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The Effect of *N*-Alkyloxycarbonyl Group on the Anticonvulsant Activities of *N*-Alkyloxycarbonyl-α-aminoglutarimides

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In connection with the development of new anticonvulsant agents with a broad spectrum, we reported that *N-Cbz*-α-aminoglutarimides, combining common structures of other anticonvulsants such as N-CO-C-N and cyclic imides in a single molecule, showed significant anticonvulsant activities in the MES (maximal electroshock seizure) and PTZ (pentylenetetrazole induced seizure) tests. In these studies, a series of (R) and (S) *N*-alkyloxycarbonyl-α-aminoglutarimides **7a~7e** and **8a~8e**, which were substituted with various alkyloxycarbonyl group instead of *Cbz* group, were prepared from the corresponding (R) and (S) *N-Cbz*-glutamic acid **3** and **4**, and were evaluated with their anticonvulsant activities against the MES and PTZ tests, including neurotoxicity, in order to define the effect of *N*-alkyloxycarbonyl group on the anticonvulsant activities of *N*-alkyloxycarbonyl-α-aminoglutarimides. Among them, (S) *N*-4-nitrobenzyloxycarbonyl-α-amino-*N*-methylglutarimide **8e** was the most active in MES (ED_{50}=35.6 mg/kg, PI=2.7) and PTZ tests (ED_{50}= 15.6, PI=6.1). Interestingly, (R) and (S) *N*-4-nitrobenzyloxycarbonyl-α-amino-*N*-methylglutarimide **7e** and **8e** and (R) *N*-phenoxycarbonyl-α-amino-*N*-methylglutrimide **7d** showed significant anticonvulsant activities in both the MES and PTZ tests and other compounds showed anticonvulsant activities in only the PTZ test. In addition, it was found that their anticonvulsant activities were dependent on their stereochemistries and *N*-substituted alkyloxycarbonyl groups.

Key words : MES test, PTZ test, Anticonvulsant, Aminoglutarimide, *N*-Alkyloxycarbonyl-α-aminoglutarimide

INTRODUCTION

The previous papers (Park *et al.*, 1996; Lee *et al.*, 1996) reported that *N*-Cbz-*N*-alkylglutarimides showed significant anticonvulsant activities in both the MES (maximal electroshock seizure) test and pentylene tetrazole as they induced seizure test (PTZ) and (R) and (S) *N-Cbz-N*-methylglutarimide **1** and **2** was most active among them enough to be recommended as new anticonvulsant agents (Lee *et al.*, 1996, 1997). Therefore we selected the (R) and (S) *N-Cbz*-α-amino-*N*-methylglutarimide **1** and **2** as the lead compounds for the futher investigation. In connection with these studies, we prepared a series of *N*-alkyloxycarbonyl-*N*-methylglutarimides **7** and **8**, as shown in Fig. 1, which were substituted with various alkyloxycarbonyl group instead of *Cbz* group and evaluated their anticonvulsant activities to define the effect of alkyloxycarbonyl group with their anticonvulsant activities.

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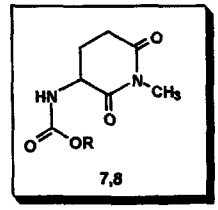
Here we wish to report the synthesis and anticonvulsant activities of *N*-alkyloxycarbonyl-α-amino-*N*-methylglutarimide **7** and **8**. In this paper, we focused on the effects of *N*-substituted alkyloxycarbonyl group with their anticonvulsant activities.

MATERIALS AND METHODS

Melting points were determined by a Electrothermal digital melting point apparatus and were incorrected. IR spectra were taken in KBr disk with JASCO FT/IR 200 and were recorded in cm^{-1}. ^{1}H-NMR spectra were recorded in $CDCl_3$ on JNM-EX90A and chemical shifts



7 a: (R), R=C_2H_5
b: (R), R=Allyl
c: (R), R=4-nitrobenzyl
d: (R), R=phenyl
e: (R), R= tert.butyl

8 a: (S), R=C_2H_5
b: (S), R=Allyl
c: (S), R=4-nitrobenzyl
d: (S), R=phenyl
e: (S), R= tert.butyl

Fig. 1. *N*-alkyloxycarbonyl-α-amino-*N*-methylglutarimide **7** and **8**.

were reported as δ values in parts per million from TMS as an internal standard. The pharmacological tests were carried out according to the proctocol of the Antiepileptic Drug Development Program of the National Institute of Neurological Disorders and Stroke (Swinyard *et al.*, 1989).

