan, Tokyo, April 1983.

3) *a*) M. A. Ondetti, B. Rubin, and D. W. Cushman, *Science*, **196**, 441 (1977); *b*) D. W. Cushman, H. S. Cheung, E. F. Sabo, and M. A. Ondetti, *Biochemistry*, **16**, 5484 (1977).

4) *a*) I. Mita, J. Iwao, M. Oya, T. Chiba, and T. Iso, *Chem. Pharm. Bull.*, **26**, 1333 (1978); *b*) A. A. Patchett, E. Harris, E. W. Tristram, M. J. Wyvratt, T. Wu, D. Taub, E. R. Peterson, T. J. Ikeler, J. ten Broeke, L. G. Payne, D. L. Ondeyka, E. D. Thorsett, W. J. Greenlee, N. S. Lohr, R. D. Hoffsommer, H. Joshua, W. V. Rayle, J. W. Rothrock, S. D. Aster, A. L. Maycock, F. M. Robinson, R. Hirschmann, C. S. Sweet, E. H. Ulm, D. M. Gross, T. C. Vassil, and C. A. Stone, *Nature* (London), **288**, 280 (1980); *c*) R. F. Meyer, E. D. Nicolaides, F. J. Tinney, E. A. Lunney, A. Holmes, M. L. Hoefle, R. D. Smith, A. D. Essenburg, H. R. Kaplan, and R. G. Almquist, *J. Med. Chem.*, **24**, 964 (1981); *d*) R. F. Meyer, A. D. Essenburg, R. D. Smith, and H. R. Kaplan, *ibid.*, **25**, 996 (1982); *e*) R. E. Galardy, *Biochem. Biophys. Res. Commun.*, **97**, 94 (1980); *f*) D. H. Kim, C. J. Guinosso, G. C. Buzby, Tr., D. R. Herbst, R. J. McCaully, T. C. Wicks, and R. L. Wendt, *J. Med. Chem.*, **26**, 394 (1983); *g*) J. L.

Stanton, N. Gruenfeld, J. E. Babiarz, M. H. Ackerman, R. C. Friedmann, A. M. Yuan, and W. Macchia, *ibid.*, **26**, 1267 (1983). *h*) N. Gruerfeld, J. L. Stanton, A. M. Yuan, F. H. Ebetino, L. J. Browne, C. Gude, and C. F. Huebner, *ibid.*. **26**, 1277 (1983).

5) *a*) M. E. Condon, E. W. petrillo, Jr., D. E. Ryono, J. A. Reid, R. Neubeck, M. Puar, J. E. Heikes, E. F. Sabo, K. A. Losee, D. W. Cushman, and M. A. Ondetti, *J. Med. Chem.*, **25**, 250 (1982); *b*) E. W. Petrillo, Jr., and M. A. Ondetti, *Medicinal Research Reviews*, **2**, 1 (1982).
6) C. Hansch and T. Fujita, *J. Am. Chem. Soc.*, **86**, 1616 (1964).
7) *a*) R. T. Dean and H. Rapoport, *J. Org. Chem.*, **43**, 2115 (1978); *b*) K. Hayashi, Y. Ozaki, K. Nunami, and N. Yoneda, *Chem. Pharm. Bull.*, **31**, 312 (1983).
8) T. Wakamiya, H. Uratani, T. Teshima, and T. Shiba, *Bull. Chem. Soc. Jpn.*, **48**, 2401 (1975).
9) Y. Iwakura, M. Sato, and Y. Matsuo, *Nippon Kagaku Zasshi*, **80**, 502 (1959).
10) *a*) K. Morsch, *Monatsch*, **63**, 220 (1933); *b*) S. David and P. Sinay, *Bull. Soc. Chim. Fr.*, **1965**, 2301.
11) J. M. Pfeffer, M. A. Pfeffer, and E. D. Frohileh, *J. Lab. Clin, Med.*, **78**, 957 (1971).