(E)-4-[2-(2,3-Dihydro-3,3-dimethylbenzo[b]thien-5-yl)-1-propenyl]benzoic Acid (6d). Heteroarotinoid 6c (1.20 g, 3.55 mmol) in a degassed solution (N_2, 10 min) of dry KOH (0.62 g, 11 mmol) in absolute ethanol (9 mL) and H_2O (3 mL) was heated to reflux (10 min), after which time the mixture became a solution. This solution was heated at reflux (45 min) and then cooled to room temperature. Quenching was effected with acetic acid (15%, 10 mL) and saturated brine (10 mL). Ethyl acetate (100 mL) was added, and the two layers separated. Extraction of the aqueous layer was done with ethyl acetate (50 mL), and the original organic layer and extract were combined and washed (brine, 2 × 25 mL; water, 25 mL). After drying (Na_2SO_4), the solution was filtered and evaporated to a white solid. Two recrystallizations (absolute ethanol), followed by washes with cold, absolute ethanol and hexanes, gave white needles of acid 6d (0.45 g, 56.4%); mp 203.7-204.8 °C. Another 61 mg (5.3%) of 6d could be obtained via concentration of the mother liquors and repeated recrystallizations of the residual solid for a total weight of 0.71 g (61.7%): IR(KBr) 3250-2000 (CO_2H) cm^{-1}; ^1H NMR ($DCCl_3$) δ 1.42 [s, 6 H, H(8,9)], 2.31 [d, 3 H, H(11)], 3.23 [s, 2 H, H(2)], 6.84 [br s, 1 H, H(12)], 7.18-7.24 [m, 2 H, H(4) and H(7)], 7.32 [dd, 1 H, H(6)], 7.48 [d, 2 H, H(14, 18)], 8.14 [d, 2 H, H(15,17)]; ^{13}C NMR ($DCCl_3$) ppm 17.9 [C(11)], 27.4 [C(8,9)], 47.3 [C(3)], 47.5 [C(2)], 120.3 [C(4)], 122.2 [C(7)], 125.4 [C(6)], 125.8 [C(12)], 129.2 and 130.2 [C(14,18) and C(15,17)], 171.8 [C(19)]; other quaternary carbons are at 126.9, 139.9, 140.1, 140.3, 144.1, and 148.2 ppm; mass spectral data for $C_{20}H_{20}C_2S$ m/z (M^+) 324.1184, found 324.1184. Anal. ($C_{20}H_{20}O_2S$) C, H.

Biological Screening Procedures. The procedures for determining the effect of a test retinoid on TPA-induced ODC activity in mouse epidermis have been described.[10,30] For ID_{50} determinations, various doses (0.1, 1.0, 5.0, 10, and 50 nmol) of test retinoids 7-17 were applied 1 h before the application of 10 nmol of TPA to mouse skin. The ODC activity was determined 4.5 h after the TPA treatment. Three mice per group per compound were used. The ID_{50} values were obtained from dose-response curves. The experimental procedure for the HL-60 cell line has been reported in full.[10,12,28]

For standard 1 and systems 6c and 6d, 34 nmol were used and resulted in 0.13, 0.062, and 0.09 nmol of CO_2/30 min per mg of protein, respectively. The control of TPA-induced ODC activity exhibited 1.02 nmol of CO_2/30 min per mg of protein. Again, three groups of mice consisting of two mice/group were used in this assay. Various doses (0.1, 1.0, 5.0, 10, and 50 nmol) were applied 1 h before applicatin of 10 nmol of TPA to mouse skin. The ODC activity was determined 4.5 h after TPA treatment.[10,30] The ID_{50} value for each compound was determined from dose-response curves. Known procedures to determine the HL-60 cell differentiation were applied to these retinoids.[10,36]

Acknowledgment. We acknowledge partial support by the College of Arts and Sciences in the form of salary (K.D.B). We also gratefully acknowledge partial support by the National Science Foundation for funds to upgrade the XL-300 NMR spectrometer (Grant DMB-8603684) and to purchase the 400-MHz spectrometer (Grant CHE-8971-8150). We are pleased to acknowledge the aid of Dr. Kurt Loening (retired), Director of Nomenclature at Chemical Abstracts Service, for the correct names for compounds cited herein. Partial support by OCAST (Grant Number HR8-056) to upgrade the 300-MHz spectrometer and to purchase the XL-400 NMR unit (Grant Number FMG-3478) is also gratefully acknowledged.

Design, Synthesis, and Physicochemical Properties of a Novel, Conformationally Restricted 2,3-Dihydro-1,3,4-thiadiazole-Containing Angiotensin Converting Enzyme Inhibitor Which Is Preferentially Eliminated by the Biliary Route in Rats

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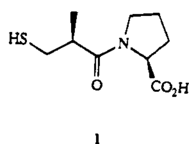
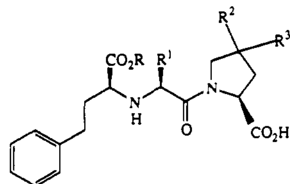
Two novel series of dihydrothiadiazole ring containing inhibitors of angiotensin converting enzyme have been designed and synthesized. The compounds are highly potent enzyme inhibitors and, as a consequence of conformational restriction, chemically stable with respect to undesirable cyclization reactions. The most interesting compound from this series, 5a (FPL 63547), is the monoethyl ester prodrug of the highly potent "aminocarboxy" inhibitor 5b (FPL 63674). It produces an antihypertensive effect of long duration in animal models after oral dosing. Unlike other ACE inhibitors, 5b is eliminated almost entirely by biliary clearance in the rat. The favorable pharmacological properties of 5a and 5b are rationalized in terms of their unique physicochemical profiles. The clear preference for biliary clearance seen with 5b is consistent with its lipophilicity and its high degree of net ionization at physiological pH, which results from the very low pK_a of the C-terminus carboxylic acid function. FPL 63547 is presently undergoing clinical investigation in man.

Introduction

The clinical success of the angiotensin converting enzyme inhibitors captopril (1)[1] and enalapril (2a)[2] in the treatment of both hypertension and chronic heart failure is well-established.[3] Many clinicians now believe that drugs of this class may become the agents of choice for the





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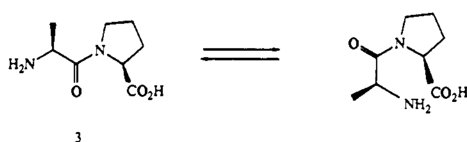
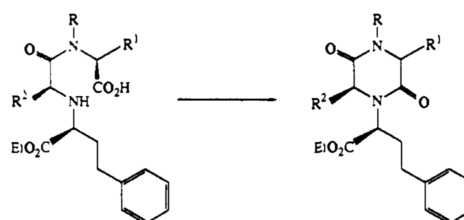
Scheme I. Cis/Trans Isomerism of L-Alanyl-L-proline (3)



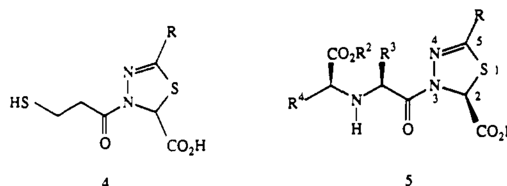
treatment of such cardiovascular disorders.[4] One problem, however, which has emerged after extended use of ACE inhibitors relates to their excretion profile. Captopril, enalaprilat (**2b**, the active diacid derived from the prodrug enalapril), and the more recently launched lisinopril (**2c**)[5] are eliminated from the body almost entirely by renal clearance.[6] Drug data sheets for these compounds warn of the potential dangers associated with their administration to patients with impaired renal function. The desirability of discovering a potent ACE inhibitor which has a significant biliary component to its elimination profile has been widely discussed[7] and this became the major objective of our studies in the area. Although little has been documented concerning the structural characteristics necessary for molecules to be excreted in the bile,[8] a number of factors have been highlighted as being important, notably lipophilicity, pK_a, and molecular weight.

