In conclusion, we have shown that ester-prodrug methodology can be a useful method for increasing a drugs ability to pass the blood-brain barrier. These results have led to a better understanding of the factors controlling the brain penetration of 6,7-ADTN.

Experimental Section

Melting points were determined in open glass capillaries on a Büchi Tottoli apparatus and are uncorrected. Elemental analyses were performed in the Department of Chemistry, University of Groningen. Where elemental analyses are indicated, results obtained were within ±0.4% of the theoretical values. Infrared spectra were run on a Beckman Acculab 2. Mass spectra were obtained using a Finnigan 3300.

2-Amino-6,7-diacetoxy-1,2,3,4-tetrahydronaphthalene Hydrobromide (1). Under a nitrogen atmosphere, 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene hydrobromide[9] (0.520 g, 0.002 mol) was added to a solution of acetyl bromide (0.786 g, 0.0064 mol) in trifluoroacetic acid (8.0 mL). The solution was stirred at room temperature for 1.5 h. The excess acetyl bromide and trifluoroacetic acid was then removed under reduced pressure, and 50 mL of dry ether was added. The resulting white precipitate was filtered off to yield 0.570 g (83%) of the HBr salt. After crystallization from methanol–ether, a white crystalline solid was obtained: mp 198–199.5 °C; IR (KBr) 1755 (C=O) cm^{-1}; MS, m/e 263 (M^+). Anal. ($C_{14}H_{17}NO_4$·HBr) C, H, N, Br.

2-Amino-6,7-bis(isobutyryloxy)-1,2,3,4-tetrahydronaphthalene Hydrobromide (2). Under a nitrogen atmosphere, 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene hydrobromide[9] (0.520 g, 0.002 mol) was added to a solution of isobutyryl chloride (0.680 g, 0.0064 mol) in trifluoroacetic acid (8.0 mL), and using the same general procedure as above, 0.640 g (80%) of a white HBr salt was obtained. Crystallization from methanol–ether produced a white crystalline solid: mp 210–211 °C; IR (KBr) 1765 (C=O) cm^{-1}; MS, m/e 319 (M^+). Anal. ($C_{18}H_{25}NO_4$·HBr) C, H, N, Br.

2-Amino-6,7-bis(pivaloyloxy)-1,2,3,4-tetrahydronaphthalene Hydrobromide (3). When the same general method was used, 2-amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene hydrobromide[9] (0.520 g, 0.002 mol) and pivaloyl chloride (0.770 g, 0.0064 mol) in trifluoroacetic acid (8 mL) yielded, after workup, 0.520 g (61%) of a white crystalline solid, mp 275–276 °C; IR (KBr) 1755 (C=O) cm^{-1}; MS, m/e 347 (M^+). Anal. ($C_{20}H_{29}NO_4$·HBr) C, H, N, Br.

2-Amino-6,7-bis(benzoyloxy)-1,2,3,4-tetrahydronaphthalene Maleate (4). 2-Amino-6,7-dihydroxy-1,2,3,4-tetrahydronaphthalene hydrobromide[9] (1.0 g, 0.0038 mol) and benzoyl bromide (2.26 g, 0.0122 mol) in trifluoroacetic acid (12 mL) under the above standard reaction conditions yielded an oily semisolid HBr salt that could not be induced to crystallize. This material was dissolved in 50 mL of water and carefully made basic to litmus paper by the addition of 1 N $NaHCO_3$. This solution was then extracted with ether (4 × 150 mL), and the ether extract was then dried over anhydrous $MgSO_4$. The dried ether extract was then evaporated under reduced pressure to yield an oil. An equivalent amount of maleic acid in isopropyl acetate was added to the oil, and this produced a white solid: 1.60 g (82.5%). The maleate was crystallized from methanol–ether to produce a white crystalline solid: mp 148–150 °C; IR (KBr) 1740 (C=O) cm^{-1}; MS, m/e 387 (M^+). Anal. ($C_{24}H_{21}NO_4$·$C_4H_4O_4$) C, H, N.

