86177-58-4; **69**, 86196-52-3; V (X = 4-CF_3), 18960-29-7; V (X = 4-PhO), 86177-59-5; VIa (X = 3,4-Cl_2; R_2 = Ph; R_2 = H), 86177-02-8; VII (R_1 = F_3; R_2 = H), 372-31-6; VIII (R_1 = CF_3; R_2 = H) Na salt, 86177-60-8; 4-(trifluoromethyl)benzenamine, 455-14-1; 4-phenoxybenzenamine, 139-59-3; 2-(chloromethyl)-1-methoxy-4-nitrobenzene, 93-06-1; 2-methoxy-*N*,*N*-dimethyl-4-nitrobenzenemethanamine, 86177-61-9; *N*-(4-hydroxyphenyl)-acetamide, 103-90-2; 4-(acetylamino)-2-[(dimethylamino)-methyl]phenol hydrochloride, 13886-11-8; *N*-[3-[(diethylamino)methyl]-4-(phenylmethoxy)phenyl]acetamide, 31842-08-7; 5-nitro[1,1′-biphenyl]-2-ol, 4291-29-6; *N*-[6-hydroxy[1,1′-biphenyl]-3-yl]acetamide, 29785-41-9; *N*-[5-[(diethylamino)-methyl]-6-hydroxy[1,1′-biphenyl]-3-yl]acetamide, 86177-62-0; *N*-cyanoguanidine, 461-58-5; *p*-aminobenzophenone, 1137-41-3.

Angiotensin Converting Enzyme Inhibitors: N-Substituted Monocyclic and Bicyclic Amino Acid Derivatives

James L. Stanton,* Norbert Gruenfeld, Joseph E. Babiarz, Michael H. Ackerman, Robert C. Friedmann, Andrew M. Yuan, and William Macchia

Research and Development Department, Pharmaceuticals Division, CIBA-GEIGY Corporation, Ardsley, New York 10502.
Received November 15, 1982

The synthesis of *N*-(3-mercaptopropionyl)-*N*-arylglycines (**14a–x**), -*N*-arylalanines (**15a,b**), -*N*-cycloalkylglycines (**16a–k**), and -1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids (**17a-d**), -1,2,3,4-tetrahydroquinoline-2-carboxylic acids (**18a–f**), and -indoline-2-carboxylic acids (**19a–k**) is described. In vitro inhibition of angiotensin converting enzyme (ACE) is reported for each compound, and the structure–activity relationship for each series is discussed. The in vivo inhibition of ACE and antihypertensive effects of representative compounds from each series are discussed. The most potent compound, **19d**, had an in vitro ACE IC_{50} of 2.6×10^{-9} M and lowered blood pressure in spontaneous hypertensive rats 85 mm at a dose of 10 mg/kg po.

Since the discovery[1] of the angiotensin converting enzyme (ACE) inhibitor 1-[(2*S*)-3-mercapto-2-methylpropionyl]-L-proline (captopril) and its use as an effective antihypertensive agent for essential and renal hypertension,[2] several papers have appeared describing a variety of analogues.[3] We have investigated the effect of replacing the proline portion of captopril with various N-substituted amino acids. In this report we describe the preparation and structure–activity relationship for a series of *N*-arylglycines,[4] *N*-arylalanines, *N*-cycloalkylglycines,[4,5] 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acids,[6] 1,2,3,4-tetrahydroquinoline-2-carboxylic acids[6d,7] and indoline-2-carboxylic acids.[6d,8]

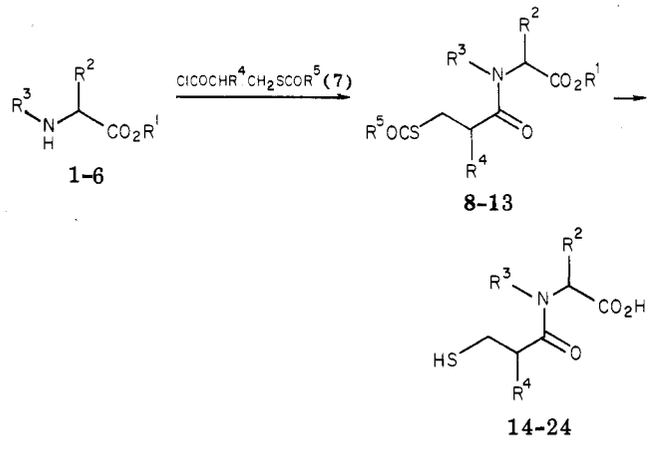
Chemistry. The desired compounds were obtained as shown in Scheme I. Amino esters **1–6** were transformed to amides **8–13** by treatment with acid chloride **7** in the presence of anhydrous potassium carbonate. Alkaline hydrolysis of **8–13** (R^5 = CH_3) led to the final products **14–24** (Table I).

The starting amino esters **1** or **2** required for **14** or **15** were prepared by alkylation of substituted anilines with ethyl chloroacetate or methyl 2-bromopropionate at 100 °C for 4–48 h in the presence of sodium acetate.[9] Amino esters **3** were obtained by reductive amination of aldehydes or ketones with glycine ethyl ester and sodium cyanoborohydride. Amino esters **4** were generated by cyclization of phenylalanine or substituted phenylalanine with formalin and hydrochloric acid,[10] followed by esterification. Amino esters **5** were synthesized from the corresponding quinaldic esters by hydrogenation at atmospheric pressure

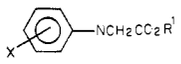
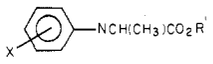
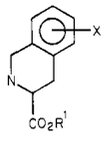
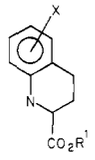
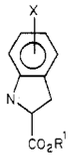
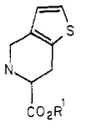
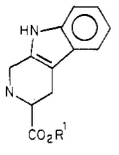
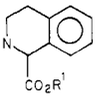
(1) D. W. Cushman, H. S. Cheung, E. F. Sabo, and M. A. Ondetti, *Biochemistry*, **16**, 5484 (1977).
(2) (a) E. L. Bravo and R. C. Tarazi, *Hypertension*, 1, 39 (1979). (b) H. R. Brunner, H. Gavras, B. Waeber, G. R. Kershaw, G. A. Turini, R. A. Vukovich, and D. N. McKinstry, *Ann. Intern. Med.*, **90**, 19 (1979). (c) D. B. Case, S. A. Atlas, J. H. Laragh, J. E. Sealey, P. A. Sullivan, and D. N. McKinstry, *Prog. Cardiovasc. Dis.*, **21**, 195 (1978). (d) H. Gavras, H. R. Brunner, G. A. Turini, G. R. Kershaw, C. P. Tifft, S. Cuttelod, I. Gavras, R. A. Vukovich, and D. N. McKinstry, *N. Engl. J. Med.*, **298**, 991 (1978).
(3) (a) I. Mita, J. Iwao, M. Oya, T. Chiba, and T. Iso, *Chem. Pharm. Bull.*, **26**, 1333 (1978). (b) M. Oya, J. Matsumoto, H. Takashina, T. Watanabe, and J. Iwao, *Chem. Pharm. Bull.*, **29**, 940 (1981). (c) R. E. Galardy, *Biochem. Biophys. Res. Commun.*, **97**, 94 (1980). (d) M. E. Condon, E. W. Petrillo, 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). (e) A. A. Patchett, E. Harris, E. W. Tristram, M. J. Wyvratt, M. 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).
(4) Following completion of this work a related patent appeared: J. T. Suh, J. W. Skiles, B. E. Williams, and A. Schwab, U.S. Patent 4 256 761 (1981).
(5) Following completion of this work the following related publication appeared: Morton-Norwich Products, Inc., Belgian Patent 889 152 (1981).
(6) After completion of this work several related publications appeared: (a) K. Hayashi, J. Kato, T. Uchida and N. Yoneda, European Patent Application 12 845 (1980). (b) Y. Oko and K. Nishikawa, European Patent Application 18 104 (1980). (c) Morton-Norwich Products, Inc., Belgian Patent 883 320 (1980). (d) R. Geyer, V. Teetz, B. Schölkens, and H. Wissmann, European Patent Application 29 488 (1981). (e) M. Vincent, G. Remond, and M. Lauble, European Patent Application 31 741 (1981). (f) J. T. Suh, B. E. Williams, and J. W. Skiles, European Patent Application 39 804 (1981).
(7) Following completion of this work the following related publication appeared: G. C. Wright and D. E. Portlock, German Patent 3 004 370 (1980).
(8) After this work was completed several related publications appeared: (a) Santen Seiyaku, Japanese Kokai 55 145 664 (1980). (b) D. H. Kim and R. J. McCaully, European Patent Application 24 852 (1981). (c) D. H. Kim, C. J. Guinosso, G. C. Buzby, D. R. Herbst, R. J. McCaully, T. C. Wicks, and R. L. Wendt, *J. Med. Chem.*, **26**, 394 (1983).
(9) G. C. Finger, D. R. Dickerson, L. D. Starr, and D. E. Orlopp, *J. Med. Chem.*, **8**, 405 (1965).
(10) S. Archer, *J. Org. Chem.*, **16**, 430 (1951).

0022-2623/83/1826-1267$01.50/0

Scheme I



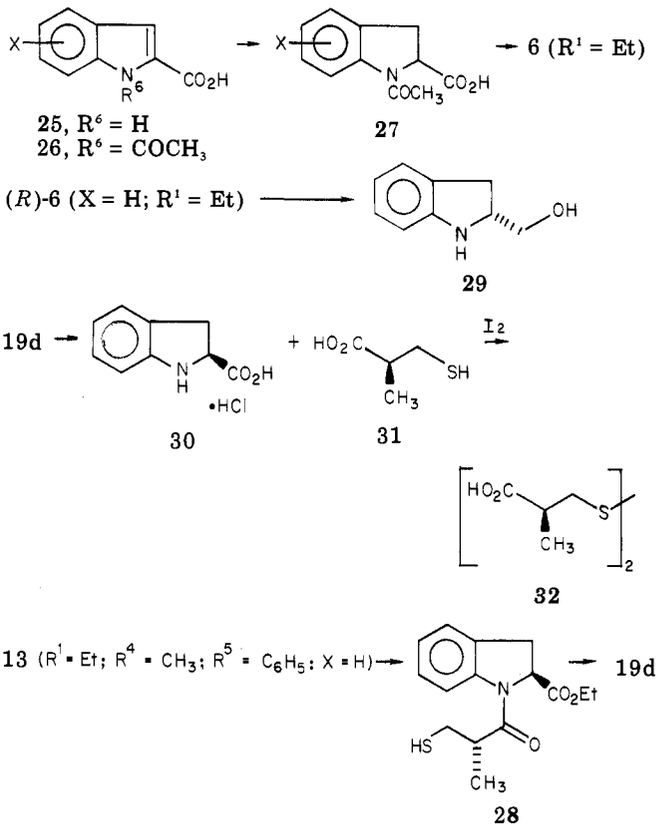
$NR^3CH(R^2)CO_2R'$

1, 8, 14	
2, 9, 15	
3, 10, 16	cycloalkyl-$NHCH_2CO_2R^1$
4, 11, 17	
5, 12, 18	
6, 13, 19	
20	$C_6H_5CH_2NCH_2CO_2R^1$
21	$NHCH(C_6H_5)CO_2R^1$
22	
23	
24	

in the presence of 10% palladium on carbon. The quinaldic esters were prepared from the corresponding acids. The quinaldic acids either were commercially available (for **5a–c**), were synthesized from commercially available quinolines by using the Reissert reaction[11] followed by hydrolysis (for **5d,f**), or were prepared by the Skraup reaction followed by the Reissert sequence (**5e**). Amino esters **6** needed for **19** were produced from **25** (Scheme II). These acids were commercially available or were prepared

(11) W. E. McEwen and R. L. Cobb, *Chem. Rev.*, **55**, 511 (1955).

