Angiotensin Converting Enzyme Inhibitors: Structure–Activity Profile of 1-Benzazepin-2-one Derivatives

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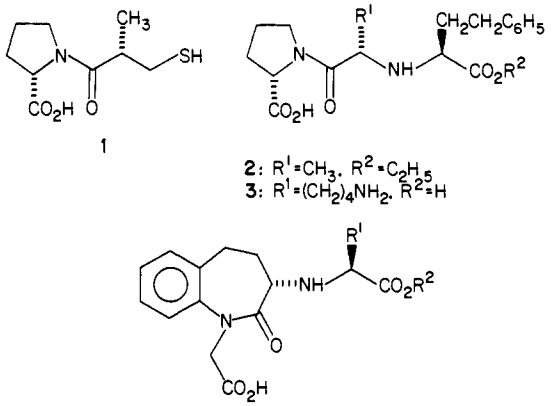
Received January 7, 1985

The preparation of a series of 3-amino-2-oxo-2,3,4,5-tetrahydro-1*H*-1-benzazepine-1-acetic acid derivatives **5a–y** by reductive amination of 2,3,4,5-tetrahydro-1*H*-1-benzazepine-2,3-dione (**7**) with L-amino acid derivatives is described. The compounds were tested for inhibition of angiotensin converting enzyme. The structure–activity profile of the series is discussed. Compound **5a** was especially potent when tested in dogs for inhibition of angiotensin I pressor response, having an ID_{50} = 0.07 mg/kg po.

Angiotensin converting enzyme (ACE) inhibitors such as captopril (**1**), enalapril (**2**), and lisinopril (**3**) are becoming increasingly important therapeutic agents for the treatment of hypertension and congestive heart failure.[1]



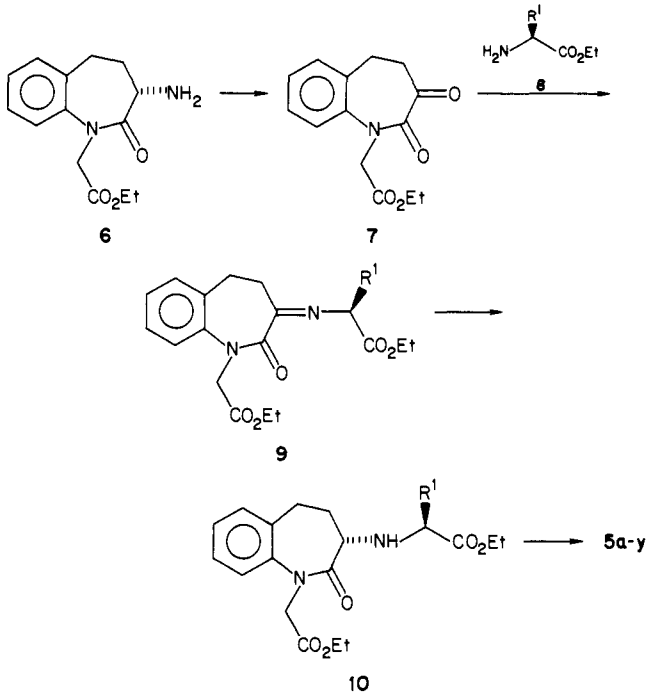
Investigation into the active conformation of these compounds has led to the discovery of 1-benzazepin-2-one derivative **4**, which possesses ACE inhibitory potency comparable to **2**.[2] On the basis of the activity of **4**, a study was carried out to elucidate the structure–activity profile of these bicyclic lactam derivatives. Herein the results of variation of the R^1 side chain on the bicyclic lactam ring system **5** are reported.

Chemistry. The desired compounds were prepared from amino lactam **6**.[2c] Oxidation with *tert*-butyl nitrite followed by *m*-chloroperbenzoic acid[3] gave dione **7**, which was converted to imine **9** by condensation with L amino esters **8** in the presence of di-*n*-butyltin dichloride.[4] Borch reduction of **9** afforded amino esters as a mixture of diastereomers, which could be separated by flash chromatography or preparative HPLC to yield **10**. Hydrolysis with 1 or 2 equiv of sodium hydroxide led to acid esters or diacids **5a–y**, respectively.