Neurochemistry. Female Wistar albino rats (C.D.L. Groningen) weighing 150–200 g were used in all experiments. They were injected with solutions of the prodrugs prepared in a mixture of polyethylene glycol 400–ethanol–water (4:3:3, v/v). After various time intervals, the rats were sacrificed, their brains were removed, and the corpus striatum and cerebellum were dissected on dry ice. Tissue samples were then stored at −80 °C until assayed for 6,7-ADTN and 6-hydroxy-7-methoxy-2-aminotetralin levels. Details of the experimental procedure for the isolation and subsequent analysis of these two substances using an HPLC C_{18} reverse-phase chromatography system linked to a rotating electrochemical detector have already been published.[7,8,11] All reported values have been corrected for recovery, which was determined by spiking brain samples from untreated rats.

Angiotensin Converting Enzyme Inhibitors: Modifications of a Tripeptide Analogue

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Modified nonhydrolyzable tripeptide analogues of (*S*)-1-[5-(benzoylamino)-1,4-dioxo-6-phenylhexyl]-L-proline (1), designed to impart oral angiotensin converting enzyme (ACE) inhibitory activity, were made and evaluated in vivo and in vitro. The *N*-methyl and C_5-methyl analogues of 1 were inactive. Insertion of heteroatoms (O, S, NH) into the C–C chain of 1 gave a series of compounds with high in vitro activity in the guinea pig serum ACE assay. The O-analogue was the most potent with an $IC_{50} = 4.4 \times 10^{-9}$ M compared to 1 with an $IC_{50} = 3.2 \times 10^{-9}$ M. The structure–activity relationships in this series of compounds lead one to speculate that the heteroatom provides an additional binding site to the surface of the enzyme; however, these compounds were inactive when tested for antihypertensive activity in the renal hypertensive rat at 30 mg/kg by the oral route (captopril is active at 1.0 mg/kg po).

Angiotensin converting enzyme (ACE) inhibitors hold great promise in the treatment of hypertension.[1] Recently, the efficient synthesis[2] of a ketomethylene analogue (1)[3] of the tripeptide Bz-Phe-Gly-Pro was described, which showed potent in vitro ACE-inhibitory activity and in vivo activity during continuous iv infusion. This analogue was less active in vivo when given either by iv bolus injection or by the oral route. It was suggested that limited in vivo activity by iv bolus injection may be due to rapid metabolic

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(1) (a) Cushman, D. W.; Cheung, H. S.; Sabo, E. F.; Ondetti, M. A. *Biochemistry* **1977**, *196*, 441. (b) Ondetti, M. A.; Rubin, B.; Cushman, D. W. *Science* **1977**, *16*, 5484.
(2) Meyer, R. F.; Nicolaides, E. D.; Tinney, F. J.; Lunney, E. A.; Holmes, A.; Hoefle, M. L.; Smith, R. D.; Essenburg, A. D.; Kaplan, H. R.; Almquist, R. G. *J. Med. Chem.* **1981**, *24*, 964.
(3) Almquist, R. G.; Chao, W.-R.; Ellis, M. E.; Johnson, H. L. *J. Med. Chem.* **1980**, *23*, 1392.