Scheme II



by using the Fischer indole synthesis with pyruvic acid. Conversion of **25** to *N*-acetylindole **26** was achieved with acetic anhydride and triethylamine at 100 °C. Alternatively, under catalysis of 4-(dimethylamino)pyridine, the reaction proceeded at room temperature. Hydrogenation of **26** at atmospheric pressure in the presence of platinum oxide led to indoline **27**.[12] Transformation of **27** to **6** (R^1 = Et) was achieved by first hydrolyzing **27** to the intermediate amino acid **6** (R^1 = H) with 2 N aqueous hydrochloric acid and then esterifying this intermediate with ethanolic hydrochloric acid. Alternatively, **27** could be converted directly to **6** (R^1 = Et) in refluxing ethanolic hydrochloric acid.

A synthesis of optically active **19d** was carried out to provide the biologically active *SS* enantiomer. In order to obtain the chiral amino ester (*S*)-**6** (X = H), resolution of **26** (X = H) was conducted by formation of a salt with cinchonidine, followed by recrystallization of this salt from ethanol. In this way, both antipodes of **26** (X = H) were isolated in 25–35% yield. Optical purity of the isomers, which had equal but opposite rotations, was determined on the corresponding methyl esters by NMR chiral shift studies with Eu-FOD, in which none of the other isomers could be detected in either sample.

By analogy to previous work,[1] the biologically active isomer **19d** should incorporate an amino acid in the *S* configuration, which corresponds to the naturally occurring L-amino acids. Determination of which of the resolved isomers of **26** had the *S* configuration was achieved by conversion of the enantiomer derived from the less soluble salt via amino ester **6** (R^1 = Et) (X = H) to hydroxymethyl derivative **29** by reduction with lithium aluminum hydride (Scheme II). Compound **29** has previously been correlated with L-phenylalanine.[13] Comparison of the optical rotation

(12) Y. Omote, Y. Fujinoma, K. T. Kuo, and N. Sugiyama, *Nippon Kagaku Zasshi*, **87**, 760 (1966).

of crude **29** ($[\alpha]_D$ −51.3°) with the reported value ($[\alpha]_D$ +60.5°) indicated that **29** had the *R* configuration. Thus, the more soluble salt contained 1-acetyl-(2*S*)-indoline-2-carboxylic acid.

The required chiral acid chloride, 3-(benzoylthio)-2-(*S*)-methylpropionyl chloride, was obtained by conversion of the corresponding racemic acid to a diastereomeric salt with dehydroabietylamine, followed by two recrystallizations from ethanol. The use of an acetyl protecting group in place of the benzoyl group resulted in a more difficult resolution. Verification of the optical purity and absolute configuration of the chiral propionic acid was achieved by comparison of the optical rotation with the reported value[14] and by NMR chiral-shift studies on the corresponding methyl ester. The chiral acid was converted to chiral acid chloride (2*S*)-**7** ($R^4 = CH_3$; $R^5 = C_6H_5$) with oxalyl chloride. Finally, each of the resolved compounds (*S*)-**6** (X = H) and (*R*)-**6** (X = H) was converted to products **19d** and **19e** with (2*S*)-**7** ($R^4 = CH_3$; $R^5 = C_6H_5$) by a modification of the general method described above. Thus, conversion of **13** (R^1 = Et; $R^4 = CH_3$; $R^5 = C_6H_5$; X = H) to **19** was conducted in two steps. Reaction of **13** (R^1 = Et; $R^4 = CH_3$; X = H; $R^5 = C_6H_5$) with hydrazine led to the formation of the corresponding mercapto ester **28**. In this way, the benzoyl group was converted to benzoylhydrazine, which could be removed from the reaction by washing with dilute aqueous hydrochloric acid. Then alkaline hydrolysis of **28** yielded **19d,e**.

A number of studies were conducted to support the optical purity of **19d**. In addition to the NMR chiral-shift studies described above which verified the optical purity of **6** (X = H) and **7** ($R^4 = CH_3$; $R^5 = C_6H_5$), intermediate **13** (X = H; R^1 = Et; $R^4 = CH_3$; $R^5 = C_6H_5$) and the methyl ester of **19d** were each found to be homogeneous under similar NMR chiral-shift studies. Furthermore, the carbon-13 NMR spectrum of **19d** showed no evidence of additional isomers. Finally, **19d** was hydrolyzed in 1 N hydrochloric acid to give amino acid **30** and 3-mercapto-2-methylpropionic acid **31**. The optical rotation of **30** ($[\alpha]_D$ −76.5°) was found to be unchanged from the amino acid used to prepare **19d**. The other hydrolysis product, propionic acid **31**, was oxidized with iodine to disulfide **32**. The optical rotation of **32** ($[\alpha]_D$ −223.8°) was found to be comparable to the reported value ($[\alpha]_D$ −219.7°).[15] Thus, **19d** was free from racemization at either chiral center.

The starting amino acids required for **20**, **21**, and **24** were commercially available. The starting amino acids 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine-6-carboxylic acid[16] and 1,2,3,4-tetrahydro-9*H*-pyrido[3,4-*b*]indole-3(*S*)-carboxylic acid[17] required for **22** and **23**, respectively, were prepared by published methods.

Results and Discussion

Compounds **14–19** from each of the series described above were evaluated for in vitro inhibition of angiotensin converting enzyme, and the results are included in Table I. A number of these compounds had potency comparable or superior to the reference compound, captopril. The structure–activity pattern was investigated for each series.

Considering the *N*-arylglycine series, the effect of attaching an aryl group to the nitrogen of the amino acid proved to be highly beneficial, as seen by comparison of **14a** ($IC_{50} = 3.0 \times 10^{-8}$ M) with the reported glycine analogue, *N*-(3-mercaptopropionyl)glycine ($IC_{50} = 2.8 \times 10^{-6}$ M).[1] Thus, attachment of a phenyl substituent to the nitrogen of glycine has led to an approximately 100-fold increase in activity.

The effect of substituents on the aromatic ring on activity of the *N*-arylglycine series proved to be considerably less dramatic. Sterically, ortho substitution (see **14k,o,x**) led to about a 10-fold reduction in potency. Since ortho substitution forces the aromatic ring out of the plane of the amide carbonyl, these results could imply that the active conformation requires the aromatic ring and the amide carbonyl to be approximately coplanar. 3,5-Disubstituted aromatic analogues (**14n,p**) were also about ten times less active, whereas simple 3-substituted (such as **14l**) or 3,4-disubstituted (such as **14i**) derivatives showed undiminished or slightly enhanced potency. The activity profile of the series further indicates that the size of the substituent at the 4-position of the aromatic ring can be increased up to about five atoms, at which point the activity declines (see **14e–g,h**).

It appears that electron-donating groups at position-3 and/or position-4 of the aromatic ring of this series slightly enhance activity (see **14i,l,r,t,u,w**). Based on this trend, the optically active 3,4-dimethoxy derivative **14j** was prepared with chiral (*S*)-**7** ($R^4 = CH_3$) and it had an $IC_{50} = 5.5 \times 10^{-9}$ M, which represents the most active compound found in the *N*-arylglycine series. Other changes in the structure of the glycine derivatives generally led to reduced potency. Thus, *N*-benzylglycine analogue **20** and α-phenylglycine derivative **21** were less potent compared to the *N*-phenylglycine analogue **14a**. Thus, the *N*-aryl group is essential for potency.

The *N*-arylalanine derivatives **15a,b** had superior in vitro potency compared to the *N*-arylglycine counterparts (compare **14b** and **14i** with **15a** and **15b**, respectively). The difference in potency, approximately a factor of 2–3, is similar to the difference reported for the corresponding parent alanine and glycine analogues.[1]

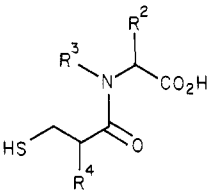
The unexpected favorable effect of introducing an *N*-aryl group to *N*-(3-mercaptopropionyl)glycines or -alanines prompted us to more fully explore the effect on ACE activity of other N-substituted amino acid derivatives. In particular, *N*-cycloalkylglycine derivatives **16a–k** were investigated. As shown in Table I, inhibitory activity is retained or slightly increased in going from an *N*-phenyl- to an *N*-cyclohexylglycine derivative.

The activity of the *N*-cycloalkylglycine series appears to be maximal for five to seven-membered rings affixed directly to nitrogen. These compounds most closely approximate the size and shape of the *N*-arylglycine derivatives. Moreover, an acyclic 3-pentyl analogue, **16c**, which corresponds to a ring-opened cyclopentyl derivative, had somewhat lower activity. The *N*-adamantylglycine **16k** also had somewhat reduced potency, possibly due to excessive steric bulk. Finally, as seen for ortho-substituted glycines, the *N*-(2-phenylcyclohexyl)glycine analogue **16i** had substantially reduced potency compared to **16h** and **16a**. Thus, it again appears that in the active conformation the ring and the amide carbonyl should be approximately coplanar.

