Angiotensin Converting Enzyme Inhibitors as Antihypertensive Agents: 1-[(2-Mercaptocycloalkyl)carbonyl]-L-prolines

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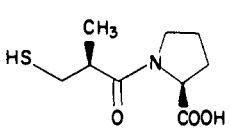
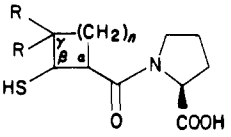
The synthesis of 1-[(2-mercaptocyclopentyl)carbonyl]-L-prolines, 1-[(2-mercaptocyclobutyl)carbonyl]-L-prolines and related benzoyl derivatives as pure isomers is described. The abilities of all the compounds to inhibit angiotensin converting enzyme (ACE) in vitro and in vivo and to lower the systolic blood pressure in renal hypertensive dogs were determined. Three of them, namely 1-[[2-(benzoylthio)cyclopentyl]carbonyl]-L-proline (**10f**(*R,S*)), 1-[(2-mercaptocyclopentyl)carbonyl]-L-proline (**10g**(*R,S*)), and 1-[[2-(benzoylthio)cyclobutyl]carbonyl]-L-proline (**16f**(*R,S*)), were found to be as potent as captopril in reducing blood pressure. The influence of chirality and ring size on the ACE inhibition is described.

The discovery by Ondetti et al.[1] of a new class of orally active angiotensin converting enzyme (ACE) inhibitors that act as antihypertensive agents,[2] of which captopril was reported to be the most potent compound, has prompted a great deal of work in this new field.[3-11] In this paper we report the synthesis and the ACE inhibitory activity of a new class of compounds, **1**, related to captopril but with a semirigid structure and hence a restricted number of conformations.



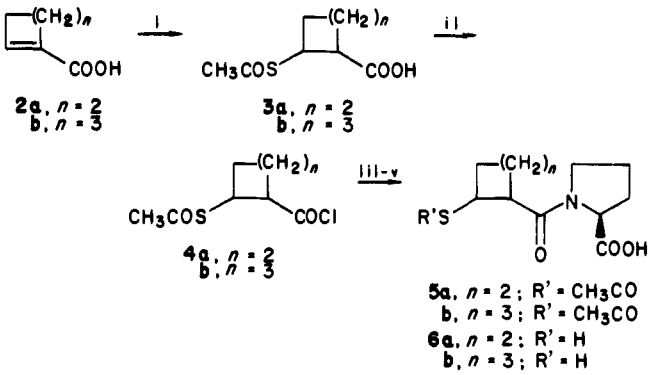
captopril



1, *n* = 1, 2, 3. R = H, CH_3

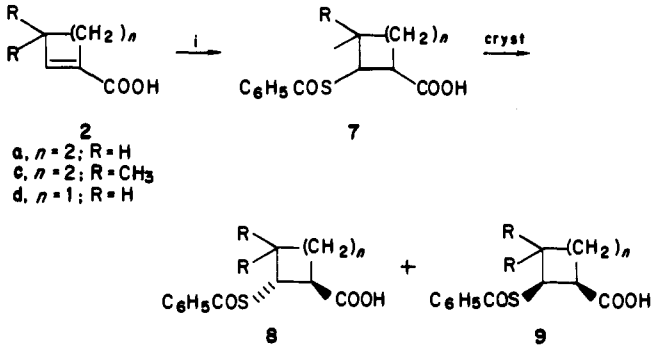
Chemistry. Compounds **6a** and **6b** were prepared as

Scheme I[a]



[a] i, CH_3COSH; ii, $SOCl_2$; iii, L-proline/NaOH-H_2O; iv, NH_3-CH_3OH; v, HCl.

Scheme II[a]



[a] i, C_6H_5COSH, 120 °C.

oily mixtures of the four diastereoisomers from **2a** and **2b** (Scheme I). The unsuccessful efforts to separate the four isomers of **6a** by classical methods suggested to us to do the Michael reaction on **2a** with thiobenzoic acid in order to obtain solid intermediates that should be easier to separate than the liquid mixtures **3a**,**4a**. This reaction gave a trans–cis solid mixture **7a** (Scheme II) from which the two isomers **8a** and **9a** were separated by crystallization and condensed with L-proline 1,1-dimethylethyl ester[12] (procedure A) to give the diastereoisomeric mixtures **10e**,**11e** and **12e**,**13e** (Schemes III and IV). These were separated by preparative liquid chromatography and then deprotected first with CF_3COOH[1b] (procedure B) and then with NH_4OH[1b] (procedure C) to give **10**–**13g** in good yields. The Michael reaction of **2c** with thiobenzoic acid gave only

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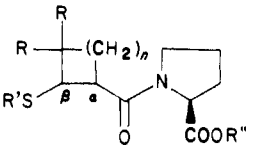
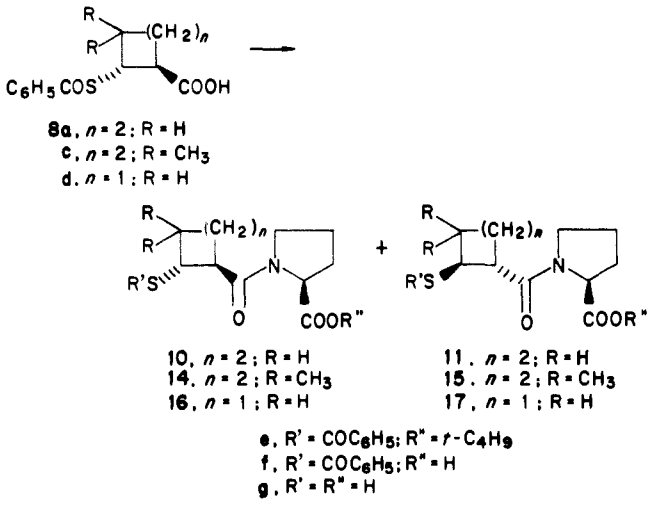
Table I. Physical Properties of 1-[(2-Mercaptocycloalkyl)carbonyl]-L-proline and in Vitro ACE Inhibitory Activity