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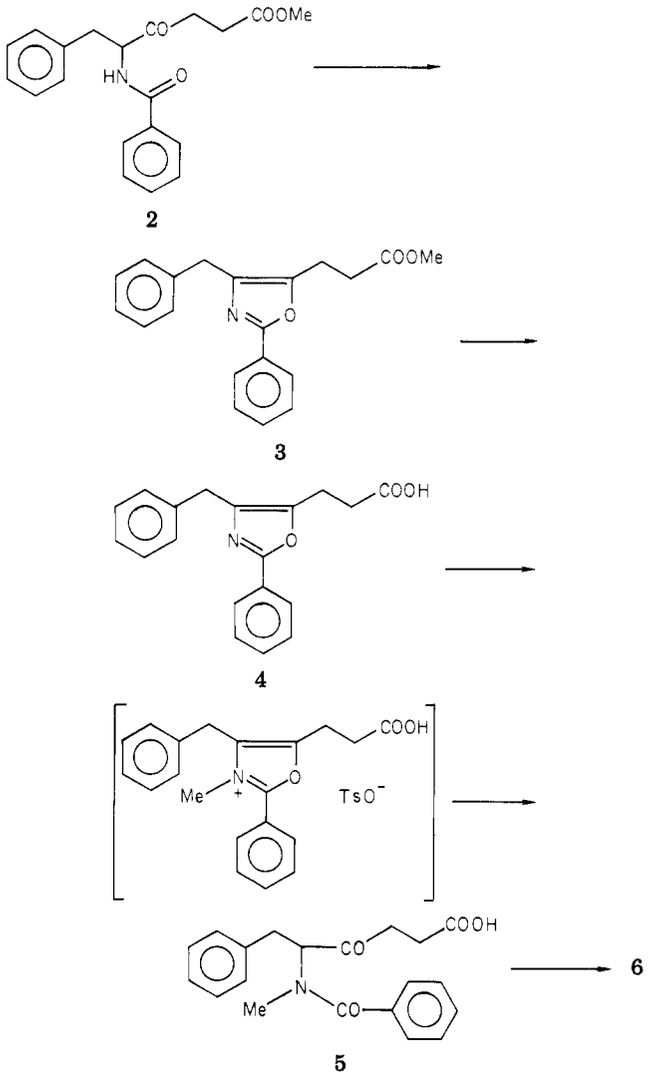
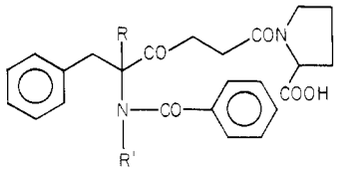
Scheme I



degradation. A possible solution to this problem of metabolic instability might be found by blocking possible sites of degradation, for instance by N-methylation of the benzamido moiety or by C-methylation α to it.

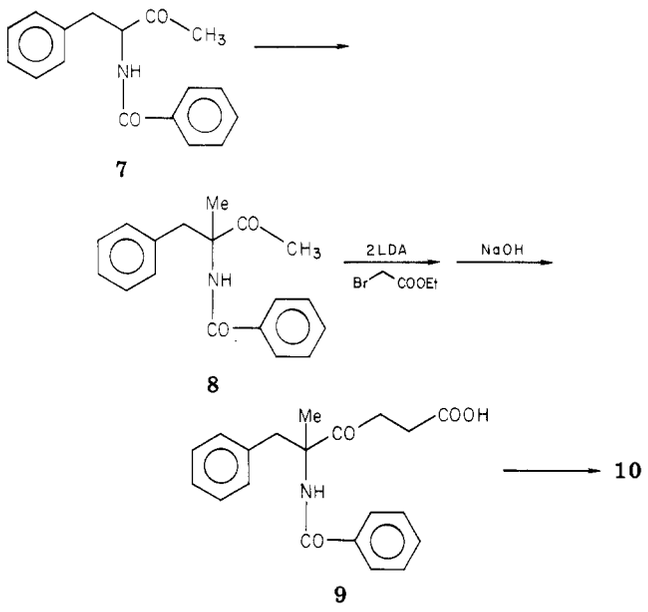


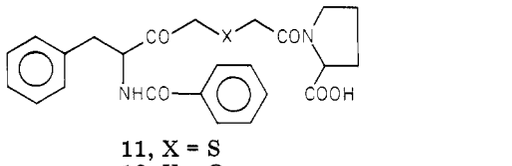
1, R, R′ = H
6, R = H; R′ = Me
10, R = Me; R′ = H

Recently, some interesting isosteric modifications of the amide bond between Phe-Ala of the tripeptide Bz-Phe-Ala-Pro were presented,[4] but none of these isosteric analogues even approached the potency of the ketomethylene analogue 1. The conclusion was that the presence of the carbonyl group is important for binding of tripeptides and their analogues to ACE.[4]

It was thought to be of interest to determine if the inhibitory potency of 1 could be further increased by providing additional binding sites for the enzyme by insertion of heteroatoms, such as O, S, or N, into the C–C chain.

