(Mercaptopropanoyl)indoline-2-carboxylic Acids and Related Compounds as Potent Angiotensin Converting Enzyme Inhibitors and Antihypertensive Agents

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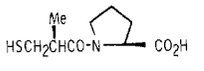
1-(3-Mercapto-2-methyl-1-oxopropyl)indoline-2-carboxylic acids (**7b**) and related compounds were synthesized in order to examine their ability to inhibit angiotensin converting enzyme (ACE) and to reduce the systolic blood pressure of spontaneously hypertensive rats (SHR). All four possible stereoisomers of the precursor 1-[3-(benzoylthio)-2-methyl-1-oxopropyl]indoline-2-carboxylic acid (**6b**) were characterized with absolute stereochemical assignment. The removal of the benzoyl group of the precursor to give **7b** was conveniently carried out by treatment with 2-methoxyethylamine. Three of the four stereoisomers of the benzoyl derivative **6** showed in vitro ACE inhibitory activity in the following order: **6b**(*S,S*) > **6b**(*S,R*) > **6b**(*R,S*). The stereoisomer having the *R,R* configuration was essentially inactive. The substitution at the C_5 of the indoline nucleus with the Et or OMe group caused only marginal changes in the inhibitory activity. The mercaptan **7b**(*S,S*) was the most active ACE inhibitor synthesized in this study, showing in vitro potency 3 times that of captopril. The augmentation of the potency may be due to the increased hydrophobicity of **7b**(*S,S*) compared with captopril and suggests the presence of a hydrophobic pocket at the active site of ACE. When tested in spontaneously hypertensive rats, **7b**(*S,S*) exhibited oral antihypertensive activity 27 times that of captopril. The corresponding benzoyl derivative **6b**(*S,S*) was 24 times as potent as captopril. The thio lactone **10** obtained by cyclization of **7b**(*S,S*) as a potential prodrug was less potent than the parent compound, **7b**(*S,S*), in the ACE inhibitory and antihypertensive tests.

Captopril[1,2] is a highly potent, orally effective, and



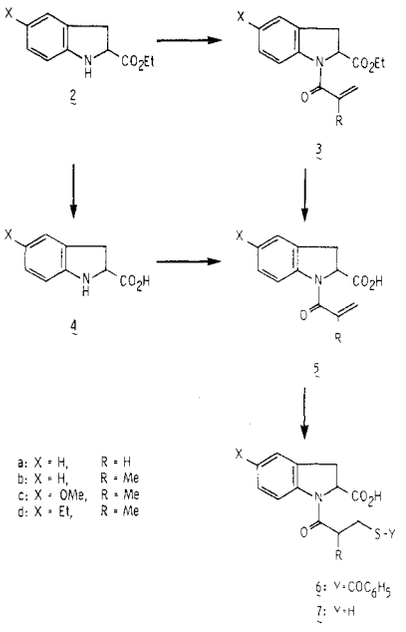
1 (CAPTOPRIL)

nonpeptidic inhibitor of angiotensin converting enzyme (ACE). It is clinically useful for the treatment of hypertension.[3] Since the discovery of this compound, numerous analogues have been prepared[4-13] in the hope of improving its pharmacological profile and/or to probe the hypothetical active-site model of the enzyme proposed by Ondetti and Cushman.[1,2] The basic structural requirements for the ACE inhibition of these compounds involve (a) a carboxylic acid group or its isosteres at one end of the molecule, (b) a carbonyl group, preferably of an amidic nature, (c) a methyl group α to the carbonyl bond, (d) a group such as sulfhydryl or phosphoryl that chelates with zinc in the enzyme, and (e) *S,S* absolute configuration at both chiral centers. Furthermore, (f) the presence of pyrrolidine at the CO_2H terminus of the molecules was found to be an important requirement for high inhibitory potency.[2,12,14,15]

Hydrophobicity is known to play an important role in the binding of substrate or inhibitor to the active site of an enzyme.[16] The effect of improved hydrophobic character, especially at the pyrrolidine portion of the therapeutically effective ACE inhibitor (captopril), on the enzyme inhibitory activity was of interest to us. This paper describes the synthesis and preliminary pharmacology of (–)-(*S*)-1-[(*S*)-3-mercapto-2-methyl-1-oxopropyl]indoline-2-carboxylic acid and related compounds.

Chemistry. Ethyl indoline-2-carboxylate (**2**)[17] was acylated in excellent yield with methacryloyl chloride to give **3**, which was then hydrolyzed to **5** under basic conditions. The acid **5** was alternatively obtained by the

Scheme I



acylation of **4** in the presence of Et_3N. The acid **4** was readily prepared from **2** by mild basic hydrolysis. Subsequent treatment of **5** with thiobenzoic acid afforded **6**

† Medicinal Chemistry Section.
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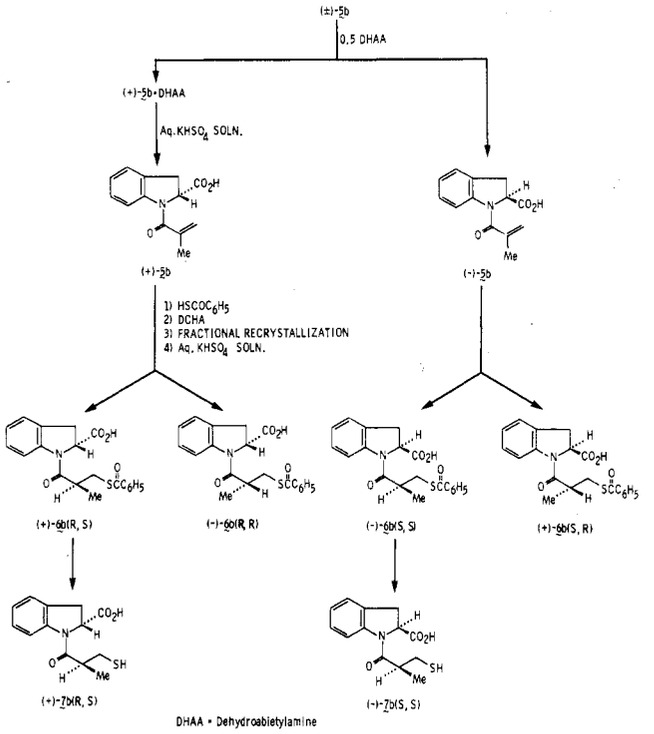
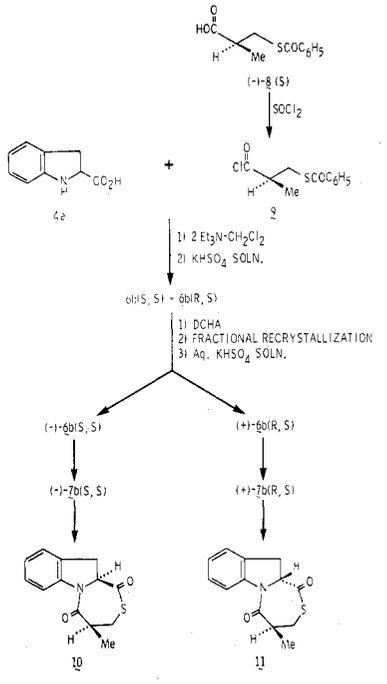
(1) M. A. Ondetti, B. Rubin, and D. W. Cushman, *Science*, **196**, 441 (1977).
(2) D. W. Cushman, H. S. Cheung, E. F. Sabo, and M. A. Ondetti, *Biochemistry*, **16**, 5484 (1977).
(3) (a) H. Gavras, H. R. Brunner, G. A. Turini, G. R. Kershaw, C. P. Tifft, S. Cuttelod, I. Gavras, R. A. Vukovich, and D. N. McKinstry, *N. Engl. J. Med.*, **298**, 991 (1978). (b) H. R. Brunner, H. Gavras, G. A. Turini, B. Waeber, P. Chappuis, and D. M. McKinstry, *Clin. Sci. Mol. Med.*, **55**, 293s (1978). (c) D. B. Case, S. A. Atlas, J. H. Laragh, J. E. Sealey, P. A. Sullivan, and D. N. McKinstry, *Progr. Cardiovasc. Dis.*, **21**, 195 (1978).
(4) I. Mita, J.-I. Iwao, M. Oya, T. Chiba, and T. Iso, *Chem. Pharm. Bull.*, **26**, 1333 (1978).
(5) E. W. Petrillo, Jr., M. A. Ondetti, D. W. Cushman, E. R. Weaver, and J. E. Heikes, "Abstracts of Papers", 176th National Meeting of the American Chemical Society, Miami Beach, FL, Sept 11–14, 1978, American Chemical Society, Washington, DC, 1978, Abstr MEDI 27.
(6) A. Sugie and J. Katsube, *Chem. Pharm. Bull.*, **27**, 1708 (1979).

0022-2623/83/1826-0394$01.50/0

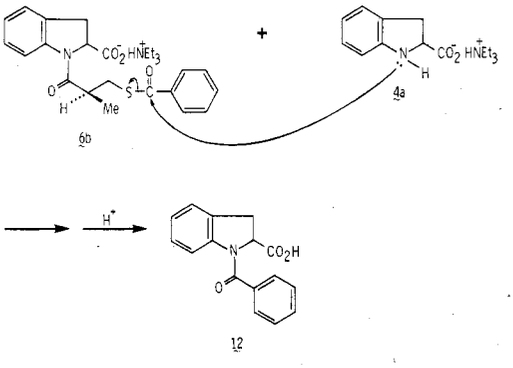
Scheme II



Scheme III



Scheme IV



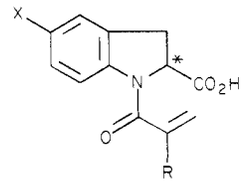
in a resinous form, from which crystalline racemic **6b**(*R,R* + *S,S*) was deposited upon addition of a small amount of ethanol. The other racemic diastereomer, **6b**(*R,S* + *S,R*) was isolated from the mother liquor (for stereochemical assignments, see below). The diastereoisomeric ratio of the thiobenzoic acid addition product was highly dependent on the nature of the reaction medium. Whereas **6b**(*R,S* + *S,R*) was the predominant product (70%) when the reaction was carried out in CH_2Cl_2, **6b**(*R,R* + *S,S*) was the major product in acetone solution. The formation of the latter in acetone medium was further enhanced by the addition of a catalytic amount of 4-(dimethylamino)-pyridine to give **6b**(*R,R* + *S,S*) and **6b**(*R,S* + *S,R*) in a ratio of 3:1. Removal of the benzoyl group by treatment of both racemic **6b**'s with NH_3–MeOH by a conventional method afforded the corresponding **7b**(*R,R* + *S,S*) and **7b**(*R,S* + *S,R*), respectively. The use of acryloyl chloride instead of methacryloyl chloride in the above synthesis gave **6a** and **7a** (Scheme I).

