SYNTHESIS OF 2-AMINOTHIAZOLYL ANALOGS OF ERGOTHIONEINE

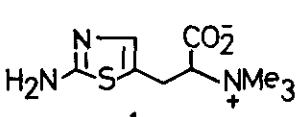
Katsuhiro Konno, Haruhisa Shirahama and Takeshi Matsumoto

Department of Chemistry, Faculty of Science, Hokkaido University

Sapporo 060, JAPAN

Abstract —— Two new thiazolyl betaines 1 and 2, isomers of *ergothioneine*, have been synthesized as model compounds of a novel betaine isolated from a toxic mushroom.

In the course of our studies[1] on the chemical constitutents of poisonous mushroom, Clitocybe acromelalga, a small amount (~1 mg) of a new, amorphous betaine[2] (M^+ 229.0880, $C_9H_{15}N_3O_2S$) isomeric with ergothioneine was isolated. The spectral properties of the new betaine were similar to those of ergothioneine, but behavior in paper electrophoresis of the former was clearly different from the latter. Therefore, synthesis of the following two 2-aminothiazolyl analogs (1 and 2) of ergothioneine was undertaken in order to compare their properties to those of the newly isolated compound from the mushroom. Although the synthetic compounds were found not identical with the natural product, we report herein the synthesis of 1 and 2, since they may be active as antagonists of ergothioneine[3]. Moreover some 2-aminothiazole derivatives are shown to act as thyroid inhibitor[4].



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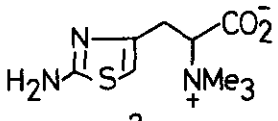
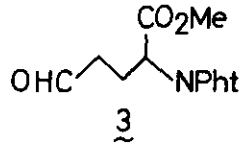


2

Acid chloride[5] of α-methyl phthaloyl-L-glutamate was reduced to an aldehyde 3 [NMR: δ ($CDCl_3$) 2.4—2.7 (4H, m, $-CH_2CH_2-$), 3.74 (3H, s, $-CO_2CH_3$), 4.7—5.0 (1H, m, α-proton), 7.6—8.0 (4H, m, -NPht), 9.70 (1H, s, -CHO), MS: m/e 275.0791(M^+), calcd. for $C_{14}H_{13}NO_5$ 275.0880, $[\alpha]_D^{25°}$ -25.1° (C=1.17, $CHCl_3$)] by $(\phi_3P)_2CuBH_4$[6] (62% yield, 2 eq. ϕ_3P, 1 eq. $(\phi_3P)_2CuBH_4$ in acetone, rt. 1.5 hr). Thus obtained aldehyde 3 was converted by phenyltrimethylammonium perbromide in THF (rt. 1.5 hr) to α-bromoaldehyde, which was condensed without purification with thiourea in THF (reflux,16 hr) to give a 2-aminothiazole derivative 4 [NMR: δ ($CDCl_3$) 3.5—3.8 (2H, m, $-CH_2-$),

3.76 (3H, s, $-CO_2CH_3$), 5.0—5.2 (1H, m, α-proton), 6.68 (1H, s, thiazole 4-H), 7.6—8.0 (4H, m, -NPht), MS: m/e 332.0661 [$(M+1)^+$], calcd. for $C_{15}H_{14}N_3O_4S$ 332.0703] in 71% yield. After blocking of the aromatic amino group by carbobenzoxy group in the usual manner (88% yield) to give 5 [NMR: δ ($CDCl_3$) 3.64 (2H, d, J=8.5 Hz, $-CH_2-$), 3.76 (3H, s, $-CO_2CH_3$), 5.02 (1H, t, J=8.5 Hz, α-proton), 5.16 (2H, s, $-O\underline{CH_2}\phi$), 6.83 (1H, s, thiazole 4-H), 7.34 (5H, s, $-OCH_2\underline{\phi}$), 7.6—8.0 (4H, m, -NPht), MS: m/e 465.0994 (M^+), calcd. for $C_{23}H_{14}N_3O_6S$ 465.0994, mp. 161—162°, $[\alpha]_D^{25°}$ -65.3° (C=0.92, $CHCl_3$)], the phthaloyl group was removed by heating 5 with hydrazine acetate (10 eq., 55°C, 16 hr, in MeOH-THF, 77% yield) to afford 6 [NMR: δ ($CDCl_3$) 3.9—4.1 (2H, m, $-CH_2-$), 3.70 (3H, s, $-CO_2CH_3$), 3.5— 3.9 (1H, m, α-proton), 5.23 (2H, s, $-O\underline{CH_2}\phi$), 6.90 (1H, s, thiazole 4-H),