Since the structure–activity picture that emerged from series **14** and **16** suggested that the biologically active conformation for these derivatives could be one in which the aromatic ring and the amide carbonyl are relatively coplanar, we prepared a series of 1,2,3,4-tetrahydroquinaldic acids, **18**, which fix the aromatic group in a rigid

(13) E. J. Corey, R. J. McCaully, and H. S. Sachdev, *J. Am. Chem. Soc.*, **92**, 2476 (1970).
(14) I. Junichi, B. Toshio, and I. Tadashi, European Patent Application 1978 (1979).
(15) G. Stallberg, *Ark. Kemi*, **12**, 131 (1957).
(16) J. P. Maffrand, German Patent 2 800 596 (1978).
(17) A. Brossi, A. Focella, and S. Teitel, *J. Med. Chem.*, **16**, 418 (1973).

Table I. N-Substituted Mono- and Bicyclic Amino Acid Derivatives 14-24



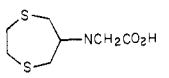
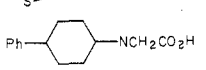
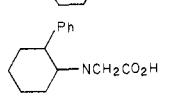
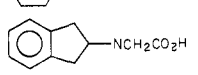
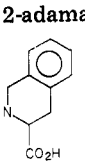
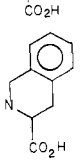
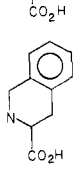
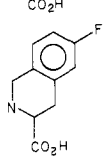
compd	$R^3NCH(R^2)CO_2H$	R^4	remarks[a]	mp,[b] °C	ACE IC_{50}, nM
14a	$C_6H_5NCH_2CO_2H$	H		99-101	30
14b[c]	$C_6H_5NCH_2CO_2H$	CH_3		170-171	13
14c	$4\text{-}FC_6H_4NCH_2CO_2H$	CH_3		163-165	11
14d	$3\text{-}ClC_6H_4NCH_2CO_2H$	CH_3		130-132	16
14e	$4\text{-}(n\text{-}C_4H_9)C_6H_4NCH_2CO_2H$	CH_3	DCHA[d]	124-126	56
14f	$4\text{-}(C_6H_5O)C_6H_4NCH_2CO_2H$	CH_3		128-130	42
14g	$4\text{-}(C_6H_5CH_2O)C_6H_4NCH_2CO_2H$	CH_3		137-139	66
14h	$4\text{-}(n\text{-}C_6H_{13}O)C_6H_4NCH_2CO_2H$	CH_3	DCHA[d]	157-160	470
14i	$3,4\text{-}(CH_3O)_2C_6H_3NCH_2CO_2H$	CH_3		81-83	15
14j	$3,4\text{-}(CH_3O)_2C_6H_3NCH_2CO_2H$	CH_3	*S* isomer	140-142	5.5
14k	$2\text{-}(CH_3O)C_6H_4NCH_2CO_2H$	H		110-112	150
14l	$3\text{-}(CH_3O)C_6H_4NCH_2CO_2H$	CH_3		149-151	10
14m	$4\text{-}(CH_3O)C_6H_4NCH_2CO_2H$	CH_3	DCHA[d]	145-147	7.7
14n	$3,5\text{-}(CH_3O)_2C_6H_3NCH_2CO_2H$	CH_3		125-127	120
14o	$2,4\text{-}(CH_3O)_2C_6H_3NCH_2CO_2H$	H		124-127	93
14p	$3,4,5\text{-}(CH_3O)_3C_6H_2NCH_2CO_2H$	CH_3		132-134	130
14q	$3,4\text{-}(C_2H_5O)_2C_6H_3NCH_2CO_2H$	CH_3	DCHA[d]	138-140	30
14r	$4\text{-}(C_2H_5O)C_6H_4NCH_2CO_2H$	CH_3		105-107	9.2
14s	$4\text{-}(n\text{-}C_3H_7O)C_6H_4NCH_2CO_2H$	CH_3		90-92	23
14t	$3,4\text{-}(OCH_2O)C_6H_3NCH_2CO_2H$	CH_3		99-101	7.2
14u	$3,4\text{-}(OCH_2CH_2O)C_6H_3NCH_2CO_2H$	CH_3		153-155	10
14v	$3,4\text{-}(CH_3)_2C_6H_3NCH_2CO_2H$	CH_3		99-101	12
14w	$3,4\text{-}[(CH_2)_3]C_6H_3NCH_2CO_2H$	CH_3		111-113	9.5
14x	$2,6\text{-}(CH_3)_2C_6H_3NCH_2CO_2H$	CH_3		143-144	190
15a	$C_6H_5NCH(CH_3)CO_2H$	CH_3	DCHA[d]	131-132	4.3
15b	$3,4\text{-}(CH_3O)_2C_6H_3NCH(CH_3)CO_2H$	CH_3	DCHA[d]	155-157	6.7
16a[e,f]	$c\text{-}C_6H_{11}NCH_2CO_2H$	CH_3	DCHA[d]	160-162	7.5
16b[g]	$c\text{-}C_5H_9NCH_2CO_2H$	CH_3	DCHA[d]	143-144	7.0
16c	$(CH_3CH_2)_2CHNCH_2CO_2H$	CH_3	DCHA[d]	138-139	34
16d	$C_6H_{11}CH_2NCH_2CO_2H$	CH_3	DCHA[d]	171-173	51
16e	$c\text{-}C_5H_9SNCH_2CO_2H$	CH_3	DCHA[d]	170-174	19
16f[h]	$c\text{-}C_7H_{13}NCH_2CO_2H$	CH_3	DCHA[d]	143-145	7.1
16g		CH_3	DCHA[d]	179-182	7.6
16h		CH_3	DCHA[d]	186-187	19
16i		CH_3	DCHA[d]	150-154	8000
16j		CH_3	DCHA[d]	180-183[i]	12
16k	2-adamantyl-NCH_2CO_2H	CH_3	Tris[j]	84-87[k]	87
17a[l,m]		H	L isomer, $[\alpha]_D$ +32° (*c* 2.3, EtOH)	145-147	27
17b[n]		CH_3	DCHA[d]	147-149	20
17c		CH_3		121-123	290
17d		H		153-155	36

Table I (*Continued*)

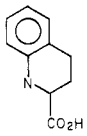
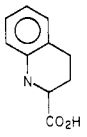
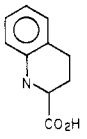
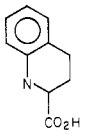
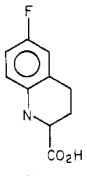
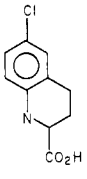
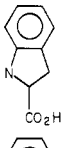
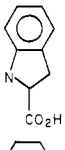
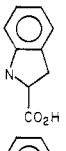
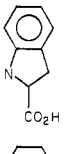
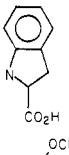
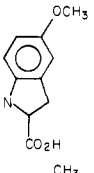
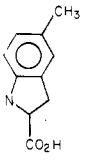
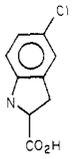
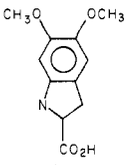
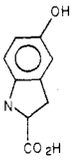
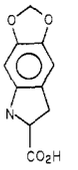
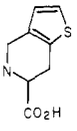
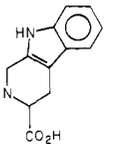
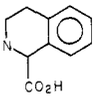
compd	$R^3NCH(R^2)CO_2H$	R^4	remarks[a]	mp,[b] °C	ACE IC_{50}, nM
18a[o]		H		115-118	13
18b[p]		CH_3		127-129	900
18c[p-r]		CH_3		130-134	25
18d[s]		H	DCHA[d]	174-176	9.0
18e		H		97-99	4.7
18f		H	DCHA[d]	200-202	5.0
19a		H		140-142	8.0
19b		H	*S* isomer, $[\alpha]_D$ −112° (*c* 0.55, EtOH)	158-159	2.6
19c[t]		CH_3	DCHA[d]	181-186	23
19d[u]		CH_3	*SS* isomer, $[\alpha]_D$ −178° (*c* 0.9, EtOH)	141-142	2.6
19e		CH_3	*RS* isomer, $[\alpha]_D$ +43° (*c* 0.9, EtOH)	98-101	50 000
19f		CH_3	DCHA[d]	199-202	23
19g		CH_3	DCHA[d]	179-181	19

Table I (*Continued*)

compd	$R^3NCH(R^2)CO_2H$	R^4	remarks[a]	mp,[b] °C	ACE IC_{50}, nM
19h[t]		CH_3	DCHA[d]	198-203	25
19i		H		182-184	270
19j		CH_3	DCHA[d]	208-211	20
19k		CH_3	DCHA[d]	194-196	26
20[v]	$C_6H_5CH_2NCH_2CO_2H$	H		152-154	540
21	$NHCH(C_6H_5)CO_2H$	H		102-106	64
22[w]		H		108-112	620
23[w]		H		190-191	540
24		H	DCHA[d]	163-166	1800
captopril[x]					15

[a] All products were racemic or a 1:1 mixture of diastereomers unless otherwise noted. [b] All compounds had satisfactory C, H, and N elemental analyses and exhibited IR and ^1H NMR spectra consistent with the structures. [c] Literature[4] mp 168-170 °C. [d] Dicyclohexylamine salt. [e] Literature[4] IC_{50} = 29 nM. [f] Reference 5. [g] Literature[4] IC_{50} = 17 nM. [h] Literature[4] IC_{50} = 31 nM. [i] Compound contained 1 equiv of water. [j] Tris(hydroxymethyl)aminomethane salt. [k] Compound contained 1.5 equiv of water. [l] Literature[6c] mp 151-155 °C; $[\alpha]_D$ +29.6 (*c* 0.5, MeOH). [m] Literature[6a] IC_{50} 81 nM. Literature[6f] mp 146-147 °C. [n] References 6b-d. [o] Literature[7] mp 109-111 °C. [p] Compounds **18b** and **18c** are racemic diastereomers separated by fractional crystallization of the intermediate ester **12**. [q] Literature[7] mp 98-101 °C. [r] Reference 6d. [s] Literature[7] mp 195-197 °C. [t] Reference 8a. [u] Literature[8a] mp 140.5-142 °C; $[\alpha]_D$ -178.1° (*c* 1.1, EtOH). [v] M. A. Ondetti and D. W. Cushman, U.S. Patent 4 053 651 (1977). [w] Reference 6f. [x] Literature[1] IC_{50} = 23 nM.

conformation. In vitro, compounds **18** retained the activity seen for the *N*-arylglycine derivatives, and several members of the series (**18e,f**) were somewhat more potent than the reference compound, captopril. Thus, this ring system holds the *N*-aryl group in a geometry suitable for effective binding. As seen for the *N*-arylglycine series, the effect of aromatic substitution on activity was small. The marked difference in potency between diastereomer **18b** and **18c** illustrates the previously observed requirement for inhibitory potency of having an L-amino acid with a 2-methylpropionyl group in the *S* configuration.[1,18] Thus, diastereomer **18c** has been assigned as the *RR,SS* diastereomer based on its biological activity. In contrast to most other captopril analogues and to the other series discussed here, the tetrahydroquinoline series (**18**) showed no significant increase in potency going from the 3-mercaptopropionyl group to the 3-mercapto-2-methylpropionyl group (compare **18a** with **18c**). A similar unusual structure–activity picture was apparently observed for some 2-arylthiazolidine-5-carboxylic acid derivatives.[19]

An isomeric bicyclic amino acid that also fixes the geometry of the aromatic ring is represented by derivatives **17a–d**. The in vitro potency of isoquinoline **17b** was

(18) (a) S. Oparil, T. Koerner, G. W. Tregear, B. A. Barnes, and E. Haber, *Circ. Res.*, **32**, 415 (1973). (b) D. W. Cushman, J. Pluscec, N. J. Williams, E. R. Weaver, E. F. Sabo, O. Kocy, H. S. Cheung, and M. A. Ondetti, *Experientia*, **29**, 1032 (1973).