The use of resolved **5b** afforded all four possible stereoisomers of **6b** and **7b** (Scheme II). When racemic **5b** was treated with an 0.5 molar equiv amount of dehydroabietylamine, (+)-**5b** preferentially formed a crystalline salt, leaving the (−) enantiomer in solution. Treatment of (−)-**5b**, obtained from the mother liquor of (+)-**5b** dehydroabietylamine salt, with thiobenzoic acid afforded a diastereoisomeric mixture of **6b**(*S,S*) and **6b**(*S,R*), which was readily separated by fractional recrystallization of the dicyclohexylamine (DCHA) salts from ethanol or 2-propanol. Similarly, **6b**(*R,S*) and **6b**(*R,R*) were prepared. Amminolysis of the benzoyl derivatives with 2-methoxyethylamine afforded the corresponding mercapto compounds (**7b**). Unlike benzamide or benzoic acid generated in the conventional debenzoylation reaction, the *N*-(methoxyethyl)benzamide that is formed by the brief contact with 2-methoxyethylamine is a liquid and was readily separable from **7b**.

The NMR spectrum of **6b**(*S,S*) deserves comment: Although the spectrum obtained in Me_2SO-d_6 showed the

(7) M. E. Condon, J. A. Reid, K. A. Losse, D. W. Cushman, and M. A. Ondetti, "Abstracts of Papers", ACS/CSJ Chemical Congress, Honolulu, HI, Apr 2–6, 1979, American Chemical Society, Washington, DC, 1979, Abstr MEDI 64.
(8) E. W. Petrillo, Jr., and E. R. Spitzmiller, *Tetrahedron Lett.*, 4929 (1979).
(9) R. E. Galardy, *Biochem. Biophys. Res. Commun.*, **97**, 94 (1980).
(10) R. G. Almquist, W.-R. Chao, M. E. Ellis, and H. L. Johnson, *J. Med. Chem.*, **23**, 1392 (1980).
(11) D. H. Kim, *J. Heterocycl. Chem.*, **17**, 164 (1980).
(12) S. Klutchko, M. L. Hoefle, R. D. Smith, A. D. Essenburg, R. B. Parker, V. L. Nemeth, M. J. Ryan, D. H. Dugan, and H. R. Kaplan, *J. Med. Chem.*, **24**, 104 (1981).
(13) 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. Ruyle, 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).
(14) (a) D. W. Cushman and M. A. Ondetti, *Prog. Med. Chem.*, **17**, 41 (1980). (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).
(15) D. W. Cushman, H. S. Cheung, E. F. Sabo, and M. A. Ondetti, *Progr. Cardiovasc. Dis.*, **21**, 176 (1978).
(16) B. R. Baker, in "Medicinal Chemistry", 3rd ed., Part I, A. Burger, Ed., Wiley-Interscience, New York, 1970, Chapter 12.
(17) E. J. Corey, R. J. McCaully, and H. S. Sachdev, *J. Am. Chem. Soc.*, **92**, 2476 (1970).

Table I. Physical Data and ACE Inhibitory Testing (in Vitro) Results of *N*-Acryloyl- and *N*-(2-Methacryloyl)indoline-2-carboxylic Acids and Analogues



compd	X	R	synth method[b]	mp, °C	$[\alpha]_D$, deg (*c*, EtOH); temp, °C	recrystn solvent	yield, %	formula[c]	IC_{50},[d] M
5a(*R* + *S*)	H	H	A	167-169		EtOAc	56	$C_{12}H_{11}NO_3$	$>10^{-5}$
5b(*R* + *S*)	H	Me	A-C	138-140		Et_2O	52, 95, 52	$C_{13}H_{13}NO_3$	$>10^{-5}$
5b(*R*)	H	Me	*b*	148-150	+133.45 (1.11); 23.5	Et_2O	77	$C_{13}H_{13}NO_3$	$>10^{-5}$
5b(*S*)	H	Me	*b*	153-154	−135.9 (0.94); 25	Et_2O	69	$C_{13}H_{13}NO_3$	$>10^{-5}$
5c(*R* + *S*)	OMe	Me	B	115-118		EtOAc	77	$C_{14}H_{15}NO_4 \cdot {}^1/_6H_2O$	10^{-5}

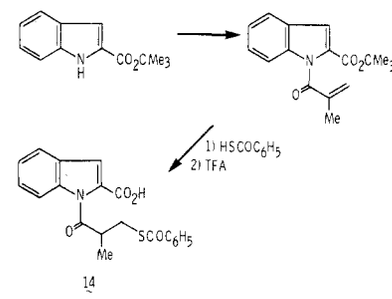
[a] Parenthetical *R* and *S* designations indicate absolute stereochemical configuration. [b] See Experimental Section. [c] All compounds were analyzed for C, H, and N. [d] Molar concentration required for 50% inhibition by the method of Cushman and Cheung.[23]

methyl proton signals as a doublet at δ 1.28, the proton signals observed in $CDCl_3$ appeared as a pair of doublets that coalesced as the temperature of the sample probe was raised, giving a broad singlet at δ 1.14. A similar solvent-dependent NMR phenomenon was also observed with **7b**(*S,S*) and its diastereomers. Apparently, the compound exists as more than one rotamer,[18] especially in a nonpolar solvent.

A practical synthesis of **7b**(*S,S*) starts with (−)-**8**(*S*)[19] and racemic **4a** (Scheme III). Treatment of (−)-**8**(*S*) with thionyl chloride and condensation of the resulting acid chloride with **4a** in the presence of 2 molar equiv of Et_3N afforded an approximately equimolar mixture of **6b**(*S,S*) and **6b**(*R,S*).[20] The rapid addition of the acid chloride was found to be extremely important for high yield of the product. Slow addition (1 h) gave **12**, which was presumably formed from the reaction of freshly generated **6b** with the intact **4a** as shown in Scheme IV. The crude diastereoisomeric mixture of **6b**(*S,S*) and **6b**(*R,S*) was converted into DCHA salts, and the salts were separated by repeated washing with MeCN followed by recrystallization from ethanol to give **6b**(*S,S*)·DCHA in 34% yield. Treatment of the salt with aqueous $KHSO_4$ followed by debenzoylation with 2-methoxyethylamine gave **7b**(*S,S*). Similarly, **7b**(*R,S*) was prepared from **6b**(*R,S*), which was isolated from the MeCN washings. Cyclization of **7b**(*S,S*) and **7b**(*R,S*) with DCC in the presence of a catalytic amount of 4-(dimethylamino)pyridine afforded thio lactones **10** and **11**, respectively.

The absolute stereochemistry of the indoline-2-carboxylic acid moiety of **6b**(*S,S*) and **7b**(*S,S*) was established to be the *S* configuration as shown below: Acidic hydrolysis of **7b**(*S,S*) gave (+)-**4a**. Reduction of the optically active **4a** with lithium aluminum hydride gave (+)-2-(hydroxymethyl)indoline. The latter has been previously correlated with L-phenylalanine to have the *S* absolute configuration. The stereochemical assignments for racemic **6b**(*R,R* + *S,S*) and **6b**(R,*S* + *S,R*) were based on their chromatographic (TLC and HPLC) characteristics

Scheme V

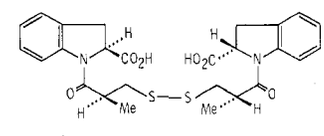


14

when compared with respective resolved enantiomers. A NMR spectral study of the thio lactones **10** and **11** warrants special comment: Examination of their molecular models indicated that whereas the C_4 Me group of **10** is positioned away from the thio lactone carbonyl group, the corresponding Me group of its diastereomer **11** is situated in close proximity to the group well within the range of the deshielding zone. Thus, as expected from the model, the C_4 Me of **10** showed signals at δ 1.35 as a doublet, and the corresponding Me protons of **11** exhibited their signals at δ 1.48.

1-[3-(Benzoylthio)-2-methyl-1-oxopropyl]-1*H*-indole-2-carboxylic acid (**14**) was prepared as shown in Scheme V. Attempts at the debenzoylation of **14** were unsuccessful under various conditions. Instead, cleavage of the amide bond occurred.

Bis-disulfide **13** was a minute impurity found in **7b**(*S,S*), which was possibly formed during the workup. It was also obtainable by a mild oxidation of **7b**(*S,S*) by the method of Yiannios and Karabinos.[21,22]



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(18) D. H. Kim, *J. Heterocycl. Chem.*, **13**, 1187 (1976).
(19) The resolved (−)-**8**(*S*) was obtained from Chemical Dynamics Corp.
(20) After we had developed this synthetic procedure, a patent (EP-008831) appeared that described the synthesis of 1-[D-3-(benzoylthio)-2-methyl-1-oxopropyl]-L-proline (*S,S*) by a similar method.
(21) C. N. Yiannios and J. V. Karabinos, *J. Org. Chem.*, **28**, 3246 (1963).
(22) Conventional methods, such as the use of iodine, caused oxidation of the indoline moiety to indole in addition to disulfide formation.