The chemical structures of captopril, enalapril, and the majority of inhibitors which are reported[9] to be undergoing development toward the clinic are related to that of the dipeptide L-alanyl-L-proline (**3**). It is well-known[10] that dipeptides of this type exist in solution as mixtures of cis/trans isomers caused by restricted rotation about the amide bond (Scheme I). Molecular modeling studies indicate[11] that the biologically active conformation of ACE inhibitors corresponds to the trans geometry about this bond. Further evidence which may support the active inhibitor conformation is provided by the good potency of several actual compounds which, inter alia, have covalently fixed trans amide bonds such as cilazapril, benazepril, libenzapril, and RS-5142.[9] At equilibrium the presence of the undesired cis isomer in the conformationally more flexible inhibitors may not only detract from the activity of the molecule but will (in the case of the "aminocarboxy" inhibitors) also facilitate irreversible cyclization to the inactive diketopiperazines (Scheme II). Such cyclic products have been observed during drug formulation and have been detected in the body fluids of animals treated with a variety of ACE inhibitors.[12]

Scheme II. Cyclization of "Aminocarboxy" ACE Inhibitors



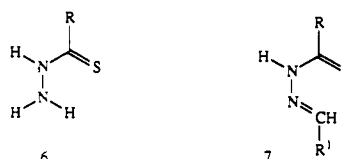
With the foregoing considerations in mind we prepared two series of substituted dihydrothiadiazoles (**4** and **5**).



We believed that repulsion between the lone pairs of electrons on the oxygen of the amide carbonyl and on N-4 of the heterocyclic ring in these molecules should ensure that the desired trans conformation would predominate in solution.[13] These molecules possess a heterocyclic ring substituent with which molecular weight, lipophilicity, and steric parameters can be manipulated and have a carboxy-terminus pK_a (1.8) which is considerably lower than that of other ACE inhibitors. A number of compounds from these series have satisfied the objectives of our research program, and the results are presented below.

Chemistry

Literature reports of molecules which possess the simple alkyl- or aryl-substituted dihydro-1,3,4-thiadiazole ring system are scarce. Indeed, until recently it was thought that the reaction of a carbothioic acid hydrazide (**6**) with an aldehyde produced the acyclic thiohydrazone **7**.[14] In



1982 the cyclic nature of these products was confirmed by NMR spectroscopy and it was inferred in a communication[15] that the resulting dihydrothiadiazole ring could be smoothly acylated on N-3.

Compounds of general structure **4** and **5** were prepared by routes A and B (Scheme III), respectively. The dihydrothiadiazole rings (**8**) were constructed by cyclization of the appropriate carbothioic acid hydrazide **6** with either ethyl or benzyl glyoxylic ester. Acylation of 5-*tert*-butyldihydrothiadiazole **8a** with 3-(acetylthio)propanoyl chloride[16] gave ester **9a** which, after deprotection with potassium hydroxide in aqueous methanol, afforded the crystalline racemic inhibitor **4a**.

Condensation of 2 equiv of racemic 5-*tert*-butyldihydrothiadiazole **8b** with the enantiomerically pure amino acid **10a** (*S,S* stereochemistry)[17] using dicyclohexylcarbo-

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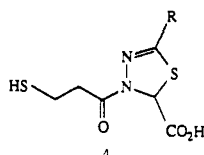
Table I. Melting Point and ACE Inhibition Data for Compounds of General Structure 4



compd[a]	R	mp, °C	rel act.[c]
4a	t-C_4H_9	128–31	5.6
4b[b]	CH_3	150–3	2.5
4c[b]	c-C_6H_{11}	174–6	6.3
4d	1-adamantyl	183–4	1.3
4e	C_6H_5	145–6	1.3
4f	4-$CH_3OC_6H_4$	164	1.3
4g	4-$CF_3C_3H_4$	73–5	1.6
4h	2-naphthyl	171–3	3.1
4i	2-furanyl	105–8	1.0

[a] All compounds give satisfactory C, H, N, S, analysis. [b] Dicyclohexylamine salt. [c] Higher values correspond to more potent compounds.

diimide and 1-hydroxybenzotriazole produced the *S,S,R* isomer (**11a**) in a diastereoselective reaction. Only a trace of the desired *S,S,S* isomer (**12a**) could be detected in the reaction mixture. Epimerization of the asymmetric center at the 2-position of the heterocyclic ring was achieved by treatment of **11a** with pyrrolidine in acetonitrile and gave an equilibrium mixture of **11a** and **12a** from which **12a** was isolated by chromatography. Reequilibration of recovered **11a** produced further batches of **12a**. Deprotection of **12a** by hydrogenation over palladium on carbon yielded the desired inhibitor prodrug **5a**. The relative stereochemistry at the three asymmetric carbon atoms of **5a** (and hence of **12a**) was confirmed by inspection of its X-ray crystal structure (Figure 1). The *S,S,S* absolute stereochemistry was deduced from the chiral integrity of the starting amino acid (**10a**).[17]

The active diacid inhibitors (**5b** and **5d**) were also produced by the chemistry of route B, but with benzyl esters **10b** and **10d** in the condensation step. Palladium on carbon catalyzed hydrogenation of *S,S,S* diesters **12b** and **12d** caused exhaustive debenzylation and the required products were recovered in high yield.

The inhibitor **5c**, containing the lysine moiety, was synthesized by following the chemistry of route B with

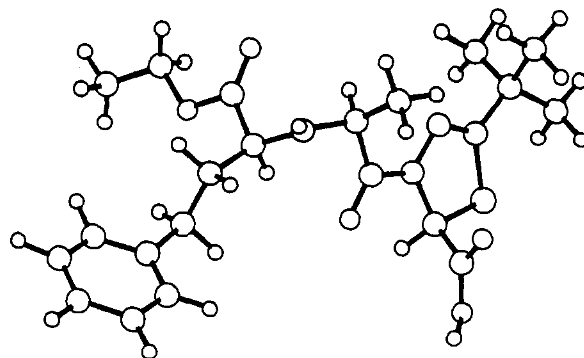


Figure 1. X-ray crystal structure of 5a.

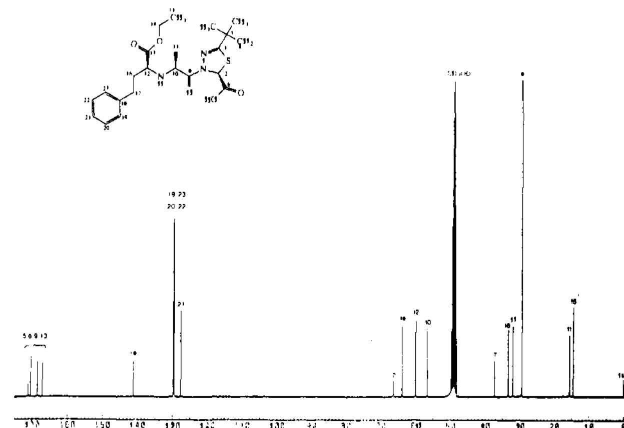


Figure 2. ^{13}C NMR spectrum of 5a in CD_3OD.

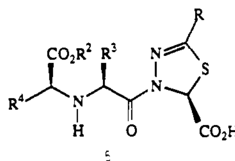
benzyl-protected intermediate **10c**.

Intermediates **10b–e** were prepared according to Scheme IV. After selection of the appropriate protecting groups, hydroxy esters **13** were converted into epimeric mixtures of diesters **14** and **15** by reaction with suitably protected amino acid derivatives. Chromatographic separation followed by deprotection of the required *S,S* diastereoisomers **14** afforded monoesters **10**.

Melting point data and biological activity against angiotensin converting enzyme in vitro for the compounds of types **4** and **5** are summarized in Tables I and II, respectively.

