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Synthesis and Anticonvulsant Activity of (*R*)- and (*S*)-3-(Carbobenzyloxy-amino-1-glutarimidooxy)esters

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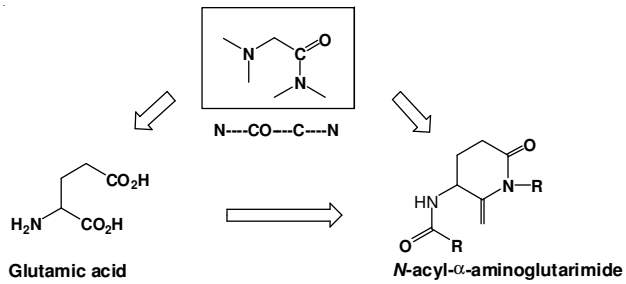
A series of (*R*)- and (*S*)-3-carbobenzyloxy-amino-1-glutarimidooxy-esters (**5a-e**) ((*R*)-and (*S*)-methyl-1-(3-carbobenzyloxy-amino-glutarimidooxy)acetate (**5a**), (*R*)-and (*S*)-ethyl-1-(3-carbobenzyloxy-amino-glutarimidooxy)acetate (**5b**), (*R*)- and (*S*)-ethyl-1-(3-carbobenzyloxy-amino-glutarimidooxy)propionate (**5c**), (*R*)- and (*S*)-methyl-2-(3-carbobenzyloxy-amino-glutarimidooxy)butyrate (**5d**), (*R*)- and (*S*)-ethyl-2-(3-carbobenzyloxy-amino-glutarimidooxy)butyrate (**5e**) were synthesized and investigated their anticonvulsant activities.

Key Words: Epilepsy, Glutamic acid, (*R*)- and (*S*)-Glutarimidooxy ester, Anticonvulsant activity, ED_{50}.

INTRODUCTION

Epilepsy is a common and diverse set of chronic neurological disorders characterized by seizures[1]. Epileptic seizures result from abnormal, excessive or hypersyn chronous neuronal activity in the brain. Epilepsy is usually controlled, but not cured, with medication. However, over 30 % of people with epilepsy do not have seizure control even with the best available medications[2-6]. Futheremore, the antiepileptic drug presently used in clinical practics suffer from a broad range of adverse side effects including sedation, tetratogenecity, cognitive dulling and liver toxicity. And clinically the epilepsy consists of various forms of seizure, so that there is a need for combination and repeat therapy to control the such complex convulsion. Owing to this multitherapy, there is a danger of toxic and troublesome side effect[7-10]. Consequently, there is a need for the development of new antiepileptic compound having broader clinical spectrum and lower toxic side effects. Recently, there has been many trials for the development of new typed anticonvulsant compounds including derivatives of various amino acids such as alanine derivatives and N-benzoyl and N-phenyl glycine amide and structural modification of currently used drug such as hydantoin, succinimdes and glutarimides and various GABA related compounds[11-15].

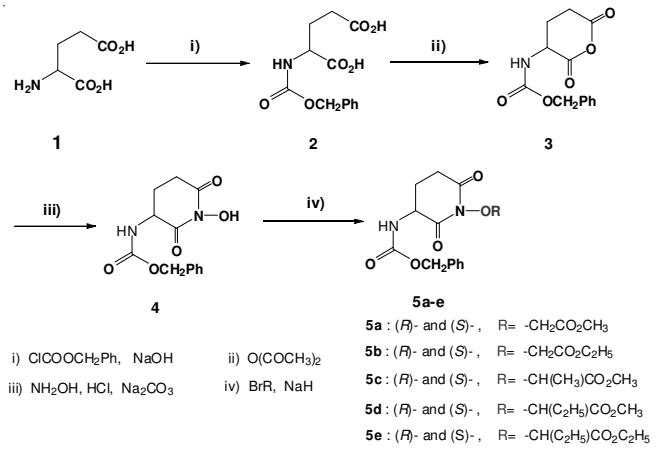
But these compounds had some limitation in clinical use that some drug showed anticonvulsant effect only in maximal electric shock seizure test (MES) or pentylene-tetrazole induced seizure test (PTZ). So we were interested in the development of new anticonvulsant compounds of broad spectrum. In connection with the studies for the development of anticonvulsants, we tried examining the structural similarities of currently available anticonvulsant compounds, known to act by different pharmacological mechanisms each other. From the studies of structural similarities of anticonvulsants, we find out the interesting facts that anticonvulsant compounds included the common structural moieties such as NH-CO-C-N and imide in their structures and also some MNDA antagonist, showing anticonvulsive effect, had structural similarity to glutamic acid, known as excitatory amino acid, in view of bioisoster. So we thought that the new anticonvulsants could be possibly developed from the glutamic acid in view of their structural sences. And we designed the following imides such as A, having aforesaid common structures such as NH-CO-C-N, imide and aminocarbonyl of GABA in their structure originated from glutamic acid as shown in **Scheme-I**.



