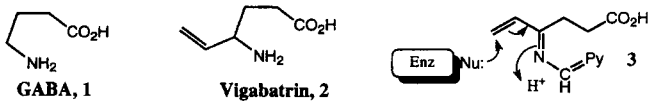
Epoxidized Derivatives of Vigabatrin as a GABA-AT Inhibitor

Min-soo Park, Jong-won Choi, Jin-hee Lee†, Pan-suk Kwon†, and Tae-woo Kwon†*

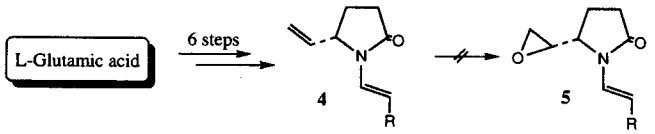
Department of Pharmacy and †Department of Chemistry, Kyungsung University, 110-1, Daeyeon-Dong, Nam-Gu, Pusan 608-736, Korea

Received March 7, 1998

GABA (4-Aminobutanoic acid, **1**) is an important neurotransmitter in mammalian central nervous system (CNS).[1] GABA deficiency has been associated with a variety of neurological disorders including Parkinson's disease,[2] epilepsy,[3] and Huntington's chorea.[4] Increasing the brain concentrations of GABA can have an anticonvulsant effect. The convulsions associated with epilepsy can be diminished by administration of GABA directly into the brain.[5] Since synthetic GABA itself does not effectively penetrate the blood-brain-barrier, there has been a need for agents such as prodrug of GABA or GABA-AT (aminotransferase) inhibitors that could enhance the concentration of GABA in brain.[6] Vigabatrin **2** is typical GABA-AT inhibitor in clinical use for the treatment of epilepsy.[7] The mechanism for the inhibition of aminobutyrate transaminase by 4-amino-hex-5-enoic acid **2** was proposed previously in which a Shiff's base **3** formed and then a Michael type addition of nucleophiles in the enzyme followed.[8]



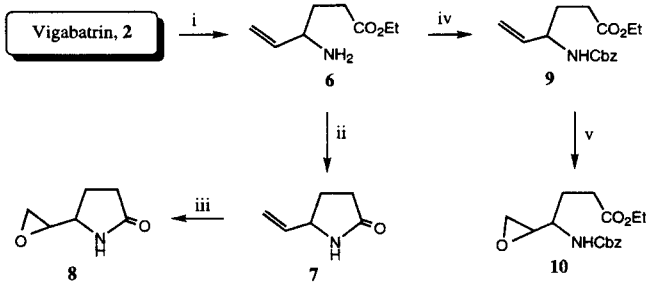
Very recently, *N*-alkenyl-5-ethenyl-pyrrolidin-2-one derivatives (**4**, R=ethyl, hexyl, phenyl) were prepared from L-glutamic acid (6 steps)[9] and we were interested in obtaining the epoxides of **4** since anticonvulsant activities might be expected from such compounds on the basis of the mechanism mentioned above. However, the epoxidation using 3-chloroperoxy benzoic acid did not give the desired product (**5**) which could be converted into epoxidized vigabartrin



R=CH_2CH_3, $CH_2(CH_2)_4CH_3$, Ph

derivatives. ^{1}H NMR of the oxidation product revealed that the vinyl (CH-CH=CH_2, 5.83-5.08 ppm) group was unreacted eventhough GC/MS showed M+16 peaks. There exist a variety of possibilities regarding the nature of the product structure. However, the structural elucidation has not yet been successful due to the instability of the compound. For the current purpose, the difficulty could be bypassed by employing the *N*-Cbz protecting group. Thus, commercial tablets of vigabatrin (**2**) were grounded and dissolved in minimum amount of water, then resulting solution was centrifuged for 30 minutes. The aqueous layer was decanted from white precipitates and evaporated under high vacuum. The purified vigabatrin was treated with thionyl chloride in absolute ethanol to give in quantitative yield 4-amino-hex-5-enoic ethyl ester (**6**) as a white solid. Refluxing the ethyl ester (**6**) for 40 hours in toluene gave the cyclized lactam derivatives (**7**) after column chromatography on silica gel[10] and **7** was further reacted with 3-chloroperoxybenzoic acid to give 5-(1,2-epoxy)-pyrrolidin-2-one (**8**) as a pale yellow oil.