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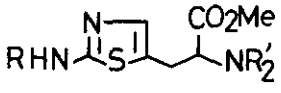
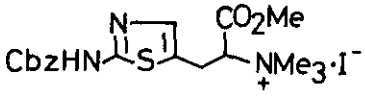


4 R = H , R_2' = Pht
5 R = Cbz , R_2' = Pht
6 R = Cbz , R_2' = H_2



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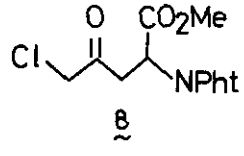
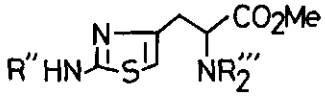
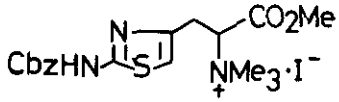


8



9 R'' = H R_2''' = Pht
10 R'' = Cbz R_2''' = Pht
11 R'' = Cbz R_2''' = H_2



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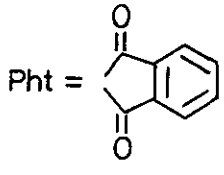

Cbz = $-CO_2CH_2\phi$

7.36 (5H, s, $-OCH_2\underline{\phi}$), MS: m/e 335.0872 (M^+), calcd. for $C_{15}H_{17}N_3O_4S$ 335.0938, mp. 123°]. Quaternary methiodide 7 [NMR: δ (CD_3OD) 3.2—3.5 (11H, bs, $-N^+(CH_3)_3$ and $-CH_2-$), 3.76 (3H, s, $-CO_2CH_3$), 4.54 (1H, dd, J=7, 12 Hz, α-proton) 5.28 (2H, s, $-O\underline{CH_2}\phi$), 7.25 (1H, s, thiazole 4-H), 7.40 (5H, s, $-OCH_2\underline{\phi}$), $C_{18}H_{24}N_3O_4SI$[7], mp. 195° (dec.)] was obtained through a) dimethylation (37% HCHO/$NaBH_3CN$, rt, 2 hr, in CH_3CN) and b) subsequent quaternarization[8] (CH_3I/MeOH, rt, 16 hr, 70% overall yield). Removal of the protective groups (62% yield, a. CF_3CO_2H, reflux, 1.5 hr, b. Et_3N-H_2O-MeOH (1:4:6), 60 °C, 16 hr) completed the synthesis of 2 [NMR: δ (D_2O) 3.2—3.4 (11H, bs, $-N^+(CH_3)_3$ and $-CH_2-$), 3.85 (1H, dd, J=5, 11 Hz, α-proton), 7.00 (1H, s, thiazole 4-H), MS: m/e 229.0880, calcd. for $C_9H_{15}N_3O_2S$ 229.0885, mp. 210° (dec.), $[\alpha]_D^{25°}$ -2.7°[9] (C=0.6, H_2O)].

Synthesis of the other isomer 3 was started from condensation of 8[10] with thiourea (63% yield, THF, reflux, 1.5 hr) to give 9 [NMR: δ ($CDCl_3$) 3.41 (2H, d, J=8 Hz, $-CH_2-$), 3.72 (3H, s, $-CO_2CH_3$), 5.23 (1H, t, J=8 Hz, α-proton), 5.50 (2H, bs, $-NH_2$), 6.07 (1H, s, thiazole 5-H), 7.5—7.9 (4H, m, -NPht), MS: m/e 332.0647 [$(M+1)^+$] calcd. for $C_{15}H_{14}N_3O_4S$ 332.0703, mp. 173—175°], which afforded, through the same sequence of reactions with 4→2, intermediates 10, 11, 12,[11] and the final product 3 [NMR: δ (D_2O) 3.2—3.4 (11H, bs, $-N^+(CH_3)_3$ and $-CH_2-$), 3.95 (1H, dd, J=5, 10 Hz, α-proton), 6.45 (1H, s, thiazole 5-H), MS: m/e 229.0876 (M^+) calcd. for $C_9H_{15}N_3O_2S$ 229.0882, amorphous, $[\alpha]_D^{25°}$ -3.6°[9] (C=0.52, H_2O)] (48% from 12).

