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(54) **ANTICONVULSANT ENANTIOMERIC AMINO ACID DERIVATIVES**

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Related U.S. Patent Documents

Reissue of:

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 Filed: **Mar. 17, 1997**

U.S. Applications:

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(51) **Int. Cl.⁷** **A61K 31/165**; C07C 233/05
 (52) **U.S. Cl.** **514/616**; 564/155; 564/158
 (58) **Field of Search** 514/616; 564/155, 564/158

(56) **References Cited**

U.S. PATENT DOCUMENTS

5,378,729 A 1/1995 Kohn et al. 514/231.2
 5,654,301 A 8/1997 Kohn et al. 514/231.2

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EP 0 194 464 9/1986

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Anderson, et al. *J. Am. Chem. Soc.* 89:19 pp. 5012–5017, (1967).

Kohn, Harold, et al. "Preparation and anticonvulsant activity of a series of functionalized. alph.-heteroatom-substituted amino acids", *J. Med. Chem.* 34, 2444–2452 (1991).

Kohn, Harold, et al. "Marked stereospecificity in a new class of anticonvulsants", *Chemical Abstracts*, 109 (1988) Abstract No. 183045.

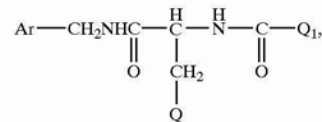
Choi, Daeock, et al. "Synthesis and Anticonvulsant Activities of N-Benzyl-2-acetamidopropionamide Derivatives", *J. Med. Chem.*, 39: 1907–1916 (1996).

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(57) **ABSTRACT**

The present invention is directed to a compound in the R configuration about the asymmetric carbon in the following formula:



pharmaceutical compositions containing same and the use thereof in treating CNS disorders in animals.

13 Claims, No Drawings

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ANTICONVULSANT ENANTIOMERIC AMINO ACID DERIVATIVES

Matter enclosed in heavy brackets [] appears in the original patent but forms no part of this reissue specification; matter printed in italics indicates the additions made by reissue.

RELATED APPLICATION

This application claims priority from U.S. provisional application No. 60/013,522 filed on Mar. 15, 1996.

GOVERNMENT SUPPORT

This invention was made with Government support under Grant/Contract No. NIH MS 15604 awarded by the National Institute of Health. The Government has certain rights in the invention.

FIELD OF THE INVENTION

The present invention relates to novel enantiomeric compounds and pharmaceutical compositions useful in the treatment of epilepsy and other CNS disorders.

BACKGROUND OF THE INVENTION

The predominant application of anticonvulsant drugs is the control and prevention of seizures associated with epilepsy or related central nervous system disorders. Epilepsy refers to many types of recurrent seizures produced by paroxysmal excessive neuronal discharges in the brain; the two main generalized seizures are petit mal, which is associated with myoclonic jerks, akinetic seizures, transient loss of consciousness, but without convulsion; and grand mal which manifests in a continuous series of seizures and convulsions with loss of consciousness.

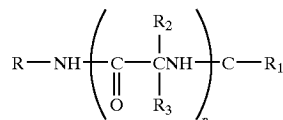
The mainstay of treatment for such disorders has been the long-term and consistent administration of anticonvulsant drugs. Most drugs in use are weak acids that, presumably, exert their action on neurons, glial cells or both of the central nervous system. The majority of these compounds are characterized by the presence of at least one amide unit and one or more benzene rings that are present as a phenyl group or part of a cyclic system.

Much attention has been focused upon the development of anticonvulsant drugs and today many such drugs are well known. For example, the hydantions, such as phenytoin, are useful in the control of generalized seizures and all forms of partial seizures. The oxazolinediones, such as trimethadione and paramethadione, are used in the treatment of non-convulsive seizures. Phenacemide, a phenylacetylurea, is one of the most well known anticonvulsants employed today, while much attention has recently been dedicated to the investigation of the diazepines and piperazines. For example, U.S. Pat. Nos. 4,002,764 and 4,178,378 to Allgeier, et al. disclose esterified diazepine derivatives useful in the treatment of epilepsy and other nervous disorders. U.S. Pat. No. 3,887,543 to Nakanishi, et al. describes a thieno [2,3-e][1,4]diazepine compound also having anticonvulsant activity and other depressant activity. U.S. Pat. No. 4,209,516 to Heckendorn, et al. relates to triazole derivatives which exhibit anticonvulsant activity and are useful in the treatment of epilepsy and conditions of tension and agitation. U.S. Pat. No. 4,372,974 to Fish, et al. discloses a pharmaceutical formulation containing an aliphatic amino acid compound in which the carboxylic acid and primary amine are separated by three or four units. Administration of

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these compounds in an acid pH range are useful in the treatment of convulsion disorders and also possess anxiolytic and sedative properties.