Results and Discussion

The compounds were tested in vitro for inhibition of ACE. As indicated in Table I, replacement of the phenylethyl group in **4** with a variety of side chains of L-amino acids or their derivatives resulted in compounds with potency comparable to **4**. On the basis of this finding, as well as data on a limited number of reported enalapril analogues,[6] it appears that the S_1 subsite of the ACE active site[7] does not have a very specific structural requirement. Previously reported results[6a] indicate that short side chains

Scheme I



(R^1 = H, Me, Et) result in reduced binding. The present work shows that alkyl, heteroalkyl, or aralkyl groups as

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0022-2623/85/1828-1603$01.50/0

Table I. 1-Benzazepin-2-one Derivatives **5a–y**[5]

compd	R^1	R^2	salt	mp,[a] °C	$[\alpha]_D$, deg (c)	ACE IC_{50}, nM
5a	$(CH_2)_4NH_2$[b]	H		179	−179 (1.0, H_2O)	7.0
5b	$(CH_2)_4NH_2$[c]	Et	HCl	85–87	−149 (0.75, MeOH)	40
5c	$(CH_2)_4NHCbz$[d]	H	HCl	216–218	−88 (1.3, MeOH)	13
5d	$(CH_2)_4NHCbz$[d]	Et	HCl	104–106	−113 (1.0, MeOH)	15
5e	$(CH_2)_4NHBoc$[e]	H		228–229	−142 (1.0, MeOH)	4.0
5f	$(CH_2)_4NHCOPh$	Et	HCl	107–109	−80 (1.0, MeOH)	
5g	CH_2OCH_2Ph[f]	H	HCl	168–170	+42 (1.0, MeOH)	10
5h	CH_2OCH_2Ph[f]	Et	HCl	198–201	+3.0 (1.0, MeOH)	
5i	CH_2SCH_2Ph	H		213–215	−207 (1.0, DMF)	2.9
5j	CH_2SCH_2Ph[f]	Et	HCl	183–185	−13 (1.1, EtOH)	
5k	$CH_2SCH_2CH_2Ph$	H		197–199	−46 (0.8, DMF)	7.0
5l	CH_2SPh	H		206–208	−111 (0.7, DMF)	4.0
5m	CH_2SPh[f]	Et	HCl	120–126	+59 (0.8, EtOH)	
5n	CH_2Ph	H		229–231	−134 (0.7, EtOH)	8.5
5o	CH_2Ph	Et	HCl	130–135	−135 (1.1, EtOH)	
5p	CH_2-3-indolyl[f]	H		195–200		13
5q	CH_2-3-indolyl[f]	Et	HCl	148	+24 (1.1, EtOH)	540
5r	CH_2CHMe_2	H		248–249		45
5s	CH_2CHMe_2	Me	HCl	206–207	−179 (1.3, EtOH)	1000
5t	*n*-Bu	H		251–252		5.0
5u	*n*-Bu	Et	HCl	215–216	−152 (1.0, EtOH)	2600
5v	$(CH_2)_2SMe$	H		236		6.5
5w	$(CH_2)_2SMe$	Et	HCl	196–197		
5x	*n*-Pr	H		269	−274 (1.3, NH_4OH)	6.0
5y	*n*-Pr	Et	HCl	204–205	−180 (1.2, EtOH)	
4						g
1						15[h]
2						4.5[i]

[a] All compounds had satisfactory C, H, and N elemental analyses and exhibited IR and NMR spectra consistent with the structure. [b] Prepared by hydrogenation of **5c**. [c] Prepared by hydrogenation of **5d**. [d] Cbz = CO_2CH_2Ph. [e] Boc = CO_2Bu-*t*. [f] Diastereomeric mixture at 3-benzazepine position. [g] IC_{50} of diacid = 1.7 nM. [h] Literature[11] IC_{50} = 23 nM. [i] Value for the corresponding diacid; literature value[6a] 1.2 nM.