Scheme-I: Structure of N-acyl-α-aminoglutarimide

Usually the stereoisomers exhibited different pharmacological activities, so we tried preparing all the (*R*)- and (*S*)-compounds in order to investigate the pharmacological

differences between their stereoisomers. The compounds (**1a-d**) could be prepared from the corresponding (*R*)- or (*S*)-glutamic acid in moderate yields by known chemical reactions as shown in **Scheme-II**.



Scheme-II: Synthetic pathway

EXPERIMENTAL

Melting points were determined on a Büchi 510 capillary melting point apparatus and uncorrected. Infrared spectra were recorded on a Perkin-Elmer 683 spectrophotometer. NMR spectra were recorded on a Varian XL-300 or Bruker AC 200 FT-NMR spectrometer in $CDCl_3$ containing Me_4Si as an internal reference. Mass spectra were obtained by using JEOL JMS DX 303 or HP 5892 Mass Spectrometer. (*R*)-3-carbobenzyloxyamino glutamic acid (**2**): To a solution of (*R*)-glutamic acid (**1**) 5.88 g, 40 mmol) and NaOH (1.60 g, 40 mmol) in H_2O (16 mL) and acetone (32 mL) at 0 ºC was added solution of carbobenzyloxy chloride (6.82 g, 40 mmol) and NaOH (1.6 0g, 40 mmol) in H_2O (16 mL) and acetone (17 mL). The reaction mixture was stirred at room temperature for 7 h. After reaction solution was concentrated *in vacuo*, it was carefully acidified (pH = 2) with conc HCl. Then the white solid was obtained in good yield (9.60 g, 86 %). (R)-3-carbobenzyloxy-amino-glutamic acid (**2**): yield 86 %; m.p. 122-123 ºC; R_f 0.46 (TLC eluent; benzene: THF: formic acid = 15:5:2, v/v/v); IR (KBr, ν_{max}, cm^{-1}): 3400, 3300, 3100, 1750, 1700, 1680; ^1H NMR (DMSO-d_6): δ 1.70~2.00 (m, CH_2, 2H), 2.20~2.40 (m, CH_2, 2H), 4.00~4.20 (m, CH, 1H), 5.03 (s, CH_2, 2H), 7.30 (s, ph, 5H). (*S*)-3-carbobenzyloxy-amino-aspartic acid (**2**): yield 80 %; the IR and ^1H NMR spectra of (*S*)-**2** was identical with the IR and ^1H NMR spectra of (*R*)-**2**. (*R*)-3-carbobenzyloxy-amino-glutamic anhydride (**3**): A mixture of synthesized (*R*)-**2** (5 g, 18 mmol) and acetic anhydride (50 mL) was stirred at room temperature for 2 h. The reaction mixture was concentrated *in vacuo*. After concentrating added 100 mL diethyl ether . Then the white solid was obtained in good yield (4.38 g, 94 %) m.p.: 96-97 ºC; R_f: 0.8 (T.L.C eluent; EtOAc); IR (KBr, ν_{max}, cm^{-1}): 1700, 1750, 1820, 3300. (S)-3-carbobenzyloxy-amino-glutamic anhydride (**3**): m.p. 130-131 ºC ; The IR and ^1H NMR spectra of (*S*)-**3** was identical with the IR and ^1H NMR spectra of (*R*)-**3**. (R)-3-carbobenzyloxy-amino-1-hydroxyglutarimide (**4**): A mixture of synthesized (R)-3-carbobenzyloxy-amino-glutamic anhydride (**3**) (2.63 g, 10 mmol) and hydroxylamine hydrochloride (0.83 g, 12 mmol) in H_2O (2 mL) with Na_2CO_3 (0.64 g) was stirred at 0 ºC for 1 h. The reaction solution was concentrated *in vacuo*. The white crystal (2.47 g, 89 %) was recrystallized by solution of ethanol and EtOAc. (*R*)-3-Carbobenzyloxy-amino-1-hydroxy glutarimide (**4**): yield 89 %; m.p. 136-137 ºC; R_f 0.46 (TLC eluent; benzene: THF: formic acid = 15:5:2, v/v/v) ; IR (KBr, ν_{max}, cm^{-1}): 1700, 1750, 1820, 3100, 3300 ; ^1H NMR (DMSO-d_6): δ 1.73~1.85 (m, CH_2, 2H), 2.18~2.25 (m, CH_2, 2H), 3.86~3.89 (m, CH_2, 1H), 5.00 (s, CH_2, 2H), 7.35 (s, ph, 5H). (*S*)-3-carbobenzyloxy-amino-1-hydroxy-glutarimide (**4**): yield 2.36 g (89 %). The IR and ^1H NMR spectra of (*S*)-**4** were identical with the IR and ^1H NMR spectra of (*R*)-**4**. The typical experimental procedure for synthesis of (*R*)-methyl-1-(3-carbobenzyloxy-amino-glutarimido-oxy)-acetate. A mixture of synthesized (*R*)-3-carbobenzyloxy-amino-1-hydroxyglutarimide (**4**) (0.55 g, 2.0 mmol) and $BrCH_2CO_2CH_3$ (0.37 g, 2.4 mmol) with NaH (0.096 g, 2.4 mmol) and DMF 10 mL were stirred at room temperature for 5 h. After EtOAc (200 mL) was added, The reaction mixture was added saturated $NaHCO_3$ solution (50 mL), 5 % HCl (50mL) and H_2O (50 mL) Then the confined organic layers were concentrated *in vacuo*. The obtained (*R*)-methyl-1-(3-carbobenzyloxy-amino-glutarimidooxy)acetate (**5a**) (0.53 g, 75 %) was recrystallized with EtOAc and *n*-hexane. (*R*)-Methyl-1-(3-carbobenzyloxy-amino-glutarimidooxy)acetate (**5a**): yield 75 %; R_f : 0.24 (TLC eluent; EtOAc: *n*-hexane = 1:1, v/v); IR (KBr, ν_{max}, cm^{-1}): 3350, 3000, 2900, 1750, 1250 ; ^1H NMR (DMSO-d_6): 1.93 (m, CH_2, 2H), 2.45~2.63 (m, CH_2, 2H), 3.76 ~3.78 (s, CH_3, 3H), 4.37 (m, CH_2, 2H), 4.55~4.64 (m, CH, 1H), 5.11~5.17 (m, CH_2, 2H), 7.45 (s, ph, 5H). (*S*)-methyl-1-(3-carbobenzyloxy-amino-glutarimidooxy)acetate (**5a**): yield, 0.49 g (70 %). The IR and ^1H NMR spectra of (*S*)-**5a** were identical with the IR and ^1H NMR spectra of (*R*)-**5a**. (*R*)-Ethyl-1-(3-carbobenzyloxy-amino-glutarimidooxy)acetate (**5b**): yield 67 % R_f: 0.25 (T.L.C eluent ; EtOAc: *n*-hexane = 1:1, v/v) ; IR (KBr, ν_{max}, cm^{-1}): 1200, 1750, 3000, 2900, 3350 ; ^1H NMR (DMSO-d_6): 1.24~1.31 (m, CH_3, 3H), 2.04~2.11 (m, CH_2, 2H), 2.48~2.58 (m, CH_2, 2H), 4.17~4.27 (m, CH_2, 2H), 4.47 (m, CH_2, 2H), 4.57~4.62 (m, CH, 1H), 5.08~5.13 (m, CH_2, 2H), 7.33 (s, ph, 5H). (*S*)-ethyl-2-(3- carbobenzyloxy-amino-glutarimidooxy)-acetate (**5b**): yield 70 %. The IR and ^1H NMR spectra of (*S*)-**5b** were identical with the IR and ^1H NMR spectra of (*R*)-**5b**. (*R*)-Ethyl-2-(3-carbobenzyloxy-amino-glutarimidooxy)propionate (**5c**): Yield 62 % R_f 0.17 (TLC eluent ; EtOAc : *n*-hexane = 1 : 2, v/v) ; IR (KBr, ν_{max}, cm^{-1}): 3300, 3000, 2900, 1750, 1200; ^1H NMR (DMSO-d_6): δ 1.13 ~1.23 (m, CH_3, 3H), 1.29~1.39 (m, CH_3, 3H), 1.77~1.81 (m, CH_2, 2H), 2.35 (s, CH_2, 2H), 3.92 (s, CH_2, 2H), 4.08~4.15 (m, CH, 1H), 4.41~4.44 (m, CH, 1H), 5.00 (s, CH_2, 2H), 7.34 (s, ph, 5H). (*S*)-ethyl-1-(3-carbobenzyloxy- amino-glutarimido-oxy)propionate (**5c**): yield 66 %. The IR and ^1H NMR spectra of (*S*)-**5c** were identical with the IR and ^1H NMR spectra of (*R*)-**5c**. (*R*)-Methyl-2-(3- carbobenzyloxy-amino-glutarimido-oxy)butyrate (**5d**): yield 77 % R_f 0.36 (T.L.C eluent; EtOAc: *n*-hexane = 1:1, v/v); IR (KBr, ν_{max}, cm^{-1}): 3350, 3000, 2900, 1750, 1250; ^1H NMR (DMSO-d_6): 0.97-1.07 (m, CH_3, 3H), 1.34~1.39 (m, CH_2, 2H), 1.79~1.93 (m, CH_2, 2H), 2.50~2.61 (m, CH_2, 2H), 3.51 (s, CH_3, 3H), 4.01 (s, CH, 1H), 4.42~4.45