U.S. Pat. No. 5,378,729 to Kohn, et al. discloses compounds and pharmaceutical compositions having central nervous system (CNS) activity which are useful in the treatment of epilepsy and other CNS disorders having the following general formula:



R is hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl, aryl lower alkyl, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, and R is unsubstituted or is substituted with at least one electron withdrawing group, or electron donating group.

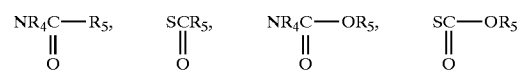
R₁ is hydrogen or lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic lower alkyl, heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, each unsubstituted or substituted with an electron donating group or an electron withdrawing group and

R₂ and R₃ are independently hydrogen, lower alkyl, lower alkenyl, lower alkynyl, aryl lower alkyl, aryl, heterocyclic, heterocyclic lower alkyl, lower alkyl heterocyclic, lower cycloalkyl, lower cycloalkyl lower alkyl, or Z—Y wherein R₂ and R₃ may be unsubstituted or substituted with at least one electron withdrawing group or electron donating group;

Z is O, S, S (O)_n, NR₄, PR₄ or a chemical bond;

Y is hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, lower alkynyl, halo, heterocyclic, or heterocyclic lower alkyl, and Y may be unsubstituted or substituted with an electron donating group or an electron withdrawing group, provided that when Y is halo, Z is a chemical bond, or

ZY taken together is NR₄NR₅R₇, NR₄OR₅, ONR₄R₇, OPR₄R₅, PR₄OR₅, SNR₄R₇, NR₄SR₇, SPR₄R₅, PR₄SR₇, NR₄PR₅R₆, PR₄NR₅R₇,



R₄, R₅ and R₆ are independently hydrogen, lower alkyl, aryl, aryl lower alkyl, lower alkenyl, or lower alkynyl, wherein R₄, R₅ and R₆ may be unsubstituted or substituted with an electron withdrawing group or an electron donating group,

R₇ is R₆, COOR₈ or COR₈,

R₈ is hydrogen, lower alkyl, or aryl lower alkyl, and the aryl or alkyl group may be unsubstituted or substituted with an electron withdrawing group or an electron donating group and

n is 1-4 and

a is 1-3.

Unfortunately, despite the many available pharmacotherapeutic agents, a significant percentage of the population with epilepsy or related disorders are poorly managed. Moreover, none of the drugs presently available are capable of achieving total seizure control, and most have disturbing side effects. Toxicities may appear upon repeated dosing that are

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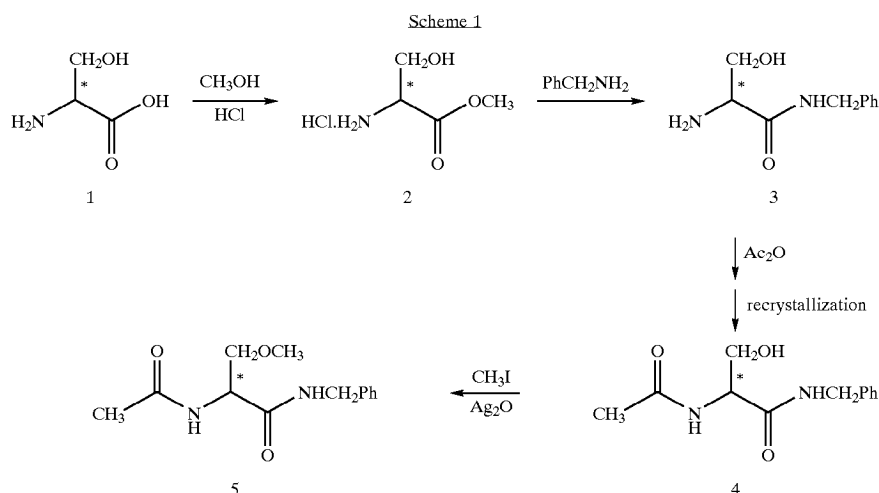
asterisk is in the R configuration. The inventor has found that the R stereoisomer at the asymmetric carbon at the asterisk is significantly more efficacious than the corresponding S enantiomer or a racemic mixture thereof.

It is preferred that the compound of the present invention be substantially pure, i.e., substantially free from impurities. It is most preferred that the compounds of the present invention be at least 75% pure (w/w) and more preferably greater than about 90% pure (w/w) and most preferably greater than about 95% pure (w/w).

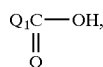
It is also preferred that the compounds of the present invention be substantially enantiomerically pure, i.e., substantially free from the corresponding S isomer. It is more preferred that the compounds of the present invention contain at least 90% (w/w) R stereoisomer, and most preferably greater than about 95% (w/w) in the R stereoisomer. Thus, the present invention contemplates compounds having at most about 10% S isomer (w/w), and even more preferably less than about 5% S isomer (w/w).