The ethyl ester (**6**) was treated with 1.2 equivalents of Cbz-Cl at 0 °C-RT to give 75% of *N*-Cbz-4-aminohex-5-enoic acid ethyl ester (**9**) as a racemic mixture. When **9** was reacted with 1.5 equivalents of 3-chloroperoxybenzoic acid for 40 hours at 0 °C, 81% of epoxidized GABA derivative (**10**) was obtained after column chromatography.



(i) $SOCl_2$, ethanol , 3hr (ii) reflux/toluene, 40hr (iii) MCPBA/CH_2Cl_2, 0°C (iv) Cbz-Cl, RT, 48hr (v) MCPBA/CH_2Cl_2, 0°C

In conclusion, we have successfully prepared the epoxides of vigabartrin derivatives (**8** and **10**) in good yields. We are currently in process of evaluating their anticonvulsant activities against MES, PTZ, Sc.Pic and Sc. Bic tests.

Experimental

5-Vinyl-pyrrolidin-2-one (7). To a stirred suspension of vigabatrin (**2**, 3 g, 23.26 mmole) in ethanol (30 mL) was added freshly distilled thionyl chloride (4.22 mL, 58.15 mmole) at 0 °C under an argon atmosphere. The solution was stirred at room temperature for 1 hour and then refluxed for 2 hours. Evaporation of the solvent below 40 °C gave a white solid and the crude product was purified by column chromatography to give a quantitative yield of **6** as a white solid. 4-Amino-hex-5-enoic acid ethyl ester, **6** (3.4 g, 21.66 mmole) in excess toluene was heated at reflux for 40 hours. Evaporation of the mixture under reduced pressure and purification by column chromatography (5% methanol+95% methylene chloride, R_f=0.32) to give 5-vinyl-pyrrolidin-2-one (**7**, 1.24 g, 11.17 mmole, 52%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.40 (1H, broard s, NH), 5.83-5.72 (1H, m), 5.23-5.17 (1H, d, J=17.12 Hz), 5.12-5.09 (1H, d, J=10.22 Hz), 4.20-4.11 (1H, m) and 2.41-2.10 (4H, m) ppm. ^{13}C NMR (300 MHz, $CDCl_3$); δ 178.94, 139.06, 116.15, 57.12, 30.26 and 28.40 ppm. IR (KBr); 3245.4,

3081.3, 1691.5, 1458.7, 1425.1, 1257.5, 994.0 and 926.9 cm^{-1}. GC/MS : CIMS 112 (M+1).

5-(1,2-epoxy)-pyrrolidin-2-one (8). To a solution of 5-vinyl pyrrolidin-2-one (0.3 g, 2.70 mmole) in methylene chloride (10 mL) at 0 °C under an argon atmosphere was added 3-chloroperoxybenzoic acid (1.40 g, 8.12 mmole). The flask was tightly stoppered and stirred for 40 hours at 0 °C, then the reaction mixtures was filtered, the filterate was evaporated and purified by column chromatography (5% methanol+95% methylene chloride, R_f= 0.31) to give 5-epoxy-pyrrolidin-2-one, (**8**, 0.21 g, 1.65 mmole, 61.1%) as a pale yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.02 (1H, broad s, NH), 3.53-3.44 (1H, m), 3.02-2.90 (1H, m), 2.88-2.51 (2H, m), 2.48-1.87 (4H, m). ^{13}C NMR (300 MHz, $CDCl_3$); δ 178.64, 55.68, 54.44, 44.65, 29.63 and 23.65 ppm. IR (neat); 3397.8, 2992.0, 1685.0, 1473.8, 1423.7, 1284.0, 1260.3, 946.1, 882.3 and 850.3 cm^{-1}. GC/MS: CIMS 128 (M+1).

***N*-Cbz-4-aminohex-5-enoic acid ethyl ester (9).** To a solution of $NaHCO_3$ (5.8 g, 69.04 mmole) in H_2O (30 mL) and 4-amino-hex-5-enoic acid ethyl ester (3.6 g, 22.93 mmole) in distilled acetone (30 mL) at 0 °C under an argon atmosphere was added Cbz-Cl (4.72 g, 3.95 mL, 27.67 mmole) in acetone (12 mL) via syringe. The mixture was stirred for 30 minutes at 0 °C and then for 48 hours at room temperature. This reaction mixture was extracted with ethyl acetate (3 times) and combined extracts were dried over $MgSO_4$, filtered, and concentrated. The crude product was purified by column chromatography on silica gel (5% methanol+95% methylene chloride, R_f=0.73) to give N-Cbz-4-aminohex-5-enoic acid ethyl ester (**9**, 5.02 g, 17.25 mmole, 75%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (5H, s), 5.75-5.67 (1H, m), 5.21-4.90 (3H, m), 5.09 (2H, s), 4.22 (1H, m), 4.12 (2H, q, J=7.11 Hz), 2.45-2.29 (2H, m), 1.97-1.79 (2H, m), 1.23 (3H, t, J=7.11 Hz). ^{13}C NMR (300 MHz, $CDCl_3$); δ 173.17, 155.78, 137.82, 136.44, 128.41, 127.99, 115.32, 66.65, 60.45, 53.01, 30.67, 29.72 and 14.09 ppm. IR (KBr); 3335.2, 3150.5-2939.6, 1731.1, 1646.0, 1529.6, 1455.0, 1376.5, 1248.5, 1182.3, 1068.1, 925.0 and 739.6 cm^{-1}. GC/MS : EIMS m/s 291 (M^+).