Scheme II





11, X = S
12, X = O
13, X = NTs
14, X = NH

Chemistry. The keto acid **5** required for the preparation of the *N*-methyl compound **6** was prepared according to Scheme I. The keto ester **2**[2] was cyclized to the oxazole ester **3** by treatment with phosphorus oxychloride. The oxazole acid **4** was converted to the oxazole quaternary salt and hydrolyzed to the *N*-methyl compound **5** according to the method[5] of N-alkylation of α-acylamino ketones. Compound **6** was isolated as a diastereomeric mixture.

The C-methyl compound **10** was prepared according to Scheme II. The known *C*-methyl compound **8**[6] was obtained in 38% yield from **7**[7] by methylation with CH_3I and NaH in DMF. Alkylation of the dianion of **8**, followed by hydrolysis with base, gave racemic **9**. Acylation[2] of L-proline yielded a diastereomeric mixture of **10**.

The intermediary keto acids **16**, **18**, and **21** for the corresponding final compounds **11**, **12**, and **13** were prepared utilizing a modification of the Dakin–West reaction as the key step[2] as described for **18** under Experimental Section.

Two of the required acid chloride intermediates, methyl 2-(chloroformylmethoxy)acetate[8] and methyl 2-(chloroformylmethylthio)acetate[9] are known. The *N*-Ts analogue required for the preparation of **21** was obtained from the acid **19** by reaction with $SOCl_2$ at ambient temperature, and the crude product was used in the Dakin–West reac-

(4) Natarajan, S.; Condon, M. E.; Nakane, M.; Reid, J.; Gordon, E. M.; Cushman, D. W.; Ondetti, M. A. In "Peptides", Proceedings of the American Peptide Symposium, 7th, Madison, WI, June 14–19, 1981; Rich, D. H.; Gross, E., Eds; p 429.

(5) Ott, D. G.; Hayes, F. N.; Kerr, V. N. *J. Am. Chem. Soc.* **1956**, *78*, 1941.

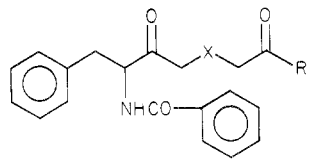
(6) Yamada, S.-I.; Terashima, S. *Chem. Pharm. Bull.* **1968**, *16*(9), 1816–1828.

(7) Aronova, N. I.; Makhova, N. N.; Unanyan, M. P.; Kondrat'eva, G. V.; Rodionova, N. A.; Zav'yalov, S. I. *Chem. Abstr.* **1969**, *70*, 88225*f*.

(8) Anschuetz, R.; Jaeger, S. *Chem. Ber.* **1922**, *55*, 677.

(9) Morrill, H. L.; Steahly, G. W.; Zienty, F. B. *J. Org. Chem.* **1961**, *26*, 4103.