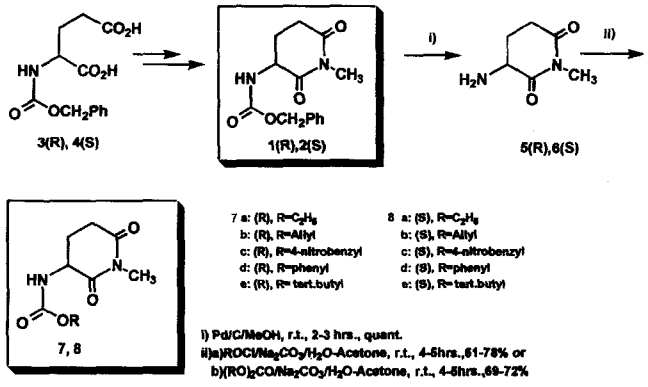
Synthesis

The synthetic methods of (R) and (S) *N-Cbz*-α-amino-*N*-methylglutarimide **7** and **8** were reported in our previous paper (Park *et al.*, 1996; Lee *et al.*, 1996;) and the final compounds for biological evaluation were prepared from the corresponding (R) or (S) *N-Cbz*-α-amino-*N*-methylglutarimide by hydrogenolysis with Pd/C and acylation with various alkoxycarbonyl chlorides or di tert. butyl-dicarbonates. The synthetic procedure is outlined in Scheme 1.

(R) α-Amino-*N*-methylglutarimide 5: (R) *N-Cbz*-α-amino-*N*-methylglutarimide (552 mg) was subjected to run catalytic hydrogenation with 10% palladium on charcoal (50 mg) in methanol (50 mL) at room temperature for 2~3 hrs. The reaction mixture was filtered and the filtrate was evaporated in vacuo to afford 270 mg of oil. This compound was subjected to run the next step without further purification. IR (neat) cm^{-1}: 1700, 1730, 3400.

(S) α-Amino-*N*-methylglutarimide 6: This compound was obtained by the same procedure as described above.

(R) *N*-ethoxycarbonyl-α-amino-*N*-methylglutarimide 7a: To the sol'n of (R) α-amino-*N*-methylglutarimide (282 mg) and Na_2CO_3 (254 mg) in acetone (3 mL) and H_2O (3 mL), the sol'n of ethoxycarbonylchloride (259 mg) in acetone (3 mL) was added. Then the reaction mixture was stirred for 4~5 hrs at room temperature. The reaction mixture was evaporated *in vacuo* and the residue was dissolved in EtOAc (200 mL). The EtOAc layer was washed with 10% aqueous $NaHCO_3$ (25 mL x 2), 5% aqueous HCl (25 mL x 2) and H_2O (25 mL x 2) and saturated NaCl (25 mL x 2) solution successively and dried over anhydrous $MgSO_4$. The EtOAc layer was evaporated to give a brown solid. This crude product was purified with silica gel column chromatography (EtOAc:hexane=3: 1) to afford 328 mg of white solid (77 %). $[\alpha]_D^{25^\circ}$: +46.752 (c=1.00%, CH_3OH); mp: 86.4°C; IR (KBr) cm^{-1}: 1670, 1710, 1730, 3300; ^{1}H-NMR (DMSO-d_6): 1.17 (3H, t, *J*=7.1), 1.60~2.10 (2H, m), 2.20~2.50 (1H, m), 2.50~2.90 (1H, m), 3.17 (3H, s), 4.02 (2H, q, *J*=7.1), 4.20~4.50 (1H, m), 5.50 (1H, br).



Scheme 1. The Preparation of *N*-alkyloxycarbonyl-α-amino-glutarimides **7** and **8**.

The following compounds were prepared according to the above procedure.

(S) *N*-ethoxycarbonyl-α-amino-*N*-methylglutarimide 8a: 78%; $[\alpha]_D^{25^\circ}$: -46.756 (c=1.00 %, CH_3OH); mp: 87.5 °C; The IR and ^{1}H NMR spectra were identical with **7a**.