The compounds of structure **5** are chemically stable with

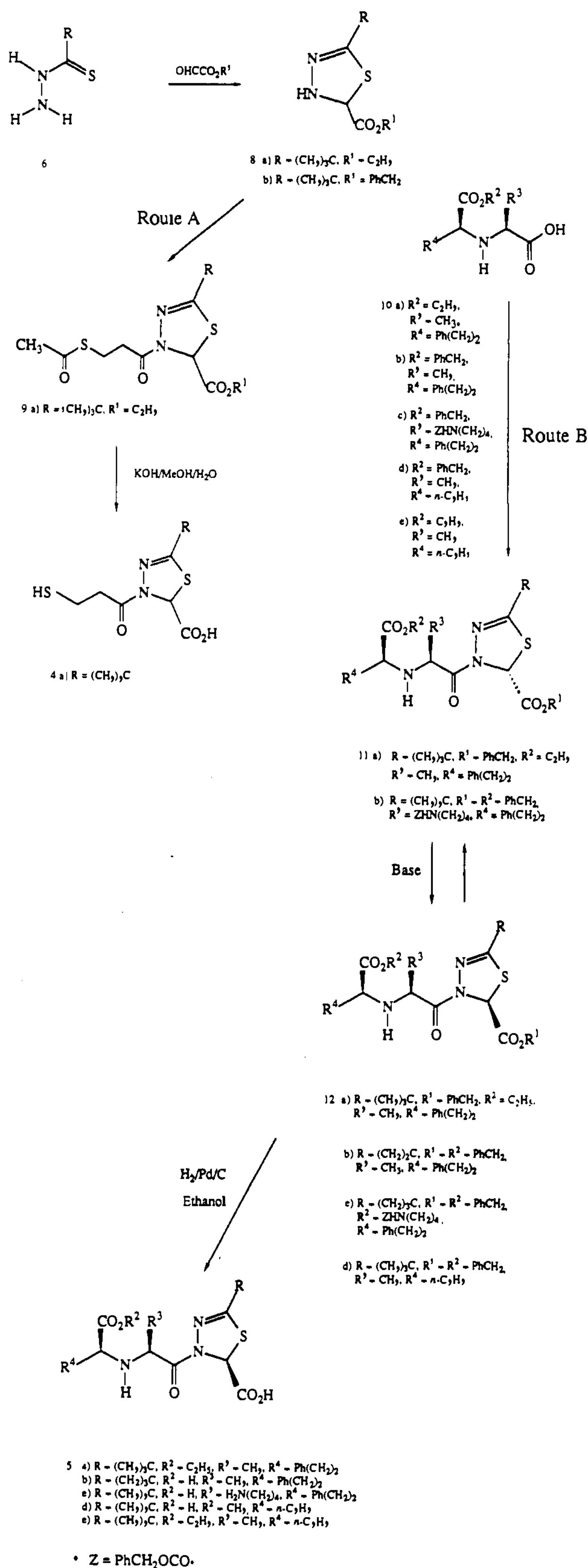
Table II. Melting Point and ACE Inhibition Data for Compounds of General Structure 5



compd[a]	R	$R^{2\,b}$	$R^{3\,b}$	$R^{4\,b}$	mp, °C	IC_{50}, nM[c]
5a	t-C_4H_9	C_2H_5	CH_3	$Ph(CH_2)_2$	162–3	NT
5b	t-C_4H_9	H	CH_3	$Ph(CH_2)_2$	179–84 d	0.51
5c	t-C_4H_9	H	$NH_2(CH_2)_4$	$Ph(CH_2)_2$	188	0.7
5d	t-C_4H_9	H	CH_3	$CH_3(CH_2)_2$	156–9	0.6
5e	t-C_4H_9	C_2H_5	CH_3	$CH_3(CH_2)_2$	183–5	NT
5f	c-C_6H_{11}	C_2H_5	CH_3	$Ph(CH_2)_2$	136–8	NT
5g	$(CH_3)_2CH$	C_2H_5	CH_3	$Ph(CH_2)_2$	151–2	NT
5h	CH_3	C_2H_5	CH_3	$Ph(CH_2)_2$	161–2	NT
5i	C_6H_5	C_2H_5	CH_3	$Ph(CH_2)_2$	183–5	NT
5j	C_6H_5	H	CH_3	$Ph(CH_2)_2$	165–70 d	1.5
5k	4-$CH_3SC_6H_4$	C_2H_5	CH_3	$Ph(CH_2)_2$	163–4	NT
5l	3-pyridyl	C_2H_5	CH_3	$Ph(CH_2)_2$	160–3	NT
enalaprilat						0.95

[a] Compounds give satisfactory C, H, N, S analysis. [b] The substituents at R^2, R^3, and R^4 were selected after consideration of those groups which have been shown to give optimum interactions with subsites on ACE (see ref 9). [c] NT = not tested (prodrug).

Scheme III



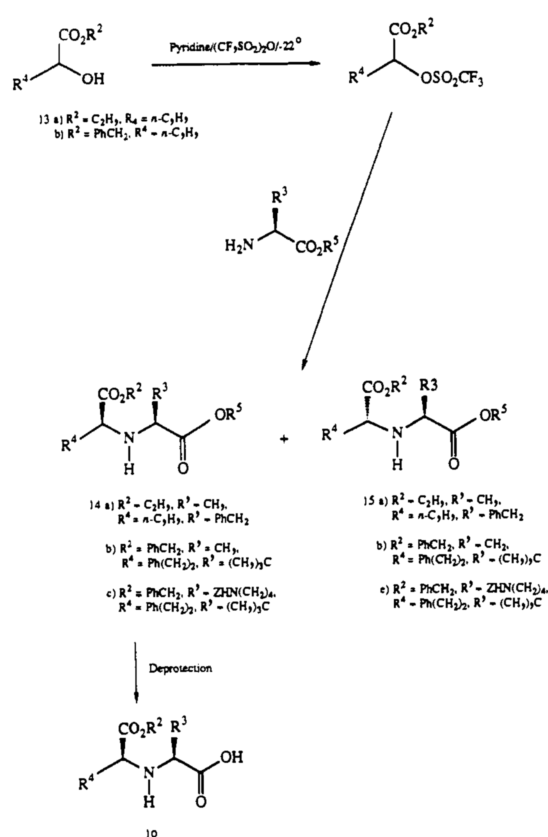
respect to diketopiperazine formation even under conditions of elevated temperature. The ^{13}C NMR spectrum of **5a** is shown in Figure 2.

Results and Discussion

Chemistry and Biology. The chemical stability of **5a** with respect to diketopiperazine formation, its X-ray crystal structure (Figure 1), and the ^{13}C NMR spectrum (Figure 2), which, unlike that of enalapril,[18] shows the signal for each carbon atom of **5a** as a discrete singlet, provide evidence to support the belief that the conformation about the heterocyclic ring–acyl bond in these compounds is restricted to that of the trans geometry (Scheme V). Ab initio quantum mechanical calculations to quantitate the energy difference between the rotamers are in progress.

It is possible, as a consequence of stereoelectronic factors, that the L-pyroglutamic acid[19] and 1-methyl-2-oxo-

Scheme IV



Scheme V

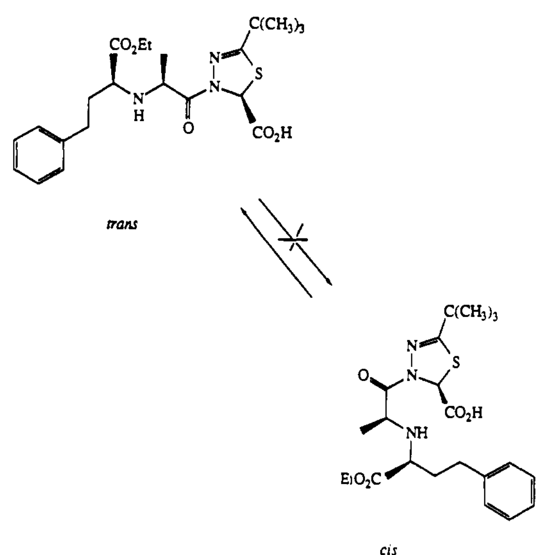


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Table III. Summary of the Physicochemical Properties of Some ACE Inhibitors and Ester Prodrugs

	pK_a	$\log D_{max}$	$\log D_{7.4}$
2a, enalapril	3.04,[a] 5.49	-0.06	-2.0
2b, enalaprilat	2.20, 3.39,[a] 8.02	-0.70	-4.8
2d, spirapril	3.0,[a] 5.5	0.87	-1.1
2e, spiraprilat	2.15, 2.72,[a] 7.53	0.27	-4.3
2c, lisinopril	1.68, 3.29,[a] 7.01, 11.12	-2.86	-3.4
5a, FPL 63547	1.79,[a] 5.40	1.61	-0.37
5b, FPL 63674	1.86,[a] 2.14, 8.00	1.19	-4.0

[a] pK_a of "C-terminus" carboxylic acid.

imidazolidine-4-carboxylic acid[20] containing inhibitors of ACE also experience conformational restriction in favor of the trans geometry at the amide bond. There is, however, no suggestion in the published literature that this may be the case nor any spectroscopic evidence presented which could help to define the stereochemistry of the molecules.