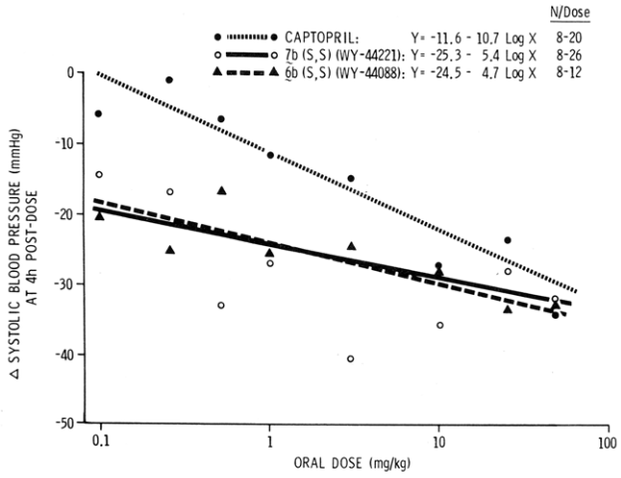


Figure 1. Dose–response relationships of antihypertensive activities of **7b**(*S,S*) (Wy-44,221), **6b**(*S,S*) (Wy-44,088), and captopril in the SHR.

Biological Results and Discussion

Compounds prepared in this study were initially tested for their in vitro ACE inhibitory activities by essentially following the procedure reported by Cushman and Cheung.[23] None of the *N*-acryloyl- or *N*-(2-methacryloyl)indoline-2-carboxylic acid intermediates displayed significant ACE inhibitory activity (Table I). Of the four stereochemical isomers of [(benzoylthio)methylpropanoyl]indoline-2-carboxylic acid, three showed inhibitory activity. The most potent compound, **6b**(*S,S*), having *S,S* absolute configuration, showed activity nearly equal to that of captopril. Its diastereoisomer, **6b**(*S,R*), exhibited only 10% of the activity of **6b**(*S,S*), and **6b**(*R,S*) was 33 times less potent than **6b**(*S,S*). Apparently, the correct stereochemical requirement (*S* configuration) at the chiral center adjacent to the CO_2H group is much more important for the activity than the one in the side chain. Compound **6b**(*R,R*) was inactive. The importance of the stereochemical requirement for inhibitory activity was further demonstrated by the indole derivative **14**, which was also inactive. The aromatic substitution with Et or MeO did not cause a significant effect on the ACE inhibitory activity (Table II).

In the series of (mercaptopropanoyl)indoline-2-carboxylic acids, **7b**(*S,S*) showed the highest activity with $IC_{50} = 3.7 \times 10^{-9}$ M, which is equivalent to 3 times that of captopril. Its diastereomer **7b**(*R,S*) showed only weak activity, again demonstrating the importance of the chiral requirement at the indoline C_2 position for the activity. As expected, racemate **7b**(*R,R* + *S,S*) was less potent than **7b**(*S,S*). The higher potency of **7b**(*R,S* + *S,R*) compared with that of optically active **7b**(*R,S*) indicates than **7b**(*S,R*) is considerably more potent than its diastereoisomer **7b**(*R,S*), as was observed with the benzoyl derivatives (Table III).

Selected compounds were studied for their in vivo ACE inhibitory activities and their ability to lower blood pressure in the spontaneously hypertensive rat (SHR) (Table IV). The former activity was assessed by calculating the oral dose required to inhibit 50% of the vasopressor response induced by intravenous administration of angiotensin I in conscious normotensive rats, using the method of Rubin et al. with slight modification.[24] Again,

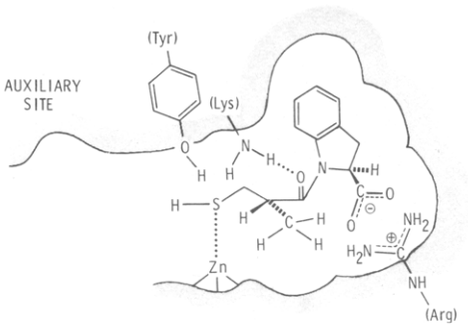


Figure 2. Active-site model of ACE.

7b(*S,S*) was the most active compound with a potency approaching 1.6 times that of captopril, whereas the potency of **6b**(*S,S*) was about one-third that of captopril. In the SHR, **7b**(*S,S*) reduced systolic blood pressure by 25 mmHg at 4 h posttreatment at a calculated oral dose of 0.88 mg/kg, whereas captopril required 17.78 mg/kg to effect the same result (Figure 1). When relative potencies were determined by the method of analysis of variance for a parallel line assay, **7b**(*S,S*) was 27 times ($p < 0.001$) as potent as captopril, and the benzoyl derivative **6b**(*S,S*) was 24 times ($p < 0.01$) more potent than captopril. The demethyl compound **6a**(*R,S*) was significantly less potent than **6b**(*S,S*). The diminished antihypertensive potency of **6c**(*S,S*) (as the DCHA salt) as compared with **6b**(*S,S*) and especially the lack of activity shown by **6d**(*S,S*) are somewhat surprising in view of the fact that both compounds exhibited good ACE inhibitory activity in vitro.

The impressive augmentation of the antihypertensive activity shown by **6b**(*S,S*) and **7b**(*S,S*) suggests possible involvement of additional hypotensive mechanisms by these compounds in addition to the peripheral ACE inhibitory effect. In fact, there is now growing evidence that the antihypertensive effect of captopril is not due solely to ACE inhibition.[25] However, factors such as improved oral absorption, differences in protein binding, and a greater contribution of central ACE inhibition may also be involved.[26]

Previously, (4*S*,9a,*S*)-hexahydro-4-methyl-1*H*,5*H*-pyrrolo[2,1-*c*][1,4]thiazepine-1,5-dione was reported to have ACE inhibitory action comparable to that of captopril.[11] Likewise, thio lactone **10** also inhibited the conversion of angiotensin I into angiotensin II in vitro and lowered blood pressure in the SHR. The potency is, however, reduced. As expected, **11** showed only moderate ACE inhibitory activity.

The active-site model of ACE proposed by Ondetti and Cushman[1,2] consists of a positively charged basic residue (arginine) that interacts with the CO_2H of the substrate, an enzyme-bound zinc ion separated from the positively charged center by the distance of a dipeptide residue, a group (lysine residue) capable of interacting with the amide carbonyl bond through hydrogen bonding, and two small circular clefts that accomodate substituents on the dipeptide backbone. Arginine, tyrosine, glutamic acid, and

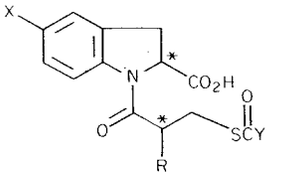
(23) D. W. Cushman and H. S. Cheung, *Biochem. Pharmacol.*, **20**, 1637 (1971).

(24) B. Rubin, R. J. Laffan, D. G. Kotler, E. H. O'Keefe, D. A. Demaio, and M. E. Goldberg, *J. Pharmacol. Exp. Ther.*, **204**, 271 (1978).

(25) S. F. Campbell and J. C. Danilewicz, *Annu. Rep. Med. Chem.*, **16**, 73 (1981).

(26) (a) J. F. E. Mann, W. Rascher, R. Dietz, A. Schomig, and D. Ganten, *Clin. Sci.*, **56**, 585 (1979). (b) Th. Unger, B. Schull, G. Speck, and D. Ganten, in "Enzyme Inhibitors", U. Brodbeck, Ed., Verlag Chemie, Weinheim, 1980, pp 223–241.

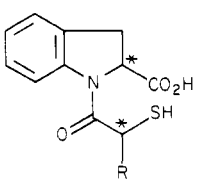
Table II. Physical Data and ACE Inhibitory Testing (in Vitro) Results of [(Benzoylthio)propanoyl]- and [(Acetylthio)propanoyl]indoline-2-carboxylic Acids and Analogues



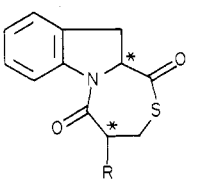
compd[a]	X	R	Y	synth method[b]	mp, °C	recrystn solvent	yield, %	$[\alpha]_D$, deg (c, EtOH); temp, °C	formula[c]	IC_{50},[d] M
6a(*R* + *S*)	H	H	C_6H_5		173-175	*e*	100		$C_{19}H_{17}NO_4S$	5.9×10^{-8}
6b(*R*,*R* + *S*,*S*)	H	Me	C_6H_5		188-190	EtOH	21		$C_{20}H_{19}NO_4S$	7.8×10^{-8}
6b(*R*,*S* + *S*,*R*)	H	Me	C_6H_5		116-117	Et_2O	25		$C_{20}H_{19}NO_4S \cdot 0.25Et_2O$	4.1×10^{-7}
6b(*S*,*S*)	H	Me	C_6H_5	A, C	144, 146	$Et_2O + C_6H_{14}$	82, 61	−186.4 (1.12); 26	$C_{20}H_{19}NO_4S$	3.8×10^{-8}
6b(*S*,*S*)·DCHA	H	Me	C_6H_5		223-224	EtOH	(88, 68)[f]	−76.6 (1.14); 22.5	$C_{20}H_{19}NO_4S \cdot C_{12}H_{23}N$	3.2×10^{-8}
6b(*S*,*R*)	H	Me	C_6H_5	B	resin		23	+65.3 (1.14); 22.5	$C_{20}H_{19}NO_4S$	3.8×10^{-7}
6b(*S*,*R*)·DCHA	H	Me	C_6H_5		132-134	MeCN	(54)	+26.0 (1.04); 22.5	$C_{20}H_{19}NO_4S \cdot C_{12}H_{23}N$	5.4×10^{-7}
6b(*R*,*R*)	H	Me	C_6H_5	A	143-145	$Et_2O + C_6H_{14}$	40	+179.3 (1.04); 25.5	$C_{20}H_{19}NO_4S$	$>10^{-5}$
6b(*R*,*R*)·DCHA	H	Me	C_6H_5		222-224	EtOH	(50)	+70.6 (0.98); 25.5	$C_{20}H_{19}NO_4S \cdot C_{12}H_{23}N$	$>10^{-5}$
6b(*R*,*S*)	H	Me	C_6H_5	B, C	resin		27, 40	−82.6 (0.97); 25	$C_{20}H_{19}NO_4S$	1.2×10^{-6}
6b(*R*,*S*)·DCHA	H	Me	C_6H_5		138.5-140	EtOAc	(34, 51)	−31.5 (1.02); 25	$C_{20}H_{19}NO_4S \cdot C_{12}H_{23}N$	3.5×10^{-6}
6c(*R*,*R* + *S*,*S*)	OMe	Me	C_6H_5	A	244-245 dec	EtOH	13		$C_{21}H_{21}NO_5S \cdot 0.25H_2O$	9.4×10^{-8}
6c(*R*,*R* + *S*,*S*)·DCHA	OMe	Me	C_6H_5		204-206	2-PrOH	(31)		$C_{21}H_{21}NO_5S \cdot C_{12}H_{23}N$	9.7×10^{-8}
6c(*S*,*S*)·DCHA	OMe	Me	C_6H_5	C	216	*g*	50	−78.2 (1.19); 25	$C_{21}H_{21}NO_5S \cdot C_{12}H_{23}N$	4.2×10^{-8}
6d(*S*,*S*)	Et	Me	C_6H_5	C	resin	*e*	60	−166.9 (1.08); 28	$C_{22}H_{23}NO_4S$	3.0×10^{-8}
6d(*S*,*S*)·DCHA	Et	Me	C_6H_5		216	*g*	(66)	−69.2 (1.09); 25.5	$C_{22}H_{23}NO_4S$	
6e(*R*,*R* + *S*,*S*)	H	Me	Me	A	123-125	EtOAc + C_6H_{14}	18		$C_{15}H_{17}NO_4S$	1.1×10^{-8}
6e(*R*,*R* + *S*,*S*)·DCHA	H	Me	Me		218-220	EtOH	(22)		$C_{15}H_{17}NO_4S \cdot C_{12}H_{23}N$	
6e(*R*,*S* + *S*,*R*)	H	Me	Me	B	94.5-96	$Et_2O + C_6H_{14}$	9		$C_{15}H_{17}NO_4S$	1.5×10^{-5}
6e(*R*,*S* + *S*,*R*)·DCHA	H	Me	Me		201-203	EtOH	(11)		$C_{15}H_{17}NO_4S \cdot C_{12}H_{23}N$	
captopril										1.1×10^{-8}