(19) M. Oya, T. Baba, E. Kato, Y. Kawashima, and T. Watanabe, *Chem. Pharm. Bull.*, **30**, 440 (1982).

Table II. Biological Results

compd	ACE IC_{50}, nM	AI % inhibn,[a] mg/kg iv	AI ED_{50}, μg/kg po	SHR[c] max Δ BP, mm (mg/kg po)
14j	5.5	30 (0.3)		−40 (50)
16a	7.5	42 (0.3)		−67 (30)
17b	20	24 (0.3)		−45 (30)
18a	13	23 (0.3)		−43 (30)
19d	2.6	95 (0.1)	58 (46-67)[d]	−85 (10)
		62 (0.01)		−56 (3)
captopril	15	70 (0.3)	550 (460-620)[d]	−45 (10)
		20 (0.03)		−25 (3)

[a] Tabulated results indicate percent inhibition of angiotensin I pressor response 15 min after intravenous administration of test compound. [b] Tabulated results indicate oral dose of test compound needed to produce 50% inhibition of angiotensin I pressor response. [c] Tabulated results indicate maximal change in blood pressure recorded during the 4-day test period. [d] 95% confidence limits.

comparable to the reference compound, captopril, but not superior to the quinolines **18a–f**. Replacement of the benzene ring of **17a** with thiophene or indole resulted in diminished potency (compare **17a** with **22** or **23**). The isomeric 1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid analogue **24** had considerably reduced activity.

In addition to the tetrahydroquinoline derivatives **18**, another series of rigid *N*-arylglycine derivatives, represented by compounds **19a–k**, was studied. In vitro, the potency of **19a–k** was found to be comparable or superior to the corresponding *N*-arylglycine derivatives. In particular, the *SS* isomer **19d** was approximately 7 times more potent in vitro than the reference compound, captopril. The structure–activity picture for compounds **19** generally paralleled that seen for the corresponding *N*-arylglycine analogues **14**. Substituted aromatic derivatives of **19c** showed only minor differences in potency. Thus, the indoline ring holds the aromatic group in a favorable orientation for binding to the ACE active site.

Representative compounds from each of the series described above were tested in vivo for inhibition of ACE as well as for antihypertensive effects.[20] Key results that clarify the structure–activity picture are summarized in Table II. The intravenous angiotensin I (AI) screen, used as the primary in vivo test, provided a qualitative measure of the relative activity of the test compounds. Percent inhibition of AI pressor response was measured at predetermined intervals over 1 h. The tabulated values, measured 15 min after administration of the test compounds, are representative of the inhibition for the test period. *N*-arylglycine **14j**, *N*-cyclohexylglycine **16a**, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid **17b**, and 1,2,3,4-tetrahydroquinoline-2-carboxylic acid **18a**, each of which had in vitro activity comparable to captopril, were found to be active in vivo but were somewhat less active than captopril. In contrast, indoline-2-carboxylic acid **19d** was found to be more potent than captopril at each submaximal dose level tested. For oral inhibition of ACE, **19d** was found to be approximately 10 times as potent as captopril. In addition, **19d** lowered blood pressure in spontaneous hypertensive rats up to 85 mmHg compared to 45 mmHg for captopril at a dose of 10 mg/kg po. This relative difference in potency was seen throughout the 4-day test period.

In conclusion, the unexpected favorable effect of introducing an *N*-aryl group to *N*-(3-mercaptopropionyl)-glycines has led to the development of rigid analogues that bind more effectively to the ACE active site than captopril. Indoline **19d** provides a better fit at the enzyme active site than naturally occurring amino acids, including proline. (*S*)-Indoline-2-carboxylic acid is not only a rigid, flat analogue of *N*-phenylglycine but can also be viewed as a rigid phenylalanine or a benzoproline analogue. The results of this work demonstrate the presence of an important binding site occupied by the benzo group and further elucidate the topography of the ACE active site. The use of this amino acid for non-mercapto ACE inhibitors is under investigation.[21]

(20) Details of the complete pharmacological profile will be reported elsewhere.

Experimental Section

Proton NMR spectra were determined on a Varian EM-390 spectrometer with Me_4Si as the internal standard. ^{13}C NMR spectra were determined on a Varian CFT-20. Infrared spectra were recorded on a Perkin-Elmer Model 457 or Perkin-Elmer Model 137 spectrophotometer. Optical rotations were measured with a Perkin-Elmer Model 141 polarimeter. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. All compounds were prepared by methods identical with those described below. Intermediate products were used directly without further purification.

Ethyl *N*-(4-Propoxyphenyl)glycinate (1, R^1 = Et; R^2 = H; R^3 = 4-*n*-$C_3H_7OC_6H_4$).[22] A mixture of 4-propoxyaniline (30.0 g, 0.20 mol), ethyl chloroacetate (24.0 g, 0.20 mol), and sodium acetate trihydrate (40.5 g, 0.30 mol) was stirred at 110 °C for 4 h. The reaction was cooled to room temperature and poured into 300 mL of H_2O. The product was collected by filtration and recrystallized from 70 mL of EtOH to give 27.0 g (57%): mp 42–43 °C; NMR ($CDCl_3$) δ 1.01 (3 H, t, J = 7 Hz), 1.28 (3 H, t, J = 7 Hz), 1.78 (2 H, sextet, J = 7 Hz), 3.88 (5 H, m), 4.31 (2 H, q, J = 7 Hz), 6.62 (2 H, d, J = 9 Hz), 6.88 (2 H, d, J = 9 Hz); IR (Nujol) 3482, 3018, 2960, 2865, 1728, 1662, 1625, 1510, 1377, 1220, 1018 cm^{-1}. Anal. ($C_{13}H_{19}NO_3$) C, H, N.

***N*-(3-Mercapto-2-methylpropionyl)-*N*-(4-propoxyphenyl)glycine (14s).** To the above amino ester (7.5 g, 31.6 mmol) and powdered anhydrous K_2CO_3 (8.7 g, 63 mmol) in 150 mL of methylene chloride at room temperature was added 3-(acetylthio)-2-methylpropionyl chloride[23] (5.7 g, 31.6 mmol). The reaction was refluxed for 2 h and then poured into 200 mL of H_2O. The reaction was extracted with 400 mL of ether. The organic layer was washed with 2 × 100 mL of 1 N aqueous HCl and 100 mL of saturated aqueous $NaHCO_3$, dried ($MgSO_4$), and rotary evaporated at room temperature to give an oily product, 8 (R^1 = Et; R^3 = 4-*n*-$C_3H_7OC_6H_4$; R^4 = R^5 = CH_3) (12.1 g, 100%), homogeneous by TLC (silica gel, 9:1 chloroform–methanol, R_f 0.6) and used without further purification: NMR ($CDCl_3$) δ 1.05 (3 H, t, J = 7 Hz), 1.21 (3 H, t, J = 7 Hz), 1.78 (2 H, sextet), 2.28 (3 H, s), 2.55–3.20 (3 H, m), 6.90 (2 H, d, J = 8 Hz), 7.29 (2 H, d, J = 8 Hz); IR (Film) 3040, 2955, 2850, 1738, 1635, 1600, 1498, 1237, 1190, 1015 cm^{-1}.

(21) N. Gruenfeld, J. L. Stanton, A. M. Yuan, F. H. Ebetino, L. J. Browne, C. Gude, and C. F. Huebner, *J. Med. Chem.*, preceding paper in this issue.
(22) P. C. Joshi, S. Parmar, and V. K. Rastogi, *J. Heterocycl. Chem.*, **16**, 607 (1979).
(23) A. Fredga and O. Martensson, *Ark. Kemi Mineral. Geol.*, **16B**, 1 (1942).

Nitrogen was bubbled through the above ester (12.1 g, 31.7 mmol) in 40 mL of methanol for 5 min. A similarly deoxygenated 2.08 N aqueous KOH solution (48 mL) was added to the above methanol solution, and the reaction was stirred at room temperature for 2 h. The reaction was quenched with 40 mL of 4 N aqueous HCl and extracted with 3 × 100 mL of methylene chloride. The combined organic portions were dried (Na_2SO_4) and rotary evaporated at room temperature to give an oil (8.5 g). The oil was dissolved in 20 mL of warm diethyl ether. Petroleum ether was added until the solution became slightly turbid. Crystallization occurred on standing at room temperature. The product was collected by filtration to give 5.2 g (52%): mp 90–92 °C; NMR ($CDCl_3$) δ 1.02 (3 H, t, J = 6 Hz), 1.08 (3 H, d, J = 6 Hz), 1.63 (3 H, m), 2.29 (1 H, m), 2.73 (2 H, m), 3.92 (2 H, t, J = 6 Hz), 4.35 (2 H, s), 6.92 (2 H, d, J = 7 Hz), 7.38 (2 H, d, J = 7 Hz), 11.33 (1 H, s); IR (Nujol) 3200–2500, 1730, 1645, 1499, 1455, 1345, 1165, 980, 848 cm^{-1}. Anal. ($C_{15}H_{21}NO_4S$) C, H, N.