Table I. ACE Inhibitors and Intermediates



no.	X	R	mp, °C	recrystn solvent	yield,[b] %	formula	anal.	$[\alpha]^{23}_D$ (c 1, $CHCl_3$)	IC_{50}[c]
11	S	L-proline	40-55		82	$C_{24}H_{26}N_2O_5S$	C, H, N	-59.6	1.2×10^{-8}
12	O	L-proline	40-50		78	$C_{24}H_{26}N_2O_6 \cdot 0.5H_2O$	C, H, N	-32.4	4.4×10^{-9}
12[a]	O	L-proline	190-200	*i*-PrOH		$C_{36}H_{49}N_3O_6$	C, H, N	-5.2	
13	NTs	L-proline	50-80		93	$C_{31}H_{33}N_3O_7S \cdot H_2O$	C, H, N	-41.1	2.2×10^{-5}
14	NH	L-proline	150-155	Me_2CO	32	$C_{24}H_{27}N_3O_5$	C, H, N	-21.7	9.6×10^{-7}
15	S	OMe	102-103	*i*-PrOH	34	$C_{20}H_{21}NO_4S$	C, H, N		
16	S	OH	138-140	EtOAc	54	$C_{19}H_{19}NO_4S$	C, H, N		
17	O	OMe	117-119	*i*-Pr_2O	79	$C_{20}H_{21}NO_5$	C, H, N		
18	O	OH	140-142	EtOAc	65	$C_{19}H_{19}NO_5$	C, H, N		
20	NTs	OEt	143-144	EtOAc	61	$C_{28}H_{30}N_2O_6S$	C, H, N		
21	NTs	OH	184-186	EtOAc	78	$C_{26}H_{26}N_2O_6S$	C, H, N		
1[d]		L-proline							3.2×10^{-9}
22[d]	CH_2	L-proline							4.2×10^{-8}

[a] DCHA salt. [b] Calculated yield is based on the last reaction step(s) from a characterized intermediate. [c] Molar concentration required for 50% inhibition. If no value is given, compound was not tested. [d] Reference 2.

tion. The final compounds **11–13** were obtained as a mixture of diastereomers and tested as such. Compound **14** was obtained from acetone as an amorphous powder. The stereochemistry of the chiral center β to the phenyl group is unknown. The final products and intermediates are tabulated in Table I.

Biological Results and Discussion

Compounds **6** and **10**, the *N*-methyl and the *C*-methyl analogues of the parent ketomethylene compound **1**, were void of in vitro ACE inhibitory activity, which indicated the high structural specificity of this part of the molecule. Insertion of a heteroatom into the C–C chain of **1** was the most successful in the case of oxygen. Compound **12**, a mixture of diastereomers, when tested in vitro, was about as active as **1**, which is the pure *S*,L isomer. The sulfur analogue **11** was approximately one-third as active, and the NH analogue **14** was several hundred times less active. The bulky *N*-Ts compound **13** was essentially inactive.

The high degree of in vitro activity of **12** and **11**, both being several times more potent that compound **22**, a homologue of **1**, suggests that these polar heteroatoms provide additional binding sites to the surface of the angiotensin converting enzyme, presumably through hydrogen bonding.

Compounds **11**, **12**, and **14** did not show antihypertensive activity in the renal hypertensive rat when administered orally at 30 mg/kg.

No experiments were performed to evaluate for in vivo ACE inhibitory activity, since our main objective was to find an orally active antihypertensive agent. However, the lack of oral antihypertensive activity in the renal rat at 30 mg/kg suggests that oral ACE inhibitory activity is lacking, since captopril and other orally active ACE inhibitors are potent antihypertensive agents in the renal hypertensive rat at 1–3 mg/kg on oral administration.

Experimental Section

Melting points (mp) were determined in a Thomas-Hoover capillary melting point apparatus or a Mel-Temp apparatus. Infrared (IR) data were recorded on a Beckman IR-9 or IR-7 prism grating instrument on a Digilab FTS-14 interferometer. Nuclear magnetic resonance measurements (NMR) were made on a Bruker WH-90 pulsed Fourier transform instrument. IR and NMR were compatible with the assigned structures. Homogeneity of the products was determined by ascending thin-layer chromatography (TLC) on precoated TLC sheets (silica gel 60F 254, Merck), using principally the solvent system $CHCl_3$–MeOH–H_2O (60:45:10). The TLC of all analytical compounds were homogeneous single spots when visualized with UV and/or I_2 vapor. Microanalytical results reported by symbols of the elements were within ±0.4% of theory.