Biological activities of synthetic betaines are now under investigation.

References and Notes

1) K. Konno, K. Hayano, H. Shirahama, H. Saito and T. Matsumoto, Tetrahedron Letters, 481 (1977).

2) NMR: δ (D_2O) 3.24 (11H, bs), 4.15 (1H, m), 7.0 (1H, s), UV: $\lambda_{max}^{H_2O}$ 246 nm, MS: m/e 229.0880 (M^+, $C_9H_{15}N_3O_2S$), 184.0858 ($C_8H_{14}N_3S$), 126.0243 ($C_5H_6N_2S$), 59.0727 (C_3H_9N), 58.0654 (C_3H_8N), CI—MS: m/e 230 $(M+1)^+$, FD—MS: m/e 230 $(M+1)^+$.

3) For physiological activities of ergothioneine see M. Fujii, Kagaku to Seibutsu (Chemistry and Life), 15, 638 (1977); M. Fujii, N. Hirano, T. Izumi, T. Furuya, Sci. Pap. Fac. Agr. Saga Univ., 36, 95 (1974).

4) R.H. Williams, G.A. Kay and B. Solomon, Amer. J. Med. Sci., 213, 198 (1947); D. Bovet, J. Bablet and J. Fournel, Ann. Inst. Pasteur, 72, 105 (1946).

5) F.E. King, J.W. Clark-Lewis and Roy Wade, J. Chem. Soc., 886 (1957).

6) G.W.J. Fleet, C.J. Fuller and P.J.C. Harding, Tetrahedron Letters, 1437 (1978); T.N. Sorrell and R.J. Spillane, ibid, 2473 (1978).

7) Satisfactory elementary analytical data was obtained for this compound.

8) V.N. Reinhold, Y. Ishikawa and D.B. Melville, J. Med. Chem., 11, 258 (1968).

9) The product might have been partially racemized. For an example of ready racemization of betaines see, H. Heath, A. Lawson and C. Rimington, J. Chem. Soc., 2215 (1951).

10) J.C. Sheehan and W.A. Bolhofer, J. Amer. Chem. Soc., 72, 2469 (1950).

11) 10 (92% yield) [NMR: δ ($CDCl_3$) 3.48 (2H, d, J=7 Hz, $-CH_2-$), 3.70 (3H, s, $-CO_2CH_3$), 5.13 (1H, t, J=7 Hz, α-proton), 5.21 (2H, s, $-OCH_2\phi$), 6.45 (1H, s, thiazole 5-H), 7.24 (5H, s, $-OCH_2\phi$), 7.4—7.8 (4H, m, -NPht). MS: m/e 465.1020 (M^+) calcd. for $C_{23}H_{19}N_3O_6S$ 465.0995],

11 (48% yield) [NMR: δ ($CDCl_3$) 2.8—3.0 (2H, m, $-CH_2-$), 3.62 (3H, s, $-CO_2CH_3$), 3.6—3.8 (1H, m, α-proton), 4.40 (2H, bs, $-NH_2$), 5.20 (2H, s, $-OCH_2\phi$), 6.44 (1H, s, thiazole 5-H), 7.27 (5H, s, $-OCH_2\phi$), MS: m/e 335.0953 (M^+) calcd. for $C_{15}H_{17}N_3O_4S$ 335.0900, $[\alpha]_D^{25°}$ -12.0° (C=1.0, $CHCl_3$)],

12 (72% yield) [NMR: δ (CD_3OD) 3.2—3.5 (11H, bs, $-N^+(CH_3)_3$ and $-CH_2-$), 3.72 (3H, s, $-CO_2CH_3$), 4.55 (1H, dd, J=5.5, 10 Hz, α-proton), 5.22 (2H, s, $-OCH_2\phi$), 6.90 (1H, s, thiazole 5-H), 7.32 (5H, s, $-OCH_2\phi$), $C_{18}H_{24}N_3O_4SI$[7], mp. 189—191° (dec.).

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