Ethyl *N*-(3,4-Dimethoxyphenyl)glycinate [1, R^1 = Et; R^2 = H; R^3 = 3,4-$(CH_3O)_2C_6H_3$]. A mixture of 3,4-dimethoxyaniline (20.0 g, 0.13 mol), ethyl chloroacetate (16.0 g, 0.13 mol), and sodium acetate trihydrate (26.5 g, 0.195 mol) was stirred at 110 °C for 22 h. The reaction was cooled to room temperature and then poured into 250 mL of H_2O. The product was collected by filtration and recrystallized from ethanol to give 15.1 g (48%) of product: mp 41–43 °C; NMR (Me_2SO-d_6) δ 1.13 (3 H, t, J = 7 Hz), 3.61 (3 H, s), 3.65 (3 H, s), 3.84 (2 H, d, J = 6 Hz), 4.13 (2 H, q, J = 7 Hz), 5.58 (1 H, t, J = 6 Hz), 6.04 (1 H, dd, J = 8 and 2 Hz), 6.34 (1 H, d, J = 2 Hz), 6.73 (1 H, d, J = 8 Hz); IR (Nujol) 3362, 2925, 2855, 1736, 1615, 1512, 1441, 1210, 1028 cm^{-1}. Anal. ($C_{12}H_{17}NO_4$) C, H, N.

***N*-(3,4-Dimethoxyphenyl)-*N*-[3-mercapto-2(*S*)-methylpropionyl]glycine (14j).** To the above ester (2.5 g, 10.4 mmol) and powdered anhydrous K_2CO_3 (2.9 g, 21 mmol) in 30 mL of methylene chloride at room temperature was added 3-(acetylthio)-2(*S*)-methylpropionyl chloride[24] (1.9 g, 10.4 mmol). The reaction was stirred at room temperature for 2 h. Then the reaction was diluted with 100 mL of methylene chloride and washed with 25 mL of H_2O, 25 mL of 1 N aqueous HCl, and 25 mL of saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$) and rotary evaporated at room temperature to give 4.0 g (100%) of a colorless oil [8, R^1 = Et; R^3 = 3,4-$(CH_3O)_2C_6H_3$; R^4 = R^5 = CH_3], homogeneous by TLC (9:1 chloroform–methanol, R_f 0.45) and used without further purification: NMR ($CDCl_3$) δ 1.11 (3 H, t, J = 7 Hz), 1.29 (3 H, d, J = 7 Hz), 2.27 (3 H, s), 2.65–3.20 (3 H, m), 3.87 (6 H, s), 4.28 (4 H, m).

A solution of the above ester (4.0 g, 10.4 mmol) in 20 mL of MeOH was deoxygenated by bubbling N_2 through the solution for 5 min. A similarly deoxygenated 2.06 N aqueous KOH solution (32.8 mL) was added to the above solution. The reaction was stirred for 2 h at room temperature and then quenched with 110 mL of 0.5 N aqueous HCl. The reaction was extracted with 2 × 50 mL of methylene chloride. The combined organic portions were dried (Na_2SO_4) and rotary evaporated at room temperature. The residue (2.7 g) was recrystallized from 1:1 hexane–ether to give 2.4 g (73%) of product (14j): mp 140–142 °C; $[\alpha]_D$ 11.5° (c 1.0, EtOH); NMR ($CDCl_3$) δ 0.95 (3 H, d, J = 7 Hz), 1.45 (1 H, t, J = 8 Hz), 2.18 (1 H, m), 2.68 (2 H, m), 3.72 (3 H, s), 3.74 (3 H, s), 4.31 (2 H, s), 6.93 (3 H, m), 10.95 (1 H, s); IR (Nujol) 3190–2600, 1735, 1635, 1510, 1461, 1235, 1199, 1135, 1015 cm^{-1}. Anal. ($C_{14}H_{19}NO_5S$) C, H, N.

***N*-(3-Mercapto-2-methylpropionyl)-*N*-(1,4-dithiacyclohept-6-yl)glycine (16g).** To 1,4-dithiacycloheptan-6-one[25] (7.41 g, 50.0 mmol) and ethyl glycinate hydrochloride (14.0 g, 100.0 mmol) in 100 mL of ethanol at room temperature was added solid sodium cyanoborohydride (6.30 g, 100.0 mmol). The reaction was stirred for 3 days at room temperature. Aqueous HCl (4 N, 10 mL) was added, and the reaction was stirred for 1 h at room temperature. The reaction was rotary evaporated. The residue was dissolved in 70 mL of 10% aqueous NaOH and extracted with 3 × 100 mL of methylene chloride. The combined organic portions were dried (K_2CO_3) and rotary evaporated at room temperature to give an oil (5.5 g). The crude product was dissolved in 200 mL of ether, and HCl gas was bubbled through the solution. The hydrochloride salt was collected by filtration, dissolved in 100 mL of 10% aqueous NaOH, and extracted with 3 × 100 mL of methylene chloride. The combined organic portions were dried (K_2CO_3) and rotary evaporated to give the product 3 (R^1 = Et; R^3 = 1,4-dithiacyclohept-6-yl) as an oil (4.4 g, 39%), homogeneous by TLC (silica gel, 9:1 chloroform–methanol, R_f 0.4) and used without further purification: NMR ($CDCl_3$) δ 1.21 (3 H, t, J = 7 Hz), 2.00 (1 H, br s), 2.72–3.33 (5 H, m), 2.92 (4 H, s), 3.41 (2 H, s), 4.18 (2 H, q, J = 7 Hz).

To the above ester (4.20 g, 18.8 mmol) and powdered anhydrous K_2CO_3 (5.20 g, 37.6 mmol) in 60 mL of methylene chloride at room temperature was added dropwise 3-(acetylthio)-2-methylpropionyl chloride (7, R^4 = R^5 = CH_3) in 10 mL of methylene chloride. The reaction was refluxed 2 h, cooled to room temperature, poured into 100 mL of H_2O, and extracted with 3 × 50 mL of methylene chloride. The combined organic portions were dried ($MgSO_4$) and rotary evaporated at room temperature to give an oil (10, R^1 = Et; R^3 = 1,4-dithiacyclohept-6-yl; R^4 = R^5 = CH_3) (6.8 g, 100%), homogeneous by TLC (silica gel, 9:1 chloroform–methanol, R_f 0.8); NMR ($CDCl_3$) δ 1.25 (6 H, m), 2.33 (3 H, s), 2.45–3.35 (7 H, m), 2.95 (4 H, s), 4.05–4.67 (5 H, m).

A solution of the above ester (6.8 g, 18.0 mmol) in 50 mL of MeOH and 27.4 mL of an aqueous 2.06 N KOH solution were each deoxygenated by bubbling N_2 through the stirring solutions for 5 min. The latter solution was added to the former, and the reaction was stirred at room temperature under N_2 for 2 h. Aqueous HCl (4 N, 14.5 mL) was added, and the reaction was extracted with 3 × 100 mL of methylene chloride. The combined organic portions were dried (Na_2SO_4) and rotary evaporated to give an oil (5.1 g). This crude product was dissolved in 100 mL of ether, and dicyclohexylamine (3.0 g, 16.5 mmol) was added, producing a white precipitate. The product was collected by filtration and dried in vacuo at 40 °C to give 3.1 g (35%) of product **16g**: mp 179–182 °C; NMR (TFA-*d*) δ 1.05–1.6 (15 H, m), 1.6–2.3 (8 H, m), 2.45–3.25 (3 H, m), 3.02 (4 H, s), 3.37 (6 H, m), 4.59 (2 H, s), 4.88 (1 H, m), 6.35 (3 H, br s); IR (Nujol) 3050–2360, 2635, 1568, 1455, 1382, 1222 cm^{-1}. Anal. ($C_{23}H_{42}N_2O_3S_3$) C, H, N.

2-(3-Mercaptopropionyl)-6-fluoro-1,2,3,4-tetrahydroisoquinoline-3-carboxylic Acid (17d). A mixture of *dl*-4-fluorophenylalanine (25.0 g, 0.137 mol) and 80 mL of 37.8% aqueous formaldehyde in 250 mL of concentrated aqueous HCl was stirred at 100 °C for 3.5 h and then overnight at room temperature. The product 4 (R^1 = H; X = 6-F) was collected by filtration, washed with 4 × 15 mL of ice-cold H_2O, and dried in vacuo at 45 °C to give 4 (R^1 = H; X = 6-F) (21.7 g, 68%), used without further purification: NMR (Me_2SO-d_6) δ 3.05 (2 H, m), 4.31 (2 H, s), 4.38 (1 H, m), 7.25 (3 H, m), 10.75 (1 H, br s).

To a stirred solution of the above acid (21.5 g, 0.11 mol) in 200 mL of MeOH at −15 °C was added thionyl chloride dropwise, keeping the reaction temperature below −10 °C. After the addition was complete, the reaction was refluxed overnight and then rotary evaporated. The residue was suspended in 200 mL of ether. Triethylamine (30 mL) was added, and the mixture was stirred for 2 h at room temperature. The triethylamine hydrochloride was removed by filtration and washed with 2 × 50 mL of ether. The combined filtrate was rotary evaporated to give the product 4 (R^1 = CH_3; X = 6-F) as an oil (18.7 g, 81%), homogeneous by TLC (silica gel, 90:7:3 ethyl acetate–ethanol–NH_4OH, R_f 0.7) and used without further purification: NMR ($CDCl_3$) δ 2.35 (1 H, s), 2.98 (2 H, m), 3.72 (1 H, m), 3.75 (3 H, s), 4.08 (2 H, s), 6.96 (3 H, m).

To a mixture of the above amino ester (9.0 g, 43.0 mmol) and powdered anhydrous K_2CO_3 (11.9 g, 86.0 mmol) in 45 mL of methylene chloride at room temperature was added dropwise 3-(acetylthio)propionyl chloride[26] (7.2 g, 43.0 mmol) in 45 mL of methylene chloride. The reaction was washed with 50 mL of H_2O, 25 mL of 2 N aqueous HCl, and 25 mL of saturated aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$) and rotary evaporated to give 12.7 g of crude product. The product was stirred in 50 mL of ether and collected by filtration to give 11

(24) Yoshitomi Pharmaceutical Industries Ltd., Belgian Patent 868532 (1978).
(25) V. P. Arya and S. P. Ghate, *Ind. J. Chem.*, **9**, 904 (1971).
(26) H. V. Daeniker and J. Druey, *Helv. Chim. Acta*, **40**, 2148 (1957).

($R^1 = R_5 = CH_3$; $R^4 = H$) (10.3 g, 70%): mp 108–110 °C; NMR ($CDCl_3$) δ 2.31 (3 H, s), 2.82 (2 H, m), 3.25 (4 H, m), 3.67 (3 H, s), 4.65 (2 H, s), 5.48 (1 H, m), 6.97 (3 H, m); IR (Nujol) 3045, 2965, 2842, 1722, 1663, 1651, 1435, 1259 cm^{-1}. Anal. ($C_{16}H_{18}FNO_4S$) C, H, N.