compd[a]	n	R	R′	R″	rel config Cβ–Cα	IC_{50},[b] μM	mp, °C	recrystn solvent	procedure[c]	yield, %	$[\alpha]^{20}_D$, deg (c 1, $CHCl_3$)	formula	anal.
6a	2	H	H	H	mixture	1.64	glass			75.4		$C_{11}H_{17}NO_3S$	
6b	3	H	H	H	mixture	11.35	glass			95.0		$C_{12}H_{19}NO_3S$	C,[d] H, N, S
10e(*R,S*)	2	H	COC_6H_5	t-C_4H_9	trans	250	73.5	hexane[e]	A	42.1	−107.5	$C_{22}H_{29}NO_4S$	C, H, N, S
11e(*S,R*)	2	H	COC_6H_5	t-C_4H_9	trans	250	67	hexane[e]	A	40.5	+4.8	$C_{22}H_{29}NO_4S$	C, H, N, S
12e(*S,S*)	2	H	COC_6H_5	t-C_4H_9	cis	250	81.5	hexane[e]	A	50.1	−153.5	$C_{22}H_{29}NO_4S$	C, H, N, S
13e(*R,R*)	2	H	COC_6H_5	t-C_4H_9	cis	124	68	hexane[e]	A	44.6	−2.7	$C_{22}H_{29}NO_4S$	C, H, N, S
14e(*S,S*)	2	CH_3	COC_6H_5	t-C_4H_9	trans	250	170	Et_2O[e]	A	42.3	−82.5	$C_{24}H_{33}NO_4S$	C, H, N, S
15e(*R,R*)	2	CH_3	COC_6H_5	t-C_4H_9	trans	250	119, 136[f]	Et_2O[e]	A	43.2	−34.6	$C_{24}H_{33}NO_4S$	C, H, N, S
16e(*R,S*)	1	H	COC_6H_5	t-C_4H_9	trans	250	103	Et_2O[e]	A	36.4	−138.8	$C_{21}H_{27}NO_4S$	C, H, N, S
17e(*S,R*)	1	H	COC_6H_5	t-C_4H_9	trans	250	112	Et_2O[e]	A	42.5	+12.8	$C_{21}H_{27}NO_4S$	C, H, N, S
10f(*R,S*)	2	H	COC_6H_5	H	trans	0.58	106	EtOAc	B	95.0	−119.9	$C_{18}H_{21}NO_4S$	C, H, N, S
11f(*S,R*)	2	H	COC_6H_5	H	trans	144	88	Et_2O	B	94.0	−81.8	$C_{18}H_{21}NO_4S$	C, H, N, S
12f(*S,S*)	2	H	COC_6H_5	H	cis	144	152	EtOAc	B	95.1	−183.4	$C_{18}H_{21}NO_4S$	C, H, N, S
13f(*R,R*)	2	H	COC_6H_5	H	cis	250	glass		B	95.0	−59.7	$C_{18}H_{21}NO_4S$	
14f(*S,S*)	2	CH_3	COC_6H_5	H	trans	250	187	EtOAc	B	85.0	−90.5	$C_{20}H_{25}NO_4S$	C, H, N, S
15f(*R,R*)	2	CH_3	COC_6H_5	H	trans	250	153	Et_2O[e]	B	74.3	−141.2	$C_{20}H_{25}NO_4S$	C, H, N, S
16f(*R,S*)	1	H	COC_6H_5	H	trans	5.50	107	Et_2O[e]	B	76.0	−119.6	$C_{17}H_{19}NO_4S$	C, H, N, S
17f(*S,R*)	1	H	COC_6H_5	H	trans	250	124	Et_2O[e]	B	95.0	−86.3	$C_{17}H_{19}NO_4S$	C, H, N, S
10g(*R,S*)	2	H	H	H	trans	1.11	118	Et_2O	C	72.2	−237.4	$C_{11}H_{17}NO_3S$	C, H, N, S
11g(*S,R*)	2	H	H	H	trans	34.25	102, 110[f]	Et_2O	C	77.8	−61.6	$C_{11}H_{17}NO_3S$	C, H, N, S
12g(*S,S*)	2	H	H	H	cis	19.50	88	Et_2O	C	77.7	−149.6	$C_{11}H_{17}NO_3S$	C, H, N, S
13g(*R,R*)	2	H	H	H	cis	206	97	Et_2O	C	76.2	−181.7	$C_{11}H_{17}NO_3S$	C, H, N, S
14g(*S,S*)	2	CH_3	H	H	trans	215	139	Et_2O[e]	C	65.8	−132.8	$C_{13}H_{21}NO_3S$	C, H, N, S
15g(*R,R*)	2	CH_3	H	H	trans	250	147	Et_2O[e]	C	80.0	−63.7	$C_{13}H_{21}NO_3S$	C, H, N, S
16g(*R,S*)	1	H	H	H	trans	1.26	145	Et_2O[e]	C	85.0	−192.3	$C_{10}H_{15}NO_3S$	C, H, N, S
17g(*S,R*)	1	H	H	H	trans	12.73	137	Et_2O	C	86.0	−44.2	$C_{10}H_{15}NO_3S$	C, H, N, S
captopril						0.59							

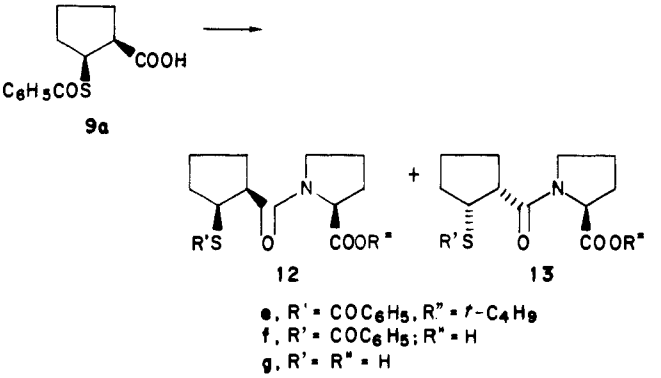
[a] Parenthetical *R* and *S* designations indicate the absolute stereochemistry. The first letter in the grouping refers to the β carbon configuration and the second letter to the α carbon configuration. [b] Micromolar concentration required for 50% ACE inhibition. [c] See Experimental Section. [d] C: calcd, 56.00; found, 56.61. [e] Solvent used to triturate the solid residue. [f] Two crystalline forms.

Scheme III



the trans isomer **8c**. The cis isomer probably was not formed because of the considerable steric interaction that a cis arrangement of the methyl, thiobenzoyl, and carboxylic groups would have. The trans isomer **8c** was condensed with L-proline, 1,1-dimethylethyl ester, and the resulting isomers **14e** and **15e** were separated and deprotected as before to give **14g** and **15g** (Scheme III). In a similar way **2d** was converted to the trans–cis mixture **7d**, the two isomers **8d** and **9d** were separated by crystallization (Scheme II), and the trans isomer **8d** was transformed to **16g** and **17g** (Scheme III).

Scheme IV



The relative configurations of **8** and **9** were established on the basis of the chemical shifts and coupling constants of the two methine protons from the literature.[13] The absolute configurations of the α and β cycloalkylic carbon atoms of the four pairs of compounds **10e,11e**, **12e,13e**, **14e,15e**, and **16e,17e** (Table I) were assigned tentatively on the basis of their ^1H NMR spectra, which displayed different populations of trans and cis conformers around the prolyl–amide bond[9,14] (Table III). In fact, the NMR

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Table II. ACE Inhibitory Activity in Conscious Normotensive Rats and Antihypertensive Activity in Conscious Renal Hypertensive Dogs

compd	dose, mg/kg iv	% reduction of Ang I response[c]	antihypertensive act. mg/kg po	antihypertensive act. % SBP decrease[a,d]	IC_{50}, μM
10f(*R,S*)	10	−80**	30	−18°°	0.58
	1	−65**	10	−15°°	
16f(*R,S*)	10	−60**	30	−17°°	5.5
	1	−45**	10	−15°	
17f(*S,R*)	10	−30*	30	−19°°	>250
	1	−18	10	<10	
10g(*R,S*)	10	−75**	30	−21°°	1.11
	1	−42**	10	−18°°	
12g(*S,S*)	10	−41**	30	<10	19.5
	1	−22**			
16g(*R,S*)		NT[b]	30	<10	1.26
captopril	0.13	−80**	30	−19°°	0.59
	0.03	−50**	10	−15°°	

[a] Maximum decrease in systolic blood pressure (SBP) 5-h postdose. [b] NT indicates not tested. [c] (**) $p < 0.01$, (*) $p < 0.05$ postdrug responses vs. predrug responses calculated by Student's t test. [d] (°°) $p < 0.01$, (°) $p < 0.05$ vs. 0 time, calculated by Dunnett's t test.