(m, CH, 1H), 5.02~5.13 (m, CH_2, 2H), 7.46 (s, ph, 5H). (*S*)-Methyl-2-(3-carbobenzyloxy-amino-glutarimidooxy)butyrate (**5d**): yield 76 %. The IR and ^{1}H NMR spectra of (*S*)-**5d** were identical with the IR and ^{1}H NMR spectra of (*R*)-**5d**. (*R*)-Ethyl-2-(3-carbobenzyloxy-amino-glutarimidooxy)butyrate (**5e**): yield 71 % R_f: 0.30 (TLC eluent ; EtOAc: *n*-hexane = 1:2, v/v); IR (KBr, ν_{max}, cm^{-1}): 3350, 3000, 2900, 1750, 1200; ^{1}H NMR (DMSO-d_6): δ 0.97~1.03 (m, CH_3, 3H), 1.25~1.35 (m, CH_3, 3H), 1.88~2.01 (m, CH_2, 2H), 2.45~2.54 (m, CH_2, 2H), 2.79~2.90 (m, CH_2, 2H), 3.50 (s, CH, 1H), 4.20~4.27 (m, CH_2, 2H), 4.46 ~4.52 (m, CH, 1H), 5.13 (s, CH_2, 2H), 7.45 (s, ph, 5H). (*S*)-Ethyl-2-(3-carbobenzyloxy-amino- glutarimidooxy)butyrate (**5e**): yield 69 %. The IR and ^{1}H NMR spectra of (*S*)-**5e** were identical with the IR and ^{1}H NMR spectra of (*R*)-**5e**.