Inspection of the enzyme inhibition data for compounds of general structure **4** and **5** (Tables I and II) shows that activity varies little with changes of substituent at the 5-position of the dihydrothiadiazole ring. Compounds **4b** ($R = CH_3$) and **4d** (R = 1-adamantyl), for example, have very similar potencies. However, we have consistently found in these series that optimal activity is achieved with small bulky substituents such as *tert*-butyl (**4a** and **5b**) and cyclohexyl (**4c**) at this site. The presence of a sterically undemanding hydrophobic pocket at the S_2' subsite on the enzyme is also indicated by the good inhibitory potency achieved when the proline moiety of captopril or enalapril is substituted by a variety of lipophilic groups.[9]

The major objectives of our studies in this area were to discover an inhibitor of ACE which produces antihypertensive effects of long duration in vivo and which is capable of being eliminated from the body by biliary clearance. When dosed orally in animal models, **5a** is both potent and long-acting and is also more effective than captopril, enalapril, and lisinopril at reducing blood pressure in the spontaneously hypertensive rat.[21] Furthermore, **5b**, the active diacid derived from prodrug **5a**, is unusual among ACE inhibitors in being preferentially eliminated by the biliary route in rats. These data have been reported elsewhere[22] but in the following section some comparative results are discussed and rationalized in terms of the unique physicochemical profiles of **5a** and **5b**.

Physical Chemistry: Biological Absorption and Elimination. The physicochemical properties of enalapril (**2a**), spirapril (**2d**), lisinopril (**2c**), and compound **5a**, together with the corresponding diacid derivatives, are summarized in Table III. The compounds are ionized

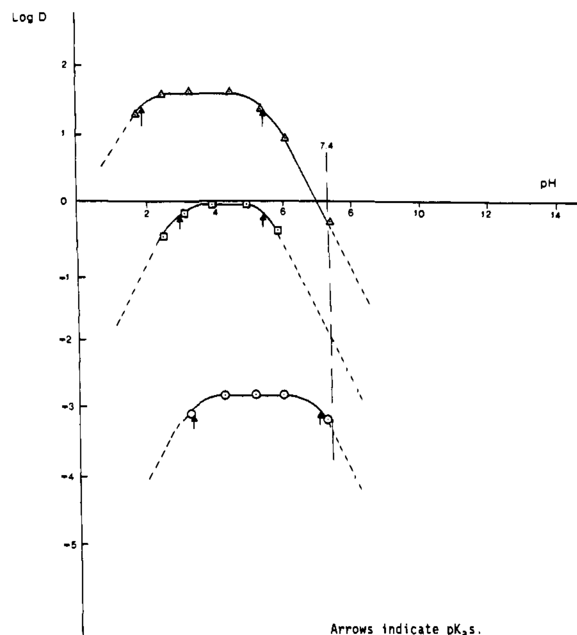

Figure 3. Relationship between distribution and pH for enalapril (**2a**, ⊡), lisinopril (**2c**, ⊙), and 5a (▲).

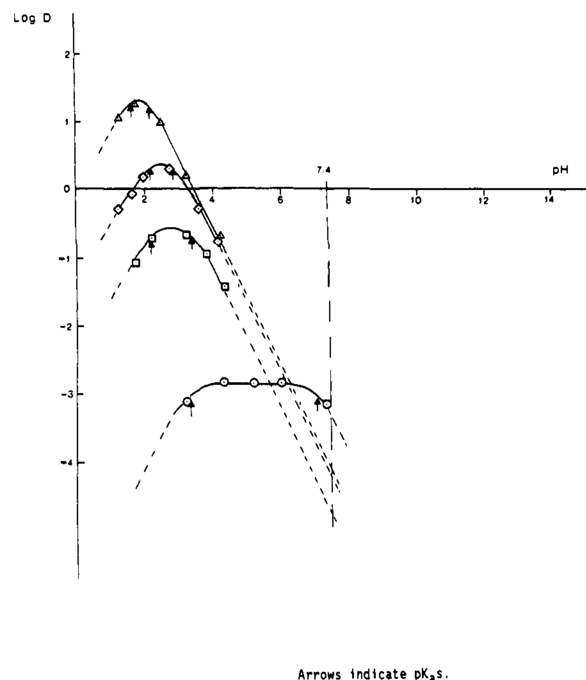

Figure 4. Relationship between distribution and pH for enalaprilat (**2b**, ⊡), spiraprilat (**2e**, ◇), lisinopril (**2c**, ⊙), and **5b** (▲).

throughout the physiological pH range and show relationships between pH values and distribution coefficient (Figures 3 and 4) which are characteristic of zwitterionic species.[23] Such distribution–pH curves are readily calculable by using established mathematical relationships.[24,25] The "C-terminus" carboxyl groups of **5a** and its diacid **5b** are considerably more acidic (pK_a 1.8) than those of enalapril, spirapril, and lisinopril (pK_a approximately 3). A plateau of maximum lipophilicity ($\log D_{max}$)[21] occurs in the region between pK_{a1} and pK_{a2}. Compound

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Table IV. Comparison of Biliary and Urinary Excretion of ACE Inhibitors in the Male Rat after IV Dosing[19]

	bile to urine ratio	$\log D_{max}$	$\log D_{7.4}$	MW	$\log I/U^b$
2c, lisinopril	0.06:1	−2.86	−3.4	405	0.39
2b, enalaprilat[a]	0.7:1	−0.7	−4.8	348	4.01
2e, spiraprilat	2.6:1	0.27	−4.3	493	4.01
5b, FPL 63674	14.6:1	1.19	−4.0	426	5.60

[a] Dosed as the monoester enalapril. [b] Logarithm of the ratio of anionic to un-ionized species at pH 7.4. The fraction ionized was calculated by using the equation:[30]

$$\text{fraction ionized} = \frac{1}{1 + 10^{(\text{p}K_a - \text{pH})}}$$

5a and its diacid **5b** have higher maximum lipophilicity than the other compounds studied.

The pH-partition theory for weak acids and bases[26] proposed that important determinants for absorption include both their lipophilicity and the proportion of compound un-ionized at the pH of the gastrointestinal (g-i) tract. In the absence of a neutral, un-ionized fraction, the observed absorption of the present compounds might be explained by a facilitated uptake mechanism such as that involved in the absorption of amino acids.[27] However, the overall "neutral" zwitterionic form of the compound may behave as the neutral un-ionized form proposed in the pH-partition theory. In favor of the latter possibility, lisinopril, which is neutral in electronic charge (distribution coefficient constant in value) at most g-i tract pH values (Figure 3), is reasonably well absorbed (29%) in the rat after oral administration[28] despite its lack of lipophilicity. The "neutral" zwitterionic ester prodrugs enalapril (**2a**) and **5a** are much more lipophilic (higher $\log D_{max}$) and hence more effectively orally absorbed (**5a**, 78%;[29] enalapril, 34%[30]).

Preference for biliary elimination of a compound has been interpreted in terms of a high molecular weight (>325 in the case of the rat), together with a combination of lipophilicity and a high degree of ionization (amphipathic properties).[8] The importance of amphipathic character has already been identified in the extraction into the bile of taurocholic acid ($\text{p}K_a$ 1.4) and glycocholic acid.[31] The $\text{p}K_a$ of the latter is likely to be approximately 3.7, as in *N*-acetylglycine, rather than the high referenced value.[24] Further examples of compounds eliminated through the bile include the highly ionized antiasthma compound disodium cromoglycate ($\text{p}K_a$ 1.0, 1.9)[32] and the lipophilic leukotriene antagonist FPL 55712 ($\text{p}K_a$ 1.8).[33]

The lipophilicity at physiological pH, $\log D_{7.4}$, and the net degree of ionization at this pH (ratio of ionized to un-ionized species, log I/U) were estimated (Table IV) for lisinopril (**2c**) and for the diacidic derivatives of enalapril (**2a**), spirapril (**2d**), and **5a** using established mathematical relationships.[24,25] Neither $\log D_{7.4}$ nor the molecular weight correlated with the elimination data (log B/U) despite the latter parameter being within the range required for biliary elimination in the rat.[8] However both the net degree of ionization (log I/U) and the maximum lipophilicity ($\log D_{max}$) were well-correlated (Table V and eqs 1, 2). The

Table V. Correlation Coefficients, *r*, of Bile to Urine Elimination Ratio and Physical-Chemical Properties (Table IV)

MW	log I/U	$\log D_{max}$	$\log D_{7.4}$	log B/U	
1.00	0.27	0.37	0.24	0.37	MW
	1.00	0.97	−0.67	0.94	log I/U
		1.00	−0.49	0.99	$\log D_{max}$
			1.00	−0.40	$\log D_{7.4}$
				1.00	log B/U

$$\log B/U = \underset{(\pm 0.05)}{0.57} \log D_{max} + 0.35 \quad (1)$$

$$(n = 4,\ r^2 = 0.99,\ F = 146.7,\ p = 0.007,\ \text{sd} = 0.14)$$

$$\log B/U = \underset{(\pm 0.11)}{0.43} \log I/U - 1.50 \quad (2)$$

$$(n = 4,\ r^2 = 0.89,\ F = 16.6,\ p = 0.055,\ \text{sd} = 0.23)$$

intercorrelation of these two physicochemical parameters prevents an unambiguous selection between them.