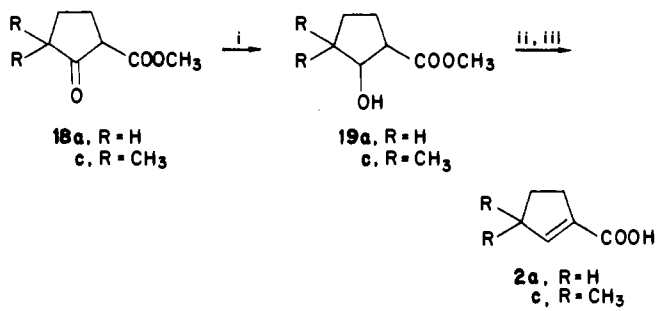
spectra of **10e**, **12e**, **14e**, and **16e** showed the presence of the two conformers in an approximate ratio of 2:8 while for **11e**, **13e**, **15e**, and **17e** this ratio was approximately 1:1. Examination of the four CPK stereomodels of the pair **10e,11e** indicated that in one of the two trans configurations (β*R*, α*S*), the cis-amide conformation showed a steric interaction between the two rings of the molecule stronger than that observed for the trans-amide conformation (**10e**), while for the opposite trans configuration (β*S*, α*R*), both cis- and trans-amide conformations displayed the same steric interaction (**11e**). Similar steric interactions were observed for the other three pairs of compounds. These assignments are supported by the relative in vitro ACE activities. Compounds with the α*S* configuraions were more potent than the related α*R* isomers, as formerly found for captopril,[1] enalapril,[5] and their congeners.

Synthesis of α,β-Unsaturated Cycloalkenecarboxylic Acid. Unsaturated acids **2a** and **2b** were prepared by a known method.[15] Compound **2a** could also be prepared from 2-oxocyclopentanecarboxylic acid methyl ester as described for 3,3-dimethyl-1-cyclopentane-1-carboxylic acid (**2c**, Scheme V). Reduction of ketones **18a,c** with $NaBH_4$ in MeOH[16] or with hydrogen and catalyst[17] gave **19a,c**, with yields that did not exceed 60%. When the same reduction was carried out with $NaBH_4$ in citrate buffer, the yields of **19a,c** were better (80%). Treatment of **19a,c** with fused NaOH gave after acidification the acids **2a,c** in good yields. 3,3-Dimethyl-2-oxocyclopentanecarboxylic acid methyl ester (**18c**) was prepared by reaction of 2,2-dimethylcyclopentanone[18] with NaH and dimethyl carbonate. 1-Cyclobutene-1-carboxylic acid (**2d**) was prepared form cyclobutanecarboxylic acid.[15]

Results and Discussion

The in vitro inhibition of plasma angiotensin converting enzyme of **6a** and **6b** (Table I) showed that **6b** was approximately one-seventh as potent as **6a**, thus focusing our interest on the preparation of the four pure diastereoisomers of this latter compound. After that all the other compounds (**14–17e–g**) were prepared as pure diastereoisomers and their in vitro ACE inhibitory activities determined. The results are reported in Table I. Among the series of the diastereoisomeric 1-[(2-mercaptocyclopentyl)carbonyl]-L-prolines (**10–13g**), **10g**(*R,S*) was found to be one-half as potent as captopril while **11g**(*S,R*), **12g**(*S,S*), and **13g**(*R,R*) were $^1/_{30}$th, $^1/_{17}$th and $^1/_{185}$th as potent as **10g**(*R,S*) respectively. Among the related benzoylthio derivatives (**10–13f**), **11**, **12**, and **13f** were practically inactive, while to our surprise **10f**(*R,S*) was twice as potent as **10g**(*R,S*). We cannot explain this apparent discrepancy, but similar discrepancies have been observed for other classes of ACE inhibitors.[10,19] The introduction of two methyl groups at C-γ into the cyclopentane ring of 1-[(2-mercaptocyclopentyl)carbonyl]-L-prolines gave the inactive **14g** and **15g**. This inactivity could be ascribed to excessive steric hindrance inhibiting binding to the ACE active site. Among the series of 1-[(2-mercaptocyclobutyl)-carbonyl]-L-prolines, **16g**(*R,S*) was equipotent with **10g**(*R,S*) and approximately 4 times as potent as the related benzoylthio derivative **16f**(*R,S*).[20] These results indicate that with the exception of **14,15g** the chirality of the C-α is more important than that of the C-β. ACE inhibitory activities of these compounds were studied in vivo in conscious normotensive rats and antihypertensive activities in conscious renal hypertensive dogs and the results are

Scheme V[a]



[a] i, $NaBH_4$-buffer; ii, NaOH, 160 °C; iii, HCl.

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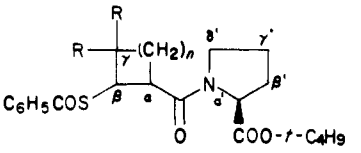
(20) The compounds obtainable from the cis isomer **9d** were not prepared because of the poor yield in synthesis of **9d** and the poor in vitro and in vivo activities of the cis derivatives **12**, **13e–g** in the five-membered ring series.

Table III. ^{1}H NMR Spectral Data[a] of 10e–17e



compd	H-α[e]	H-β	H-α'[b]	H-δ' (2 H)	R	C_6H_5	t-C_4H_9
10e	2.78 (dt, J = 8, 8.5) 20% cc[c]	4.30 (m)	4.43 (m)	3.59 (m)	1.6–2.5 (m)	7.3–7.9 (m)	1.42 (s) 20%
	3.06 (dt, J = 6.5, 8.5) 80% tc[d]						1.44 (s) 80%
11e	2.85 (dt, J = 7, 7) 50% cc	4.17 (dt, J = 6.5, 8) 50%	4.35 (m) 50% cc	3.4–3.8 (m)	1.6–2.5 (m)	7.4–8.0 (m)	1.43 (s) 50%
	3.08 (dt, J = 5.5, 8) 50% tc	4.28 (dt, J = 5.5, 5.5) 50%	4.44 (m) 50% tc				1.44 (s) 50%
12e	3.07 (m) 10% cc	4.21 (m)	4.34 (m)	3.59 (m)	1.6–2.3 (m)	7.4 8.0 (m)	1.35 (s) 10%
	3.37 (ddd, J = 8, 8, 5) 90% tc						1.44 (s) 90%
13e	3.2–3.7 (m)	4.13 (dt, J = 8, 8) 40%	4.34 (m) 40% cc	3.2–3.7 (m)	1.6–2.3 (m)	7.4–8.0 (m)	1.38 (s) 40%
		4.22 (dt, J = 8, 8) 60%	4.42 (m) 60% tc				1.47 (s) 60%
14e	2.84 (ddd, J = 10, 10, 5) 10% cc	4.31 (d, J = 10) 90%	4.20 (m) 10% cc	3.55 (m)	0.93 (s) 10%	7.3–8.0 (m)	1.43 (s) 10%
	3.12 (ddd, J = 10, 10, 5) 90% tc	4.53 (d, J = 10) 10%	4.38 (m) 90% tc		0.98 (s) 90%		1.45 (s) 90%
15e	2.96 (ddd, J = 10, 10, 5) 50% cc	4.13 (d, J = 10) 50%	4.30 (m) 50% cc	3.4–3.8 (m)	1.09 (s) 100% 0.96 (s) 50%	7.3–8.0 (m)	1.27 (s) 50%
	3.12 (ddd, J = 10, 10, 5) 50% tc	4.36 (d, J = 10) 50%	4.42 (m) 50% tc		0.98 (s) 50%		1.48 (s) 50%
16e	3.2–3.7 (m)	4.57 (dt, J = 9, 9) 80%	4.17 (m) 20% cc	3.2–3.7 (m)	1.12 (s) 100% 1.8–2.6 (m)	7.4–8.0 (m)	1.44 (s) 20%
		4.71 (dt, J = 9, 9) 20%	4.44 (m) 80% tc				1.48 (s) 80%
17e	3.2–3.7 (m)	4.49 (dt, J = 9, 9) 50%	4.30 (m) 50% cc	3.2–3.7 (m)	1.8–2.7 (m)	7.4–8.0 (m)	1.44 (s) 50%
		4.52 (dt, J = 9, 9) 50%	4.39 (m) 50% tc				1.47 (s) 50%