RESULTS AND DISCUSSION

From our standpoint about structural property of the imidooxy and carbobenzoyloxy glutarimide, we synthesized (*R*)- and (*S*)-methyl-1-(3-carbobenzyloxy-amino-glutarimidooxy)acetate (**5a**), (*R*)- and (*S*)-ethyl-1-(3-carbobenzyloxy-amino-glutarimidooxy)acetate (**5b**), (*R*)- and (*S*)-ethyl-1-(3-carbobenzyloxy-amino-glutarimidooxy)propionate (**5e**), (*R*)- and (*S*)-methyl-2-(3-carbobenzyloxy-amino-glutarimidooxy)-butyrate (**5d**), (*R*)- and (*S*)-ethyl-2- (3-carbobenzyloxy-amino-glutarimidooxy)butyrate (**5e**). All products gave satisfactory spectral data. So the compounds **5a-e** were submitted to the following anticonvulsant tests. It was reported that MES test was correlated to generalized tonic clonic seizure and PTZ test to generalized absence seizure. So the primary anticonvulsant activity of (*S*)-N-Cbz-α-amino-glutarimidoxy acetic acid ester are very meaningful for the clinical prediction of anticonvulsant drug candidates. Therefore we investigated the anticonvulsant activity for those compounds ((*R*)-**5a-e** and (*S*)-**5a-e**) in maximal electric shock seizure test (MES test) and pentylenetetrazole induced seizure test (PTZ test). The results of anticonvulsant activity are summarized in Table-1.

TABLE-1
PRIMARY ANTICONVULSANT ACTIVITY OF (*S*)-N-Cbz-α-AMINO-GLUTARIMIDOXY ACETIC ACID ESTER **5a-e** AGAINST THE STRYCHNINE TEST

Compound	Config	R	ED_{50} [a]
5a	S	$-CH_2CO_2CH_3$	45.8
5b	S	$-CH_2CO_2C_2H_5$	53.5
5c	S	$-CH(CH_3)CO_2CH_3$	69.2
5d	S	$-CH(C_2H_5)CO_2CH_3$	161.7
5e	S	$-CH(C_2H_5)CO_2C_2H_5$	98.3

[a]All compounds were dissolved in polyethyleneglycol and administered i.p to ICR male mice. Dos was denoted in mg/kg. [c]The Str. test: Subcutaneous strychnine (1.20 mg/kg) 0.5 h post administration of test compound.

We continue to synthesize their analogs and evaluate their anticonvulsant activities in order to develop more active anticonvulsant compounds and define the structure-activity relationship more distinctly.