Table II. In Vivo Biological Results

compd	rat AI[a] ID_{50}, mg/kg po	SHR[b] max ΔBP, mm (mg/kg po)	dog AI[c] ID_{50}, mg/kg po
5a	1.7 (1.3–2.4)[d]	−69 (30)	0.07 (0.03–0.12)[d]
4	0.10 (0.02–0.22)[d]	−50 (3.0)	0.25[e]
2[f]	0.14 (0.080–0.20)[d]	−54 (3.0)	0.15[e]

[a] Tabulated results indicate oral dose of test compound needed to produce 50% inhibition of angiotensin I pressor response in normotensive rats. [b] Tabulated results indicte maximal change in blood pressure recorded during the 4-day test period in spontaneous hypertensive rats. [c] Tabulated results indicate oral dose of test compound needed to produce 50% inhibition of angiotensin I pressor response in normotensive dogs. [d] 95% confidence limits. [e] Nonlinearity of dose–response curve did not allow the determination of 95% confidence limits. [f] Literature[9] rat AI ID_{50} = 0.28 mg/kg po; SHR max = −35 (1.0 mg/kg po) and dog AI ID_{50} = 0.096 mg/kg po.

short as in **5x**, as long as in **5d**, or as bulky as in **5e** provide effective substrates for binding to ACE.

During the primary in vivo testing of **5a** at 3 mg/kg po for inhibition of angiotensin I (AI) pressor response in rats, it was noted that, although not especially potent, **5a** produced increasing inhibition over the 4-h test period. Since this observation suggested that **5a** might have a slow onset but long duration of action, further testing was carried out. The key in vivo results are summarized in Table II.[8] It should be noted that 60–70% of the antihypertensive effect of **5a** was sustained for 24 h at a dose of 30 mg/kg po in the spontaneous hypertensive rat (SHR). Furthermore, **5a** was found to be especially potent when administered orally to normotensive dogs. With an ID_{50} of 0.07 mg/kg po, **5a** was more potent than **4** or **2**, which had ID_{50}'s of 0.25 and 0.15 mg/kg po, respectively. As was observed in rats, **5a** had a slow onset of activity in dogs, taking 1–2 h after oral dosing for appreciable AI response inhibition to occur. In conclusion, **5a** appears to have good ACE activity in rats and dogs with an indication of a long duration of action. It is of interest that **5a** has good in vivo activity without the requirement of an ester function to improve absorption. In this regard, it is reminiscent of lisinopril.[1g,h]

Experimental Section

Proton NMR spectra were determined on a Varian EM-390, Varian XL-100, or Perkin-Elmer R-600 spectrometer with Me_4Si as the internal standard. Infrared spectra were recorded on a Perkin-Elmer Model 457, Perkin-Elmer Model 137, or Perkin-Elmer Model 521 spectrophotometer. Optical rotations were measured with a Perkin-Elmer Model 141 or Perkin-Elmer Model

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241 polarimeter. Melting points were taken on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Mass spectra were recorded on an A.E.I. MS 902 spectrometer. All compounds were prepared by methods identical with those described below. Intermediate products were used directly without further purification. The experimental details for the biological tests have been described previously.[10]

1-[(Ethoxycarbonyl)methyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepine-2,3-dione (7). A solution of 3-amino-1-[(ethoxycarbonyl)methyl]-2,3,4,5-tetrahydro-1*H*-1-benzazepin-2-one (**6**)[2c] (8.0 g, 30.5 mmol), acetic acid (0.4 mL), and *tert*-butyl nitrite (4.5 mL) in $CHCl_3$ (150 mL) was refluxed for 2.5 h. The reaction mixture was cooled to 0 °C, and *m*-chloroperbenzoic acid (6.0 g, 34.7 mmol) was added in four portions. After stirring at room temperature for 45 min, the reaction mixture was washed with saturated $NaHCO_3$ (3 × 200 mL) and saturated NaCl (200 mL). The organic phase was dried (Na_2SO_4) and evaporated, and the product was crystallized from ethyl acetate (100 mL) to give **7** (5.5 g, 70%): mp 118–119 °C; NMR ($CDCl_3$) δ 1.28 (3 H, t, *J* = 7 Hz), 3.18 (4 H, m), 4.21 (2 H, q, *J* = 7 Hz), 4.62 (2 H, s), 7.35 (4 H, m); IR ($CHCl_3$) 3065, 2945, 1747, 1728, 1667, 1607, 1420, 1225 cm^{-1}. Anal. ($C_{14}H_{15}NO_4$) C, H. N.