[a] Spectra were recorded with a Bruker WH-270 spectrometer in $CDCl_3$ and chemical shifts (δ) are relative to internal tetramethyl silane. Coupling constants are in hertz. [b] All the other CH_2 absorb between δ 1.5 and 2.5, according to their structures. [c] Percent value refers to the relative abundance of the cis conformer (cc). [d] Percent value refers to the relative abundance of the trans conformer (tc). [e] dt = doublet of triplets; m = multiplet; s = singlet; ddd = doublet of doublets of doublets; d = doublet; br = broad; ddt = doublet of doublets of triplets.

reported in Table II.[21] Compounds **10f**(*R,S*), **16f**(*R,S*), **10g**(*R,S*), and **12g**(*S,S*) were active as ACE inhibitors in vivo. The peak effect was reached 15–30 min after iv injection, and it had completely disappeared after 120 min. The most interesting compounds, **10f**(*R,S*), **16f**(*R,S*), and **10g**(*R,S*) were $^1/_{30}$th as potent as captopril as ACE inhibitors. These compounds significantly reduced blood pressure in renal hypertensive dogs. The reduction in blood pressure was dose related over the same range (30–10 mg/kg) as for captopril. The effects of the compounds appeared to be long lasting, since their peak effects were reached about 5 h after treatment and hypotension was still present at the end of the observation period (7 h). Compounds **10f**(*R,S*), **16f**(*R,S*), and **10g**(*R,S*) have hypotensive effects comparable to that of captopril but a considerably lower in vivo ACE inhibition. This would suggest that their hypotensive activity may not be completely related to plasma ACE inhibition, as already hypothesized by Unger et al.[22]

In conclusion, compounds with a cyclopentane and cyclobutane ring are equipotent in vitro ACE inhibitors (**10g**(*R,S*) and **16g**(*R,S*). The in vivo inactivity of **16g**(*R,S*) in renal hypertensive dogs is not easily explainable in view of its good in vitro activity and of the similarity of its structure with the other analogues with the same configurations. It is possible that an unfavorable pharmacokinetic profile is responsible of this discrepancy. The compound **17f**(*S,R*) has the same activities as **16f**(*R,S*), at the highest dose only.

(21) Compounds that are not reported in this table were inactive in both the tests.

(22) Unger, T.; Gauten, D.; Lang, R. E. *TIPS* **1983**, 514.

Experimental Section

Melting points were measured with a Du Pont 990 thermal analyzer with a differential scanning calorimetric cell (DSC) and scan speed of 10 °C/min and are corrected. ^{1}H NMR spectra were obtained with a Bruker WH-270 spectrometer or on a Varian A-60 (VA60) when specified. Spectra were recorded in $CDCl_3$ and data are reported as δ values with respect to Me_4Si. IR spectra, obtained with a Perkin-Elmer 580 spectrophotometer, were recorded in $CDCl_3$ unless otherwise noted and data are reported in reciprocal centimeters. Low-resolution mass spectra were obtained with a Hitachi Perkin-Elmer RMU-6L mass spectrometer, using the direct insertion system. Optical activities, determined with a Perkin-Elmer 241 polarimeter, were recorded in $CHCl_3$. Preparative liquid chromtography was carried out in a Waters Prep LC/System 500 A instrument. Column chromatography was done on Merck 60 silica gel (70–230 mesh). Thin-layer chromatography (TLC) was used to monitor reactions and column fractions and to establish the homogeneity of products. TLC were run on Merck 60 F_{254} silica gel plates (0.25-mm thick). When elemental analyses are indicated only by symbols of the elements, the analytical results obtained were within ±0.4% of the theoretical values. Anhydrous $MgSO_4$ was used to dry organic extracts. NMR spectral data for compounds **10e**–**17e** are reported in Table III.

2-(Acetylthio)cyclopentanecarboxylic Acid (3a). A mixture of **2a** (22.4 g, 0.2 mol) and freshly distilled thioacetic acid (17.5 mL, 0.26 mol) was heated for 1 h on a steam bath, left at room

temperature for 15 h, and then concentrated under vacuum. Purification of the residue by column chromatography, with a mixture of hexane in Et_2O as eluent, gave 21 g (55.8%) of liquid **3a** as a 7:3 mixtue of trans–cis isomers: NMR δ 1.5–2.3 (6 H, m, 3 CH_2), 2.33–2.34 (3 H, 2 s, $COCH_3$), 2.79 (0.7 H, dt, J_{CH-CH} = 8.5 Hz, J_{CH-CH_2} = 7.5 Hz, CHCO, trans), 3.17 (0.3 H, dt, J_{CH-CH} = 8.5 Hz, J_{CH-CH_2} = 8 Hz, CHCO, cis), 3.49 (0.7 H, dt, J_{CH-CH_2} = 8 Hz, CHS, trans), 3.99 (0.3 H, dt, J_{CH-CH_2} = 8 Hz, CHS, cis), 9.1–10.5 (1 H, br, COOH); TLC (hexane–Et_2O, 7:3).

2-(Acetylthio)cyclohexanecarboxylic Acid (3b). With use of **2b** (9 g, 0.07 mol) as starting material and following the procedure described above, column chromatography gave 4.5 g of the starting material and 4 g (56.5%) of liquid **3b** as a 4:6 mixture of trans–cis isomers: NMR δ 1.3–2.2 (8 H, m, 4 CH_2), 2.32–2.33 (3 H, 2 s, $COCH_3$), 2.52 (0.4 H, ddd, J_{CH-CH} = 9 Hz, J_{CH-CH} = 9, 4 Hz, CHCO, trans), 2.85 (0.6 H, ddd, J_{CH-CH} = 4 Hz, J_{CH-CH_2} = 4, 9 Hz, CHCO, cis), 3.74 (0.4 H, ddd, J_{CH-CH} = 4, 9 Hz. CHS, trans), 4.12 (0.6 H, ddd, J_{CH-CH_2} = 6, 4 Hz, CHS, cis), 8.7–11.8 (1 H, br, COOH); TLC (hexane–Et_2O, 4:6).