The clear preference for biliary elimination seen with **5b** is consistent with its lipophilicity and its high degree of net ionization resulting from its uniquely low "C-terminus" $\text{p}K_a$.

Conclusion

A novel class of thiadiazoline ring containing inhibitors of angiotensin converting enzyme has been designed and synthesized. Repulsion between the lone pairs of electrons on the oxygen of the amide carbonyl and on N-4 of the heterocyclic ring ensures that these molecules adopt the trans conformation both in the solid state and in solution. The drugs are highly potent and, as a consequence of the conformational restraint, chemically stable with respect to diketopiperazine formation.

The most interesting compound from this series, **5a** (FPL 63547),[39] is the monoethyl ester prodrug of the highly potent "aminocarboxy" inhibitor **5b** (FPL 63674). It produces an antihypertensive effect of long duration in animal models after oral dosing. Unlike other ACE inhibitors, FPL 63674 is eliminated almost entirely by biliary clearance in the rat. The clear preference for biliary clearance seen with this compound is consistent with its lipophilicity and its high degree of net ionization at physiological pH, which results from the uniquely low carboxy terminus $\text{p}K_a$.

FPL 63547 is presently undergoing clinical investigation in man.

Experimental Section

Melting points were determined in open capillary tubes with a Büchi melting point apparatus and are uncorrected. The structures of all compounds are consistent with spectroscopic data (IR, ^{1}H NMR, and MS) and satisfactory elemental analyses were obtained where stated. NMR spectra were recorded on a Bruker AM360 360-MHz spectrometer using TMS as standard. The chemical shifts are in ppm (δ), in the solvents indicated. Mass spectra were recorded on a VG 70-250SEQ machine and optical rotations were measured with a Bendix Model 243 automatic polarimeter. Flash chromatography was performed with thick-walled glass columns on silica gel (Matrex Silica 60, 35–70 μm) according to the method of Still.[34] In the text, petroleum ether refers to the fraction boiling in the range 40–60 °C. Following aqueous extractions, organic solutions were dried over anhydrous sodium sulfate prior to evaporation. *N*-[1(*S*)-(Ethoxy-

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carbonyl)-3-phenylpropyl]-L-alanine (**10a**) was purchased from Kanegafuchi Chemical Industry Co., Ltd.

Ionization constants were obtained by potentiometric titration[25] at 25 °C using a thermostated Radiometer automatic titration apparatus. The pK_a values obtained were calculated from the pH-volume data with computer programs.[25] In the case of **5a**, ionization constants were determined by the partition method[25] in Miglyol 812-aqueous buffer[35] systems. Miglyol 812 was purchased from Dynamit Nobel (UK) Ltd. (Slough, U.K.).

All distribution coefficients were obtained by using the shake-flask method[36] in octanol-aqueous buffer systems and the measurements were carried out in triplicate. The values quoted are the mean of the three results and in all cases the standard deviation was <0.04. Octanol, specially purified for the determination of partition coefficients, was obtained from Fisons Scientific Apparatus (Loughborough, U.K.).

The following aqueous phases were used: pH <2 (aqueous HCl), pH 2.2-4.8 (McIlvaine's citrate-phosphate buffer), pH >5 (Sorensen's phosphate buffer). Buffer solutions were of ionic strength 0.02. Appropriate phases were assayed before and after partitioning with UV spectroscopy or reversed-phase HPLC.

HPLC analyses were carried out with a Hewlett-Packard 1084B liquid chromatograph and a 300-mm μBondpak C_{18} column. The mobile phase consisted of methanol-ammonium acetate (0.5%) (20:80 v/v). The flow rate was 2 mL/min and the analyses were carried out at 35 °C. Detection was by UV spectroscopy at 230 nm. A saturated solution of each compound was prepared in the appropriate solvent and filtered through an Anotop filter of pore size 0.2 μm; 20 μL of each solution was injected.

Substituted carbothioic acid hydrazides (6) were prepared by routes which have been previously described in the literature:[14,37] **6a** (R = t-C_4H_9), mp 93-4 °C (lit. mp 93-4 °C); 6b (R = CH_3), not isolated in crystalline form (lit. mp 73-75 °C); **6c** (R = c-C_6H_{11}), mp 105-7 °C (lit. mp 106-7 °C); **6d** (R = 1-adamantyl), mp 202-4 °C (novel); **6e** (R = C_6H_5), mp 72-3 °C (lit. mp 72-3 °C); **6f** (R = 4-$CH_3OC_6H_4$), mp 115-7 °C (lit, mp 123-4 °C); **6g** (R = 4-$CF_3C_6H_4$), mp 114-5 °C (novel); **6h** (R = 2-naphthyl), mp 166-7 °C (lit. mp 163-5 °C); **6i** (R = 2-furanyl), mp 129-30 °C (lit. mp 130-1 °C); **6j** (R = $(CH_3)_2CH$) not isolated in crystalline form (novel); **6k** (R = 4-$CH_3SC_6H_4$), mp 152-3 °C (novel).

5-*tert*-Butyl-2,3-dihydro-3-(3-mercapto-1-oxopropyl)-1,3,4-thiadiazole-2-carboxylic Acid (4a). The synthesis is an example of route A.

Ethyl 5-*tert*-Butyl-2,3-dihydro-1,3,4-thiadiazole-2-carboxylate (8a). A solution of 1,1-dimethylethanethioic acid hydrazide (6a; 1.32 g, 0.01 mol) and ethyl glyoxylate (1.2 g, 0.012 mol) in ethanol (20 mL) was stirred under nitrogen at room temperature for 16 h. The solvent was removed by evaporation to yield the crude, unstable dihydrothiadiazole (2.2 g, 100%) as a clear, golden oil: NMR ($CDCl_3$) δ 1.24 (s, 9 H, $C(CH_3)_3$), 1.30 (t, 3 H, CH_3), 4.24 (q, 2 H, CH_2), 5.43 (s, 1 H, heterocyclic CH).

Ethyl 3-[3-(Acetylthio)-1-oxopropyl]-5-*tert*-butyl-2,3-dihydro-1,3,4-thiadiazole-2-carboxylate (9a). A stirred suspension of polyvinylpyridine (2.0 g) in a solution of **8a** (2.2 g, 0.01 mol) in dry toluene (80 mL) under nitrogen was treated dropwise at room temperature with 3-(acetylthio)propanoyl chloride[16] (1.7 g, 0.01 mol). After 16 h the mixture was filtered and the filtrate was stirred vigorously for 2 h with saturated sodium bicarbonate solution. The organic phase was separated, washed with water, dried, and evaporated to an oil. Purification of the product by flash chromatography on silica gel using petroleum ether/ethyl acetate (10:1) as eluent gave **9a** (2.4 g, 73%) as a clear gum: NMR ($CDCl_3$) δ 1.25 (s, 9 H, $C(CH_3)_3$), 1.28 (t, 3 H, CH_3), 2.33 (s, 3 H, CH_3CO), 2.9-3.3 (m, 4 H, $(CH_2)_2$), 4.23 (m, 2 H, CH_2), 6.12 (s, 1 H, CH).

5-*tert*-Butyl-2,3-dihydro-3-(3-mercapto-1-oxopropyl)-1,3,4-thiadiazole-2-carboxylic Acid (4a). A solution of diester **9a** (2.0 g, 0.0058 mol) in methanol (30 mL) was cooled to 0 °C under nitrogen and treated dropwise with a solution of potassium hydroxide (1.16 g) in water (5 mL). After 2 h at 10 °C the reaction mixture was added to a mixture of ethyl acetate (100 mL) and water (100 mL), and the aqueous phase was acidified with dilute hydrochloric acid. The organic phase was separated, dried, and evaporated to a mobile oil. Purification of the product by flash chromatography on silica gel using petroleum ether/ethyl acetate/acetic acid (5:5:0.2) as eluent gave 4a (1.1 g, 69%) as a white, crystalline solid: mp 128-31 °C; NMR (DMSO-d_6) δ 1.22 (s, 9 H, $C(CH_3)_3$), 2.46 (t, 1 H, SH), 2.71 (m, 2 H, SCH_2), 2.93 (t, 2 H, CH_2CO), 6.25 (s, 1 H, heterocyclic CH), 13.53 (br s, 1 H, CO_2H). Anal. ($C_{10}H_{16}N_2O_3S_2$) C, H, N, S.