3(*S*)-[[(1*S*)-5-Amino-1-carboxypentyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepine-1-ethanoic Acid Monohydrate (5a) from 7 via 5c.[12] A solution of **7** (35.3 g, 0.135 mol), N^{ϵ}-(benzyloxycarbonyl)-L-lysine methyl ester (39.7 g, 0.136 mol), and di-*n*-butyltin dichloride (2.28 g, 7.5 mmol) in 800 mL of $CHCl_3$ was refluxed with water separation for 4.5 h. The reaction mixture was concentrated to give crude imine (82.7 g), used without further purification.

To the above imine in 1.5 L of MeOH and 64 mL of acetic acid was added $NaBH_3CN$ (62.8 g, 0.137 mol) in portions over 1 h. The reaction mixture was stirred at room temperature overnight and evaporated. The residue in 300 mL of H_2O was adjusted to pH 10 with concentrated NH_4OH and extracted with 3 × 250 mL of CH_2Cl_2. The organic portions were washed with 100 mL of saturated NaCl, dried ($MgSO_4$), and evaporated to give an oil (74.7 g). Purification using preparative HPLC (Waters 500A Prep LC using 2 Prep Pak 500 columns and 3:2 toluene–ethyl acetate as eluting solvent) gave the less polar *R,S* isomer (35.1 g) and the more polar *S,S* isomer (22.6 g, 39.2%); NMR (Me_2SO-d_6) δ 1.13 (3 H, t, *J* = 7 Hz), 1.33 (4 H, m), 1.75–2.45 (4 H, m), 3.07 (5 H, m, 1 exchangeable H), 3.45 (3 H, s), 4.05 (2 H, m), 4.18 (2 H, q, *J* = 7 Hz), 4.59 (2 H, AB q, *J* = 2, 18 Hz), 5.06 (2 H, s), 7.35 (5 H, m), 7.41 (5 H, s).

A solution of the above diester (22.6 g, 42.0 mmol) in 580 mL of MeOH and 84 mL of 1 N aqueous NaOH was stirred at room temperature for 19 h and evaporated. The residue in 300 mL of H_2O was washed with 2 × 300 mL of diethyl ether. The aqueous layer was adjusted to pH 2.0 with 12 N HCl, producing a precipitate. The product was collected by filtration, washed with 25 mL of H_2O, and dried at 80 °C to give **5c**·HCl (16.3 g, 78%): mp 216–218 °C; $[\alpha]_D$ −88° (*c* 1.3, MeOH); NMR (Me_2SO-d_6) δ 1.38 (6 H, m), 1.78–2.75 (4 H, m), 2.80–3.50 (4 H, m), 4.54 (2 H, AB q, *J* = 7, 20 Hz), 5.05 (2 H, s), 7.33 (5 H, m), 7.41 (5 H, s), 8.48 (4 H, br s). Anal. ($C_{26}H_{31}N_3O_7$·HCl) C, H. N.