1-[[2-(Acetylthio)cyclopentyl]carbonyl]-L-proline (5a). A solution of **3a** (20 g, 0.106 mol) in $SOCl_2$ (8.7 mL, 0.12 mol) was left at room temperature for 20 h. The reaction mixture was concentrated under vacuum and the residue was distilled under reduced pressure [bp 130–135 °C (2.8–4 mmHg)] to yield 17.4 g (79.2%) of **4a** as a liquid mixture of two isomers: NMR (VA60) δ 1.5–2.6 (6 H, m, 3 CH_2), 2.35 (3 H, s, $COCH_3$), 3.28 (1 H, dt, J_{CH-CH} = 8.5 Hz, J_{CH-CH} = 8 Hz, CHCO), 4.15 (1 H, dt, J_{CH-CH} = 8 Hz, CHS). Compound **4a** (16 g, 0.0774 mol) was added dropwise to a stirred solution, cooled to 0 °C, of L-proline (18 g, 0.156 mol) in 1 N NaOH (156 mL, 0.156 mol) and the reaction mixture was maintained at that temperature for 2 h. The ice bath was removed, and the mixture was stirred for 12 h and then acidified with concentrated HCl to about pH 1. The aqueous phase was extracted with Et_2O. The organic phase was washed with brine, dried, and concentrated to give 21 g (95%) of **5a** as a viscous oil: NMR δ 1.5–2.5 (10 H, m, 5 CH_2), 2.26–2.40 (3 H, m, $COCH_3$), 2.7–3.1 (1 H, m, CHCO), 3.3–3.8 (2 H, m, CH_2N), 3.9–4.2 (1 H, m, CHS), 4.5–4.8 (1 H, m, CHCOO), 7.8 (1 H, br, COOH); TLC (hexane–CH_2Cl_2–THF–CH_3COOH, 6:2:2:1).

1-[[2-(Acetylthio)cyclohexyl]carbonyl]-L-proline (5b). With use of **3b** (4 g, 0.02 mol) as the starting material and proceeding as described above, 3.9 g (88%) of liquid **4b** [bp 120 °C (0.3 mmHg)] was obtained: NMR δ 1.3–2.2 (8 H, m, 4 CH_2), 2.35 (3 H, s, $COCH_3$), 2.97 (0.4 H, dd, J_{CH-CH} = 9 Hz, J_{CH-CH2} = 4.9 Hz, CHCO, trans), 3.24 (0.6 H, dd, J_{CH-CH} = 4 Hz, J_{CH-CH_2} = 9, 4 Hz, CHCO, cis), 3.77 (0.4 H, dd, J_{CH-CH_2} = 9, 3.5 Hz, CHS, trans), 4.24 (0.6 H, dd, J_{CH-CH_2} = 4, 6 Hz, CHS, cis). With use of **4b** (3.7 g, 0.0168 mol) as the starting material and proceeding as described above, 5.0 g (98%) of **5b** was obtained as a viscous oil: NMR δ 1.3–2.24 (12 H, m, 6 CH_2), 2.29–2.31 (3 H, 2 s, $COCH_3$), 2.6–3.2 (1 H, m, CHCO), 3.5–4.2 (3 H, m, CH_2N and CHS), 4.4–4.7 (1 H, m, CHCOO), 7.16 (1 H, br, COOH).

1-[(2-Mercaptocyclopentyl)carbonyl]-L-proline (6a). A solution of **5a** (21 g, 0.0736 mol) in 5 N methanolic ammonia (215 mL) was stored at room temperature under argon for 5 h.[1b] The solution was concentrated. The residue was dissolved in water (250 mL), acidified with acetic acid (pH 5), and extracted with EtOAc. The combined organic phases were washed with brine, dried, and concentrated. The residue was converted to a DCHA salt in EtOAc and after cooling 30 g (96%) of the salt (mp 164–167 °C) was collected. Anal. ($C_{11}H_{17}NO_3S \cdot C_{12}H_{23}N$) C, H, N, S. The DCHA salt of **6a** (16 g, 0.0377 mol) was distributed between ethyl acetate and 5% aqueous $NaHSO_4$. The organic phase was dried and concentrated to give 7.2 g (78.5%) of **6a** as a resinous mixture of diastereoisomers: NMR δ 1.5–2.5 (11 H, m, 5 CH_2 and SH), 2.8–4.0 (4 H, m, CH_2N, CHCO, and CHS), 4.5–4.7 (1 H, m, CHCOO), 9.9 (1 H, br, COOH); MS (methyl derivative), m/z 257 [M^+·] (100), 225 [M – CH_3OH]$^+$·, 224 [M – SH ·]$^+$, 198 [M – $COOCH_3$]$^+$, 128 [M – ·C_6H_9SO]$^+$; TLC (hexane–CH_2Cl_2–THF–CH_3COOH, 6:2:2:1).

1-[(2-Mercaptocyclohexyl)carbonyl]-L-proline (6b). A solution of **5b** (5 g, 0.0167 mol) in 5 N methanolic ammonia (50 mL) was stored at room temperature under argon for 5 h. The solution was concentrated, and the residue was dissolved in water (40 mL), acidified with acetic acid (pH 5), extracted with EtOAc, dried, and concentrated to give 4.08 g (95%) of **6b**, as a resinous mixture of diastereoisomers: NMR δ 1.1–2.5 (13 H, m, 6 CH_2, SH), 2.8–4.0 (4 H, m, CH_2N, CHCO, CHS), 4.5–4.7 (1 H, m, CHCOO), 6.75 (1 H, br, COOH); MS (methyl derivative), m/z 271 [M^+·], 238 [M – ·SH]$^+$, 212 [M – ·$COOCH_3$]$^+$, 128 [M – ·$C_7H_{11}NO_2$]$^+$, 70 [C_4H_8N]$^+$ (100); TLC (hexane–CH_2Cl_2–THF–CH_3COOH, 6:2:2:1).

2-(Benzoylthio)cyclopentanecarboxylic Acid 8a and 9a. A solution of **2a** (210 g, 1.87 mol) in freshly distilled thiobenzoic acid (265 mL, 2.25 mol) was heated at 120 °C overnight under argon. After cooling, the mixture of trans–cis isomers (about 7:3)[23] was stirred in cyclohexane (1.6 L) and filtered to give a solid mixture of the trans isomer **8a** containing approximately 25% of the cis isomer **9a**. After several crystallizations from Et_2O this mixture yielded 129 g (27.6%) of the pure trans isomer **8a** as white crystals: mp 100 °C; IR (Nujol) 3500–2300 (OH), 1700 (acid, C=O), 1665 (thiol ester, C=O) cm^{-1}; NMR δ 1.7–2.5 (6 H, m, 3 CH_2), 3.0 (1 H, dt, J_{CH-CH} = 7.5 Hz, J_{CH-CH_2} = 7.5 Hz, CHCO), 4.27 (1 H, dt, J_{CH-CH_2} = 7.5 Hz, CHS), 7.4–8.1 (6 H, m, aromatics and COOH); MS, m/z 250 [M^+·], 236 [M – H_2O]$^+$·, 204 [M – HCOOH]$^+$·, 144 [M – C_7H_6O]$^+$ ·, 105 [M – C_6H_9S]$^+$ (100), 100 [144 – CO_2]$^+$·. Anal. ($C_{13}H_{14}O_3S$) C, H, S.