Methyl 2-Phenyl-4-(phenylmethyl)-5-oxazolepropanoate (3). A solution of **2**[2] (51 g, 0.15 mol) and $POCl_3$ (30.5 mL, 0.3 mol) in 1500 mL of toluene was refluxed for 1 h. The cooled reaction mixture was washed with ice-cold aqueous $KHCO_3$, dried (K_2CO_3), and evaporated to give 43.3 g (90%) of **3**, mp 48–49 °C. Recrystallization from hexane gave white needles, mp 49–50 °C. Anal. ($C_{20}H_{19}NO_3$) C, H, N.

2-Phenyl-4-(phenylmethyl)-5-oxazolepropanoic Acid (4). A solution of **3** (43.3 g, 0.135 mol) and 160 mL of aqueous NaOH (1 N) in 750 mL of MeOH was refluxed for 1 h. The MeOH was evaporated at reduced pressure, and the solution was acidified to pH 4 with dilute HCl. The product was collected by filtration, washed with H_2O, and recrystallized from *i*-Pr_2O to give 31.7 g (76%) of analytically pure **4**, mp 141–142 °C. Anal. ($C_{19}H_{17}NO_3$) C, H, N.

δ-(*N*-Benzoyl-*N*-methylamino)-γ-oxobenzenehexanoic Acid (5). A mixture of **4** (5 g, 0.163 mol) and methyl *p*-toluenesulfonate (9.1 g, 0.49 mol) was heated at 200 °C for 5 min. The cooled reaction mixture was partitioned between ether and H_2O. The aqueous layer was washed with ether and made alkaline with NaOH (25 mL, 2 N). The resulting emulsion was warmed to 50 °C for 5 min. The resulting solution was adjusted to pH 4 with dilute HCl. The product was taken up in CH_2Cl_2 and washed with H_2O. Evaporation gave a tan gum, which could not be crystallized. It was converted to a dicyclohexylamine salt, which crystallized from MeCN to give 6.9 g (81%) of **5** (DCHA salt), mp 135–140 °C. Anal. ($C_{32}H_{44}N_2O_4$) C, H, N.

The above DCHA salt (5.5 g) was converted to **5** (3.8 g), a colorles gum: NMR ($CDCl_3$) δ 5.1–5.3 (m, 1, *H*CNCO), 2.7 (s, 3, N-CH_3). Anal. ($C_{20}H_{21}NO_4$) C, H, N.

1-[5-(*N*-Benzoyl-*N*-methylamino)-1,4-dioxo-6-phenylhexyl]-L-proline (6). Compound **5** (3.4 g) was converted into 3.9 g (90%) of **6** following the known procedure.[2] Compound **6** was obtained as a colorless amorphous solid from MePh: mp 40–60 °C; $[\alpha]^{23}_D$ -64.2° (*c* 1.09, $CHCl_3$). Anal. ($C_{25}H_{28}N_2O_5 + {}^1/_7$MePh) C, H, N.

The DCHA salt crystallized from ether as a white solid, mp 140–145 °C. Anal. ($C_{37}H_{51}N_3O_5$) C, H, N.

δ-(Benzoylamino)-δ-methyl-γ-oxobenzenehexanoic Acid (9). A solution of **8**[6] (5.6 g, 0.02 mol) in THF (30 mL) was added at -50 °C to a solution of lithium diisopropylamide (0.04 mol) in THF (100 mL). After 0.5 h, ethyl bromoacetate (2.2 mL, 0.02

mol) was added dropwise at −50 °C with stirring. The reaction mixture was allowed to warm to ambient temperature, stirred for 16 h, and then adjusted to neutral pH with HOAc (3.5 mL, 0.06 mol). Evaporation of the THF solution at reduced pressure gave the crude ethyl ester of **9** (7.1 g), which was hydrolyzed according to the previously published procedure[2] to give 2.4 g (35%) of **9** as a light tan foam: NMR ($CDCl_3$) δ 6.5 (s, 1, NH), 1.5 (s, 3, C-CH_3). Anal. ($C_{20}H_{21}NO_4$) C, H, N.