Melting point data for other compounds of general structure 4 which were prepared according to Scheme A are detailed in Table I.

5-*tert*-Butyl-3-[*N*-[1(*S*)-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2(*S*)-carboxylic Acid (5a). The synthesis is an example of route B.

Benzyl 5-*tert*-Butyl-2,3-dihydro-1,3,4-thiadiazole-2-carboxylate (8b). A solution of 1,1-dimethylethanethioic acid hydrazide (6a; 28.6 g, 0.216 mol) and benzyl glyoxylate (36 g, 0.22 mol) in ethanol (500 mL) was stirred at room temperature under nitrogen for 16 h. The solvent was removed by evaporation and the residue was purified by flash chromatography on silica gel using petroleum ether/ether (3:1) as eluent to give the unstable dihydrothiadiazole (51.1 g, 84%) as a clear oil: NMR ($CDCl_3$) δ 1.2 (s, 9 H, $C(CH_3)_3$), 5.2 (q, 2 H, CH_2Ph), 5.49 (s, 1 H, heterocyclic CH), 7.36 (s, 5 H, aromatic CH).

Benzyl 5-*tert*-Butyl-3-[*N*-[1(*S*)-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(*R*)-carboxylate (11a). A mixture of **8b** (1.14 g, 0.004 mol), *N*-[1(*S*)-(ethoxycarbonyl)-3-phenylpropyl]-L-alanine (**10a**; 0.57 g, 0.002 mol), 1-hydroxybenzotriazole (0.28 g, 0.002 mol), and dicyclohexylcarbodiimide (0.42 g, 0.002 mol) in dichloromethane (50 mL) was stirred under nitrogen at room temperature for 16 h. The suspended solid was removed by filtration and the filtrate was evaporated to a gum. The residue was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate (4:1) as eluent to give the product (0.82 g) as a clear gum: NMR ($CDCl_3$) δ 1.24, (s, 9 H, $C(CH_3)_3$), 1.26 (t, 3 H, CH_2CH_3), 1.33 (d, 3 H, $CHCH_3$), 1.9-2.1 (m, 2 H, $PhCH_2CH_2$), 2.70 (m, 2 H, $PhCH_2CH_2$), 3.40 (t, 3 H, $CHCO_2$), 4.1-4.3 (m, 3 H, $CHCH_3$ and CH_2CH_3), 5.18 (q, 2 H, OCH_2Ph), 6.20 (s, 1 H, heterocyclic CH), 7.1-7.4 (m, 10 H, aromatic CH).

Benzyl 5-*tert*-Butyl-3-[*N*-[1(*S*)-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2-(*S*)-carboxylate (12a). A solution of **11a** (1.0 g, 0.002 mol) and pyrrolidine (1 g, 0.014 mol) in dry acetonitrile (30 mL) was stirred over crushed 3A molecular sieves at room temperature for 6 h. The volatile components were removed by evaporation, and the desired *S,S,S* epimer (**12a**) was separated from the more polar starting material (**11a**) by flash chromatography on silica gel using petroleum ether/ethyl acetate (4:1) as eluent. The product (0.45 g, 45%) was isolated as a clear gum: NMR ($CDCl_3$) δ 1.24 (s, 9 H, $C(CH_3)_3$), 1.28 (t, 3 H, CH_2CH_3), 1.32 (d, 3 H, $CHCH_3$), 1.90-2.10 (m, 2 H, $PhCH_2CH_2$), 2.65-2.80 (m, 2 H, $PhCH_2CH_2$), 3.31 (t, 1 H, $CHCO_2$), 4.04 (q, 1 H, $CHCH_3$), 4.18 (m, 2 H, CH_2CH_3), 5.18 (s, 2 H, OCH_2Ph), 6.20 (s, 1 H, heterocyclic CH), 7.15-7.40 (m, 10 H, aromatic CH). Further batches of **12a** could be obtained by reequilibration of recovered **11a** as above.

5-*tert*-Butyl-3-[*N*-[1(*S*)-(ethoxycarbonyl)-3-phenylpropyl]-L-alanyl]-2,3-dihydro-1,3,4-thiadiazole-2(*S*)-carboxylic Acid (5a). A solution of **12a** (0.67 g) in ethanol (100 mL) was stirred over 10% palladium on carbon (0.6 g) under an atmosphere of hydrogen for 16 h at room temperature. The catalyst was removed by filtration and the solvent was reduced to ca. 2 mL by evaporation. The cooled solution soon yielded 5a (0.3 g, 53%) as colorless crystals: mp 165-8 °C; $[\alpha]_D^{23} = -260°$ (*c* 0.4, EtOH); NMR ($CDCl_3$) δ 1.20 (s, 9 H, $C(CH_3)_3$), 1.26 (t, 3 H, CH_2CH_3), 1.48 (d, 3 H, $CHCH_3$), 2.13 (m, 2 H, $PhCH_2CH_2$), 2.72 (br t, 2 H, $PhCH_2CH_2$), 3.56 (t, 1 H, $CHCO_2$), 4.19 (m, 2 H, CH_2CH_3), 4.29 (q, 1 H, $CHCH_3$), 6.09 (s, 1 H, heterocyclic CH), 7.10-7.30 (m, 5 H, aromatic CH), 8.10 (br s, 2 H, CO_2H and NH); MS shows an $(M + H)^+$ species at *m/z* 450 (MW 449). Anal. ($C_{22}H_{31}N_3O_5S$) C, H, N, S.

***N*-[1(*S*)-(Ethoxycarbonyl)butyl]-L-alanine (10e).** The synthesis is an example of the chemistry depicted in Scheme IV.

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N-[1(S)-(Ethoxycarbonyl)butyl]-L-alanine Benzyl Ester (14a) and N-[1(R)-(Ethoxycarbonyl)butyl]-L-alanine Benzyl Ester (15a). Trifluoromethanesulfonic anhydride (50 g, 0.175 mol) was added dropwise to a vigorously stirred solution of dry pyridine (15.2 mL, 0.188 mol) in dichloromethane (500 mL) at −22 °C and the mixture was stirred at this temperature for a further 15 min. A solution of ethyl 2-hydroxypentanoate, (13a; 21.0 g, 0.144 mol) in dichloromethane (50 mL) was added over a 2-min period and the resulting slurry was allowed to warm to room temperature over 1 h. The white solid was removed by filtration and the filtrate was evaporated to an oil. A solution of the residue in petroleum ether was passed through a short pad of silica gel and the eluent was reevaporated to give the crude trifluoromethanesulfonate ester an a clear oil (30.3 g, 75%). A solution of the ester (19.2 g, 0.07 mol) in dichloromethane (50 mL) was added to a mixture of L-alanine benzyl ester (12.4 g, 0.07 mol) and triethylamine (15.3 mL, 0.11 mol) in the same solvent (200 mL). The reaction was stirred for 16 h at room temperature and then heated at reflux for 1 h. The solvent was removed by evaporation to provide a crude mixture of the S,S isomer 14a (more polar) and the corresponding R,S diastereoisomer 15a (less polar), as an orange oil (19.5 g). The residue was purified by flash chromatography on silica gel using petroleum ether/ether (5:1) to yield 14a (9.3 g, 44%) and 15a (8.7 g, 41%) as clear oils.

14a: NMR ($CDCl_3$) δ 0.89 (t, 3 H, CH_3), 1.26 (t, 3 H, OCH_2CH_3), 1.31 (d, 3 H, $CHCH_3$), 1.3–1.7 (m, 4 H, CH_2CH_2), 3.27 (t, 1 H, CH), 3.39 (q, 1 H, $CHCH_3$), 4.16 (q, 2 H, OCH_2CH_3), 5.15 (q, 2 H, CH_2Ph), 7.34 (s, 5 H, aromatic CH).