The mother liquors from these crystallizations were combined and concentrated to give 230 g of a 6:4 mixture of trans–cis isomers. These last were crystallized from Et_2O to give 130 g of 7:3 mixture of trans–cis isomers. The filtrate was concentrated, giving 94 g of trans–cis mixture of approximately the same amount. The mother liquors obtained from the treatment with cyclohexane were concentrated, and the residue was purified by column chromatography, using hexane with increasing amounts of Et_2O as eluent, giving 90 g of a trans–cis mixture in approximately equal amounts. The mixtures, containing the trans–cis isomers in equal amounts (1:1), were combined (184 g, 0.73 mol), dissolved in EtOAc (2.5 L), cooled to 5 °C, and treated with dicyclohexylamine (DCHA) (145 g, 0.8 mol). The resulting salt (314 g, 99%) was filtered and crystallized five times from EtOAc to give 99 g of DCHA salt of pure **9a** as white crystals: mp 175 °C. Anal. ($C_{13}H_{14}O_3S \cdot C_{12}H_{23}N$) C, H, N, S. The DCHA salt of **9a** (84 g, 0.195 mol) was distributed between EtOAc (1.5 L) and 5% aqueous $NaHSO_4$ (700 mL). The organic phase was dried and concentrated to give 35 g (72%) of **9a** as white crystals: mp 93.5 °C; IR (Nujol) 3500–2300 (OH), 1700 (acid, C=O), 1665 (thiol ester, C=O) cm^{-1}; NMR δ 1.7–2.2 (6 H, m, 3 CH_2), 3.26 (1 H, dt, J_{CH-CH} = 6 Hz, J_{CH-CH} = 6.5 Hz, CHCO), 4.19 (1 H, dt, J_{CH-CH} = 6.5 Hz, CHS), 7.4–8.0 (5 H, m, aromatics), 10.4–11.4 (1 H, br, COOH); MS, m/z 250 [M^+·], 105 [M – ·C_6H_9S]$^+$ (100), 77 [105 – CO]$^+$. Anal. ($C_{13}H_{14}O_3S$) C, H, S.

2-(Benzoylthio)-3,3-dimethylcyclopentanecarboxylic Acid (8c). A solution of **2c** (35 g, 0.25 mol) in freshly distilled thiobenzoic acid (48 mL, 0.41 mol) was heated at 120 °C under argon overnight. After cooling to room temperature the solid mixture was triturated with cyclohexane to give 32 g of pure **8c** with mp 131 °C. The mother liquors, after cooling in an ice bath, gave 5 g of **8c** with the same purity (53.16%). A small amount was crystallized from Et_2O: mp 131 °C; IR 3510, 3440–2300 (OH), 1740, 1710 (acid, C=O), 1665 (thiol ester, C=O) cm^{-1}; NMR δ 0.97–1.10 (6 H, 2 s, $C(CH_3)_2$), 1.5–2.3 (4 H, m, 2 CH_2), 2.93 (1 H, dt, J_{CH-CH} = 9 Hz, J_{CH-CH} = 9 Hz, CHCO), 4.17 (1 H, d, CHS), 7.2–8.2 (5 H, m, aromatics), 8.8–9.8 (1 H, br, COOH); MS, m/z 278 [M^+], 172 [M – C_7H_6O]$^+$·, 105 [M – ·$C_8H_{13}S$]$^+$ (100), 77 [105 – CO]$^+$; TLC (Et_2O). Anal. ($C_{15}H_{18}O_3S$) C, H, S.

2-(Benzoylthio)cyclobutanecarboxylic Acid 8d and 9d. A solution of **2d** (41.5 g, 0.42 mol) in freshly distilled thiobenzoic acid (83 mL, 0.71 mol) was heated at 100 °C under argon overnight. After cooling to room temperature, the mixture was triturated with cyclohexane to give a crude compound. Crystallization from Et_2O yielded 60.1 g (60.14%) of pure **8d** as white crystals: mp 106.5 °C; IR 3510, 3440, 2300 (OH), 1740, 1710 (acid, C=O), 1660 (thiol ester, C=O) cm^{-1}; NMR δ 2.1–2.6 (40 H, m, 2 CH_2), 3.32 (1 H, dt, J_{CH-CH} = 9 Hz, J_{CH-CH_2} = 9 Hz, CHCO), 4.5 (1 H, dt, J_{CH-CH} = 9 Hz, CHS), 7.4–8.0 (5 H, m, aromatics), 9.8–11.4 (1 H, br, COOH); MS, m/z 236 [M^+·], 218 [M – H_2O]$^+$·,

(23) Composition of the mixtures was roughly evaluated from the relative UV absorptions of the two spots on TLC (Et_2O–CH_2Cl_2, 2:8; **8a** more polar compound, **9a** less polar).

130 [M – C_7H_6O]$^{+\cdot}$, 105 [M – $\cdot C_5H_7O_2S$] (100), 86 [130 – CO_2]$^{+\cdot}$, 77 [105 – CO]$^+$; TLC (Et_2O). Anal. ($C_{12}H_{12}O_3S$) C, H, S.

The mother liquors from the treatment with cyclohexane were concentrated. The residue was purified by column chromatography with hexane and increasing amounts of Et_2O to give a solid mixture of **8d** and **9d** (24.7 g). Crystallization from cyclohexane yielded 5.3 g of pure **9d** (5.30%) as white crystals: mp 120 °C; IR 3510, 3460–2300 (OH), 1740, 1705 (acid, C=O), 1660 (thiol ester, C=O) cm^{-1}; NMR δ 2.2–2.6 (4 H, m, 2 CH_2), 3.65 (1 H, m, CHCO), 4.73 (1 H, ddd, J_{CH-CH} = 9 Hz, J_{CH-CH_2} = 9, 9 Hz, CHSCO), 7.42–7.93 (5 H, dd, dd, d, aromatics); MS, m/z 236 [M$^{+\cdot}$], 218 [M – H_2O]$^{+\cdot}$, 130 [M$^+$ – C_7H_6O]$^{+\cdot}$, 105 [C_7H_5O]$^+$ (100), 77 [C_6H_5]$^+$; TLC (Et_2O). Anal. ($C_{12}H_{12}O_3S$) C, H, S.

Procedure A. 1-[[2-(Benzoylthio)cyclopentyl]carbonyl]-L-proline 1,1-Dimethylethyl Ester 10e and 11e. Compound **8a** (10 g, 0.04 mol) was added to a stirred solution of L-proline 1,1-dimethylethyl ester (6.85 g, 0.04 mol) cooled to 0–5 °C and freshly distilled dicyclohexylcarbodiimide (8.25 g, 0.04 mol) in dry CH_2Cl_2 (55 mL). The reaction was allowed to proceed at 0–5 °C for 4 h and then overnight at room temperature. Dicyclohexylurea was filtered off and the filtrate was concentrated. The residue was purified by preparative liquid chroamtography, with EtOAc–hexane (25:75) as eluent, to give the two diastereoisomers. After trituration with hexane, the less polar fraction gave 6.8 g (42.1%) of **10e** and the more polar fraction gave 6.54 g (40.5%) of **11e** as white solid compounds.

