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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, plasmaprotein binding, TD_{50} and potentiating effect of phenobarbitone sodium.

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

Most of the antiepileptic drugs, i.e. derivatives of barbiturates, hydantoins, contain uride structure. Kohn[1] *et al.* synthesized various selectively derivatives of α-acetamido-N-benzyl-α-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 α-phenyl substituent on α-acetamido-N-benzyl-α-phenyl acetamide by a relatively small electron-rich, heteroaromatic moiety led to a greater improvement in the anticonvulsant potency of the drug candidate. Ken[2] proposed an anticonvulsant nucleus containing the same moiety. Takashi[3] extracted a seizure producing substance (K-substance) during seizure condition from dog's brain and explained that the substance contained $-COO^-$, $-CH_2NH_2$,-CHNH, $-CH_2OH$ pharmacodynamic moieties present in the anticonvulsant nucleus.

EXPERIMENTAL METHODS

Sheehan's method[4] 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℃ for 15 min. The mixture was then cooled and recrystallized from ethanol (10%), yield, 90%, mp. 191-192℃.

Preparation of phthalylglycylchloride: A suspension of phthalylglycine (0.1 mol) and phosphorous pentachloride (0.1 mol) in 200 m*l* benzene was heated at 60℃ 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 ℃.

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 m*l* of water at 5℃. 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℃.

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