1-[5-(Benzoylamino)-5-methyl-1,4-dioxo-6-phenylhexyl]-L-proline (10). When the previously described procedure was used, compound **9** (2.3 g, 0.0068 mol) gave 1.5 g (50%) of **10** as a light tan, glossy foam: mp 90–100 °C; $[\alpha]^{23}_D$ −73.5° (*c* 1.05, $CHCl_3$). Anal. ($C_{25}H_{28}H_2O_5 \cdot 0.5H_2O$) C, H, N.

Methyl [3-(Benzoylamino)-2-oxo-4-phenylbutoxy]acetate (17). Triethylamine (7.5 mL, 0.055 mol) was added dropwise with stirring and cooling in an ice bath to a solution of 2-phenyl-4-(phenylmethyl)-5(4*H*)-oxazolone (12.55 g, 0.05 mol) and methyl 2-(chloroformylmethoxy)acetate[8] (8.35 g, 0.05 mol) in THF (100 mL). After 2 h, the ice bath was removed, and the suspension was allowed to stand overnight. The filtrate was evaporated at reduced pressure at <50 °C to give a quantitative yield of acylated oxazolone [TLC (*i*-Pr_2O) R_f 0.64]. The crude product was dissolved in pyridine (60 mL), warmed to 80 °C, and HOAc (45 mL) was added in one lot. The solution was heated on a steam bath with stirring for 1 h and evaporated at reduced pressure. The crude product was crystallized from *i*-Pr_2O to yield 14 g (79%) of **17**, mp 117–119 °C. Anal. ($C_{20}H_{21}NO_5$) C, H, N.

[3-(Benzoylamino)-2-oxo-4-phenylbutoxy]acetic Acid (18). A solution of **17** (13.8 g, 0.039 mol) in 200 mL of THF and 90 mL of aqueous NaOH (0.5 N) was warmed to 40 °C and then allowed to stand for 20 h at ambient temperature. THF was evaporated at reduced pressure at <40 °C, and the solution was acidified to pH 4 with dilute HCl. The product was collected by filtration, washed with H_2O, and recrystallized from EtOAc to give 8.6 g (65%) of **18**, mp 140–142 °C. Anal. ($C_{19}H_{19}NO_5$) C, H, N.

Ethyl *N*-(Carboxymethyl)-*N*-[(4-methylphenyl)-sulfonyl]glycinate (19). Ethyl *N*-[(4-methylphenyl)sulfonyl]-glycinate[10] (49 g, 0.19 mol) in DMF (190 mL) was converted to the Na salt with NaH (0.19 mol) and alkylated with benzyl chloroacetate (35 g, 0.19 mol). The crude product, showing one spot only on TLC, was catalytically debenzylated in the presence of Pd/C in THF. The crude product was slurried in *i*-Pr_2O (300 mL) to give 43.4 g (72%) of **19**, mp ~100 °C. A sample was recrystallized from *i*-Pr_2O to give a white solid, mp 104–105 °C. Anal. ($C_{13}H_{17}NO_6S$) C, H, N.

1-[[[3-(Benzoylamino)-2-oxo-4-phenylbutyl]amino]-acetyl]-L-proline (14). To a solution of **13** (7.9 g, 0.013 mol) in liquid NH_3 (300 mL) was added finely cut Na (2.9 g, 0.126 mol) until the reaction mixture remained dark blue. After 0.5 h, NH_4Cl (7.5 g, 0.14 mol) was added. Liquid NH_3 was allowed to evaporate. The residue was slurried in H_2O (100 mL). The pH was adjusted to ~5 with HOAc. The product was taken up in CH_2Cl_2 and was washed with H_2O. The crude product (2.8 g) was dissolved in boiling acetone and precipitated on concentration and cooling as a tan powder: yield 1.8 g (32%); mp 150–155 °C. Anal. ($C_{24}H_{27}N_3O_5$) C, H, N.