Procedure B. 1-[[2-(Benzoylthio)cyclopentyl]carbonyl]-L-proline (10f). A solution of **10e** (11 g, 0.0273 mol), anisole (53 mL), and CF_3COOH (77 mL) was left to stand at room temperature for 5 h and monitored by TLC (hexane–CH_2Cl_2–Et_2O–CH_3COOH, 6:2:2:3). At the end the reaction mixture was concentrated under vacuum, and the residue was dissolved in EtOAc and extracted several times with saturated aqueous $NaHCO_3$. The aqueous phase was acidified with 10% HCl, saturated with NaCl, and extracted with EtOAc. The organic phase was dried and concentrated to a small volume, from which a white product was crystallized. Filtration gave 9 g (95%) of pure **10f**.

Procedure C. 1-[(2-Mercaptocyclopentyl)carbonyl]-L-proline (10g). Concentrated aqueous ammonium hydroxide (16.5 mL) was added to a stirred suspension of **10f** (9 g, 0.0259 mol) in water (25 mL) and the resulting solution was stirred under argon for 2 h at room temperature. At the end [as evidenced by TLC (hexane–CH_2Cl_2–Et_2O–CH_3COOH, 6:2:2:3] the reaction mixture was diluted with brine (100 mL), the precipitate of benzamide was filtered off, and the filtrate was washed with EtOAc, acidified with 10% HCl, and extracted with EtOAc. This organic phase was dried and concentrated. The residue was crystallized from Et_2O to yield 4.55 g (72.2%) of **10g** as white crystals.

3,3-Dimethyl-2-oxocyclopentanecarboxylic Acid Methyl Ester (18c). 2,2-Dimethylcyclopentanone (39.96 g, 0.357 mol) and MeOH (0.5 mL) were added dropwise to a stirred suspension of 65% NaH in mineral oil (15.37 g, 0.417 mol) in dimethyl carbonate (390 mL). The suspension was heated and a mild exothermic reaction started at 70 °C. The heating bath was removed and the temperature was maintained at 70–75 °C with an ice bath. When the exothermic reaction had finished, the reaction mixture was heated at 82 °C for 5 h and then cooled to 0 °C. MeOH (15 mL) was added dropwise, followed by CH_3COOH (28 mL). The resulting suspension was treated with water (200 mL) and extracted with CH_2Cl_2, the organic phase was dried and concentrated. The residue was distilled under reduced pressure [bp 105–113 °C (15 mmHg)] to give 48.6 g (79.5%) of **18c**: IR (neat) 1750 (ketone, C=O), 1730 (ester, C=O) cm^{-1}; NMR δ 1.08 (6 H, s, 2 CH_3), 1.5–2.6 (4 H, m, 2 CH_2), 3.23 (1 H, dd, J_{CH-CH_2} = 8, 9 Hz, CHCO), 3.70 (3 H, s, $COOCH_3$).

2-Hydroxy-3,3-dimethylcyclopentanecarboxylic Acid Methyl Ester (19c). A solution of **18c** (47 g, 0.28 mol) in MeOH (190 mL) was added at room temperature to a stirred solution of citric acid (27 g, 0.14 mol) and 95% NaOH pellets (5.5 g, 0.13 mol) in water (300 mL). Solid $NaBH_4$ (25 g, 0.75 mol) and citric acid (30 g) were added portionwise, each portion of the former being followed by a portion of the latter in order to maintain the pH between 5 and 6.5. When the addition was complete, the pH was adjusted to 6, the MeOH was distilled off in vacuo, and the solution was extracted with CH_2Cl_2. The combined organic phases were dried and concentrated, and the residue was distilled under reduced pressure [bp 60–65 °C (0.6 mmHg)] to give 38 g (79%) of **19c** as a mixture of isomers: IR (neat), 3550 (OH), 1735 (ester, C=O) cm^{-1}; NMR (VA60) δ 0.90–1.06 (6 H, 2 s, 2 CH_3), 1.3–2.3 (4 H, m, 2 CH_2), 2.8–3.3 (2 H, m, CHCO + OH), 3.75 (3 H, s, $COOCH_3$), 3.6–3.9 (1 H, m, CHO).

3,3-Dimethyl-1-cyclopentenecarboxylic Acid (2c). Compound **19c** (33 g, 0.192 mol) was poured over solid KOH (330 g) in a 1-L flask. The flask was frequently rotated to avoid accumulation of the liquid on the bottom. A moderate exothermic reaction took place and after 2 h complete solidification of the mass was observed. The reaction mixture was heated on an oil bath at 180 °C for 2 h and cooled, and water (700 mL) was added cautiously through a reflux condenser. Complete solution occurred within 1 h and the temperature of the solution rose to 60 °C. The solution was cooled to 0 °C, transferred to a 5-L beaker, and acidified (congo red) by stirring with concentrated HCl. The precipitate was filtered, washed with water (200 mL), and crystallized from water (3 L) to give 23 g (84%) of **2c** as white crystals: mp 67–69 °C; IR (Nujol) 3500–2100 (OH), 1690 (acid, C=O), 1635 (C=C) cm^{-1}; NMR δ 1.15 (6 H, s, 2 CH_3) 1.78 (2 H, t, $J_{CH_2-CH_2}$ = 8 Hz, CH_2C=), 2.63 (2 H, dt, J_{CH-CH_2} = 1.5 Hz, CH_2C=), 6.70 (1 H, t, CHC=), 11.63 (1 H, br, COOH). Anal. ($C_8H_{12}O_2$) C, H.

In Vitro ACE Inhibitory Activity. In vitro assays were adapted form the method of Poulsen et al.[24] and it was described previously.[25] To a plastic tube containing 12 μg of the test compound, 50 μL of dialyzed plasma and 10 μL of the Ab-AgII (antibody against angiotensin II) were added. The tube was incubated 30 min at 37 °C and the reaction was quenched by cooling at 0 °C. Fifty microliters of TAB (Tris-albumin buffer: 0.2 M Tris-HCl, pH 7.5, containing 0.3% bovine serum albumin) and 1 mL of the cold and labeled AgII (unlabeled AgII was purchased from NIBSC, Holly Hill, Hampstead, London NW3 6RB, England; labeled AgII was purchased from Ormonoterapia Richter, Cinisello, Milan, Italy) solution (ca. 100 pg of [^{125}I]AgII) were added, and then the mixture was left 18 h at 4 °C. After this 200 μL of a suspension of charcoal coated dextran was added and separated by centrifugation at 3000 rpm for 15 min at 2 °C. The supernatant was collected and counted in a solid scintillator gamma counter (Packard 5330). The AgII produced in the presence and in the absence (control) of the test compound was read off the curve for radioactivity. When a compound was active, scalar amounts were tested and the corresponding inhibition percentages calculated. IC_{50} values (concentration for 50% inhibition) were determined by plotting the inhibition percentage prohibits against log concentration over a 20–80% inhibition range.