To the above ester (7.0 g, 20.6 mmol) in 125 mL of methanol at room temperature was added 62 mL of 1 N aqueous NaOH. The reaction was stirred at room temperature for 4 h. The reaction was concentrated to remove the methanol. The remaining aqueous solution was diluted with 50 mL of H_2O and washed with 2 × 25 mL of methylene chloride, which was discarded. The aqueous layer was acidified with 15 mL of 6 N HCl and extracted with 3 × 50 mL of methylene chloride. These combined organic portions were dried (Na_2SO_4) and rotary evaporated. The residue was slurried in 15 mL of ether and filtered, and the filtrate was dried in vacuo to give the product **17d** (4.1 g, 70%): mp 153–155 °C; NMR (Me_2SO-d_6) δ 2.15–2.88 (5 H, m), 3.07 (2 H, m), 4.10–4.90 (2 H, m), 5.12 (1 H, m), 7.13 (3 H, m), 12.85 (1 H, br s); IR (Nujol) 3150–2750, 1729, 1610, 1498, 1442, 1249, 1199 cm^{-1}. Anal. ($C_{13}H_{14}FNO_3S$) C, H, N.

1-(3-Mercaptopropionyl)-6-fluoro-1,2,3,4-tetrahydroquinoline-2-carboxylic Acid (18e). To KCN (13.3 g, 0.204 mol) in 100 mL of H_2O at room temperature was added 6-fluoroquinoline[27] (10.0 g, 0.068 mol). Benzoyl chloride (19.1 g, 0.14 mol) was added over 2 h. After stirring for an additional 2 h, the reaction mixture was decanted. The gummy residue was washed with 100 mL of H_2O, 2 × 75 mL of 1 N HCl, and 100 mL of H_2O. The gum was dissolved in 120 mL of hot ethanol. On cooling to 0 °C, the product crystallized out and was collected by filtration to give 7.8 g (41%), which was used without further purification: IR (Nujol) 3030, 2915, 2845, 2418, 1645, 1595, 1455, 1292, 1098, 1055 cm^{-1}.

The above nitrile (15.5 g, 55.9 mmol) in 160 mL of 12 N aqueous HCl was refluxed overnight. The reaction was cooled to room temperature and washed with 2 × 100 mL of ether. The aqueous layer was rotary evaporated. The residue was dissolved in 100 mL of H_2O and adjusted to pH 3 with concentrated NH_4OH. The solution was cooled to 0 °C. The product was collected by filtration to give 7.5 g (85%): mp >250 °C; (Me_2SO-d_6) δ 7.55–8.45 (3 H, m), 8.25 (1 H, d, J = 8 Hz), 8.68 (1 H, d, J = 8 Hz), 13.25 (1 H, br s).

To a suspension of the above acid (7.5 g, 39.2 mmol) in 70 mL of toluene was added thionyl chloride (14.0 g, 118 mmol). The reaction was refluxed for 4 h. The reaction was concentrated to about 40 mL. Methanol (40 mL) was added. The reaction was left standing for 30 min and then rotary evaporated until solid started to appear. The reaction was then diluted with 100 mL of ether. The product was collected by filtration to give methyl 6-fluoroquinaldate (7.8 g, 82%), used without further purification: NMR (Me_2SO-d_6) δ 4.05 (3 H, s), 7.67–8.05 (2 H, m), 8.21 (1 H, d, J = 8 Hz), 8.35 (1 H, m), 8.62 (1 H, d, J = 8 Hz).

A solution of the above ester (2.6 g, 10.7 mmol) in 70 mL of methanol was hydrogenated at 1 atm of pressure in the presence of 200 mg of platinum oxide. The reaction was filtered, and the filtrate was rotary evaporated. The residue in 50 mL of 5% aqueous $NaHCO_3$ was extracted with 2 × 50 mL of ether. The combined organic portions were dried (K_2CO_3) and rotary evaporated to give the product as an oil **5** ($R^1 = CH_3$; X = 6-F) (2.2 g, 100%), used without further purification: NMR ($CDCl_3$) δ 2.15 (2 H, m), 2.75 (2 H, m), 3.72 (3 H, s), 3.95 (1 H, m), 4.31 (1 H, br s), 6.69 (2 H, m), 6.81 (1 H, s).

To **5** ($R^1 = CH_3$, X = 6-F) (2.4 g, 11.5 mmol) and anhydrous K_2CO_3 (3.2 g, 23 mmol) in 20 mL of methylene chloride at room temperature was added 3-(acetylthio)propionyl chloride (1.9 g, 11.5 mmol) in 10 mL of methylene chloride dropwise in 5 min. The reaction was refluxed for 2 h and then extracted with 25 mL of H_2O, 25 mL of 2 N HCl, and 25 mL of 10% aqueous $NaHCO_3$. The organic layer was dried ($MgSO_4$) and rotary evaporated to give the oily product **12** ($R^1 = R^5 = CH_3$; R^4 = H; X = 6-F) (3.3 g, 84%), used without further purification: NMR ($CDCl_3$) δ 2.28 (3 H, s), 2.72 (4 H, m), 3.21 (4 H, m), 3.69 (3 H, s), 5.28 (1 H, t, J = 7 Hz), 6.95–7.35 (3 H, m).

(27) A. Sveinbjornsson, H. L. Bradlow, S. Oae, and C. A. Vanderwerf, *J. Org. Chem.*, 16, 1450 (1951).

To a solution of the above ester (3.3 g, 9.7 mmol) in 20 mL of methanol, deoxygenated by bubbling N_2 through the solution for 5 min, was added 14 mL of a similarly deoxygenated 2.15 N aqueous KOH solution. The reaction was stirred for 2 h at room temperature. The reaction was acidified with 20 mL of 4 N aqueous HCl and diluted with 100 mL of H_2O. The reaction was extracted with 2 × 50 mL of methylene chloride. The combined organic portions were dried (Na_2SO_4) and rotary evaporated to give an oil (2.4 g). The crude product was dissolved in 25 mL of ether. Hexane was added until the solution became turbid. The product crystallized out and was collected by filtration to give **18e** (1.7 g, 62%): mp 97–99 °C; NMR ($CDCl_3$) δ 1.52 (1 H, t, J = 8 Hz), 2.4–3.15 (8 H, m), 5.22 (1 H, t, J = 7 Hz), 7.13 (3 H, m), 11.67 (1 H, br s); IR (Nujol) 3060, 2935, 2880, 1720, 1650, 1495, 1378, 1262, 1142 cm^{-1}. Anal. ($C_{13}H_{14}FNO_3S$) C, H, N.

(*S*)-1-Acetylindoline-2-carboxylic Acid [(*S*)-26]. 1-Acetylindoline-2-carboxylic acid[12] (120 g, 0.58 mol) and *l*-cinchonidine (172 g, 0.58 mol) were dissolved in 1.2 L of hot EtOH. The solution was allowed to stand at room temperature overnight and then at 0 °C for 4 days. A white crystalline salt (144 g) was filtered off. The filtrate was rotary evaporated, 1 L of H_2O was added, and the solution was adjusted to pH 1 with concentrated HCl. After 15 min, the product was collected by filtration, washed with 3 × 250 mL of 2 N aqueous HCl, 2 × 100 mL of H_2O, and 2 × 100 mL of EtOH to give 38 g (31.6%) of product [(*S*)-**26**]: mp 214–215 °C; $[\alpha]_D$ −133.3° (c 1.165, EtOH); NMR (Me_2SO-d_6) δ 2.15 (3 H, s), 3.39 (2 H, m), 5.21 (1 H, m), 7.17 (3 H, m), 8.16 (1 H, d, J = 7 Hz), 13.30 (1 H, br s); IR (Nujol) 3015, 2955, 2939, 2700, 2590, 1721, 1616, 1582, 1463, 1247, 1219, 942 cm^{-1}. Anal. ($C_{11}H_{11}NO_3$) C, H, N.

(*S*)-Indoline-2-carboxylic Acid Hydrochloride Hydrate [(*S*)-6, R^1 = X = H]. A suspension of (*S*)-**26** (37.5 g, 0.18 mol) in 380 mL of 2 N aqueous HCl was deoxygenated by bubbling N_2 through the reaction for 5 min. Then the reaction was refluxed for 2 h, cooled to room temperature, and filtered through Celite. The filtrate was rotary evaporated and crystallized from ether–2-propanol. Filtration gave a white crystalline product, (*S*)-**6** (R^1 = X = H) (35.7 g, 91%): mp 133 °C dec; $[\alpha]_D$ −70.4° (c 1.0, EtOH); NMR (Me_2SO-d_6) δ 3.41 (2 H, m), 4.86 (1 H, dd, J = 7 and 8 Hz), 7.37 (4 H, s), 9.19 (3 H, br s); IR (Nujol) 3220, 3045, 2985, 2920, 2525, 1685, 1603, 1465, 1275 cm^{-1}. Anal. ($C_9H_{12}NO_3Cl$) C, H, N.

Ethyl (*S*)-Indoline-2-carboxylate Hydrochloride [(*S*)-6, R^1 = Et; X = H]. A solution of the above amino acid (34.0 g, 0.17 mol) in 350 mL of EtOH was saturated with gaseous HCl without external cooling. The reaction was stirred for 2 h at room temperature, and then the solvent was removed under reduced pressure until crystallization began. The reaction was poured into 400 mL of ether and cooled at 0 °C for 1 h. Filtration gave the product (*S*)-**6** (R^1 = Et; X = H) (31 g, 80%): mp 179–181 °C; $[\alpha]_D$ −63° (c 1.385, EtOH); NMR (Me_2SO-d_6) δ 1.27 (3 H, t, J = 7 Hz), 3.41 (2 H, m), 4.26 (2 H, q, J = 7 Hz), 4.82 (1 H, dd, J = 7 and 8 Hz), 7.28 (4 H, m), 10.95 (2 H, s); IR (Nujol) 3075, 2978, 2960, 2855, 1755, 1580, 1462, 1245, 1021 cm^{-1}. Anal. ($C_{11}H_{13}NO_2Cl$) C, H, N.

