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Synthesis of 1,4-Thiazepine Derivatives Having Angiotensin-Converting Enzyme Inhibitory Property [1)]

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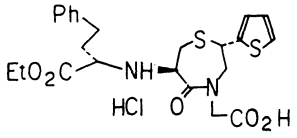
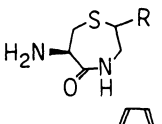
Reduction of (6R)-6-amino-6,7-dihydro-2-thienyl-1,4-thiazepin-5(4H)-one derivatives with Mg-MeOH gave the corresponding perhydrothiazepinones. Protection with trityl group at the 6-amino group gave predominantly the 2S,6R isomer which was converted to the potent angiotensin-converting enzyme (ACE) inhibitor. The ACE inhibitor having the 6,7-dihydro-1,4-thiazepin-5(4H)-one ring was also prepared.

Inhibition of angiotensin-converting enzyme (ACE) which plays an important role in renin-angiotensin-aldosterone system results in a lowering of blood pressure and the ACE inhibitors have become antihypertensive agents. [2)] We have recently reported that the perhydrothiazepinone **1** had a potent inhibitory activity against ACE and was a candidate for an antihypertensive agent. [3)] The key intermediate in the synthesis of **1** is (2S,6R)-6-amino-2-thienylperhydrothiazepin-5-one **2** which is separated from by-product **3** by fractional recrystallization. This paper describes the effective utilization of **3**, that is, the preparation of **1** from **3** via the 6,7-dihydro-1,4-thiazepin-5(4H)-ones obtained easily by oxidation of **3** and the synthesis of an ACE inhibitor having the 6,7-dihydro-1,4-thiazepine ring.



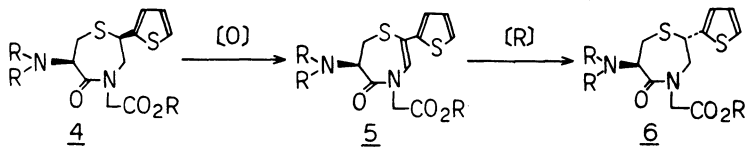
1



2 R=

3 R=

According to the conformational energy calculation of 6-amino-5-oxo-2-phenylperhydrothiazepin-4-ylacetic acid[3] the 2S,6R isomer **6** takes a chair conformation possessing two pseudoequatorial substituents at the 2 and 6 positions, while the 2R,6R one **4** takes the same conformation except for the 6-amino group which is located in a pseudoaxial orientation. Hence it was expected that **6** would be more predominantly produced than **4** by reduction of the 6,7-dihydro-1,4-thiazepin-5(4H)-one **5** which would be derived from **4** by oxidation.[4]