To a solution of **5c** (3.77 g, 7.60 mmol) in 800 mL of 80% aqueous EtOH was added 0.50 g of 10% Pd/C. The mixture was hydrogenated at room temperature under 3 atm of pressure for 40.5 h, filtered through Celite, treated with activated charcoal, filtered, and evaporated. The residue was taken up in and evaporated from toluene (3 × 200 mL) to produce a white powder, which was dried to vacuo overnight at 80 °C to give **5a** monohydrate (2.47 g, 86%): mp 179 °C (dec); $[\alpha]_D$ −179° (*c* 1.0, H_2O); NMR (D_2O) δ 1.62 (6 H, m), 2.11–3.15 (4 H, m), 3.52 (1 H, m), 3.84 (1 H, m), 4.45 (2 H, q, *J* = 18 Hz), 7.39 (4 H, s); IR (Nujol) 3450, 3090, 2990, 2700, 1680, 1665, 1620, 1530, 1478, 1382 cm^{-1}. Anal. ($C_{18}H_{27}N_3O_6$) C, H. N.

3-[[(1*R*)-2-(Benzylthio)-1-(ethoxycarbonyl)ethyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepine-1-ethanoic Acid Hydrochloride (5j).[5,12] To a solution of **7** (5.0 g, 19.0 mmol) were added (*S*)-benzyl-L-cysteine ethyl ester (4.4 g, 19.0 mmol) and di-*n*-butyltin dichloride (0.35 g, 1.0 mmol) in $CHCl_3$ (250 mL), and the solution was refluxed for 16 h with a water separator. The solvent was evaporated to give 11.0 g of crude imine **9** (R^1 = CH_2SCH_2Ph), which was used without further purification. The imine (11.0 g) was dissolved in MeOH (250 mL) and acetic acid (45 mL). $NaBH_3CN$ (1.4 g, 23.0 mmol) was added, and the reaction mixture was stirred at room temperature for 16 h. Concentrated HCl (15 mL) was added, and the reaction mixture was stirred 1 h and evaporated. The residue was dissolved in 500 mL of 10% NH_4OH and extracted with 3 × 200 mL of ether. The combined ether portions were washed with 200 mL of saturated NaCl, dried (Na_2SO_4), and evaporated to give 7.2 g of crude amine, which was purified by flash column chromatography using 200 g of 70–230 mesh silica gel and 20% ethyl acetate in toluene as the eluting solvent to give **10** (R^1 = CH_2SCH_2Ph) (3.8 g, 41% overall from **7**) as a mixture of diastereomers: NMR ($CDCl_3$) δ 1.20 (6 H, t, *J* = 7 Hz), 2.28 (6 H, m), 3.30 (3 H, m), 3.70 and 3.80 (2 H, s, SCH_2Ph), 4.20 (4 H, q, *J* = 7 Hz), 4.55 (2 H, m), 7.30 (9 H, m); IR (Nujol) 1730, 1650 cm^{-1}.

A solution of **10** (R^1 = CH_2SCH_2Ph) (1.0 g, 2.0 mmol) in EtOH (30 mL) containing 2 N aqueous KOH (1.0 mL, 2.0 mmol) was stirred at room temperature for 16 h and evaporated. The residue in 30 mL of H_2O was washed with 30 mL of diethyl ether. The aqueous layer was adjusted to pH 2.0 with 6 N HCl and extracted with 3 × 25 mL of ethyl acetate. The combined ethyl acetate portions were dried (Na_2SO_4), evaporated, redissolved in 75 mL of CH_2Cl_2, saturated with HCl gas, and evaporated. The residue was crystallized from ether or give **5j**·HCl (250 mg, 25%): mp 183–195 °C; $[\alpha]_D$ 13° (*c* 1.1, EtOH). HPLC analysis using a Whatman ODS-3 reversed-phase column and 25% H_2O in MeOH containing 0.025% HOAc showed the product to be a 1:1 mixture of diastereomers: NMR (Me_2SO-d_6) δ 1.15 (3 H, d of t), 2.15–2.95 (4 H, m), 3.05–3.35 (1 H, m), 3.48–4.20 (5 H, m), 4.50 (2 H, m), 7.35 (11 H, m, 2 exchangeable H); IR (Nujol) 1735, 1680 cm^{-1}; MS (*m/e*) M^+ 456 (2), 190 (28), 319 (100), 91 (90). Anal. ($C_{24}H_{28}N_2O_5S$·HCl) C, H, N.