[a] Parenthetical *R* and *S* designations indicate the absolute stereochemistry. The first letter in the grouping refers to the stereochemistry of the indoline and the second letter indicates the stereochemistry of the propanoyl tail. These designations combined with a plus sign indicate a mixture of stereoisomers. [b] See Experimental Section. [c] All compounds were analyzed for C, H, and N. [d] Molar concentration required for 50% inhibition; tested by the method described by Cushman and Cheung.[23] Potency of salt was based on the active moiety. [e] The product was sufficiently pure for pharmacological evaluation and need not be purified. [f] Yields reported in parentheses indicate the yields of DCHA salts, and yields described without parentheses are overall yields of final products. [g] The reaction product was repeatedly washed with MeCN until it became homogeneous by TLC and reached acceptable melting point range.

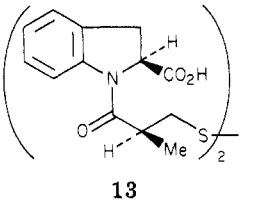
Table III. Physical Data and ACE Inhibitory Testing (in Vitro) Results of (Mercaptopropanoyl)indoline-2-carboxylic Acids and Tetrahydro-1*H*,5*H*-[1,4]thiazepino[4,3-*a*]indole-1,5-diones, and 1,1'-[Dithiobis[(*S*)-2-methyl-1-oxo-3,1-propanediyl]]bis[(*S*)-indoline-2-carboxylic acid]



7



10, 11



13

compd[a]	R	mp, °C	$[\alpha]_D$, deg (c, EtOH); temp, °C	yield, %	formula[b]	IC_{50},[c] M
7a(*R* + *S*)	H	146-148		17[d]	$C_{12}H_{13}NO_3S$	1.4×10^{-7}
7b(*R*,*R* + *S*,*S*)	Me	*e*		42	$C_{13}H_{15}NO_3S$	3.0×10^{-7}
7b(*R*,*S* + *S*,*R*)	Me	resin		75	$C_{13}H_{15}NO_3S$	7.4×10^{-8}
7b(*S*,*S*)	Me	140.5-142	−178.1 (1.14); 24	82	$C_{13}H_{15}NO_3S$	3.7×10^{-9}
7b(*R*,*S*)	Me	resin	+31.56 (1.35); 24.5	71[f]	$C_{13}H_{15}NO_3S$	1.4×10^{-5}
10	Me	140-141	+35.26 (1.085);[g] 25	63	$C_{13}H_{13}NO_2S$	1.4×10^{-8}
11	Me	145.5-147	−32.66 (0.97);[g] 25	28	$C_{13}H_{13}NO_2S$	2.0×10^{-5}
13		*e*	−24.99 (1.1); 25	67	$C_{26}H_{28}N_2O_6S \cdot HOAc$	1.3×10^{-6}
captopril						1.1×10^{-8}

[a] Parenthetical *R* and *S* designations indicate the absolute stereochemical configuration. The first letter in the grouping refers to the stereochemistry of the indoline, and the second letter indicates the stereochemistry of the mercaptopropanoyl tail or the thiazepino moiety. These designations combined with a plus sign indicate a mixture of stereoisomers. [b] All compounds were analyzed for C, H, and N. [c] Molar concentration required for 50% inhibition; tested by the method described by Cushman and Cheung.[23] [d] Prepared by treatment with NH_3-MeOH as described for 7b(*R*,*R* + *S*,*S*) under Experimental Section. [e] See Experimental Section. [f] Prepared as described for 7b(*S*,*S*) with $MeOCH_2CH_2NH_2$ and then purified via the DCHA salt. [g] Optical rotation was obtained in EtOAc solution.

Table IV. ACE Inhibitory Effect against Angiotensin I in Conscious Rats and Antihypertensive Activity Measured in Spontaneously Hypertensive Rats of Selected Compounds

compd	ACE inhibitory act., po ID_{50},[a] mg/kg	antihypertensive act., po ED_{25mmHg},[b] mg/kg
6a(*R* + *S*)	1.95 (4)[c]	12.5 (4)[c]
6b(*S*,*S*)	2.0 (7)	1.03 (8-12)
6b(*S*,*R*)·DCHA	NT[d]	39 (8)
6b(*R*,*S*)	NT	100 (4)
6c(*S*,*S*)·DCHA	NT	20 (4)
6d(*S*,*S*)	NT	>100 (4)
6e(*R*,*R* + *S*,*S*)	NT	13 (4)
7a(*R* + *S*)	1.6 (3)	NT
7b(*R*,*S* + *S*,*R*)	2.0 (6)	5.6 (4)
7b(*S*,*S*)	0.36 (9)	0.88 (8-26)
7b(*R*,*S*)	NT	inactive
10	NT	2.0 (4)
13	NT	24 (8)
captopril	0.57 (12)	17.78 (8-20)

[a] Dose (mg/kg, po) required to inhibit 50% of the angiotensin I induced vasopressor response. [b] Dose (mg/kg, po) required to lower blood pressure of SHR by 25 mmHg at 4-h postdose. [c] Number of rats used at each dose. [d] NT indicates not tested.

lysine were later found to be involved in the enzyme–substrate interaction.[27,28] Unlike the active site of the closely related carboxypeptidase A, the original model of Ondetti and Cushman did not include the presence of a hydrophobic pocket. The present study, however, tends to indicate the presence of such a pocket also in the active site of ACE. Thus, the augmentation of the inhibitory activity by 7b(*S*,*S*) compared with captopril may be due to a stronger binding of 7b(*S*,*S*) with the active site than that of captopril through an added interaction of the indoline nucleus with the hydrophobic pocket, as shown in Figure 2. In agreement with such modification of the active-site model, Cheung et al. recently reported that ACE preferentially reacts with substrates containing hydrophobic groups at the position closest to the CO_2H terminus.[28] Such a pocket has also been suggested by Bünning et al.[27] Very recently, Oya et al. reported that in a series of mercaptoacyl amino acids, 2-mercaptopropanoyl-L-tryptophan and 2-mercaptopropanoylphenylalanine possess much higher ACE inhibitory activity than 2-mercaptopropanoylglycine itself.[29,30]

The most active compound, 7b(*S*,*S*) (Wy-44,221) is currently under toxicological evaluation as a potential therapeutic agent for treatment of hypertension.

Experimental Section

The melting points were obtained on a Thomas-Hoover melting point apparatus and are uncorrected. Elemental analyses were performed with a Perkin-Elmer Model 240 elemental analyzer by the Analytical Section of these laboratories. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values. IR spectra were recorded as KBr pellets on a Perkin-Elmer 299 infrared spectrophotometer. NMR spectra were obtained on a Jeolco Model C-60HL, a Varian XL-100, or a Varian FT-88 NMR spectrometer with Me_4Si as the internal standard. Mass spectra were recorded with an Associated Electrical Industries MS-9 high-resolution mass spectrometer. Optical rotations were measured with a Carl Zeiss polarimeter. Homogeneity of intermediates and final products was determined by TLC on Merck silica gel 60-F-254 plates developed with the solvent system CH_2Cl_2/EtOH/NEt_3/toluene (8:2:1:1). Reactions were routinely

(27) P. Bünning, B. Holmquist, and J. F. Riordan, *Biochem. Biophys. Res. Commun.*, **83**, 1442 (1978).
(28) H.-S. Cheung, F.-L. Wang, M. A. Ondetti, E. F. Sabo, and D. W. Cushman, *J. Biol. Chem.*, **255**, 401 (1980).
(29) M. Oya, J. Matsumoto, H. Takashina, T. Watanabe, and J. Iwao, *Chem. Pharm. Bull.*, **29**, 940 (1981).
(30) M. Oya, J. Matsumoto, H. Takashina, J. Iwao, and Y. Funae, *Chem. Pharm. Bull.*, **29**, 63 (1981).

performed under dry N_2 atmosphere, and purified reaction products were dried in vacuo over P_2O_5.