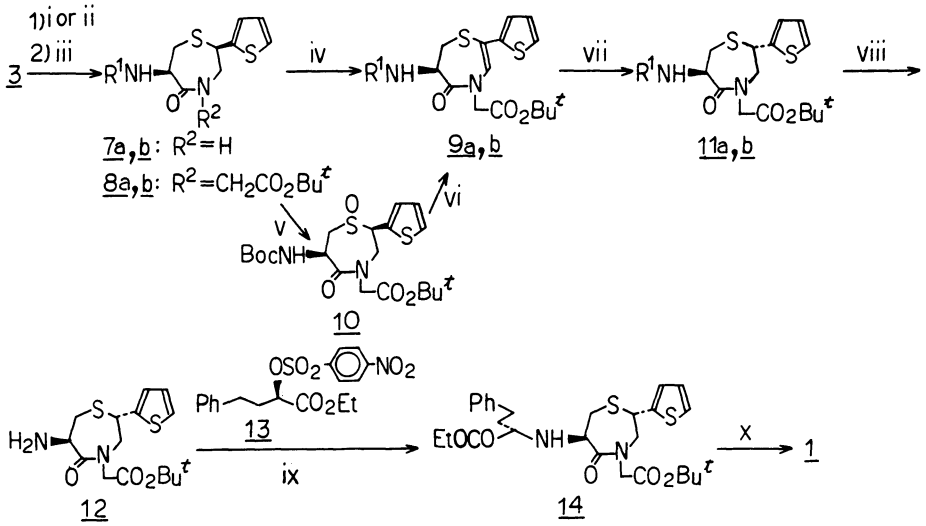


4 **5** **6**

Treatment of **3** with trityl chloride or di-tert-butyl dicarbonate followed by alkylation with tert-butyl bromoacetate gave **8a,b**,[5] respectively, which were oxidized with tert-butyl hypochlorite in the presence of a base to give 6,7-dihydro-1,4-thiazepin-5(4H)-ones **9a,b**,[5] respectively, in moderate yields. **9b** was also obtained from **8b** through the sulfoxide **10**.[5] ^{1}H NMR spectra of **9a,b** show singlets at 6.38 and 6.82, respectively, due to the olefinic proton at the 3 position of the thiazepine ring. Reduction of **9a,b** was carried out with magnesium in methanol to give a diastereoisomeric mixture of **8a,b** and **11a,b**[5] which were separated by flash chromatography. The proportion of these isomers is dependent on the protecting group at the 6-amino group, i.e., the trityl derivative **9a** gave **8a** and **11a** in a ratio of 1:4.4, while the tert-butoxycarbonyl (Boc) derivative **9b** afforded **8b** and **11b** in a ratio of 1:1.6. These results indicate that the reduction of the 6,7-dihydro-1,4-thiazepin-5(4H)-one having bulky substituents at the 2 and 6 positions produces preferentially the corresponding perhydrothiazepinone having the pseudoequatorial substituents at the 2 and 6 positions in the chair conformation. Removal of the trityl and Boc groups in **11a,b** with aqueous acetic acid and p-toluenesulfonic acid, respectively, gave the amino compound **12**,[5] which was converted to the diester **14**[3] by N-alkylation with the sulfonate **13**. Removal of the tert-butyl group with acid gave the potent ACE inhibitor **1**.[3]

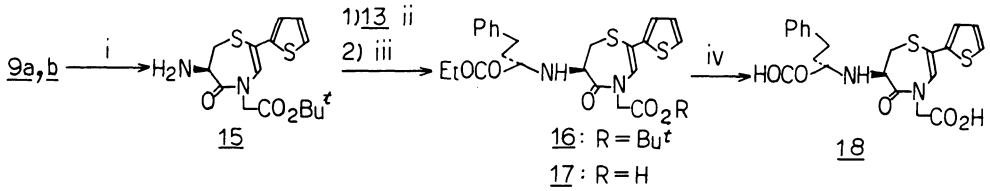
Next, the ACE inhibitor **17**[5] having the 6,7-dihydro-1,4-thiazepine ring was synthesized from **9a,b** by the same procedure as in the preparation of **1** from **11a,b**, i.e., removal of the amino-protecting group followed by N-alkylation with **13** and removal of the tert-butyl group. The low yield in **17** was caused by instability of **17** in acidic media. Alkaline hydrolysis of **17** afforded the

dicarboxylic acid **18** [5,6] which was less potent than the corresponding dicarboxylic acid (IC_{50}=3.6 nM)[7] of **1** but still had potent inhibitory activity (IC_{50}=6.8 nM).[7]



a, R^1=Ph_3C; b, R^1=t-BuOCO (Boc)

Reagents, reaction conditions and yields. i) Ph_3CCl, Et_3N in DMF; r.t., 1.5 h, 84%. ii) Boc_2O, Et_3N in DMF; r.t., 3 h; 85%. iii) $BrCH_2CO_2Bu^t$, NaH in DMF; 5 °C, 1 h → r.t., 1 h; 98%. iv) N-Methylmorpholine(1.1 mol equiv.), Bu^tOCl(1.03 mol equiv.) in toluene; -40--50 °C, 3 h → r.t., 2 h; **9a**, 81%; **9b**, 72%. v) mcpba in CH_2Cl_2; -30 °C, 1 h; quantitative. vi) Ac_2O; 130 °C, 8 h; 52%. Vii) Mg turnings(12 atom equiv.) in MeOH; 30 °C, 4 h, portionwise addition; **11a**, 65%; **8a**, 15%; **11b**, 51%; **8b**, 30%. viii) For **11a**; 80% aq. AcOH; 50 °C, 0.5 h; 83%: for **11b**; p-TSA.H_2O in dioxane; r.t., 6 h; 96%. ix) **13**(1.1 mol equiv.), Et_3N(2 mol equiv.) in DMA; 50 °C, 24 h; 96%; x) 4 mol dm^{-3} HCl-dioxane; r.t., 16 h; 78%.



Reagents, reaction conditions and yields. i) For **9a**; 80% aq. AcOH; 50 °C, 0.5 h; 83%: for **9b**; p-TSA.H_2O in dioxane; r.t., 6 h; 99%. ii) **13**(1.1 mol equiv.), Et_3N(2 mol equiv.) in DMA; 50 °C, 24 h; 98%. iii) CF_3CO_2H, r.t., 3.5 h followed by neutralization with aq. $NaHCO_3$; 15%. iv) 1 mol dm^{-3} NaOH; r.t., 5 h; 83%.

References

1) Part 3 of "Angiotensin-Converting Enzyme Inhibitors." Part 2: H. Yanagisawa,

S. Ishihara, A. Ando, T. Kanazaki, S. Miyamoto, H. Koike, Y. Iijima, K. Oizumi, Y. Matsushita, and T. Hata, J. Med. Chem., 31, 422 (1988).

