

## Designing of Antiepileptic Ligands by Esterification and Acetylation of Dipeptides

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**Abstract** □ Glycylglycine, alanylalanine and alanylglycine were synthesized, their free carboxylic and amino groups were converted to methyl esters of N-acetylglycylglycine, N-acetylalanylglycine and N-acetylalanylalanine.

The synthesized compounds were evaluated for antiepileptic activity, plasma protein binding,  $TD_{50}$  and potentiating effect of phenobarbitone sodium.

**Keywords** □ N-acetyl glycylglycine methyl ester, N-acetylalanylglycine methyl ester, N-acetylalanylalanine methyl ester, plasma protein binding, antiepileptic activity.

Most of the antiepileptic drugs, i.e. derivatives of barbiturates, hydantoins, contain uride structure. Kohn<sup>1)</sup> *et al.* synthesized various selectively derivatives of  $\alpha$ -acetamido-N-benzyl- $\alpha$ -phenyl acetamide and evaluated in the maximal electroshock seizure (MES) and horizontal screen (tox) tests in mice. It was also reported that replacement of the  $\alpha$ -phenyl substituent on  $\alpha$ -acetamido-N-benzyl- $\alpha$ -phenyl acetamide by a relatively small electron-rich, heteroaromatic moiety led to a greater improvement in the anticonvulsant potency of the drug candidate. Ken<sup>2)</sup> proposed an anticonvulsant nucleus containing the same moiety. Takashi<sup>3)</sup> extracted a seizure producing substance (K-substance) during seizure condition from dog's brain and explained that the substance contained  $-\text{COO}^-$ ,  $-\text{CH}_2\text{NH}_2$ ,  $-\text{CHNH}$ ,  $-\text{CH}_2\text{OH}$  pharmacodynamic moieties present in the anticonvulsant nucleus.

### EXPERIMENTAL METHODS

Sheehan's method<sup>4)</sup> was adapted for the preparation of glycylglycine, alanylalanine and alanylglycine.

#### Synthesis of dipeptides

Glycylglycine was synthesized in the following steps.

**Preparation of phthalylglycine** : Glycine (0.2 mol) and phthalic anhydride (0.2 mol) was heated in an oil bath at 180-185°C for 15 min. The mixture was then cooled and recrystallized from ethanol (10%), yield, 90%, mp. 191-192°C.

**Preparation of phthalylglycylchloride** : A suspension of phthalylglycine (0.1 mol) and phosphorous pentachloride (0.1 mol) in 200 ml benzene was heated at 60°C for 2 hr with constant stirring. The reaction mixture was cooled, concentrated under reduced pressure and the residue was recrystallized from benzene and petroleum ether, yield, 75%, mp. 81-82°C.

**Preparation of phthalylglycylglycine** : A solution of phthalylglycylchloride (0.02 mol) was added slowly with constant stirring to a suspension of glycine (0.02 mol) and magnesium oxide (0.03 mol) in 75 ml of water at 5°C. After stirring for an additional 10 min at room temperature, the mixture was acidified with hydrochloric acid to get a precipitate. The precipitate was filtered and recrystallized from 90% ethanol, yield, 80%, mp. 227-228°C.

**Preparation of glycylglycine from phthalylglycylglycine** : A suspension of phthalylglycylglycine (0.01 mol) in