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Synthesis of (4*S*,9*aS*)-hexahydro-4-methyl-1*H*,5*H*-pyrrolo[2,1-*c*][1,4]thiazepine-1,5-dione, an orally active potent angiotensin converting enzyme inhibitor is described.

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Sir:

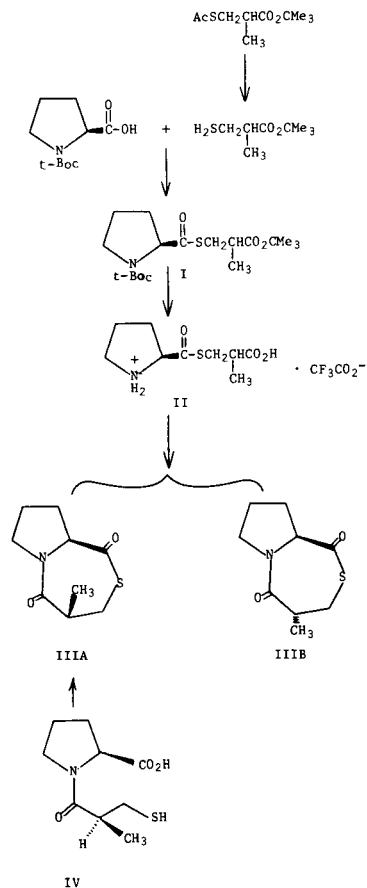
The renin-angiotensin-aldosterone system plays an important role in maintaining elevated blood pressure. Renin acts on angiotensinogen, an α -glycoprotein produced in the liver, to split off the decapeptide angiotensin I which, in turn, is converted by angiotensin converting enzyme (ACE) to the octapeptide angiotensin II. The latter is an extremely potent vasopressor, and a stimulant for the secretion of aldosterone causing a gradual and sustained increase in blood pressure (1). Inhibition of the catalytic action of ACE produces a fall in blood pressure and thus provides a means for the clinical control of hypertension (2,3).

Our efforts in the search for therapeutically useful antihypertensive agents have resulted in the synthesis of compounds which belong to a novel heterocycle, pyrrolo[2,1-*c*][1,4]thiazepine. Among these compounds, (4*S*,9*aS*)-hexahydro-4-methyl-1*H*,5*H*-pyrrolo[2,1-*c*][1,4]thiazepine-1,5-dione (IIIA) showed a potent ACE inhibitory activity and reduced high blood pressure when tested in animals. We wish to report here the synthesis of IIIA.

t-Boc-L-proline was condensed with 3-mercapto-2-methylpropanoic acid *t*-butyl ester by means of dicyclohexylcarbodiimide (DCC) in the presence of a catalytic amount of 4-dimethylaminopyridine (DMAP) (4) to give (2*S*)-2-[[[3-(*t*-butoxy)-2-methyl-3-oxopropyl]thio]carboxyl]-1-pyrrolidinecarboxylic acid *t*-butyl ester (I; ir (film): 1680-1710 cm^{-1} (COs); ms: (C.I.) m/e 374 (MH^+), 318, 274, 262) as a non-distillable oil in 90% yield. The 3-mercapto-2-methylpropanoic acid *t*-butyl ester was obtained by the methanolic ammonia treatment of the corresponding *S*-acetyl derivative (b.p. 73-78° (0.9 mm Hg)); ir (film): 1680 cm^{-1} (COs) prepared from 3-acetylthio-2-methylpropanoic acid (5) and isobutylene by a known method (6). The treatment of the crude condensation product I with a large amount of trifluoroacetic acid (TFA) at room temperature removed both the protecting groups giving 2-methyl-3-[(2*S*)-pyrrolidinylcarbonyl]thio]propanoic acid which was isolated as a TFA salt (II, m.p. 81-83°: ir (potassium bromide pellet): 1650 (CO), 1680 (CO),

and 1700 (CO) cm^{-1} ; nmr (DMSO- d_6): CH_3 at δ 1.14 ppm as a doublet. Anal. Calcd. for $\text{C}_9\text{H}_{15}\text{NO}_3\text{S}\cdot\text{CF}_3\text{CO}_2\text{H}$: C, 39.87; H, 4.87; N, 4.23.

Found: C, 40.13; H, 4.84; N, 4.18. When II was allowed to react with DCC in the presence of slightly greater than an equivalent amount of DMAP in methylene chloride at room temperature for 4 hours, a ring closure reaction occurred giving IIIA (m.p. 103-104°; ir (potassium bromide pellet): 1660 (COs) and 1590 (CON) cm^{-1} ; nmr (deuteriochloroform): CH_3 at δ 1.38 ppm as a doublet, all other proton signals were shown as complex multiplets; ms: m/e (C.I.) 200 (MH^+), 171 ($\text{MH}^+\text{-CHO}$)



(E.I.) 171, 143, 138, 129, 125, 101, 97, 70; $[\alpha]_D^{25} = -113.6$ (c = 0.835%, ethanol). *Anal. Calcd. for* C₁₉H₁₃NO₂S: C, 54.25; H, 6.57; N, 7.03. Found: C, 54.42; H, 6.72; N, 7.06) and its diastereomer IIIB (m.p. 74-76°; ir (potassium bromide pellet): 1660 (COS) and 1620 (CON) cm⁻¹, $[\alpha]_D^{24} = -36.02$ (c = 0.66%, ethanol). *Anal. Calcd. for* C₁₉H₁₃NO₂S: C, 54.25; H, 6.57; N, 7.03. Found: C, 54.27; H, 6.69; N, 7.19) in about 7:3 ratio. The ring closure reaction proceeded in 94% yield. The separation of these two diastereomers was achieved by a preparative hplc but fractional recrystallizations from ethyl acetate or anhydrous ether was also effective. Intramolecular cyclization of 1-(D-3-mercapto-2-methylpropanoyl)-L-proline (S,S) (IV, 7,8) to IIIA using DCC in the presence of DMAP (4) established the stereochemical assignment shown.

The potency of the ACE inhibitory activity of IIIA when tested by a literature procedure (9) was comparable to that of captopril. No significant inhibitory activity was found with its diastereomer IIIB (10).

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- (10) After the preparation of this manuscript, there appeared a patent (U. S. Patent 4,192,945) which described the synthesis of (4*RS*,9*aS*)-hexahydro-4-methyl-1*H*,5*H*-pyrrolo[2,1-*c*][1,4]thiazepine-1,5-dione (a diastereomeric mixture) by a similar approach.