(R) *N*-allyloxycarbonyl-α-amino-*N*-methylglutarimide 7b: 70%; $[\alpha]_D^{25^\circ}$: +48.306 (c=1.00%, CH_3OH); mp: 78.5 °C; IR (KBr) cm^{-1}; 1670, 1715, 3370; ^{1}H NMR (DMSO-d_6): 1.60~2.10 (2H, m), 2.20~2.50 (1H, m), 2.50~2.90 (1H, m), 3.16 (3H, s), 4.20~4.50 (1H, m), 4.60 (2H, d, *J*=5.4), 5.70 (1H, br), 5.80~6.10 (1H, m).

(S) *N*-allyloxycarbonyl-α-amino-*N*-methylglutarimide 8b: 61%; $[\alpha]_D^{25^\circ}$: -48.306 (c=1.00%, CH_3OH); mp: 76.4 °C; The IR and ^{1}H NMR spectra were identical with **7b**.

(R) *N*-4-nitrobenzyloxycarbonyl-α-amino-*N*-methylglutarimide 7c: 74%; mp: $[\alpha]_D^{25^\circ}$: +35.852 (c=1.00%, CH_3OH); mp: 135.4°C; IR (KBr) cm^{-1}: 1670, 1730, 3310; ^{1}H NMR (DMSO-d_6): 1.60~2.10 (2H, m), 2.20~2.50 (1H, m), 2.50~2.90 (1H, m), 3.17 (3H, s), 4.20~4.50 (1H, m), 5.24 (2H, s), 5.70 (1H, br), 7.48 (2H, d, *J*=8.1), 8.10 (2H, d, *J*=8.1).

(S) *N*-4-nitrobenzyloxycarbonyl-α-amino-*N*-methylglutarimide 8c: 76%; $[\alpha]_D^{25^\circ}$: -35.808 (c=1.00%, CH_3OH); mp: 138.3°C; The IR and ^{1}H NMR spectra were identical with **7c**.

(R) *N*-phenoxycarbonyl-α-amino-*N*-methylglutarimide 7d: 64%; $[\alpha]_D^{25^\circ}$: +53.232 (c=1.00%, CH_3OH); mp: 145.2°C; IR (KBr) cm^{-1}: 1685, 1710, 3300; ^{1}H NMR (DMSO-d_6): d 1.60~2.10 (2H, m), 2.30~2.60 (2H, m), 2.60~2.95 (1H, m), 3.21 (3H, s), 4.10~4.50 (1H, m), 5.90 (1H, br), 7.10~7.40 (5H, m).

(S) *N*-phenoxycarbonyl-α-amino-*N*-methylglutarimide 8d: 61%; $[\alpha]_D^{25^\circ}$: -53.232 (c=1.00%, CH_3OH); mp: 145.7 °C; The IR and ^{1}H NMR spectra were identical with **7d**.

(R) *N*-tert.butoxy-α-amino-*N*-methylglutarimide 7e: To the sol'n of (R) α-amino-*N*-methylglutarimide (282 mg) and Na_2CO_3 (254 mg) in acetone and H_2O, the sol'n of di tert. butyl-dicarbonate (465 mg) in acetone (5 mL) was added. Then the reaction mixture was stirred for 4~5 hrs at room temperature. The reaction mixture was evaporated *in vacuo* and the residue was dissolved in EtOAc (200 mL). The EtOAc layer was washed with 10% aqueous $NaHCO_3$ (25 mL x 2), 5% aqueous HCl (25 mL x 2) and H_2O (25 mL x 2) and saturated NaCl solution (25 mL x 2) successively

and dried over anhydrous $MgSO_4$. The EtOAc layer was evaporated to give a brown solid. This crude product was purified with a silica gel column chromatography (EtOAc:hexane=1:1) to afford 347 mg of white solid (72%). mp: 81.7°C; $[\alpha]_D^{25°}$: +40.638 (c= 1.00%, CH_3OH); IR (KBr) cm^{-1}: 1680, 1710, 1730, 3390; ^{1}H-NMR (DMSO-d_6): 1.47 (6H, s), 1.60~2.10 (2H, m), 2.30~2.60 (1H, m), 2.60~2.95 (1H, m), 3.17 (3H, s), 4.10~4.50 (1H, m), 5.50 (1H, br).