Biological Methods. The in vitro ACE inhibitory activity was determined by a radioassay procedure reported previously.[2] The oral testing for antihypertensive activity was carried out in renal hypertensive rats (n = 2) at a dose of 30 mg/kg as described previously.[2]

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(10) Fischer, E.; v. Mechel, L. *Chem. Ber.* **1916**, *49*, 1361.

Synthesis and Biological Activity of 5′-Substituted 5-Fluoropyrimidine Nucleosides

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5′-Deoxy-5-fluorouridine (5′-dFUrd, **1**) possesses a significantly higher chemotherapeutic index than other fluoropyrimidines as a result of its being selectivity cleaved in tumors to 5-fluorouracil (FUra) by uridine phosphorylase. Because **1** is a relatively poor substrate for this enzyme, we synthesized a series of 5′-deoxy-5′-substituted-5-fluorouridine (FUrd) derivatives in an effort to obtain compounds that might have improved substrate interactions compared to **1** and thus possibly be better prodrugs of FUra. Three derivatives, 5′-*O*-tosyl-FUrd (**13**), 5′-*O*-mesyl-FUrd (**14**), and 5′-deoxy-5′-bromo-FUrd (**15**), had cytostatic activity against L1210 and CCRF-CEM leukemic cells in culture superior to that of **1**. In preliminary in vivo antitumor studies against L1210 leukemic cells in mice, 5′-deoxy-5′-chloro-FUrd (**4**), 5′-*O*-mesyl-FUrd (**14**), and 5′-deoxy-5′-fluoro-FUrd (**18**) gave percent increases in life span of 64, 58, and 58, respectively, compared to a value of 20 for compound **1**.

Considerable interest has been generated recently in the newly synthesized fluoropyrimidine 5′-deoxy-5-fluorouridine (5′-dFUrd, **1**)[1,2] by the discovery that this compound (1) possesses superior antitumor activity against experimental tumors in animals and (2) causes considerably less host toxicity compared to the well-known clinically used fluoropyrimidines 5-fluorouracil (FUra), 5-fluorodeoxyuridine (FdUrd), and Ftorafur (Ft).[3,4] Because **1** lacks a 5′-hydroxy group, it cannot be directly phosphorylated by pyrimidine kinases, and so the conversion to nucleotides that is necessary for cytotoxicity must be effected via alternate pathways. There is now good evidence that the activity of **1** against tumor cells in culture depends on its cleavage to FUra by uridine phosphorylase, an enzyme which is not ubiquitously present as is thymidine phosphorylase but is distributed unequally among various tissues and organs.[5] Uridine phosphorylase activity has been found to be considerably higher in Walker carcinoma 256,[5] hepatomas,[6] and solid sarcoma 180[5,7] than in the surrounding normal tissue. These observations are

(1) H. Hřebabecký and J. Beránek, *Collect. Czech. Chem. Commun.*, **43**, 3268 (1978).
(2) A. F. Cook, M. J. Holman, M. J. Kramer, and P. W. Trown, *J. Med. Chem.*, **22**, 1330 (1979).
(3) W. Bollag and H. R. Hartmann, *Eur. J. Cancer*, **16**, 427 (1980).
(4) H. R. Hartmann and W. Bollag, *Schweiz. Med. Wochenschr.*, **110**, 1078 (1980).
(5) H. Ishitsuka, M. Miwa, K. Takemoto, K. Fukuoka, A. Itoga, and H. B. Muruyama, *Gann*, **71**, 112 (1980).
(6) E. Reid, *Br. J. Cancer*, **18**, 179 (1964).
(7) M. J. Kramer, P. W. Trown, R. Cleeland, A. F. Cook, and E. Grumberg, *Proc. Am. Assoc. Cancer Res.*, **20**, 79 (1979).

0022-2623/82/1825-0999$01.25/0