15a: NMR ($CDCl_3$) δ 0.89 (t, 3 H, CH_3), 1.24 (t, 3 H, OCH_2CH_3), 1.30 (d, 3 H, $CHCH_3$), 1.38 (m, 2 H, CH_2), 1.60 (m, 2 H, CH_2), 3.27 (t, 1 H, CH), 3.39 (q, 1 H, $CHCH_3$), 4.12 (q, 2 H, OCH_2CH_3), 5.15 (q, 2 H, CH_2Ph), 7.34 (s, 5 H, aromatic CH).

N-[1(S)-(Ethoxycarbonyl)butyl]-L-alanine (10e). A solution of 14a (6.2 g) in ethanol (250 mL) was hydrogenated over 10% palladium on carbon (0.6 g) at 3 atm of pressure for 0.5 h. The catalyst was removed by filtration and the filtrate was evaporated to ca. 10 mL. Addition of ether induced crystallization to yield 10e (3.8 g, 86%) as colorless crystals: mp 153–4 °C; NMR ($CDCl_3$ + DMSO-d_6) δ 0.92 (t, 3 H, CH_3), 1.2–1.5 (m, 8 H, OCH_2CH_3, $CHCH_3$, and CH_2), 1.55–1.75 (m, 2 H, CH_2), 3.28 (q, 1 H, $CHCH_3$), 4.18 (m, 2 H, OCH_2), 6.60 (br s, 2 H, NH and CO_2H). Anal. ($C_{10}H_{19}NO_4$) C, H, N.

10e was converted into 5e (Table II) by the chemistry of route B.

N-[1(S)-(Benzyloxycarbonyl)-3-phenylpropyl]-L-alanine (10b). The synthesis is a further example of the chemistry depicted in Scheme IV.

Benzyl 2-Hydroxy-4-phenylbutanoate (13b). A mixture of 2-hydroxy-4-phenylbutanoic acid (20.4 g, 0.11 mol), benzyl bromide (12.75 mL, 0.11 mol), and triethylamine (15.9 mL, 0.11 mol) in ethyl acetate (64 mL) was heated under reflux for 16 h. The solution was cooled and poured onto a mixture of water and ether. The separated organic extract was washed with saturated sodium bicarbonate solution and water and then dried. The solvent was removed by evaporation and the residue was purified by flash chromatography using petroleum ether/ether (10:1) to give 13b (14.0 g, 46%) as a pale yellow oil: NMR ($CDCl_3$) δ 1.92–2.17 (2, m, 2 H, CH_2CH), 2.72 (m, 2 H, $PhCH_2$), 2.87 (d, 1 H, OH), 4.23 (m, 1 H, CH_2CH), 5.17 (q, 2 H, $PhCH_2O$), 7.14–7.40 (m, 10 H, aromatic CH).

N-[1(S)-(Benzyloxycarbonyl)-3-phenylpropyl]-L-alanine *tert*-Butyl Ester (14b) and N-[1(R)-(Benzyloxycarbonyl)-3-phenylpropyl]-L-alanine *tert*-Butyl Ester (15b). The trifluoromethanesulfonate ester of 13b was reacted with L-alanine *tert*-butyl ester by using the same conditions as described for the preparation of 14a and 15a. The crude mixture of products was purified by flash chromatography on silica gel using petroleum ether/ethyl acetate (9:1) as eluent to give 14b (23% yield) and the less polar R,S isomer 15b (27% yield) as clear oils.

14b: NMR ($CDCl_3$) δ 1.26 (d, 3 H, $CHCH_3$), 1.43 (s, 9 H, $C(CH_3)_3$), 1.84–2.08 (m, 2 H, CH_2CH), 2.66 (m, 2 H, $PhCH_2CH_2$), 3.23 (q, 1 H, CH_3CH), 3.39 (t, 1 H, CH_2CH), 5.16 (q, 2 H, $PhCH_2O$), 7.1–7.4 (m, 10 H, aromatic CH).

15b: NMR ($CDCl_3$) δ 1.25 (d, 3 H, $CHCH_3$), 1.43 (s, 9 H, $C(CH_3)_3$), 1.96 (m, 2 H, CH_2CH), 2.66 (m, 2 H, $PhCH_2CH_2$), 3.22 (q, 1 H, CH_3CH), 3.31 (t, 1 H, CH_2CH), 5.14 (q, 2 H, $PhCH_2O$), 7.1–7.4 (m, 10 H, aromatic CH).

N-[1(S)-(Benzyloxycarbonyl)-3-phenylpropyl]-L-alanine (10b). A solution of 14b (2.2 g) in trifluoroacetic acid (44 mL) was stirred under nitrogen at room temperature for 5 h. The mixture was evaporated to dryness and the residue was dissolved in water (50 mL). The pH of the aqueous solution was adjusted to 6.0 and the product was extracted into dichloromethane (3 × 100 mL). Evaporation of the solvent yielded 10b (1.63 g, 87%) as a colorless, crystalline solid: mp 155–8 °C; NMR ($CDCl_3$) δ 1.42 (d, 3 H, CH_3CH), 2.06 (m, 2 H, $PhCH_2CH_2$), 2.62 (t, 2 H, $PhCH_2CH_2$), 3.36 (q, 1 H, CH_3CH), 3.56 (t, 1 H, CH_2CH), 5.16 (q, 2 H, $PhCH_2O$), 7.04–7.37 (m, 10 H, aromatic CH).

10b was converted into 5b (Table II) by the chemistry of route B.

5-*tert*-Butyl-3-[N^2-[1(S)-carboxy-3-phenylpropyl]-L-lysyl]-2,3-dihydro-1,3,4-thiadiazole-2(S)-carboxylic Acid (5c). N^6-(Benzyloxycarbonyl)-N^2-[1(S)-(benzyloxycarbonyl)-3-phenylpropyl]-L-lysine *tert*-Butyl Ester (14c). A solution of 13b (13.8 g, 0.05 mol) and pyridine (6.6 mL, 0.08 mol) in dichloromethane (140 mL) was added dropwise over 0.5 h to a stirred solution of trifluoromethanesulfonate anhydride (13 mL, 0.077 mol) in the same solvent (140 mL) at 0 °C. The mixture was allowed to warm to room temperature over 0.5 h and then washed well with water. The dried organic phase was evaporated to an oil. A solution of the residue in dichloromethane (140 mL) was added to a mixture of N^6-(benzyloxycarbonyl)-L-lysine *tert*-butyl ester[38] (15.5 g, 0.05 mol) and triethylamine (6.6 mL, 0.05 mol) in the same solvent (140 mL). The reaction was stirred at room temperature for 1 h, heated at reflux for 2.5 h, cooled, washed with water, and dried, and the solvents were removed by evaporation. The more polar of the pair of closely running products was isolated by flash chromatography on silica gel using petroleum ether/ether (5:1) as eluent to yield the desired S,S isomer 14c (8.4 g, 28%) as a clear oil: NMR ($CDCl_3$) δ 1.41 (s, 9 H, $C(CH_3)_3$), 1.33–1.66 (m, 6 H, $CH_2CH_2CH_2$), 1.84–2.05 (m, 2 H, $PhCH_2CH_2$), 2.65 (m, 2 H, $PhCH_2CH_2$), 3.09 (t, 1 H, CH_2CHNH), 3.15 (m, 2 H, CH_2NHCO), 3.34 (t, 1 H, NHCHCO), 5.14 (m, 4 H, 2 × $PhCH_2O$), 7.11–7.36 (m, 15 H, aromatic CH).

N^6-(Benzyloxycarbonyl)-N^2-[1(S)-(benzyloxycarbonyl)-3-phenylpropyl]-L-lysine (10c). A solution of 14c (0.5 g) in ether (20 mL) was cooled to −5 °C and saturated with dry HCl, and the mixture was stirred at room temperature for 18 h. Evaporation of the solvent yielded a crude sample of 10c (0.48 g, 100%) as a white solid. The NMR spectrum, although showing broad, unresolved signals, indicated the absence of a *tert*-butyl ester function. The fast atom bombardment MS showed the $(M + H)^+$ species at m/z 533 ($C_{31}H_{36}N_2O_6$, MW 532).