***N*-Cbz-4-amino-5,6-epoxy-hexanoic acid ethyl ester (10).** To a solution of *N*-Cbz 4-amino-5-enoic acid ethyl ester, **9** (0.62 g, 2.13 mmole) in methylene chloride (30 mL) at 0 °C under an argon atmosphere was added 3-chloroperoxybenzoic acid (MCPBA, 1.11 g, 6.43 mmole). The flask was tightly stoppered and stirred for 40 hours at 0 °C, then the reaction mixtures was filtered, evaporated and purified by column chromatography on silica gel (CH_2Cl_2, R_f=0.38) to give *N*-Cbz-5-epoxy GABA ethyl ester (**10**, 0.50 g, 1.72 mmole, 81%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.34 (5H, s), 5.08 (2H, s), 4.75 (1H, broad), 4.12 (2H, q, J=10.5 Hz), 4.10 (1H, m), 2.72 (2H, m), 2.57 (1H, m), 2.44 (2H, t, J=11.4 Hz), 2.01-1.97 (2H, m), 1.24 (3H, t, J=10.5 Hz) ppm. ^{13}C NMR (300 MHz, $CDCl_3$); δ 172.94, 156.18, 128.48, 128.12, 128.01, 127.95, 66.88,60.54, 53.23, 49.48, 44.07, 30.59, 28.31 and 14.13 ppm. IR (KBr); 3338.0, 3090.0-2938.3, 1727.4, 1527.8, 1455.7, 1375.7, 1339.7, 1246.5, 1183.3, 1071.5, 861.3 and 739.8 cm^{-1}. GC/MS: EIMS m/s 307 (M^+).

Acknowledgment. This work was supported by a grant of the 96 and 97' Good Health R&D Project, Ministry of Health and Welfare, R.O.K.

References

1. (a) Metcalf, B. W. *Biochemical Pharmacology* **1979**, *28*, 1705 and references cited therein (b) Krnjeric, K. *Nature, Lond* **1970**, *228*, 119.
2. Barbeau, A. *Lancet II* **1973**, 1499.
3. Roberts, E. *Biochem. Pharmac.* **1974**, *23*, 2637.
4. Perry, T. L.; Hansen, S.; Jkister, M. N. *New Engl. J. Med.* **1973**, *288*, 337.
5. Karlesson, A.; Fonnum, F.; Malthe-Sorensen, D.; Storm-Mathisen, J. *J. Biochem. Pharmacol* **1974**, *23*, 3053.
6. Roberts, E.; Kuriyama, K. *Brain Res.* **1968**, *8*, 1.
7. (a) Kwon, T. W.; Keusenkothen, P. F.; Smith, M. B. *J. Org. Chem.* **1992**, *57*, 6169. (b) Tassinari, C. A.; Michelucci, R.; Ambrosetto, G.; Salvi, F. *Arch. Neurol.* **1987**, *44*, 907-910. (c) Browne, T. R.; Mattson, R. J.; Penry, J. K.; Smith, D. B.; Treiman, D. M.; Wilder, B. J.; Ben-Mensachem, E.; Miketta, R. M.; Sherry, K. M.; Szabo, G. K. *Br. J. Clin. Pharmacol.* **1989**, *27*, 952.
8. (a) Silverman, R. B. *Mechanism-Based Enzyme Inactivation; Chemistry and Enzymology*; CRC Press: Boca Raton, FL, 1988, vol 1 and 2. (b) Silverman, R. B. *Methods Enzymol.* **1995**, *249*, 240.
9. Manuscripts in preparation.
10. Keusenkothen, P. F.; Smith, M. B. *J. Chem. Soc., Perkin Trans* **1994**, *1*, 2485.