Ethyl 1-[3-(Benzoylthio)-2(*S*)-methylpropionyl]-indoline-2(*S*)-carboxylate (13, R^1 = Et; $R^4 = CH_3$; $R^5 = C_6H_5$; X = H). To (*S*)-**6** (R^1 = Et; X = H) free base (2.3 g, 12.0 mmol) in 30 mL of methylene chloride was added powdered K_2CO_3 (3.3 g, 24.0 mmol). To this stirring mixture was added 3-(benzoylthio)-2(*S*)-methylpropionyl chloride[14] in 1 min. The reaction was stirred for 2 h at room temperature and then partitioned between 50 mL of ether and 50 mL of H_2O. The organic layer was washed with 25 mL of H_2O, 2 × 25 mL of 1 N HCl, and 25 mL of brine, dried (Na_2SO_4), and rotary evaporated to give an oil (4.8 g), which crystallized on standing. The solid was slurried in hexane and collected by filtration to give the product (4.2 g, 88%): mp 114–116 °C; $[\alpha]_D$ −195.9° (c 1.5, EtOH); NMR ($CDCl_3$) δ 1.26 (3 H, t, J = 7 Hz), 1.39 (3 H, t, J = 7 Hz), 2.85 (1 H, m), 3.38 (4 H, m), 4.15 (2 H, q, J = 7 Hz), 5.10 (1 H, m), 6.98–8.45 (9 H, m); IR (Nujol) 2945, 2885, 1740, 1671, 1630, 1465, 1199, 1028 cm^{-1}.

Ethyl 1-[3-Mercapto-2(*S*)-methylpropionyl]indoline-2-(*S*)-carboxylate (28). To the above product (2.0 g, 5.0 mmol) in 30 mL of methylene chloride was added hydrazine hydrate (0.30 g, 5.5 mmol). The reaction was stirred overnight at room temperature and then washed with 3 × 300 mL of 1 N HCl, dried (Na_2SO_4), and rotary evaporated to give an oil (**28**; 1.5 g, 100%):

NMR ($CDCl_3$) δ 1.25 (6 H, m), 2.55 (1 H, t, J = 9 Hz), 2.85–3.65 (5 H, m), 4.19 (2 H, q, J = 7 Hz), 4.95 (1 H, m), 6.92–8.35 (4 H, m).

1-[3-Mercapto-2(*S*)-methylpropionyl]indoline-2(*S*)-carboxylic Acid (19d). A solution of **28** (1.5 g, 5.0 mmol) in 30 mL of MeOH and 5.5 mL of 2.03 N aqueous KOH were each deoxygenated by bubbling N_2 through the solutions for 5 min. The latter solution was then added to the former, and the reaction was stirred 2 h at room temperature with N_2 bubbling through the solution. The reaction was diluted with 70 mL of H_2O and extracted with 2 × 50 mL of ether. The aqueous layer was acidified to pH 1 with concentrated HCl and extracted with 3 × 40 mL of methylene chloride. The combined methylene chloride portions were dried (Na_2SO_4) and rotary evaporated to give 1.0 g of crude product. Recrystallization from ether–petroleum ether gave 0.70 g (52%) of product **19d**: mp 141–142 °C; $[\alpha]_D$ −178.2° (*c* 1.785, EtOH); NMR ($CDCl_3$) δ 1.28 (3 H, m), 1.65 (1 H, t, J = 8 Hz), 2.62 (1 H, m), 2.85–3.90 (4 H, m), 4.95 (0.5 H, m), 5.24 (0.5 H, m), 7.21 (3.5 H, m), 8.26 (0.5 H, m), 11.10 (1 H, s); IR (Nujol) 3050, 2935, 2865, 1735, 1645, 1590, 1488, 1210, 1035 cm^{-1}. Anal. ($C_{13}H_{15}NO_3S$) C, H, N.

In Vitro Inhibition of Angiotensin Converting Enzyme from Rabbit Lung. ACE was prepared in crude solubilized form from lungs of male rabbits (New Zealand white, from Hare Farms, weighing approximately 5 kg and allowed free access to food and water). Fresh lungs were freed of connective tissue and processed by the method of Das and Soffer[28] to the stage of the Nonidet-P40 extract. The extract was frozen and stored at −70 °C until used in enzyme assays.

The conditions for assay of ACE were adapted from a procedure described by Cheung and Cushman,[29] in which histidylleucine liberated from the synthetic substrate hippurylhistidylleucine is quantitated. The enzyme extract was diluted to the appropriate activity with 100 mM potassium phosphate buffer (pH 8.3) containing 300 mM NaCl. Various concentrations of test drugs, as well as 5 mM hippurylhistidylleucine, were prepared in the same buffer. The reaction medium consisted of 100 μL of test drug solution (or buffer for the control), 100 μL of 5 mM hippurylhistidylleucine (or buffer for the blank), and 50 μL of enzyme solution. Reaction was started by addition of enzyme, continued for 30 min at 37 °C, and then terminated by addition of 0.75 mL of 0.6 N NaOH. The samples were treated at room temperature with 100 μL of a methanolic solution of *o*-phthaldialdehyde (2 mg/mL), followed in 10 min with 100 μL of 6 N HCl. They were then read against water in a spectrophotometer set at 360 nm, and all readings were corrected for the blank. With the aid of a standard curve (obtained by running known amounts of histidylleucine through the assay procedure), the corrected optical densities were converted to nanomoles of histidylleucine formed during the 30-min incubation. IC_{50} values were determined graphically as the concentration of test drug at which the amount of histidylleucine formed was reduced to 50% of the value found in the absence of test drug. The tabulated IC_{50} values represent the average of two runs.

Angiotensin Converting Enzyme Inhibitor Screen (Intravenous Administration).[30] Six normotensive Wistar rats were anesthetized with Inactin (100 mg/kg iv). The femoral artery and saphenous vein were cannulated for blood pressure and intravenous administration, respectively. Angiotensin I (0.33 μg/kg iv) was administered, and blood pressure was recorded. This was repeated two more times. Test compound was administered intravenously. Then angiotensin I (0.33 μg/kg iv) was administered after 5, 10, 15, 30, and 60 min, and blood pressure was recorded. Student's *t* test was used to compare pre- and postdrug values.

Angiotensin Converting Enzyme Inhibitor Screen (Oral Administration). Six male normotensive Wistar rats were implanted with carotid and jugular cannulas exteriorized for blood pressure measurement and intravenous angiotensin I administration, respectively. Rats were fasted overnight. Angiotensin I (0.66 μg/kg iv) was administered, and blood pressure was recorded. This was repeated once. Test compound was administered orally. Angiotensin I (0.66 μg/kg iv) was administered after 0.5, 1.0, 2.0, 3.0, and 4.0 h, and blood pressure was recorded. For determination of the ED_{50}, the percent inhibition was determined 1 h after administration of test compound at four dose levels, and the value was calculated by linear regression analysis of the best fit curve.

Antihypertensive Screen with Spontaneous Hypertensive Rat.[31] Six spontaneous hypertensive rats (male, 270–415 g, 16–24 weeks old, obtained from Charles River Breeding Laboratories) were given four successive daily doses of test compound. Systolic blood pressure was estimated by tail sphygmomanometry, and heart rate was counted from the pulse record, before and at intervals of 2, 4, and 24 h after each dose. The unanesthetized rats were restrained in Plexiglas holders in a compartment maintained at 32 °C. Mean resting blood pressure recorded prior to administration of test compound was 201 mmHg. Data was analyzed by student's paired *t* test.

Acknowledgment. The authors express their thanks to Dr. H. B. Renfroe for his encouragement and support of this work, Dr. E. Ku and Ms. C. Signor for the biochemical data, Dr. D. Chen and Mr. D. Miller and their staffs for the in vivo biological data, Mrs. L. Raabis for the proton NMR spectra, Dr. R. Rodebaugh for the carbon-13 NMR spectra, and Mr. G. Robertson and his staff for performing the elemental analyses.

Registry No. **1** (R^1 = Et; R^3 = 4-*n*-$C_3H_7OC_6H_4$), 70350-96-8; **1** (R^1 = Et; R^3 = 3,4-$(CH_3O)_2C_6H_3$), 86323-64-0; **3** (R^1 = Et; R^3 = 1,4-dithiacyclohept-6-yl), 86323-65-1; (±)-**4** (R^1 = H; X = 6-F), 86323-66-2; (±)-**4** (R^1 = CH_3; X = 6-F), 86323-67-3; (±)-**5** (R^1 = CH_3; X = 6-F), 86323-68-4; (*S*)-**6** (R^1, X = H), 82923-76-0; (*S*)-**6** (R^1 = Et; X = H) (base), 82923-81-7; (*S*)-**6** (R^1 = Et; X = H), 79854-42-5; (±)-**7** (R^4, R^5 = CH_3), 70354-87-9; (*R*)-**7** (R^4, R^5 = CH_3), 74345-73-6; **7** (R^4 = H; R^5 = CH_3), 41345-72-6; (*R*)-**7** (R^4 = CH_3; R^5 = Ph), 74654-91-4; (±)-**8** (R^1 = Et; R^3 = 4-*n*-$C_3H_7OC_6H_4$;R^4, R^5 = CH_3), 86323-69-5; (*S*)-**8** (R^1 = Et; R^3 = 3,4-$(CH_3O)_2C_6H_3$; R^4, R^5 = CH_3), 86323-70-8; (±)-**10** (R^1 = Et; R^3 = 1,4-dithiacyclohept-6-yl; R^4, R^5 = CH_3), 86323-71-9; (±)-**11** (R^1, R^5 = CH_3; R^4 = H), 86323-72-0; (±)-**12** (R^1, R^5 = CH_3; R^4 = H; X = 6-F), 86323-73-1; (*S,S*)-**13** (R^1 = Et; R^4 = CH_3; R^5 = C_6H_5; X = H), 86323-74-2; **14a**, 86323-75-3; (±)-**14b**, 86323-76-4; (±)-**14c**, 86323-77-5; (±)-**14d**, 86323-78-6; (±)-**14e**, 86323-80-0; (±)-**14f**, 86323-81-1; (±)-**14g**, 86323-82-2; (±)-**14h**, 86323-84-4; (±)-**14i**, 86323-85-5; (*S*)-**14j**, 86362-78-9; **14k**, 86323-86-6; (±)-**14l**, 86323-87-7; (±)-**14m**, 86323-89-9; (±)-**14n**, 86323-90-2; **14o**, 86323-91-3; (±)-**14p**, 86323-92-4; (±)-**14q**, 86323-94-6; (±)-**14r**, 86323-95-7; (±)-**14s**, 86323-96-8; (±)-**14t**, 86323-97-9; (±)-**14u**, 86323-98-0; (±)-**14v**, 86323-99-1; (±)-**14a**, 86324-00-7; (±)-**14x**, 86324-01-8; (±)-**15a**, 86324-03-0; (±)-**15b**, 86324-05-2; (±)-**16a**, 86324-06-3; (±)-**16b**, 86324-08-5; (±)-**16c**, 86324-10-9; (±)-**16d**, 86324-12-1; (±)-**16e**, 86324-14-3; (±)-**16f**, 86324-16-5; (±)-**16g**, 86324-18-7; (±)-**16g** (base), 8624-17-6; **16h**, 86324-20-1; **16i**, 86324-22-3; (±)-**16j**, 86324-24-5; (±)-**16k**, 86324-26-7; (*S*)-**17a**, 76693-38-4; (±)-**17b** (isomer 1), 86390-85-4; (±)-**17b** (isomer 2), 86390-86-5; (±)-**17c** (isomer 1), 86362-79-0; (±)-**17c** (isomer 2), 86362-82-5; (±)-**17d**, 86324-27-8; (±)-**18a**, 75433-81-7; (±)-w18b, 86324-28-9; (±)-**18c**, 86324-29-0; (±)-**18d**, 75433-82-8; (±)-**18e**, 86324-30-3; (±)-**18f**, 86324-32-5; (±)-**19a**, 78701-34-5; (*S*)-**19b**, 84171-37-9; (±)-**19c** (isomer 1), 78701-27-6; (±)-**19c** (isomer 2), 78701-30-1; (*S,S*)-**19d**, 78779-29-0; (*R,S*)-**19e**, 86362-80-3; (±)-**19f** (isomer 1), 86324-34-7; (±)-**19f** (isomer 2), 86324-54-1; (±)-**19g** (isomer 1), 86324-36-9; (±)-**19g** (isomer 2), 86324-56-3; (±)-**19h** (isomer 1), 86324-38-1; (±)-**19h** (isomer 2), 86324-58-5; (±)-**19i**, 86362-81-4; (±)-**19j** (isomer 1), 86324-40-5; (±)-**19j** (isomer 2), 86324-60-9; (±)-**19k** (isomer 1), 86324-42-7; (±)-**19k** (isomer 2), 86324-62-1; **20**, 86324-43-8; (±)-**21**, 86324-44-9; (±)-**22**, 86324-45-0; (±)-**23**, 86324-46-1; (±)-**24**,