Ethyl 1-(2-Methyl-1-oxo-2-propenyl)indoline-2-carboxylate (3b). To an ice-chilled and stirred mixture of ethyl indoline-2-carboxylate (**2a**; 4.78 g, 25.0 mmol), Et_3N (2.7 g, 26.7 mmol), and anhydrous ether (500 mL) was added dropwise methacryloyl chloride (2.9 g, 27.7 mmol) dissolved in a small amount of ether. The reaction mixture was stirred at room temperature for 4 h. The precipitate that separated was removed by filtration, and the filter residue was washed with ether. The combined filtrate and washing were washed with water and then with saline and dried over $MgSO_4$. Evaporation of the solvent on a rotary evaporator gave **3b** in quantitative yield as a thick oil, which was used directly in the following reaction: MS, m/e 259 (M^+), 186 ($M^+ - CO_2Et$); NMR ($CDCl_3$) δ 1.25 (t, 3 H, CH_3CH_2), 2.03 (s, 3 H, CH_3C=), 3.35 (ABX m, 2 H, CH_2), 4.25 (q, 2 H, CH_3CH_2), 5.05 (q, 1 H, $CHCO_2$), 5.30 (m, 2 H, CH_2=), 7.07 and 7.70 (m, 4 H, aromatic); TLC R_f 0.89.

By a similar procedure, **3a** was prepared as an oil from **2a** and acryloyl chloride in 96% yield.

Ethyl 5-methoxy-1-(2-methyl-1-oxo-2-propenyl)indoline-2-carboxylate (3c), as a thick oil, was prepared from **2c** as described for the preparation of **3b**, in 62% yield: TLC R_f 0.87; NMR ($CDCl_3$) δ 1.25 (t, 3 H, CH_3CH_2), 2.03 (s, 3 H, CH_3C=), 3.30 (ABX m, CH_2), 3.75 (s, 3 H, CH_3O), 4.23 (q, 2 H, CH_3CH_2), 5.10 (m, 1 H, $CHCO_2$), 5.35 (m, 2 H, CH_2=), 6.75 and 7.60 (m, 3 H, aromatic). Anal. ($C_{16}H_{19}NO_4$) C, H, N.

1-(2-Methyl-1-oxo-2-propenyl)indoline-2-carboxylic Acid (5b). Method A. A mixture of **3b** (3.9 g, 15 mmol), 80% aqueous Me_2SO (90 mL), and KOH (86% pellets, 1.3 g, 19.9 mmol) was stirred under N_2 for 2 days at room temperature and then evaporated under reduced pressure on a rotary evaporator to give an oily residue. The residue was dissolved in H_2O (a small amount of insoluble material was removed by filtration), and the aqueous solution was acidified carefully with dilute HCl. The oily product that separated was extracted with ether. The ether extract was washed with H_2O and then with saline and dried with $MgSO_4$. Evaporation of the extract on a rotary evaporator under reduced pressure afforded an oil, which was dissolved in acetonitrile (25 mL). Dicyclohexylamine (DCHA) was added dropwise to the solution with hand swirling until the pH of the solution reached ca. 8.5. The mixture was allowed to set at room temperature overnight. A precipitate was collected on a filter, washed with ether several times, and recrystallized from 2-propanol to give 3.5 g (56%) of **5b**·DCHA salt, mp 193–195 °C. Anal. ($C_{13}H_{13}NO_3 \cdot C_{12}H_{23}N \cdot 0.25H_2O$) C, H, N.

The salt was treated with 5% aqueous $KHSO_4$ solution (50 mL), and the free acid that separated was extracted with EtOAc. The combined extracts (120 mL) were dried ($MgSO_4$) and evaporated on a rotary evaporator under reduced pressure to give 1.8 g (52% from **3a**) as a thick oil, which solidified on standing. Recrystallization from ether gave an analytical sample of **5b**: mp 138–140 °C; IR 2500, 1743 cm^{-1} (CO_2H); NMR ($CDCl_3$) δ 2.04 (s, 3 H, CH_3), 3.40 (m, 2 H, CH_2), 5.12 (q, 1 H, CH), 5.35 (s, 2 H, $=CH_2$), 6.95–7.30 (m, 3 H, aromatic), 7.60 (br s, 1 H, C_7 H); TLC R_f 0.47.

In one experiment, the oily product obtained by evaporation of the ether extract solidified on standing for 10 days to give **5b** (68%), which was sufficiently pure for subsequent use.

Method B. To a solution of **3b** (61.4 g, 0.24 mol) in MeOH (350 mL) was added a solution of 10.68 g (0.26 mol) of NaOH pellets in H_2O (130 mL). The resulting mixture was stirred at room temperature for 1 h, poured into brine (2.5 L), and acidified with concentrated HCl (25 mL) with chilling in ice. The precipitate that separated was collected on a filter and washed with cold H_2O to give 52.7 g (95%) of **5b**, mp 135–138 °C.

Method C. To a homogeneous solution of **4a** (1.63 g, 0.01 mol) and Et_3N (2.04 g, 0.022 mol) in CH_2Cl_2 (70 mL) was added dropwise methacryloyl chloride (95%, 1.1 g, 0.01 mol) at 0 °C. The resulting mixture was stirred at 0 °C for 15 min and then at room temperature for 2.5 h, washed with 5% aqueous $KHSO_4$ solution twice and then with saline once, and dried over Na_2SO_4. CH_2Cl_2 was removed on a rotary evaporator, and the residue (2.13 g) was recrystallized from a small amount of EtOAc to give 1.2 g (52%) of **5b**, mp 138–140 °C.

Indoline-2-carboxylic Acid (4a). Method A. A mixture of **2a** (9.56 g, 0.05 mol), 80% aqueous Me_2SO (250 mL), and KOH (86% pellets, 3.26 g, 0.05 mol) was stirred at room temperature overnight and then evaporated on a rotary evaporator in vacuo to give a thick oil. The oil was dissolved in H_2O (100 mL). The solution was made slightly alkaline by addition of dilute NaOH solution; it was then washed with ether several times. Acidification of the aqueous solution with HCl while chilling in ice to pH ~5 caused separation of a precipitate. The mixture was chilled, and the precipitate was collected on a filter and washed with cold H_2O to give 8.73 g (100%) of **4a**: mp 168–170 °C dec; IR 1610 cm^{-1} (CO_2^-); TLC R_f 0.40. Anal. ($C_9H_9NO_2$) C, H, N.

Method B. A mixture of **2a** (191.2 g, 1.0 mol) and MeOH (2.0 L) was treated at 5 °C with stirring with a solution of H_2O (50 mL) and KOH (86% pellets, 65.2 g, 1.0 mol).

The mixture was stirred at room temperature for 3 h and concentrated on a rotary evaporator under reduced pressure. The concentrated solution was chilled in ice and acidified first with concentrated HCl and then with dilute HCl to pH 5. The mixture was chilled in ice, and a precipitate was collected on a filter and washed with cold H_2O to give 155 g (95%) of **4a**, mp 165–170 °C dec.

Resolution of (±)-5b. To a hot, vigorously stirred methanolic (300 mL) solution of (±)-**5b** (29 g, 0.125 mol) was added slowly a warm methanolic (60 mL) solution of dehydroabietylamine (DHAA; 18.0 g, 0.063 mol). The solution was stirred for 5 min and then allowed to set at room temperature for 10 min. The mixture was reheated to boiling, then hot water (240 mL) was added with vigorous stirring. The resulting mixture was allowed to sit at room temperature overnight. A precipitate was collected on a filter and washed 5 times with a cold mixture of MeOH (60 mL) and H_2O (50 mL) to give 27.9 g of (+)-**5b**·DHAA. The combined filtrate and washings were set aside for isolation of (−)-**5b**. Recrystallizations of the (+)-**5b**·DHAA from methanol improved the melting point to 218–220 °C, $[\alpha]^{26.5}_D$ = +91.09 (*c* 1.15%, EtOH). Anal. ($C_{13}H_{13}NO_3 \cdot C_{20}H_{31}N$) H, N; C: calcd, 76.70; found, 76.29. The salt was powdered and partitioned between 1 N NaOH solution and ether. The aqueous layer was washed with ether twice, acidified with dilute HCl, and extracted with ether 3 times. The combined extracts were washed with H_2O and then with saline and dried over Na_2SO_4. Evaporation of the ether on a rotary evaporator gave a solid residue, which was recrystallized from ether to yield 11 g (76%) of (+)-**5b**.

The original filtrate and washings were combined and evaporated carefully on a rotary evaporator to ca. 120 mL and then chilled in a refrigerator overnight. The precipitate was collected on a filter, washed with cold H_2O, and dried over P_2O_5 in vacuo to give 18.7 g of crude (−)-**5b**, mp 130–134 °C. The crude acid was pulverized and extracted with warm, anhydrous ether 4 times (total of 1.2 L). The combined extracts were allowed to set at room temperature overnight. A small amount of fluffy material that deposited was removed by filtration, and the filtrate was concentrated on a rotary evaporator to a slurry, which was chilled in a freezer. A precipitate was collected on a filter and washed with cold ether 5 times. The filter residue was dissolved in a total of 600 mL of anhydrous ether. A small amount of insoluble material was again removed by filtration. The filtrate was concentrated to ca. 300 mL and refiltered. Hexane was added to the filtrate until it became cloudy, and the mixture was chilled in a freezer overnight. The precipitate that separated was collected on a filter and washed with cold ether to give 10 g (69%) of (−)-**5b**.