2) E. W. Petrillo, Jr., and M. A. Ondetti, Med. Res. Rev., 2, 1 (1982); M. J. Wyvratt, and A. A. Patchett, ibid., 5, 483 (1985).

3) H. Yanagisawa, S. Ishihara, A. Ando, T. Kanazaki, S. Miyamoto, H. Koike, Y. Iijima, K. Oizumi, Y. Matsushita, and T. Hata, J. Med. Chem., 30, 1984(1987).

4) Attempts at inversion at the 2 position of the sulfoxide or sulfone of **4** through the carbanion at this position were unsuccessful.

5) All new compounds were characterized by elemental analyses and spectral dada. The physical and spectral data are as follows. Optical rortations were measured at a 1% solution in DMF at 25 ℃. **7a**: amorphous; $[\alpha]_D$-46.9 ° . **7b**: mp 197-199 ℃ (dec); $[\alpha]_D$-76.5 ° . **8a**: mp 150-151 ℃ (dec); $[\alpha]_D$-53.2 ° . **8b**: mp 162-164 ℃ ; $[\alpha]_D$+3.7 ° . **9a**: mp 90-91 ℃ ; $[\alpha]_D$-326.8 ° ; NMR ($CDCl_3$) δ 1.39(9H,s), 3.50(2H,ABq, $\Delta\delta$ =0.76 ppm,J=17), 3.3-4.0(4H,m), 6.38(1H,s), 6.7-7.7(18H,m). **9b**: amorphous; $[\alpha]_D$-603.5 ° ; NMR ($CDCl_3$) δ 1.43(9H,s), 1.46 (3H,s), 3.13(1H,t,J=11), 3.82(1H,d,d,J=5.5, 11), 4.17(2H,ABq, $\Delta\delta$ =0.30 ppm, J=18), 4.88(1H,d,d,d,J=5.5, 8, 11), 5.84(1H,d,J=8), 6.82(1H,s), 6.9-7.4(3H, m). **10**: mp 201-202 ℃ ; $[\alpha]_D$-125.6 ° . **11a**: amorphous; $[\alpha]_D$ +28.6 ° ; NMR ($CDCl_3$) δ 1.45(9H,s), 2.4-3.0(2H,m), 3.70(2H,ABq, $\Delta\delta$ =0.48 ppm, J=17), 3.55-4.15(3H,m), 4.57(1H,br d,J=7), 6.83(2H,d,J=4), 7.0-7.6(16H,m), **11b**: gum; $[\alpha]_D$+46.3 ° ; NMR ($CDCl_3$) δ 1.47(18H,s), 2.9-3.1(2H,m), 3.5-4.75(3H,m), 4.85-5.15(1H,m), 6.06(1H,br d,J=6), 6.85-7.35(3H,m). **12**: mp 81-82 ℃ ; NMR ($CDCl_3$) δ 1.47(9H,s), 2.29(2H,br s), 2.6-4.7(8H,m), 6.75(3H,m). **15**: mp 90 ℃ ; $[\alpha]_D$-517.5 ° ; NMR ($CDCl_3$) δ 1.47(9H,s), 1.90(2H,br s), 2.78(1H,d,d,J=11, 21), 2.5-4.2(3H,m), 4.17(2H,ABq, $\Delta\delta$ =0.50 ppm,J=17), 6.89(1H,s), 6.8-7.45 (3H,m). **16**: syrup; $[\alpha]_D$-296.8 ° ; NMR ($CDCl_3$) δ 1.20(3H,t,J=7.5),1.47(9H, s), 1.7-2.2(2H,m), 2.3-4.5(11H,m), 6.88(1H,s), 6.8-7.4(3H,m), 7.21(5H,s). **17**: mp 146-148 ℃ ; $[\alpha]_D$-506.1 ° ; NMR ($CDCl_3$) δ 1.16(3H,t,J=7.5), 1.6-2.2(2H, m), 2.3-4.6(10H,m), 6.84(1H,s), 6.7-7.4(3H,m), 7.13(5H,s). **18**: mp 215-217 ℃ (dec); NMR ($DMSO\text{-}d_6$) δ 1.6-2.0(2H,m), 2.4-2.8(3H,m), 3.0-3.3(2H,m), 3.55-4.0 (3H,m), 4.23(2H,ABq, $\Delta\delta$ =0.32 ppm,J=17), 7.0-7.6(9H,m).

6) Compounds **1** and **17** are the prodrugs which are converted to the active dicarboxylic acids in a living body by enzyme.

7) The concentration required for 50% inhibition of rabbit lung ACE with hippurylhistidylleucine as substrate.

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