(28) M. Das and R. L. Soffer, *J. Biol. Chem.*, **250**, 6762 (1975).
(29) H. S. Cheung and D. W. Cushman, *Biochim. Biophys. Acta*, **293**, 451 (1973).
(30) B. Rubin, R. J. Laffan, O. G. Kotler, E. H. O'Keefe, D. A. Demaio, and M. E. Goldberg, *J. Pharmacol. Exp. Ther.*, **204**, 271 (1978).
(31) (a) R. J. Laffan, M. E. Goldberg, J. P. High, T. R. Schaeffer, M. H. Waugh, and B. Rubin, *J. Pharmacol. Exp. Ther.*, **204**, 281 (1978). (b) E. E. Muirhead, R. L. Prewitt, B. Brooks, and W. L. Brosius, *Circ. Res.*, **43-I**, 53 (1978).

86324-48-3; (S)-27, 82950-72-9; (±)-27, 82923-75-9; (S)-27 l-cinchonidine, 85683-64-3; (S,S)-28, 86324-49-4; 2-cyano-6-fluoroquinoline, 86324-50-7; 6-fluoro-2-quinolincarboxylic acid, 86324-51-8; methyl 6-fluoro-2-quinolincarboxylate, 86324-52-9; l-cinchonidine, 485-71-2; 4-propoxyaniline, 4469-80-1; ethyl chloroformate, 105-39-5; 3,4-dimethoxyaniline, 6315-89-5; 1,4-dithiacycloheptan-6-one, 34654-19-8; ethyl glycinate hydrochloride, 623-33-6; 4-fluoro-DL-phenylalanine, 51-65-0; 6-fluoroquinoline, 396-30-5; formaldehyde, 50-00-0; angiotensin converting enzyme, 9015-82-1.

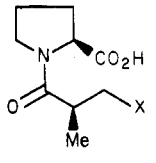
Angiotensin Converting Enzyme Inhibitors: 1-Glutarylindoline-2-carboxylic Acid Derivatives

Norbert Gruenfeld, James L. Stanton,* Andrew M. Yuan, Frank H. Ebetino, Leslie J. Browne, Candido Gude, and Charles F. Huebner

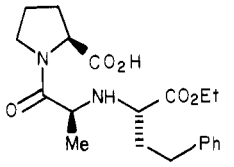
Research and Development Department, Pharmaceuticals Division, CIBA-GEIGY Corporation, Ardsley, New York 10502.
Received November 29, 1982

The preparation of a series of 1-glutarylindoline-2(S)-carboxylic acid derivatives, **6a–v** and **21a–c**, is described. The above compounds were tested for inhibition of angiotensin converting enzyme. The structure–activity relationship of the series is also discussed. Compound **6u**, the most potent member of the series, had an in vitro IC_{50} of 4.8×10^{-9} M. Compound **6v**, an ethyl ester of **6u**, lowered blood pressure 70 mm in spontaneous hypertensive rats at an oral dose of 30 mg/kg.

Captopril, 1-[(2S)-3-mercapto-2-methylpropionyl]-L-proline (**1a**), is an angiotensin converting enzyme (ACE)



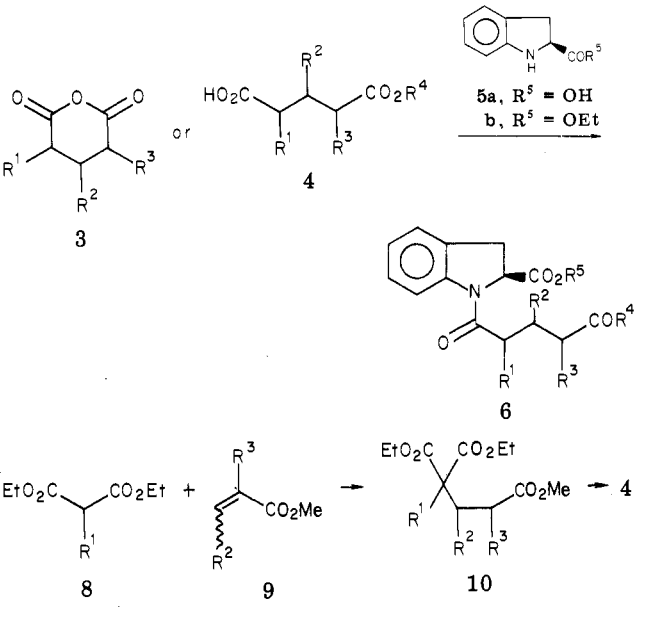
1a, X = SH
b, X = CH_2CO_2H



2

inhibitor that has been shown to be an effective antihypertensive agent in man.[1] However, the drug produces a number of side effects, most commonly, rashes and an alteration of taste.[2] These effects might be attributed to the thiol group, which binds to zinc at the enzyme active site.[3] Several effective ACE inhibitors have since been found that do not contain a thiol group.[4,5] In particular, enalapril (**2**), which contains a carboxylate group for binding to zinc at the active site, has been suggested to be a transition-state inhibitor that through its CO_2H, NH, and phenethyl groups achieves good binding. In the initial report on **1a** it was disclosed that replacement of the thiol in **1a** with a carboxylic acid to give **1b** substantially decreased the potency, increasing the IC_{50} from 2.3×10^{-8} to 4.9×10^{-6} M.[6] Despite this finding we set out to explore a series of substituted glutaric acid derivatives related to **1b** in which L-proline was replaced by (S)-indoline-2-carboxylic acid.[7] Herein we report the results of this work.

Scheme I



Chemistry. The desired compounds were prepared as shown in Scheme I. Reaction of glutaric anhydride derivative **3** with (S)-indoline-2-carboxylic acid (**5a**) or the corresponding ethyl ester (**5b**) resulted in amides **6** (method A). For unsymmetrical anhydrides, **5a** or **5b** added predominately to the least hindered carbonyl group, and the products were purified by fractional crystallization.

(1) (a) Bravo, E. L.; Tarazi, R. C. *Hypertension* **1979**, *1*, 39. (b) Brunner, H. R.; Gavras, H.; Waeber, B.; Kershaw, G. R.; Turini, G. A.; Vukovich, R. A.; McKinstry, D. N. *Ann. Intern. Med.* **1979**, *90*, 19. (c) Case, D. B.; Atlas, S. A.; Laragh, J. H.; Sealey, J. E.; Sullivan, P. A.; McKinstry, D. N. *Prog. Cardiovasc. Dis.* **1978**, *21*, 195. (d) Gavras, H.; Brunner, H. R.; Turini, G. A.; Kershaw, G. R.; Tifft, C. P.; Cuttelod, S.; Gavras, I.; Vukovich, R. A.; McKinstry, D. N. *N. Engl. J. Med.* **1978**, *298*, 991.
(2) Atkinson, A. B.; Robertson, J. J. S. *Lancet* **1979**, *2*, 836.
(3) Das, M.; Soffer, R. L. *J. Biol. Chem.* **1975**, *250*, 6762.
(4) Almquist, R. G.; Chao, W. R.; Ellis, M. E.; Johnson, H. L. *J. Med. Chem.* **1980**, *23*, 1392.
(5) Patchett, A. A.; Harris, E.; Tristram, E. W.; Wyvrett, M. J.; Wu, M. T.; Taub, D.; Peterson, E. R.; Ikeler, T. J.; ten Broeke, J.; Payne, L. G.; Ondeyka, D. L.; Thorsett, E. D.; Greenlee, W. J.; Lohr, N. S.; Hoffsommer, R. D.; Joshua, H.; Ruyle, W. V.; Rothrock, J. W.; Aster, S. D.; Maycock, A. L.; Robinson, F. M.; Hirschmann, R.; Sweet, C. S.; Ulm, E. H.; Gross, D. M.; Vassil, T. C.; Stone, C. A. *Nature (London)* **1980**, *288*, 280.
(6) Cushman, D. W.; Cheung, H. S.; Sabo, E. F.; Ondetti, M. A. *Biochemistry* **1977**, *16*, 5484.
(7) The use of this amino acid in a series of mercaptan-containing ACE inhibitors has been described: Stanton, J. L.; Gruenfeld, N.; Babiarz, J. E.; Ackerman, M. H.; Friedmann, R. C.; Yuan, A. M.; Macchia, W. *J. Med. Chem.*, following paper in this issue.

0022-2623/83/1826-1277$01.50/0