(S) *N*-tert.butoxy-α-amino-*N*-methylglutarimide 8e: 69%; $[\alpha]_D^{25°}$: -40.638 (c=1.00%, CH_3OH); mp: 84.5°C; The IR and ^{1}H NMR spectra were identical with **7e**.

Pharmacology

The anticonvulsant activities for *N*-alkyloxycarbonyl-α-amino-*N*-methylglutarimides **7** and **8** in the maximal electric shock seizure (MES) and the pentylenetetrazole induced seizure (PTZ) tests were carried out according to the protocol of the Antiepileptic Drug Developement Program of the National Institute of Neurological Disorders and Stroke (Swinyard *et al.*, 1988) They follow as such: All tested compounds were dissolved in polyethylene glycol 400 and administered ip to ICR male mice at doses of 25, 50, 75 and 100 mg/kg. The anticonvulsant tests were performed 30 min after administration in groups of 4 mice, and we determined the lowest dose that all tested animals could be induced seizures at the stage of preliminary screening. Seizure was then artificially induced by either electric shock or pentylenetetrazole. The maximal elelectric shock seizure (MES) tests were elicited with a 60-cycle a.c. of 50 mA intensity delivered for 0.2 s via corneal electrods with a ECT unit (UGO Basline, Itlay). A drop of 0.9% saline was instilled in the eye prior to application of electrods. Protection in these tests was defined as the abolition of hind limb tonic extension component of seizure. The pentylenetetrazole seizure (PTZ) test entailed the administration of 80 mg/kg of pentylenetetrazole as a 0.5% solution subcutaneously in the posterior midline of the mice, and observation lasted for 30 min. Protection was defined as the failure to observe even a threshold seizure, a single episode of chronic spasms that persist for at least 5 sec. duration, and the ED_{50}, acts as a quantitative anticonvulsant evaluations was estimated from the dose-responce data. The effects of the compounds on the forced and spontaneous motor activities were evaluated in mice by the rotorod test with a Rotorod treadmill for mice (UGO Baseline, Itlay). They follow as such: The previously trained animal was placed on an 1 inch diameter knurled plastic rod rotating at 6 rpm after the administration of the tested compounds. Normal mice can remain on a rod at this speed indefinitely. Neurological toxicity was defined as the failure of the animal to remain on the rod for 2 min. Finally, the median neurotoxic dose (TD_{50}) was estimated from the dose-response data.

RESULTS AND DISCUSSION

As seen in Scheme 1, all the tested compounds were prepared from the corresponding (R) or (S) *N*-alkoxycarbonyl-α-amino-*N*-methylglutarimide from the *N-Cbz*-α-amino-*N*-methylglutarimide via hydrogenolysis with Pd/C, and acylation by usual methods in moderate yields. All the compounds gave satisfactory spectral data. We investigated the anticonvulsant activities for those compounds in both the MES and PTZ tests. The results of preliminary anticonvulsant activities are summarized in Table I and II.

As seen in Table I and Table II, (R) and (S) *N*-4-nitrobenzyloxycarbonyl-α-amino-*N*-methylglutarimide and (R) *N*-pheoxycarbonyl-α-amino-*N*-methylglutarimide exhibited anticonvulsant activities against the MES test at a dose of 100 mg/kg. But in the PTZ tests, all the tested compounds were found to be less active than a dose of 100 mg/kg. According to the protocol

Table I. Anticonvulsant activities of (R)-*N*-alkyloxycarbonyl-α-amino-*N*-methylglutarimides (7) in mice

Compound	Config.	R	Dose[a]	MES[b]	PTZ[c]
7a	R	C_2H_5	25		4/4
			50		2/4(3/4)[d]
			75		1/4
			100	4/4	0/4
7b	R	Allyl	25		3/4(4/4)[e]
			50		2/4
			75		1/4
			100	4/4	0/4
7c	R	4-nitrobenzyl	25	4/4	3/4(4/4)[e]
			50	4/4	0/4(1/4)[d]
			75	3/4	
			100	2/4(0/4)[f]	0/4
7d	R	phenyl	25	4/4	
			50	2/4(3/4)[d]	4/4
			75	2/4	3/4(2/4)[g]
			100	0/4	1/4(0/4)[h]
7e	R	tert.butyl	25	4/4	3/4(4/4)[e]
			50		2/4
			75		1/4
			100	4/4	0/4