3(*S*)-[[(1*R*)-2-(Benzylthio)-1-carboxyethyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-benzazepine-1-ethanoic Acid (5i).[12] A solution of **10** (R^1 = CH_2SCH_2Ph) (2.1 g, 4.6 mmol) in MeOH (30 mL) containing 2 N aqueous NaOH (4.8 mL, 9.6 mmol) was stirred at room temperature for 16 h and evaporated. The residue in 100 mL of H_2O was washed with ethyl acetate (100 mL). The aqueous layer was adjusted to pH 3.0 with 12 N HCl. Fractional crystallization gave **5i** (500 mg, 27): mp 213–215 °C; $[\alpha]_D$ −207° (*c* 1.0, DMF); NMR (Me_2SO-d_6) δ 2.22 (6 H, m), 3.28 (3 H, m), 3.67 (2 H, s), 4.54 (2 H, s), 7.28 (12 H, m, 3 exchangeable protons). Anal. ($C_{22}H_{24}N_2O_5S$) C, H, N. Analytical HPLC of this sample using a Whatman ODS-3 reversed-phase column and 15% H_2O in MeOH with 0.025% acetic acid indicated only one isomer. The remaining material from the mother liquor contained both diastereomers by HPLC.

3(*S*)-[[1(*S*)-(Ethoxycarbonyl)butyl]amino]-2,3,4,5-tetrahydro-2-oxo-1*H*-1-benzazepine-1-ethanoic Acid Monohydrochloride (5y).[5,12] A solution of **7** (36.0 g, 0.138 mol), ethyl 2-amino-L-butyrate (20.0 g, 0.138 mol), and di-*n*-butyltin dichloride (2.0 g, 6.9 mmol) in 500 mL of $CHCl_3$ was refluxed with H_2O separation for 3 h. The reaction mixture was evaporated, the residue was taken up in 500 mL of MeOH, and 3 mL of acetic acid and $NaBH_3CN$ (8.7 g, 0.138 mol) were added. The reaction mixture was stirred 3 days at room temperature, 50 mL of 12 N HCl was added, and the reaction mixture was stirred 1 h and evaporated. The residue was suspended in 200 mL of H_2O, made alkaline by addition of concentrated NH_4OH, and extracted with 3 × 200 mL of ethyl acetate. The organic portions were dried (K_2CO_3) and evaporated to give 47.2 g of oil, by TLC (ether, R_f 0.15, 0.20) an approximately 1:1 mixture of diastereomers. The mixture was separated by preparative HPLC (70:30 toluene–ethyl acetate) to give 25.8 g of the less polar *R,S* diastereomer and 17.5 g of the desired isomer **10** (R^1 = *n*-Pr) as an oil: NMR ($CDCl_3$) δ 0.89 (3 H, t, *J* = 7 Hz), 1.10 (3 H, t, *J* = 7 Hz), 1.22 (3 H, t, *J*

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(12) The configuration at the newly created center was assigned on the basis of the biological activity of the product and/or products derived therefrom.

= 7 Hz), 1.45 (4 H, m), 2.12 (2 H, m), 2.55 (2 H, m), 3.20 (3 H, m), 4.03 (2 H, q, J = 7 Hz), 4.23 (2 H, q, J = 7 Hz), 4.59 (AB q, J = 10, 18 Hz), 7.29 (4 H, m).