Reaction of Resolved 5b with Thiobenzoic Acid. Method A. Preparation of (−)-(*S*)-1-[(*S*)-3-(Benzoylthio)-2-methyl-1-oxopropyl]indoline-2-carboxylic Acid [(−)-6b(*S*,*S*)]. To a stirred solution of thiobenzoic acid (95% purity, 8.0 g, 0.055 mol) in acetone (450 mL) was added 4-(dimethylamino)pyridine (0.61 g, 5 mmol). The resulting mixture was stirred for 5 min, and then (−)-**5b** (11.56 g, 0.05 mol) was added. The reaction mixture was heated under reflux for 6 h and then evaporated on a rotary evaporator to give a resinous residue. The residue was dissolved in CH_2Cl_2, and the solution was washed with cold 1 N HCl twice and with saline and then dried over $MgSO_4$. Evaporation of CH_2Cl_2 on a rotary evaporator gave a foamy, resinous material. The residue was dissolved in MeCN (250 mL). Dicyclohexylamine (9.2 g, 0.05 mol) was added slowly to the cold MeCN solution with stirring, and the resulting mixture was chilled for 2 h. The precipitate was collected on a filter and washed with MeCN and then repeatedly with EtOH to afford the DCHA salt

of (-)-**6b**(*S,S*). The combined filtrate and washings were set aside for the isolation of (+)-**6b**(*S,R*)·DCHA. Recrystallization of the crude product from ethanol gave 12.13 g (88%) of (-)-**6b**(*S,S*)·DCHA. Powdered (-)-**6b**(*S,S*)·DCHA (2.0 g, 3.6 mmol) was shaken vigorously with a mixture of 5% aqueous $KHSO_4$ (50 mL) and EtOAc (45 mL), and the organic layer was separated. The aqueous layer was extracted with EtOAc two additional times (20 and 10 mL). The combined extracts were washed with water and saline and dried over Na_2SO_4. Evaporation of the solvent on a rotary evaporator gave an oil, which solidified on standing. Recrystallization of the crude product from ether and hexane gave 1.25 g (93%) of (-)-**6b**(*S,S*): IR 1750 (CO_2H), 1660 (COS), 1620 cm^{-1} (CON); MS, *m/e* 369 (M^+), 325 ($M - CO_2$), 323 ($M - H_2 - CO_2$), 207 [$C_6H_5COSCH_2CH(Me)CO^+$], 163, 118, 105, 77; TLC R_f 0.68; NMR (Me_2SO-d_6) δ 1.28 (d, 3 H, CH_3), 2.75–3.80 (m, 5 H, $CHCH_2$ and indoline CH_2), 5.18 (m, 1 H, $CHCO_2$), 6.94–8.20 (m, 9 H, aromatic), 13.20 (br s, 1 H, CO_2H).

Method B. Preparation of (+)-(*S*)-1-[(*R*)-3-(Benzoylthio)-2-methyl-1-oxopropyl]indoline-2-carboxylic Acid [(+)-6b(*S,R*)]. A mixture of (-)-**5b** (5.78 g, 0.025 mol), thiobenzoic acid (95% purity, 5 g, 0.034 mol), and CH_2Cl_2 (70 mL) was refluxed for 8.5 h and then evaporated on a rotary evaporator to give a resinous residue. The residue was dissolved in MeCN (50 mL), and DCHA (ca. 5 g) was added dropwise to the solution with stirring until the pH of the solution reached 6.5. After the resulting mixture was chilled in ice, a precipitate [(-)-**6b**(*S,S*)·DCHA] was collected on a filter and washed with MeCN. The combined filtrate and washings were set in a hood overnight and then chilled in ice and filtered. The filtrate was treated with an additional amount of DCHA until the pH of the solution reached 8. The resulting solution was evaporated in open air until a precipitate started to separate. It was chilled in ice. The precipitate was collected on a filter and washed with MeCN to give (+)-**6b**(*S,R*)·DCHA (7.39 g, 54%). Recrystallization from MeCN gave an analytical sample. Treatment of (+)-**6b**(*S,R*)·DCHA (2.5 g, 4.5 mmol) with 5% aqueous $KHSO_4$ solution and EtOAc as described in method A gave 0.7 g (42%) of (+)-**6b**(*S,R*) in a resinous form, TLC R_f 0.62.

1-[3-(Benzoylthio)-1-oxopropyl]indoline-2-carboxylic Acid (6a). To a stirred mixture of **5a** (6.52 g, 0.03 mol) and CH_2Cl_2 (160 mL) was added dropwise thiobenzoic acid (95% purity, 4.36 g, 0.03 mol) dissolved in a small amount of CH_2Cl_2. The reaction mixture was chilled in ice during the addition and an additional 10 min, then kept at room temperature for 1 h, and refluxed for 2.5 h. It was concentrated on a rotary evaporator to ca. 30 mL and then chilled in a refrigerator for 1 day. A precipitate was collected on a filter and washed with CH_2Cl_2 to give 10.7 g of **6a**: TLC R_f 0.62.

Reaction of Racemic 5b with Thiobenzoic Acid. Thiobenzoic acid (0.75 g, 5.2 mmol) dissolved in CH_2Cl_2 (3 mL) was added dropwise to a solution of (±)-**5b** (1.2 g, 5.2 mmol) in chilled CH_2Cl_2 (25 mL). The reaction mixture was stirred at room temperature for 0.5 h and at 40 °C for 3 h and then evaporated on a rotary evaporator to give a resinous residue. Addition of a small amount of EtOH to the residue caused a partial solidification. The solid material was separated by suction filtration and recrystallized from ethanol to give 0.4 g of **6b**(*R,R* + *S,S*): TLC R_f 0.68.

The filtrate and mother liquors from the above recrystallization were combined and evaporated on a rotary evaporator. The residue was dissolved in ether, and the ether solution was concentrated under a slow stream of N_2, causing precipitation of crystals. The precipitate was collected and recrystallized from ether to give 0.5 g of **6b**(*R,S* + *S,R*): TLC R_f 0.62.

(-)-(*S*)-[(*S*)-3-(Benzoylthio)-2-methyl-1-oxopropyl]indoline-2-carboxylic Acid [(-)-6b(*S,S*)] and (-)-(*R*)-[(*S*)-3-(Benzoylthio)-2-methyl-1-oxopropyl]indoline-2-carboxylic Acid [(-)-6b(*R,S*)]. Method C. To a stirred mixture of $SOCl_2$ (40 mL) and (-)-(*S*)-3-(benzoylthio)-2-methylpropanoic acid (**8**; 22.4 g, 0.1 mol) in a 250-mL round-bottom flask capped with a $CaCl_2$ tube was added 2 drops of pyridine. The stirring was continued at room temperature for 7 h. Evaporation of the excess $SOCl_2$ on a rotary evaporator gave a clear liquid, which was kept under high vacuum for 2–3 h. The acid chloride thus obtained was dissolved in 50 mL of CH_2Cl_2 and then added over a period of 10 min to a vigorously stirred and chilled (ice bath) mixture of **4a** (16.4 g, 0.1 mol), triethylamine (20.4 g, 0.2 mol), and CH_2Cl_2 (400 mL). The reaction mixture was stirred for 15 min at 0 °C and for 2.5 h at room temperature, washed with 5% aqueous $KHSO_4$ solution 3 times (250, 200, and 150 mL) and with saline, and then dried over Na_2SO_4. Evaporation of the CH_2Cl_2 on a rotary evaporator gave a resinous residue, which was dried in vacuo. The residue was dissolved in MeCN (200 mL), and the solution was chilled to 10 °C. Dicyclohexylamine (18.2 g, 0.1 mol) was added slowly with stirring to the MeCN solution, and the resulting mixture was kept in a refrigerator for 1.5 h. The precipitate was collected on a filter and washed with MeCN repeatedly to give crude (26.3 g, 95.5%) (-)-**6b**(*S,S*)·DCHA, mp 216–218 °C. Recrystallization from ethanol improved the melting point to 223–224 °C and gave 18.6 g (68%) of pure salt. The DCHA salt was converted in 90% yield to (-)-**6b**(*S,S*) by treatment with aqueous $KHSO_4$ solution as described in method A.

The combined MeCN filtrate and washings were chilled in a freezer for 3 days. The precipitate that separated was collected on a filter and washed with cold MeCN to give 20.4 g of crude DCHA salt, mp 134–137 °C. Recrystallization from EtOAc afforded 14.0 g (51%) of (-)-**6b**(*R,S*)·DCHA. Treatment of the salt with aqueous $KHSO_4$ as described in method A afforded (-)-**6b**(*R,S*) as an oil.

1-Benzoylindoline-2-carboxylic Acid (12). The reaction was carried out as described for the preparation of (-)-**6b**(*S,S*) by method C, except for the addition time, which was extended to 1 h. After evaporation of the CH_2Cl_2 on a rotary evaporator, the residue was dissolved in MeCN (200 mL) and chilled in a freezer. A precipitate was collected on a filter, washed with MeCN, and recrystallized from ethanol to give **12** in 31% yield: mp 204–206 °C; IR 1714 (CO_2H), 1640 cm^{-1} (CON); TLC R_f 0.61. Anal. ($C_{16}H_{13}NO_3$·0.25H_2O) C, H, N.

(-)-(*S*)-1-[(*S*)-3-Mercapto-2-methyl-1-oxopropyl]indoline-2-carboxylic Acid [(-)-7b(*S,S*)]. General Debenzoylation Reaction. A mixture of **6b**(*S,S*) (5.0 g, 0.0135 mol) and 2-methoxyethylamine (40 mL) was stirred under N_2 for 15 min at 0 °C and then for 10 min at room temperature. The excess amine was evaporated on a rotary evaporator to give an oil, which was kept in vacuo for 10 min. The residue was dissolved in cold O_2-free H_2O (200 mL), and the aqueous solution was washed with freshly opened anhydrous ether 4 times. The aqueous layer was immediately acidified with dilute HCl to pH ~1 and extracted with ether 2 times. The combined extracts were washed with saline and dried over Na_2SO_4. Evaporation of the ether on a rotary evaporator and then in vacuo afforded a solid residue, which was dissolved in ca. 300 mL of hot EtOAc and filtered with a coarse, folded filter paper. The filtrate was diluted with hexane until it became cloudy and set at room temperature for 1 h and then in an ice bath for 2–3 h. The precipitate was collected on a filter and washed with a mixture of EtOAc/hexane (3:10) to give 2.95 g of **7b**(*S,S*): TLC, R_f 0.45; IR 2580 (SH), 1740 (CO_2H), 1620 cm^{-1} (CON); NMR (Me_2SO-d_6) δ 1.24 (d, 3 H, CH_3), 2.1–3.8 (m, 5 H, $CHCH_2$ and indoline CH_2), 5.08 (m, 1 H, $CHCO_2H$), 6.9–7.3 (m, 3 H, aromatic H's), 8.13 (d, 1 H, aromatic C_7 H).