[a]All compounds were dissolved in polyethyleneglycol400 and administerd i.p to ICR male mice. Dose was denoted in mg/kg.
[b]The MES test: 50 mA, 60 Hz, ac, 0.2 sec., via corneal eletrods, 30 min post administration of test compound. And the results were denoted as non-protected animals/tested animals.
[c]The PTZ test: Subcutaneous pentylenetetrazol (80 mg/kg) 30 min post administration of test compound. And the results were denoted as non-protected animals/tested animals.
[d] at a dose of 30 mg/kg. [e] at a dose of 15 mg/kg. [f] at a dose of 150 mg/kg. [g] at a dose of 90 mg/kg. [h] at a dose of 125 mg/kg.

for the development of new anticonvulsant agents, the compounds, showing the antionvulsant activity at a dose of 100 mg/kg in mice, were recommended to further investigation of quantification. So we selected the **1a,b,c,d,e,2a,b,c** and **e**, except **2d**, for the quantitative anticonvulsant evaluation and we carried out rotorod test to evaluate the neurotoxicity for the selected compounds. The results of quantitative anticonvulsant activities and rotorod test are summarized in Table III.

Table II. Anticonvulsant activities of (S)-*N*-alkyloxycarbonyl-α-amino-N-methylglutarimides (**8**) in mice

Compound	Config.	R	Dose[a]	MES[b]	PTZ[c]
8a	S	C_2H_5	25		2/4(4/4)[d]
			50		1/4
			75		0/4
8b	S	Allyl	25		4/4
			50		3/4
			75		2/4
			100	4/4	0/4(1/4)[e]
8c	S	4-nitrobenzyl	25	4/4[f]	1/4f(4/4)[d]
			50	0/4(1/4)[g]	0/4
8d	S	phenyl	100	4/4	4/4
8e	S	tert.butyl	25		3/4(4/4)[h]
			50		2/4
			75		1/4
			100	4/4(2/4)[i]	0/4

[a]All compounds were dissolved in polyethyleneglycol400 and administerd i.p to ICR male mice. Dose was denoted in mg/kg.
[b]The MES test: 50 mA, 60 Hz, ac, 0.2 sec., via corneal eletrods, 30 min post administration of test compound. The results were denoted as non-protected animals/tested animals.
[c]The PTZ test: Subcutaneous pentylenetetrazol (80 mg/kg) 30 min post administration of test compound. The results were denoted as non-protected animals/tested animals.
[d] at a dose of 5 mg/kg. [e] at a dose of 90 mg/kg. [f] at a dose of 20 mg/kg. [g] at a dose of 40 mg/kg. [h] at a dose of 15 mg/kg. [i] at a dose of 150 mg/kg.

As seen in Table III, (R) *N*-4-nitrobenzyloxycarbonyl-α-amino-*N*-methylglutarimide **7c**, (R) *N*-pheoxycarbonyl-α-amino-*N*-methylglutarimide **7d** and (S) *N*-4-nitrobenzyloxycarbonyl-α-amino-*N*-methylglutarimide **8c** among the tested compounds that exhibited anticonvulsant activities in the MES tests, but other tested compounds didn't show anticonvulsant activities in similar testing. The most active compound in the MES tests was (S) *N*-4-nitrobenzyloxycarbonyl-α-amino-*N*-methylglutarimide **8c** (ED_{50}=35.6 mg/kg. PI=2.7). The anticonvulsant activity of this compound was 7.6-fold more active than that of valproic acid, and the protective index was 1.7-fold higher than that of valproic acid. And the anticonvulsant activities of other active compounds were also comparable to currently applicable antiepileptic drugs.