To **10** (R^1 = n-Pr) (9.0 g, 23 mmol) in 90 mL of EtOH at 0 °C was added a solution of NaOH (830 mg, 21 mmol) in 10 mL of H_2O over 30 min. The reaction was stirred for 3 h at room temperature and evaporated. The residue in 200 mL of H_2O was extracted with 200 mL of diethyl ether. The aqueous layer was acidified to pH 4.3 with 1 N HCl and extracted with 2 × 200 mL of ethyl acetate. The combined ethyl acetate portions were dried (Na_2SO_4) and evaporated to give 6.3 g of a foam. A solution of the foam in 200 mL of CH_2Cl_2 was acidified by bubbling in HCl gas, evaporated, and crystallized from 3-pentanone to give 5.8 g of **5y**·HCl; mp 204–205 °C; $[\alpha]_D$ −180° (c 1.2, EtOH); NMR ($CDCl_3$) δ 0.82 (3 H, t, J = 7 Hz), 1.07 (3 H, t, J = 7 Hz), 1.40 (2 H, m), 1.82 (2 H, m), 2.45 (4 H, m), 3.28 (1 H, m), 3.98 (1 H, m), 4.02 (2 H, q, J = 7 Hz), 4.67 (2 H, s), 7.38 (4 H, s), 10.6 (2 H, br s); IR (Nujol) 3350, 3175, 2950, 2620, 2512, 1740, 1720, 1660, 1535, 1465, 1378, 1212 cm^{-1}. Anal. ($C_{19}H_{27}N_2O_5Cl$) C, H. N.

Acknowledgment. The authors express their thanks to Drs. H. W. Gschwend and H. B. Renfroe for their encouragement and support of this work, Drs. B. Petrack and J. Norman, J. Ansell, and H. Hankin for the biochemical data, Drs. F. Goodman, M. Zimmerman, and B. E. Watkins, D. Miller, and R. A. Dotson for the in vivo biological data, L. Raabis for the NMR spectra, M. Brzechffa for the mass spectral data, G. Robertson and R. Oekinghaus for microanalyses, and M. Makar for typing the manuscript.

Registry No. **5a**, 97878-35-8; **5b**, 97878-67-6; **5b**·HCl, 97878-49-4; **5c**, 95384-35-3; **5c**·HCl, 94793-91-6; **5d**, 97878-68-7; **5d**·HCl, 95384-40-0; **5e**, 97878-50-7; **5f**·HCl, 95384-34-2; (*S,S*)-**5g**, 97878-69-8; (*R,S*)-**5g**, 97878-70-1; (*S,S*)-**5g**·HCl, 97878-51-8; (*R,S*)-**5g**·HCl, 97878-52-9; (*S,S*)-**5h**·HCl, 97878-53-0; (*R,S*)-**5h**·HCl, 97878-54-1; (*S,R*)-**5i**, 95384-22-8; (*R,R*)-**5i**, 97878-41-6; (*S,R*)-**5i**·HCl, 97878-42-7; (*R,R*)-**5i**·HCl, 97878-43-8; (*S,R*)-**5j**, 97878-37-0; (*R,R*)-**5j**, 97878-38-1; (*S,R*)-**5j**·HCl, 97878-39-2; (*R,R*)-**5j**·HCl, 97878-40-5; **5k**, 95384-23-9; **5l**, 95384-24-0; (*S,R*)-**5m**·HCl, 95384-30-8; (*R,R*)-**5m**·HCl, 97878-55-2; **5n**, 97878-56-3; **50**·HCl, 97878-57-4; (*S,S*)-**5p**, 97878-59-6; (*R,S*)-**5p**, 97878-58-5; (*S,S*)-**5q**, 97889-70-8; (*R,S*)-**5q**, 97889-71-9; (*S,S*)-**5q**·HCl, 97878-60-9; (*R,S*)-**5q**·HCl, 97878-61-0; **5r**, 97878-62-1; **5s**, 97878-71-2; **5s**·HCl, 97878-63-2; **5t**, 97878-64-3; **5u**, 97878-72-3; **5u**·HCl, 97878-65-4; **5v**, 95384-25-1; **5w**·HCl, 95384-32-0; **5x**, 97878-66-5; **5y**, 97878-47-2; **5y**·HCl, 97878-48-3; (±)-**6**, 88391-85-9; **7**, 88372-49-0; **8** (R^1 = $(CH_2)_4NHCl_2$ z, methyl ester), 1155-64-2; **8** (R^1 = SCH_2Ph), 953-18-4; **8** (R^1 = n-Pr), 39256-85-4; **9** (R^1 = $(CH_2)_4NHCb$ z, methyl ester), 97878-34-7; **9** (R^1 = CH_2SCH_2Ph), 97878-36-9; **9** (R^1 = n-Pr), 97878-44-9; (*S,S*)-**10** (R^1 = $(CH_2)_4NHCbz$, methyl ester), 94811-71-9; (*R,S*)-**10** (R^1 = $(CH_2)_4NHCbz$, methyl ester), 95102-10-6; (*S,R*)-**10** (R^1 = SCH_2Ph), 95393-15-0; (*R,R*)-**10** (R^1 = SCH_2Ph), 95384-21-7; (*S,S*)-**10** (R^1 = n-Pr), 97878-46-1; (*R,S*)-**10** (R^1 = n-Pr), 97878-45-0; ACE, 9015-82-1.

