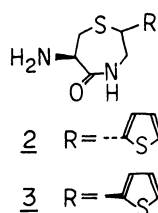
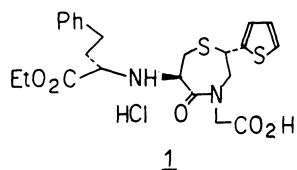


Synthesis of 1,4-Thiazepine Derivatives Having  
Angiotensin-Converting Enzyme Inhibitory Property <sup>1)</sup>

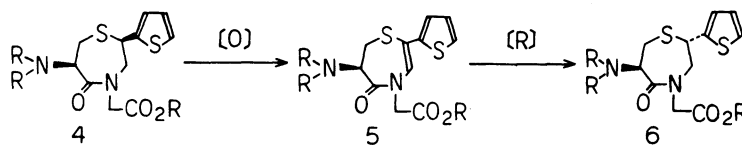
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Reduction of (6R)-6-amino-6,7-dihydro-2-thienyl-1,4-thiazepin-5(4H)-one derivatives with Mg-MeOH gave the corresponding perhydrothiazepinones. Protection with trityl group at the 6-amino group gave predominantly the 2S,6R isomer which was converted 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.<sup>2)</sup> We have recently reported that the perhydrothiazepinone 1 had a potent inhibitory activity against ACE and was a candidate for an antihypertensive agent.<sup>3)</sup> 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.



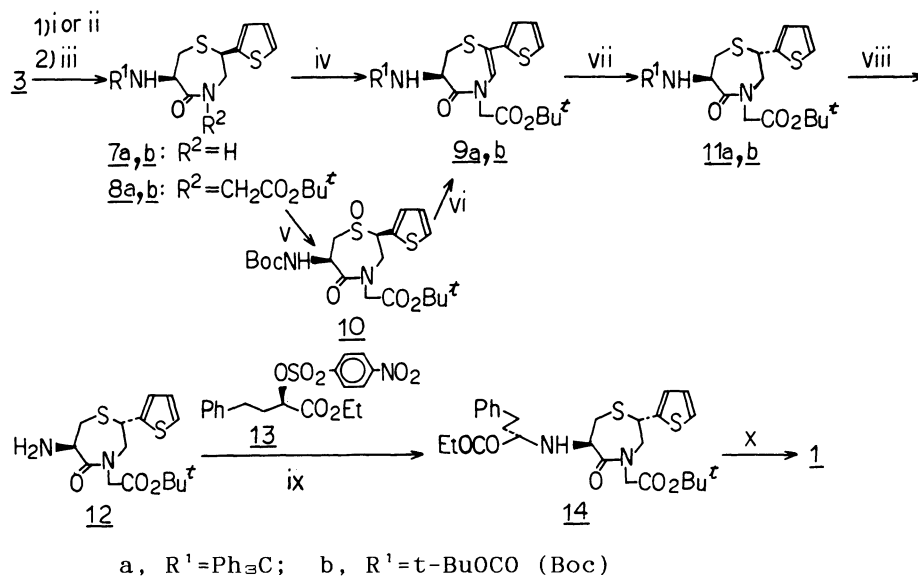
According to the conformational energy calculation of 6-amino-5-oxo-2-phenylperhydrothiazepin-4-ylacetic acid<sup>3)</sup> the 2S,6R isomer **6** takes a chair conformation possessing two pseudoequatorial substituents at the 2 and 6 positions, while the 2R,6R one **4** takes the same conformation except 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.<sup>4)</sup>



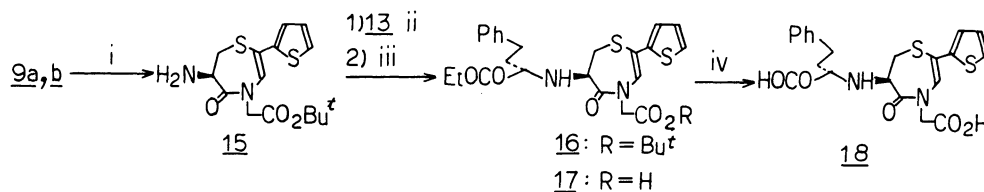
Treatment of **3** with trityl chloride or di-tert-butyl dicarbonate followed by alkylation with tert-butyl bromoacetate gave **8a,b**,<sup>5)</sup> respectively, which were oxidized with tert-butyl hypochlorite in the presence of a base to give 6,7-dihydro-1,4-thiazepin-5(4H)-ones **9a,b**,<sup>5)</sup> respectively, in moderate yields. **9b** was also obtained from **8b** through the sulfoxide **10**.<sup>5)</sup> <sup>1</sup>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**,<sup>5)</sup> 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**,<sup>5)</sup> which was converted to the diester **14**<sup>3)</sup> by N-alkylation with the sulfonate **13**. Removal of the tert-butyl group with acid gave the potent ACE inhibitor **1**.<sup>3)</sup>

Next, the ACE inhibitor **17**<sup>5)</sup> 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<sup>5,6)</sup> which was less potent than the corresponding dicarboxylic acid ( $IC_{50}=3.6$  nM)<sup>7)</sup> of 1 but still had potent inhibitory activity ( $IC_{50}=6.8$  nM).<sup>7)</sup>



Reagents, reaction conditions and yields. i)  $Ph\equiv CCl$ ,  $Et_3N$  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  $\rightarrow$  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  $\rightarrow$  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,

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- 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 data. The physical and spectral data are as follows. Optical rotations were measured at a 1% solution in DMF at 25 °C. **7a**: amorphous;  $[\alpha]_D -46.9^\circ$ . **7b**: mp 197-199 °C (dec);  $[\alpha]_D -76.5^\circ$ . **8a**: mp 150-151 °C (dec);  $[\alpha]_D -53.2^\circ$ . **8b**: mp 162-164 °C;  $[\alpha]_D +3.7^\circ$ . **9a**: mp 90-91 °C;  $[\alpha]_D -326.8^\circ$ ; NMR (CDCl<sub>3</sub>)  $\delta$  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;  $[\alpha]_D -603.5^\circ$ ; NMR (CDCl<sub>3</sub>)  $\delta$  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 °C;  $[\alpha]_D -125.6^\circ$ . **11a**: amorphous;  $[\alpha]_D +28.6^\circ$ ; NMR (CDCl<sub>3</sub>)  $\delta$  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;  $[\alpha]_D +46.3^\circ$ ; NMR (CDCl<sub>3</sub>)  $\delta$  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 °C; NMR (CDCl<sub>3</sub>)  $\delta$  1.47(9H,s), 2.29(2H,br s), 2.6-4.7(8H,m), 6.75(3H,m). **15**: mp 90 °C;  $[\alpha]_D -517.5^\circ$ ; NMR (CDCl<sub>3</sub>)  $\delta$  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;  $[\alpha]_D -296.8^\circ$ ; NMR (CDCl<sub>3</sub>)  $\delta$  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 °C;  $[\alpha]_D -506.1^\circ$ ; NMR (CDCl<sub>3</sub>)  $\delta$  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 °C (dec); NMR (DMSO-d<sub>6</sub>)  $\delta$  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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