In the case of the PTZ tests, all the tested compounds showed significant anticonvulsant activities. The most active compound in the PTZ tests was (S) *N*-4-nitrobenzyloxycarbonyl-α-amino-*N*-methylglutarimide **8c** (ED_{50}=15.6 mg/kg, PI=6.1). The anticonvulsant activity of this compound was 9.5-fold more active than that of valproic acid, and the protective index of this

Table III. The selected anticonvulsant evaluation of *N*-alkyloxycarbonyl-α-amino-*N*-methylglutarimides (**7** and **8**) in mice

Compound	Config.	R	TD_{50}[b] (mg/kg)	ED_{50} (mg/kg)[a]	
				MES (PI)[c]	PTZ (PI)[d]
7a	R	C_2H_5	150.0		56.9 (2.6)
7b	R	Allyl	125.0		51.9 (2.4)
7c	R	4-nitrobenzyl	100.0	100.0	31.9 (3.1)
7d	R	phenyl	125.0	56.9 (2.2)	88.1 (1.4)
7e	R	tert.butyl	125.0		51.9 (2.4)
8a	S	C_2H_5	105.6		32.5 (3.3)
8b	S	Allyl	113.1		69.4 (1.6)
8c	S	4-nitrobenzyl	94.4	35.6 (2.7)	15.6 (6.1)
8e	S	tert.butyl	105.6		51.9(2.0)
	Diphenylhydantoin[e]		65.4	9.5 (6.9)	f
	Phenobarbitale		69.0	21.8 (3.1)	13.1 (5.3)
	Ethosuximidee		440.8	f	130.4 (3.4)
	Methosuximidee		130.1	42.6 (3.1)	34.5 (3.7)
	Valproic aide		425.8	271.1 (1.6)	148.6 (2.9)
	Trimethadionee		1070.0	704.2 (1.5)	250.5 (4.3)

[a]All compounds were administered ip to ICR male mice and all anticonvulsant tests were performed in groups of 4 mice 30 min after test compound administration.
[b]Rotarod test for neurotoxicity in groups of 5 mice.
[c]maximal electric shock seizure test: 50 mA, 60 Hz, ac, 0.2 s. and PI is protective index (TD_{50}/ED_{50}).
[d]Subutaneous pentylenetetrazole (80 mg/kg) induced seizure test.
[e]Witak. *et al.* 1972. [f] not effect

compound was 2.1-fold higher than that of valproic acid. Also, all the tested compounds, except the *N*-phenoxycarbonyl compound, showed significant anticonvulsant activities comparable to other antiepileptic drugs.

Of interest, it was found that the N-substituted alkoxycarbonyl group had effects on the anticonvulsant activities of *N*-alkoxycarbonyl-α-amino-*N*-methylglutarimides. The order of anticonvulsant activities against the PTZ tests, as judged from the ED_{50} value for (R) series, was *N*-4-nitrobenzyloxycarbonyl > *N*-allyloxycarbonyl=*N*-tert. butoxycarbonyl > *N*-ethoxycarbonyl > *N*-phenoxycarbonyl compound; for (S) series, *N*-4-nitrobenzyloxycarbonyl > N-ethoxycarbonyl > *N*-tert. butoxycarbonyl > *N*-allyloxycarbonyl compound.

From the above results, although we could not explain the reason exactly, it was conceivable that *N*-substituted alkoxycarbonyl group played an important role for the anticonvulsant activities of *N*-alkoxycarbonyl-α-aminoglutarimides.

CONCLUSION

In conclusion, a series of (R) and (S) *N*-alkoxycarbonyl-α-amino-*N*-methylglutarimide were prepared from the corresponding *N-Cbz*-glutamic acid, and their anticonvulsant activities were evaluated in the MES and PTZ tests. These include their neuritoxicities, in order to define the effects of *N*-alkoxycarbonyl group with their anticonvulsant activities. From these studies, it was found that only (R) *N*-4-nitrobenzyloxycarbonyl-α-amino-*N*-methylglutarimide **7c**, (R) *N*-phenoxycarbonyl-α-amino-*N*-methylglutarimide **7d**, and (S) *N*-4-nitro-benzyloxycarbonyl-α-amino-*N*-methylglutarimide **8c** were active in the MES tests. However, and all the tested compounds showed significant anticonvulsant activities in the PTZ tests. (S) *N*-4-nitrobenzyloxy-α-amino-*N*-methylglutarimide was most active in both tests. As evaluated from ED_{50} value and PI index, this compound was found to be active enough to recommend a new anticonvulsant drug candidate. Also, we found that the anticonvulsant activities of these compounds were dependent on the *N*-substituted alkoxycarbonyl group. From these results, even though we could not explain the reason exactly, it was conceived that the *N*-substituted alkyloxycarbonyl group of these compounds played an important role for their anticonvulsant activities and their spectrum of anticonvulsant activities.

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