Angiotensin Converting Enzyme Inhibitors: N-Substituted D-Glutamic Acid γ Dipeptides†

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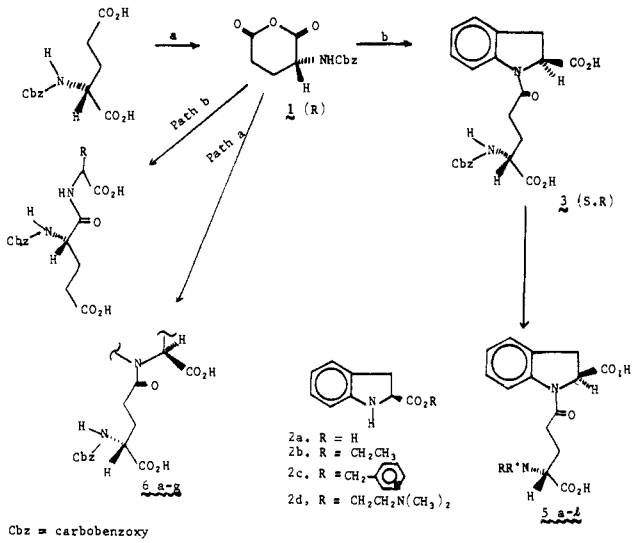
Received September 25, 1984

The preparation of two series of *N*-carbobenzoxy-γ-D-glutamyl secondary 2*S* amino acids and (N-substituted γ-D-glutamyl)indoline-2(*S*)-carboxylic acid dipeptides is described. In vitro inhibition of angiotensin converting enzyme (ACE) is reported for each compound, and the structure–activity relationship is discussed. Oral and iv inhibition of AI pressor response in vivo of selected compounds in Table II is also discussed. The most potent compounds in vitro, **3** and **6a**, had an ACE IC_{50} of 7 and 2.7 × 10^{-9} M, respectively.

Since the pioneering work of the Squibb group[1] numerous reports[2] on angiotension converting enzyme (ACE) inhibitors have appeared. Clinical studies[3] have shown ACE inhibitors to be useful in the treatment of hypertension. Bearing in mind the basic stereochemical and active-site model developed from a number of carboxyalkyl tripeptides and 2,4-disubstituted glutaric acid dipeptides, the effects of varying substituents within subsites for this model using D-glutamic acid as the backbone was investigated. Specifically, the importance of the S_2' and S_1, binding sites[4] in the absence of a S_1' site substituent was looked at by varying the substituent on the glutamyl nitrogen and by varying the C-terminal amino acid of the dipeptide.

Chemistry. D-Glutamic acid was converted to *N*-Cbz-glutamic anhydride (**1**) by a previously described[5] procedure. The literature[6] suggests that nucleophilic opening of **1** with amino acids (esters) affords mixtures of α- and γ-dipeptides, with the former predominating. However, the reaction of **1** with secondary amino acids in pyrridine afforded γ-dipeptides (path a), which provided a series of compounds **3** and **6a–g** listed in Table I, while reaction with primary amino acids gave predominantly α-dipeptides (path b, Scheme I).

Scheme I[a]



[a] Reagents: (a) Ac_2O; (b) **2a**, pyridine, 50 °C.

†Ksander, G. M., paper presented in part at the 19th National Medicinal Chemistry Symposium, Tuscon, AZ, June 1984.

0022-2623/85/1828-1606$01.50/0