Benzyl 3-[N^6-(Benzyloxycarbonyl)-N^2-[1(S)-(benzyloxycarbonyl)-3-phenylpropyl]-L-lysyl]-5-*tert*-butyl-2,3-dihydro-1,3,4-thiadiazole-2(R)-carboxylate (11b). A mixture of 10c (5.7 g, 0.01 mol), 8b (5.9 g, 0.02 mol), 1-hydroxybenzotriazole (1.4 g, 0.01 mol), and dicyclohexylcarbodiimide (2.0 g, 0.01 mol) was stirred under nitrogen at room temperature for 18 h. Triethylamine (1.4 mL, 0.01 mol) was added, and the suspended solids were removed by filtration. The solvent was removed from the filtrate by evaporation and the residue was purified by flash chromatography on silica gel using petroleum ether/ether (5:1) as eluent to yield 11b (2.1 g, 27%) as a clear oil: NMR ($CDCl_3$) δ 1.20 (s, 9 H, $C(CH_3)_3$), 1.33–1.76 (m, 6 H, $CH_2CH_2CH_2$), 1.96 (m, 2 H, $PhCH_2CH_2$), 2.61 (t, 2 H, $PhCH_2CH_2$), 3.15 (m, 2 H, CH_2NHCO), 3.44 (t, 1 H, CH_2CHNH), 4.03 (t, 1 H, NHCHCO), 5.03–5.26 (m, 6 H, 3 × $PhCH_2O$), 6.18 (s, 1 H, heterocyclic CH), 7.06–7.42 (m, 20 H, aromatic CH).

Benzyl 3-[N^6-(Benzyloxycarbonyl)-N^2-[1(S)-(benzyloxycarbonyl)-3-phenylpropyl]-L-lysyl]-5-*tert*-butyl-2,3-dihydro-1,3,4-thiadiazole-2(S)-carboxylate (12c). A mixture of 11b (2.1 g, 0.0027 mol) and pyrrolidine (1.6 mL, 0.019 mol) in dry acetonitrile (60 mL) was stirred over crushed 3A molecular sieves (2 g) for 24 h at room temperature. The solution was filtered and the filtrate was evaporated to a gum. The desired S,S,S isomer

(38) Bentley, P. H.; Stachulski, A. V. *J. Chem. Soc. Perkin Trans. 1* 1983, 1187.

(39) Note added in proof: the published proposed international proprietary name for FPL 63547 is utibapril.

12c was separated from the more polar *S,S,R* epimer 11b by flash chromatography on silica gel using petroleum ether/ether (5:1) as eluent. The product (0.47 g, 22%) was isolated as a clear oil: NMR ($CDCl_3$) δ 1.21 (s, 9 H, $C(CH_3)_3$), 1.35–1.79 (m, 6 H, $CH_2CH_2CH_2$), 1.86–2.10 (m, 2 H, $PhCH_2CH_2$), 2.65 (t, 2 H, $PhCH_2CH_2$), 3.14 (m, 2 H, CH_2NHCO), 3.32 (t, 1 H, CH_2CHNH), 3.96 (t, 1 H, NHCHCO), 5.01–5.23 (m, 6 H, 3 × $PhCH_2O$), 6.15 (s, 1 H, heterocyclic CH), 7.07–7.44 (m, 20 H, aromatic CH).

5-*tert*-Butyl-3-[N^2-[1(*S*)-carboxy-3-phenylpropyl]-L-lysyl]-2,3-dihydro-1,3,4-thiadiazole-2(*S*)-carboxylic Acid (5c). A solution of 12c (1.1 g) in ethanol (90 mL) was stirred over 10% palladium on carbon (0.9 g) under an atmosphere of hydrogen for 1 h. The catalyst was removed by filtration and the filtrate was evaporated to dryness. Recrystallization of the residue from a mixture of wet THF and ethanol gave the hemihydrate of 5c (0.24 g, 36%) as colorless crystals: mp 180–90 °C dec; NMR (DMSO-d_6) δ 1.67 (s, 9 H, $C(CH_3)_3$), 1.32–1.70 (m, 6 H, $CH_2CH_2CH_2$), 1.80 (m, 2 H, $PhCH_2CH_2$), 2.61 (m, 2 H, $PhCH_2CH_2$), 2.72 (m, 2 H, CH_2NH_2), 3.06 (t, 1 H, CH_2CHNH), 4.14 (m, 1 H, NHCHCO), 5.78 (s, 1 H, heterocyclic CH), 7.16–7.28 (m, 5 H, aromatic CH). Anal. ($C_{23}H_{34}N_4O_5S\cdot0.5H_2O$) C, H, N, S.

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Registry No. 4a, 130324-30-0; 4b, 130324-31-1; 4b·DCHA, 130324-38-8; 4c, 130324-32-2; 4c·DCHA, 130324-39-9; 4d, 130324-33-3; 4e, 130324-34-4; 4f, 130324-35-5; 4g, 130324-36-6; 4h, 130275-77-3; 4i, 130324-37-7; 5a, 109683-61-6; 5b, 109683-79-6; 5c, 109683-62-7; 5d, 109715-05-1; 5e, 109683-63-8; 5f, 109683-80-9; 5g, 109683-82-1; 5h, 109683-84-3; 5i, 112137-37-8; 5j, 109683-78-5; 5k, 112063-18-0; 5l, 109683-81-0; 6a, 93114-01-3; 6b, 62543-18-4; 6c, 92503-30-5; 6d, 109684-20-0; 6e, 20605-40-7; 6f, 62625-55-2; 6g, 109684-16-4; 6h, 95372-07-9; 6i, 68062-22-6; 6j, 130275-76-2; 6k, 109684-10-8; 8a, 130275-78-4; 8b, 121342-42-5; 9a, 130275-79-5; 10a, 82717-96-2; 10b, 89371-42-6; 10c, 107832-08-6; 10d, 130275-80-8; 10e, 82834-12-6; 11a, 109683-69-4; 11b, 109715-01-7; 12a, 109718-93-6; 12c, 109785-11-7; 13a, 126372-01-8; 13b, 95513-34-1; 14a, 112243-70-6; 14b, 117560-14-2; 14c, 107832-07-5; 15a, 112243-71-7; 15b, 130275-81-9; 15c, 130275-82-0; ACE, 9015-82-1; OHCCOOEt, 924-44-7; $OHCCOOCH_2Ph$, 52709-42-9; $AcSCH_2CH_2COCl$, 41345-72-6; (±)-$PhCH_2CH_2CH(OH)COOH$, 111611-91-7; H-Ala-OCH_2Ph, 17831-01-5; H-Ala-OBu-*t*, 21691-50-9; H-Lys(Z)-OBu-*t*, 63628-63-7.

Non-Steroidal Antiandrogens. Design of Novel Compounds Based on an Infrared Study of the Dominant Conformation and Hydrogen-Bonding Properties of a Series of Anilide Antiandrogens

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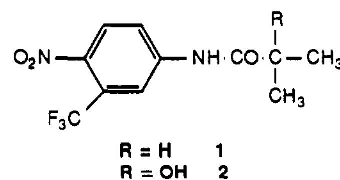
Antiandrogenic activity is observed in anilides containing a tertiary hydroxyl group, and these compounds are used to define a pharmacophore in terms of their physicochemical properties. Infrared spectroscopy shows that these anilides exist in a single conformation, which exerts a powerful influence on the hydrogen-bond donor ability of the hydroxyl group in a model system. Arguments are presented which suggest that hydrogen-bonding ability is an important contributor to biological activity. Compounds were synthesized that reproduced these properties in series not containing an amide bond. Such compounds were found to exhibit good antiandrogen activity. We suggest that quantitative information on hydrogen bonding might also be useful in other systems.

Introduction

Androgen antagonists are a potentially useful treatment for a number of hormone-dependent conditions ranging from acne and hirsutism to prostate cancer.[1] Currently, both steroidal and non-steroidal agents (such as flutamide, 1) have shown clinical benefit in the treatment of prostate cancer, but most show a range of unpleasant side effects as well as overlapping effects on other hormonal activity.[2] Our aim was to find a peripherally selective, non-steroidal, pure antagonist that would have no effect on circulating hormone levels.[2]

Clinically the most widely studied non-steroidal antagonist is flutamide (1), although the active species in vivo was subsequently identified[3] as the hydroxylated metabolite 2. However, few details of structure–activity relationships (SAR) have been reported apart from the patent literature[4] which infers that the most active compounds contain electron-withdrawing substituents in the aromatic ring and a branched alkyl chain α to the amidic carbonyl. Consequently chemical synthesis was initially directed toward exploring structure–activity with 2 as the lead compound.



These studies confirmed that electron-withdrawing groups in the aromatic ring are important for biological activity and that considerable variation is also possible α to the hydroxyl,[2,5] but it is not our intention to describe

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