(±)-1-(3-Mercapto-2-methyl-1-oxopropyl)indoline-2-carboxylic acid [(±)-7b(*R,R* + *S,S*)] was prepared by the method described by Cushman et al.[2] from (±)-**6b**(*R,R* + *S,S*) and then converted into the DCHA salt. The DCHA salt was purified by recrystallization from 2-propanol to a constant melting point of 193–195 °C. The acid was then regenerated by partitioning in 5% aqueous $KHSO_4$ solution and EtOAc, giving the product as a glassy solid. The solid material was dissolved in a small amount of anhydrous ether and added dropwise to cold hexane (150 mL) with vigorous stirring. The fluffy precipitate that separated was collected on a filter. No definite melting point could be obtained.

1,1′-[Dithiobis[(*S*)-2-methyl-1-oxo-3,1-propanediyl]]bis-[(*S*)-indoline-2-carboxylic Acid] (13). A mixture of **7b**(*S,S*) (0.3 g, 1.13 mmol) and Me_2SO (7 mL) was stirred at room temperature for 1 week and then evaporated on a rotary evaporator in vacuo to give a resinous residue. The crude product was purified by preparative HPLC (M9 C_{18} column; MeCN/H_2O/HOAc, 30:60:10) to give 0.22 g (67%) of **13** as an amorphous white solid. No definite melting point could be obtained: TLC R_f 0.34.

(4*S*,11a*S*)-3,4,11,11a-Tetrahydro-4-methyl-1*H*,5*H*-[1,4]-thiazepino[4,3-*a*]indole-1,5-dione (10). To a chilled (ice bath)

and stirred mixture of **7b**(*S,S*) (1.247 g, 4.7 mmol), 4-(dimethylamino)pyridine (0.06 g, 0.5 mmol), and CH_2Cl_2 (500 mL) was added slowly DCC (1.02 g, 4.9 mmol) in CH_2Cl_2 (10 mL). The reaction mixture was stirred at 0 °C for 15 min and then at room temperature for 4 h. The reaction mixture was concentrated on a rotary evaporator to ca. 80 mL, chilled in a dry ice–acetone bath, and filtered to remove DCU (1.0 g), which was washed with cold CH_2Cl_2. The combined filtrate and washings were washed with cold 1 N HCl twice and with saline and dried over $MgSO_4$. Evaporation of the CH_2Cl_2 on a rotary evaporator gave a solid residue, which was dissolved in warm EtOAc (75 mL). The solution was concentrated to ca. 15 mL and then chilled in a freezer overnight to give 0.73 g of **10**: IR 1664 (COS), 1600 cm^{-1} (CON); NMR ($CDCl_3$) δ 1.38 (d, 3 H, CH_3), 2.90–3.90 (m, 4 H, CH_2CH and indoline CH_2), 5.30 (m, 1 H, CHCOS), 6.92–7.25 (m, 3 H, aromatic), 8.13 (d, 1 H, aromatic C_7 H); TLC R_f 0.85.

(4*S*,11a*R*)-3,4,11,11a-Tetrahydro-4-methyl-1*H*,5*H*-[1,4]-thiazepino[4,3-*a*]indole-1,5-dione (11) was similarly prepared from (+)-**7b**(*R,S*) in 28% yield: TLC R_f 0.84.

***tert*-Butyl Indole-2-carboxylate.** To a chilled (dry ice–acetone bath) solution of indole-2-carboxylic acid (16.12 g, 0.1 mol) in 1,2-dimethoxyethane (300 mL) were added isobutylene (300 mL) and concentrated sulfuric acid (30 mL). The resulting mixture was shaken in a Parr apparatus for 3.5 days. The excess isobutylene was vented carefully in a hood, and the reaction mixture was poured into a mixture of 1 N NaOH (300 mL) and ice (200 g). The product was extracted with CH_2Cl_2. The extract was washed with 1 N NaOH, dried over Na_2SO_4 + K_2CO_3, and evaporated on a rotary evaporator. The crude product thus obtained was purified on an alumina column (neutral activity III, 450 g) eluting with CH_2Cl_2/hexane (1:1) and then was recrystallized from hexane to give the product (33%): mp 103–105 °C; IR 3355 (NH), 1669 (COOC) cm^{-1}; TLC R_f 0.87; NMR ($CDCl_3$) δ 1.65 [s, 9 H, $C(CH_3)_3$], 7.00–7.76 (m, 5 H, aromatic), 9.28 (broad exchangeable s, 1 H, NH). Anal. ($C_{13}H_{15}NO_2$) C, H, N.

***tert*-Butyl 1-(2-Methyl-1-oxo-2-propenyl)indole-2-carboxylate.** To a stirred solution of *tert*-butyl indole-2-carboxylate (4.35 g, 20 mmol) in 1,2-dimethoxyethane (100 mL) was added NaH dispersed in mineral oil (50%, 1.15 g, 24 mmol). The resulting mixture was stirred at room temperature for 40 min and then chilled in an ice–water bath. A solution of methacryloyl chloride (2.51 g, 24 mmol) in 1,2-dimethoxyethane (10 mL) was added over 5 min. The resulting mixture was stirred at room temperature for 1 h. Glacial HOAc (0.3 mL) was added, and the reaction mixture was evaporated on a rotary evaporator in vacuo. The residue was purified on a silica column (neutral activity III) eluting with $CHCl_3$/hexane (1:4). The viscous pale yellow oil thus obtained was distilled twice to give 1.41 g (25%) of product: bp 130–132 °C (0.02 mmHg); IR (film) 1721 (COOC), 1701 cm^{-1} (CON); TLC R_f 0.91, R_f ($CHCl_3$) 0.36; NMR ($CDCl_3$) δ 1.56 [s, 9 H, $C(CH_3)_3$], 2.16 (s, 3 H, CH_3), 5.14 and 5.53 (2 s, 2 H, CH_2=), 7.09–8.05 (m, 5 H, aromatic). Anal. ($C_{17}H_{19}NO_3$) C, H, N.

1-[3-(Benzoylthio)-2-methyl-1-oxopropyl]indole-2-carboxylic Acid (14). A mixture of *tert*-butyl 1-(2-methyl-1-oxo-2-propenyl)indole-2-carboxylate (7.43 g, 26 mmol), acetone (100 mL), and thiobenzoic acid (3.96 g, 28.6 mmol) was refluxed for 20 h and evaporated on a rotary evaporator in vacuo. The residue was purified by column chromatography on silica, with $CHCl_3$/hexane (1:1) as the mobile phase, to afford 10.95 g (99%) of *tert*-butyl 1-[3-(benzoylthio)-2-methyl-1-oxopropyl]indole-2-carboxylate: IR (film) 1730, 1712, 1669 cm^{-1} (ester, thio ester, and amide CO's); NMR ($CDCl_3$) δ 1.35 (d, 3 H, CH_3CH), 1.56 [s, 9 H, $(CH_3)_3$], 3.21–3.68 (m, 3 H, $CHCH_2$), 7.13–8.06 (m, 10 H, aromatic H's). A solution of the above *tert*-butyl ester (10.91 g, 25.8 mmol) and trifluoroacetic acid (79.4 mL, 1.03 mol) was kept at 25 °C for 10 min and then evaporated on a rotary evaporator in vacuo at ca. 50 °C. The residue was thoroughly triturated with cold hexane and recrystallized from acetone–hexane twice to give 4.68 g (56%) of the product: mp 120–122 °C (softens at 119 °C); IR 2577 (COOH), 1730, 1700, 1669 cm^{-1} (acid, thio ester, and amide CO's); NMR ($CDCl_3$) δ 1.31 (d, 3 H, CH_3CH), 3.08–3.80 (m, 3 H, CH_2CH), 7.08–8.04 (m, 10 H, aromatic H's), 10.26 (exchangeable s, 1 H, CO_2H); TLC R_f 0.72. Anal. ($C_{20}H_{17}NO_4S$) C, H, N.

Hydrolysis of 7b(*S,S*). A mixture of **7b**(*S,S*) (0.2 g, 0.75 mmol) and 6 N HCl (20 mL) was refluxed gently for 3 h and then evaporated on a rotary evaporator to give a dark amber oil. The residue was diluted with H_2O (1 mL). Addition of concentrated NaOH solution to pH ~2 caused separation of a precipitate. The mixture was chilled in ice, and the precipitate was collected on a filter and washed with cold H_2O, with ether, and then with EtOAc to give (+)-**4a** (0.13 g, 100%): mp 160–163 °C dec; IR 1640 cm^{-1} (CO_2^-); $[\alpha]^{25}_D$ +34.50° (*c* 0.91, DMF). Anal. ($C_9H_9NO_2 \cdot 0.125H_2O$) C, H, N.

Reduction of (+)-4a. One gram of (+)-**4a** was reduced with 1.0 g of $LiAlH_4$ in ether by a conventional method to give (+)-(*S*)-2-(hydroxymethyl)indoline[17] (0.27 g, 27%): mp 68–69 °C; $[\alpha]^{25.5}_D$ +54.3° (*c* 1.15, EtOH) [lit.[17] mp 67.8–69.3 °C; $[\alpha]^{27}_D$ +60.5° (*c* 0.89, EtOH)].

Reaction of (+)-(*S*)-4a with 9. The reaction was carried out as described for the preparation of **6b**(*S,S*) with 0.816 g (5 mmol) of (+)-(*S*)-**4a** and 1.121 g (5 mmol) of (−)-(*S*)-**8** to give a product (1.2 g, 65%) that is identical (IR, mp, mmp, optical rotation) with **6b**(*S,S*) prepared by method A.