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REFERENCES

1. (a) B.S. Chang and D.H. Lowenstein, *N. Engl. J. Med.*, **349**, 1257 (2003); (b) M.J. Brodie, A.T. Elder and P. Kwan, *Lancet Neurol.,* **8**, 1019 (2009); (c) J.S. Duncan, J.W. Sander, S.M. Sisodiya, M.C. Walker, *Lancet*, **367**, 9516 (2006); (d) R.M. Arida, E.A. Cavalheiro, F.A. Scorza and C.A. Scorza, *Neurosci. Biobehav. Rev*., **33**, 422 (2009); (e) W.B. Thomas, *Veterinary Clinics North America: Small Animal Practice*, **40**, 161 (2010).
2. (a) J.M. Liebmann and A. Schneider, *Ann. Med. Chem*., **20**, 11 (1985); (b) E.A. Swinyard, Antiepilepic Drug, Ravan Press: New York, edn. 2, p. 5 (1982).
3. D. Schmidt, *Epilepsia*, **25**, 244 (1984).
4. (a) D. Lindhart and R.J.E.A. Hopperner, *Epilepsia*, **25**, 77 (1984).
5. J.A. Vida, In ed.: W.O. Foye, Principle of Medicinal Chemistry, Lea & Febiger: Philadelphia, Ch. 11 (1995).
6. (a) H. Kohn, K.N. Sawhney, D. LeGall and J.D. Leader, *J. Med. Chem*., **34**, 2444 (1991); (b) H. Kohn, K.N. Sawhney, D. LeGall and J.D. Cinley, *J. Med. Chem*., **33**, 919 (1990); (c) J.D. Conley and H. Kohn, *J. Med. Chem*., **30**, 567 (1987).
7. (a) J. Takahashi, K. Ogui, H. Fujimura, I. Satoda, T. Fukui and Y. Yamamoto, Swiss Patent 393355, Oct. 30 (1965); (b) D.E. Thorne, US Patent. 3657341, April 8 (1972).
8. (a) W.J. Brouillette, V.P. Jestkov, M.L. Brown, M.S. Akhatar, T.M. DeLorey and G.B. Brown, *J. Med. Chem*., **37**, 3289 (1994); (b) C.H. Kwon, M.T. Iqbal and J.N.D. Eurpel, *J. Med. Chem*., **34**, 1845 (1991).
9. (a) V.A. Farrar, M. Ciechanowicz-Rutkowska, J. Grochowski, P. Serda, G. Filippini, C.N. Hinko, A. El-Assadi, J.A. Moore, I.O. Edafiogho, C.W. Andrew, M. Cory, J.M. Nicholson and K.R. Scott, *J. Med. Chem*., **36**, 3517 (1993); (b) I.O. Edafiogho, K.R. Scitt, J.A. Moore, V.A. Farrar and J.M. Nicholson, *J. Med. Chem*., **34**, 387 (1991); (c) M.R. Borenstein and P.H. Duukas, *J. Pharm. Sci*., **76**, 300 (1987); (d) M.J. Kornet, *J. Pharm. Sci*., **73**, 405 (1984).
10. (a) D.T. Witiak, S.K. Seth, E.R. Baizmann, S.L. Weibel and H.H. Wolf, *J. Med. Chem*., **19**, 1419 (1976); (b) H.Y. Aboul-Eneine, C.W. Schauberger, A.R. Hansen and L.J. Fischer, *J. Med. Chem*., **18**, 736 (1975).
11. (a) K.E. Andersen, C. Braestrup, F.C. Gronwald, A.S. Jorgensen, E.B. Nielsen, U. Sonnewald, P.O. Sorensen, P.D. Suzdak and L.J.S. Knutsen, *J. Med. Chem*., **36**, 1716 (1993); (b) V. N'Goka, G. Schlewer, J.M. Linget, J.P. Chambon and C.G. Wermuth, *J. Med. Chem*., **34**, 2547 (1991); (c) J.R. Bruke and R.B. Silvermann, *J. Am. Chem*. Soc., **113**, 9329 (1991).
12. (a) P.C.K. Pook, D.E. Jane and J.C. Watkins, *J. Med. Chem*., **37**, 4288 (1994); (b) R. Heckendorn, H. Allgeier, J. Baud, W. Grunzenhauser and C. Angst, *J. Med. Chem.,* **36**, 3721 (1993).
13. For the preparation of 4: M. Itoh, *Chem. Pharm. Bull*., **17**, 1679 (1969); For the preparation of 1 and 2: S.R. Sandler and W. Karo, Organic Functional Group preparation; Academic Press: New York, Vol. 3, p. 253 (1972).
14. (a) E.A. Swinyard, J.H. Woodhead, H.S. White and M.R. Franklin, In ed.: R. Levy, General Priciples, Experimental Section, Quantification and Evaluation of Anticonvulsants in Antiepileptic Drugs, New York, Ravan Press, edn. 3, p. 88 (1988); (b) R.L. Krall, J.K. Penry, B.G. White, H.J. Kupferberg and C.A. Swinyard, *Epilepsia*, **19**, 409 (1978).
15. R.J. Porter, J.J. Cereghino, G.D. Gladding, B.J. Hessie, H.J. Kupferberg, B. Scoville and B.G. White, *Cleveland Clin. Q*, **51**, 283 (1984).