In Vivo ACE Inhibitory Activity. The in vivo inhibitory activity was evaluated in conscious normotensive rats treated intravenously. Male Wistar rats from Charles River, weighing 300–350 g, were chronically implanted with aortic cannulae (for blood pressure monitoring) and femoral vein cannulae (for intravenous drug injection) under Nembutal (30 mg/kg) anesthesia. Three days later AI (0.3 μg/kg iv) was administered to conscious rats before and 5, 15, 30, 60, and 120 min after intravenous test drug administration. Each compound was evaluated in three rats. The maximum dose administered was 10 mg/kg. The postdrug AI responses were compared to the predrug AI responses. The significances of differences were calculated by the Student's t test. Blood pressure was recorded with a Statham P23Db pressure transducer connected to a Hewlett-Packard 7702 B recorder. A compound inducing less than a 10% reduction in the response was considered to be inactive.

Antihypertensive Activity in Dogs. The antihypertensive activity of the compounds was tested in conscious hypertensive mongrel dogs. The hypertension was induced by bilateral constriction of the renal arteries as described by Goldblatt.[26] The compounds were administered by gavage in gelatine capsules. Systolic blood pressure in the tail was measured by an indirect technique (W + WBP recorder 8005, Electronic Basel) before and

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1, 3, 5, and 7 h after treatment. A compound that induced a fall of the basal systolic pressure of less than 10% was considered to be inactive. Each compound was evaluated in three dogs. The significance of before and after treatment differences was calculated by the Dunnett's t test.

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Registry No. **2a**, 1560-11-8; **2b**, 636-82-8; **2c**, 80969-70-6; **2d**, 23519-90-6; (*cis*)-**3a**, 99343-45-0; (*trans*)-**3a**, 99343-46-1; (*cis*)-**3b**, 99343-47-2; (*trans*)-**3b**, 71551-06-9; (*cis*)-**4a**, 99343-48-3; (*trans*)-**4a**, 99343-49-4; (*cis*)-**4b**, 99343-50-7; (*trans*)-**4b**, 99355-29-0; **5a**, 80969-56-8; **5b**, 99396-52-8; **6a**, 80969-57-9; 6a·DCHA, 99571-76-3; **6b**, 99396-53-9; **7a**, 99343-51-8; **7c**, 99343-52-9; **7d**, 99343-53-0; (*trans*)-**8a**, 99343-54-1; (*trans*)-**8c**, 99343-55-2; **8d**, 99343-56-3; **9a**, 99397-53-2; 9a·DCHA, 99582-29-3; (*cis*)-**9d**, 99343-57-4; **10e**, 80969-61-5; **10f**, 80969-62-6; **10g**, 81024-74-0; **11e**, 81024-72-8; **11f**, 81024-73-9; **11g**, 81024-75-1; **12e**, 81024-76-2; **12f**, 81024-78-4; **12g**, 81024-80-8; **13e**, 80969-64-8; **13f**, 81024-77-3; **13g**, 81024-79-5; **14e**, 80969-66-0; **14f**, 80969-67-1; **14g**, 80969-71-7; **15e**, 81024-81-9; **15f**, 81024-82-0; **15g**, 81024-83-1; **16e**, 99343-58-5; **16f**, 80969-73-9; **16g**, 80969-74-0; **17e**, 99396-54-0; **17f**, 81024-84-2; **17g**, 81024-85-3; **18a**, 10472-24-9; **18c**, 80969-68-2; (*cis*)-**19a**, 933-92-6; (*trans*)-**19a**, 933-93-7; (*cis*)-**19c**, 99343-59-6; (*trans*)-**19c**, 99343-60-9; ACE, 9015-82-1; AcSH, 507-09-5; L-Pro, 147-85-3; L-Pro-OC$(CH_3)_2CH_3$, 2812-46-6; PhCOSH, 98-91-9.

Supplementary Material Available: ^1H NMR spectral data of **10–17f,g** and IR and mass spectral data of **10–17e–g** (6 pages). Ordering information is given on any current masthead page.

Synthesis and Antiviral Activity of Sulfonamidobenzophenone Oximes and Sulfonamidobenzamides

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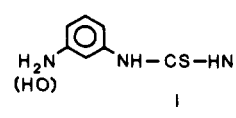
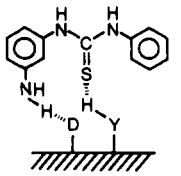
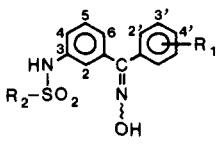
To find antiviral agents, various sulfonamidobenzophenone oximes (II) were synthesized from the appropriate *m*-sulfonamidobenzophenones by hydroxylamine reaction. The reaction products were generally obtained as syn/anti mixtures which were separable by fractional crystallization. The anti isomer had more potent antipoliovirus activity than the syn isomer. Various sulfonamidobenzamides (III) which were structurally related to II were synthesized by the reactions of amino-substituted benzamides with sulfuryl chloride or amines with (aminosulfonyl)benzoyl chloride. Antiviral activity was examined by the plaque-inhibition test. Compounds **5**, **36**, and **69** exhibited strong antipicornavirus activity. The structure–activity relationships are discussed.

m-Amino- and *m*-hydroxy-substituted diphenylthioureas (I) were reported to show antipicornavirus activity by Galabov et al.[1] Analysis of the realtionship between the chemical structure and antiviral activity in I revealed the existence of two active centers which bind the corresponding viral receptors by hydrogen bonds.[1] Our interest was directed to the synthesis of *m*-sulfonamidobenzophenone oximes (II) and *m*-sulfonamidobenzamides (III) with the partial structures of syn and anti isomers of 6-[(hydroxyimino)phenylmethyl]-1-[(1-methylethyl)-sulfonyl]-1*H*-benzimidazole-2-amine (IV),[2] which are virus-specific inhibitors of picornavirus multiplication.

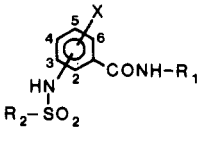


I

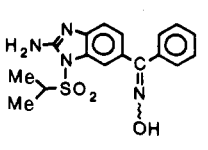




II



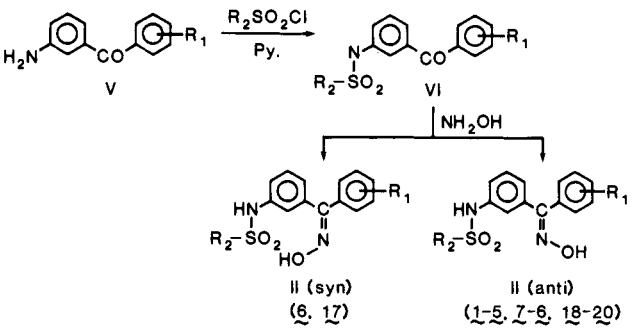
III



IV

In analogy to I, the oxime or the carbamoyl group and the sulfonamido group of II and III were expected to participate in hydrogen-bond formation with the virus-specific target. We thus prepared compounds of these sulfonamide series as shown in Scheme I and II.

Scheme I



Chemistry. The general synthetic routes for the preparation of II are illustrated in Scheme I. The starting *m*-aminobenzophenones (V) were prepared according to methods described in the literature.[3-11] *m*-Sulfonamidobenzophenone VI, prepared by the reaction of V with dimethylsulfamoyl chloride or isopropylsulfuryl chloride, was treated with hydroxylamine to obtain the desired *m*-sulfonamidobenzophenone oximes (II) (Scheme I). The

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