In Vitro ACE Inhibitory Activity. The in vitro inhibitory activity was determined by a method reported previously[23] with slight modification. The crude ACE was prepared by blending 1 g of rabbit lung acetone extract (Pel-Freeze Biologicals) with 35 mL of 50 mM potassium phosphate buffer, pH 8.3, and by centrifuging at 40000*g* for 45 min. After final addition of 0.15 mL of the enzyme supernatant solution, each 0.25 mL of assay solution was comprised of the following components: K_2PO_4 buffer, pH 8.3 (100 mM); NaCl (300 mM); and hippuryl-L-histidyl-L-leucine (HHL, 5 mM). Zero time controls were obtained by addition of 0.25 mL of 2 N HCl before the enzyme addition and all others after 30 min of incubation at 37 °C. Hippuric acid released from HHL by the enzyme action was extracted into 1.5 mL of ethyl acetate, 1.0 mL of the extract was evaporated to dryness, and the residue was suspended in 1.0 mL of H_2O. The absorbance at 228 nm was measured, and the amount of hippuric acid was calculated from a standard curve. Concentration–inhibition curves were constructed, and IC_{50} values were determined. Inhibitory activity is reported as the IC_{50}, the approximate molar concentration of compound required to cause a 50% inhibition of the control converting enzyme activity.

In Vivo Inhibitory Test in the Conscious Normotensive Rat. A slight modification of the angiotensin I challenge test in the conscious rat reported by Rubin et al.[24] was utilized. Conscious, male, Sprague–Dawley rats weighing 200–350 g were prepared, and polyethylene cannulas were inserted into the carotid artery and jugular vein for blood pressure measurement and administration of test compound, respectively. The catheters were tunneled subcutaneously and exteriorized at the back of the neck. The animals were kept in individual cylindrical Plexiglas restrainers for the duration of the experiment. Arterial blood pressure was measured with a Statham P23Gb transducer (Gould Statham, Hato Ray, Puerto Rico) and recorded on a Beckman Dynograph (Beckman Instruments, Fullerton, CA). Pressor responses to intravenous injections of angiotensin I (300 ng/kg) and angiotensin II (100 ng/kg) were compared before and at various intervals after oral dosing with 0.1, 1.0, 3.0, or 10 mg/kg of prospective ACE inhibitors. Selective inhibition of the ACE would be indicated by an attenuation of angiotensin I induced vasopressor responses with little effect on the responses to angiotensin II. Results are expressed as the ID_{50}, the approximate dose in molar concentration required to inhibit the angiotensin I pressor response by 50%.

Antihypertensive Test in the Conscious Rats. Using an indirect tail-cuff technique,[31] we recorded systolic blood pressure of SHR before and 1.5 and 4 h after single oral dose administration of 0.1, 0.25, 0.5, 1.0, 3.0, 10.0, 25.0, or 50.0 mg/kg of test compound. Antihypertensive activity is reported as the ED_{25mmHg}, the approximate dose which would lower the systolic blood pressure by 25 mmHg at 4 h, calculated from the log dose–response relationships generated by linear regression analysis.[32]

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(31) H. C. Stanton, *Methods Pharmacol.*, 1, 135–138 (1971).
(32) R. Steel and J. Torrie in "Principles and Procedures of Statistics", McGraw-Hill, New York, NY, 1960.

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Registry No. (±)-**2a**, 27719-97-7; (±)-**3a**, 78701-31-2; (±)-**3b**, 78701-23-2; (±)-**3c**, 78701-43-6; (±)-**4a**, 16851-56-2; (+)-(*S*)-**4a**, 79815-20-6; (±)-**5a**, 78701-32-3; (*R*)-**5a**, 84171-38-0; (*S*)-**5a**, 84171-40-4; (±)-**5b**, 78701-24-3; (±)-**5b**·DCHA, 78701-41-4; (+)-(*R*)-**5b**, 78701-37-8; (−)-(*S*)-**5b**, 78701-38-9; (+)-(*R*)-**5b**·DHAA, 78701-39-0; (*R*)-**5c**, 84171-33-5; (*S*)-**5c**, 84171-39-1; (±)-**6a**, 78701-33-4; (*R*)-**6a**, 84171-36-8; (*S*)-**6a**, 84171-41-5; (±)-(*R**,*R**)-**6b**, 78701-25-4; (±)-(*R**,*S**)-**6b**, 78701-28-7; (−)-(*S*,*S*)-**6b**, 78779-25-6; (−)-(*S*,*S*)-**6b**·DCHA, 78821-38-2; (+)-(*S*,*R*)-**6b**, 78779-26-7; (+)-(*S*,*R*)-**6b**·DCHA, 78821-39-3; (+)-(*R*,*S*)-**6b**, 78779-28-9; (+)-(*R*,*S*)-**6b**·DCHA, 78821-41-7; (−)-(*R*,*R*)-**6b**, 78779-27-8; (−)-(*R*,*R*)-**6b**·DCHA, 78821-40-6; (±)-(*R**,*R**)-**6c**, 84171-34-6; (±)-(*R**,*R**)-**6c**·DCHA, 84171-35-7; (*S*,*S*)-**6c**·DCHA, 84117-83-9; (*S*,*S*)-**6d**, 84117-84-0; (*S*,*S*)-**6d**·DCHA, 84117-85-1; (±)-(*R**,*R**)-**6e**, 78701-40-3; (±)-(*R**,*R**)-**6e**·DCHA, 78739-20-5; (±)-(*R**,*S**)-**6e**, 78701-54-9; (±)-(*R**,*S**)-**6e**·DCHA, 78701-55-0; (*R*)-**7a**, 84171-32-4; (*S*)-**7a**, 84171-37-9; (±)-(*R**,*S**)-**7b**, 78701-29-8; (±)-(*R**,*R**)-**7b**·DCHA, 78701-27-6; (−)-(*S*,*S*)-**7b**, 78779-29-0; (+)-(*R*,*S*)-**7b**, 83212-49-1; (−)-(*S*)-**8**, 72679-02-8; (*R*)-**9**, 74654-91-4; (*S*,*S*)-**10**, 78779-31-4; (4*S*,11a*R*)-**11**, 78701-50-5; (*S*)-**12**, 84117-80-6; **13**·H_3CCO_2H, 84130-23-4; **14**, 84117-81-7; ACE, 9015-82-1; methacryloyl chloride, 920-46-7; thiobenzoic acid, 98-91-9; *tert*-butyl indole-2-carboxylate, 84117-86-2; *tert*-butyl 1-(2-methyl-1-oxo-2-propenyl)indole-2-carboxylate, 84130-24-5; *tert*-butyl 1-[3-(benzoylthio)-2-methyl-1-oxopropyl]indole-2-carboxylate, 84117-87-3.

Antihypertensive Activity of 6-Arylpyrido[2,3-*d*]pyrimidin-7-amine Derivatives. 2. 7-Acyl Amide Analogues

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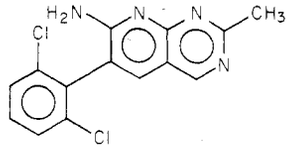
The effect of acylation with a variety of acids on the antihypertensive activity of 6-(2,6-dichlorophenyl)pyrido[2,3-*d*]pyrimidin-7-amine (**1**) is reported, and structure–activity relationships are discussed. Although several of the compounds show good oral antihypertensive activity in the conscious, spontaneously hypertensive rat (SHR), their activity profile appears to differ from **1** in that the onset of action is shortened at comparable blood pressure lowering doses, and the magnitude of effect is considerably greater at higher doses. A variety of urea, thiourea, guanidine, and amidine analogues also were prepared. Although many of these derivatives showed some antihypertensive effects when dosed orally to SHR, this activity was weaker and of shorter duration than that obtained with **1**. Aqueous solubilities and hydrolytic stabilities for four of the more active compounds were measured and suggest that these do not function as prodrugs of **1**.

In a recent paper,[1] we reported the antihypertensive activity of a novel series of 6-arylpyrido[2,3-*d*]pyrimidin-7-amine derivatives. Compound **1** emerged from that



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study as the most promising candidate for further evaluation. Although **1** met our initial objectives of oral activity and long duration, the requirements for activity of the substituent in the 7-position of the pyridopyrimidine ring had not been explored. One transformation that seemed particularly appealing in this connection was acylation. If activity could be maintained, a variety of new polar and/or nonpolar moieties could easily be introduced into the molecule. However, if inherent activity was lost on acylation, the known relative lability of this type of heterocyclic amide might provide a prodrug form of **1** with altered absorption characteristics or modified onset or duration effects. Finally, from a purely chemical standpoint, acylation of the 7-amino group could provide activation for further transformations at this position, e.g., reduction or alkylation to alkylamino analogues. We thus explored these possibilities and report in this paper the synthesis and biological activity of a series of 7-(acylamino)-6-arylpyrido[2,3-*d*]pyrimidines related to **1**.

Chemistry. When **1** was heated in the presence of acetic anhydride, a modest yield of **3** was obtained. The yield and purity of **3** were substantially improved when the reaction was run with a slight excess of acetic anhydride in refluxing ethyl acetate. In this case, **3** crystallized from the mixture on cooling. When **3** was found to have antihypertensive effects similar to **1** in the spontaneously hypertensive rat (SHR) at the screening dose of 50 mg/kg, we moved to prepare a larger series of analogues. Readily available acid anhydrides were employed initially (method A) for the preparation of several of the analogues in Table I, including the extremely labile trifluoroacetamide, **10**, which was cleaved immediately to **1** on dissolution in MeOH. We found that the standard acylating method with acid chloride/tertiary amine systems was generally unsuitable for acylating **1**, although methanesulfonamide **31** was later obtained by this procedure. Considering other acylating methods that might have application in this situation, we elected to try acylimidazolides.[2] Indeed,

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(1) (a) This paper has been presented in part; see "Abstracts of Papers", Second Chemical Congress of the North American Continent, Las Vegas, NV, Aug 24–29, 1980; American Chemical Society: Washington, DC, 1980; Abstr MEDI 52. (b) Bennett, L. R.; Blankley, C. J.; Fleming, R. W.; Smith, R. D.; Tessman, D. K. *J. Med. Chem.* **1981**, *24*, 382 (paper 1 of the series).

0022-2623/83/1826-0403$01.50/0