The compounds of the present invention in the R form are prepared by art recognized techniques from commercially available starting materials.

An exemplary procedure is outlined in Scheme 1 hereinbelow:

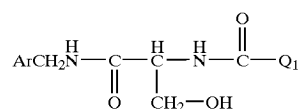


A D serine molecule (1) is esterified under acylation conditions with an alcohol, such as acidic methanol, to provide the corresponding ester (2). 2 is reacted with ArCH_2NH_2 , such as benzylamine, under acylation conditions to form the corresponding amide (3). Acylation of the free amino group, with an acylating derivative of



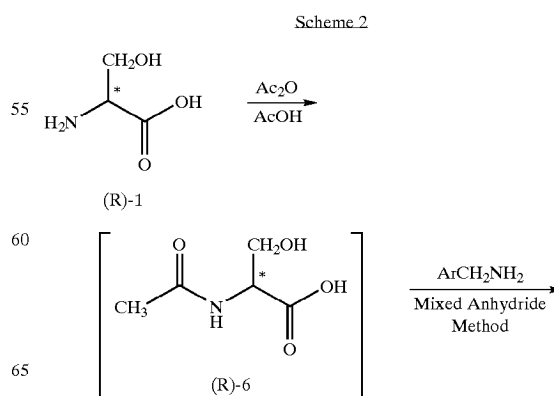
such as acetic acid, or lower alkyl ester of acetic acid, or acetic anhydride provides the hydroxymethyl derivative,

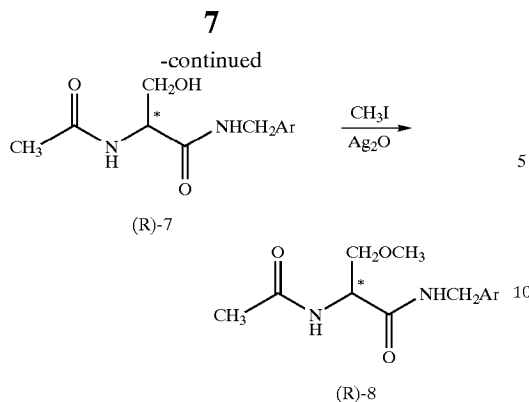
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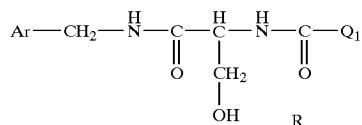
The enantiopurity of 4 was determined by techniques known in the art, including melting point, optical rotation and ^1H NMR upon addition of an organic acid in the R-configuration, such as R(-)-mandelic acid. Crystallization of 4 was repeated until the desired enantiopurity thereof was achieved. The product of 4 is converted to the ether under Williamson conditions by reacting it with QX, wherein Q is as defined herein above and X is good leaving groups, such as OTs, OMs, or halide (e.g., CH_3I) and the like in the presence of base (e.g., Ag_2O) to form the product (5) having Formula I.

Another variation is depicted in Scheme 2.



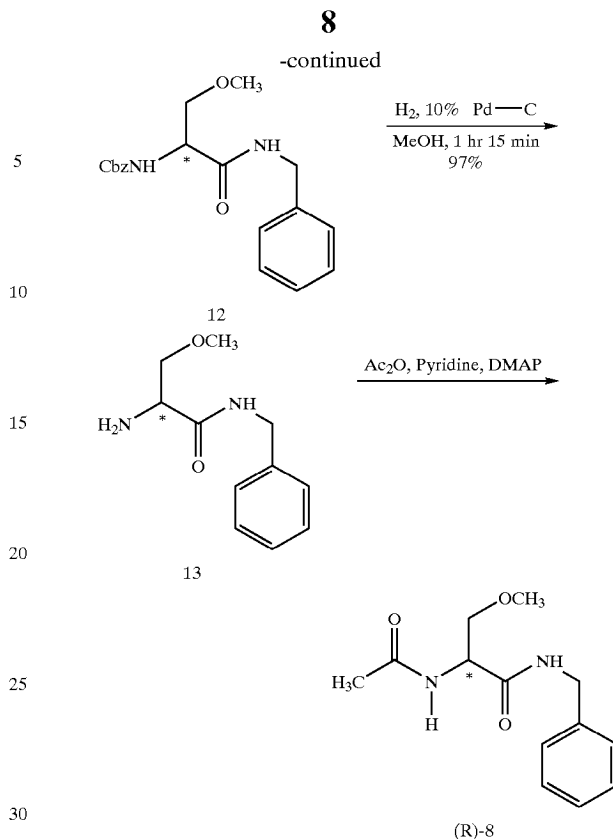
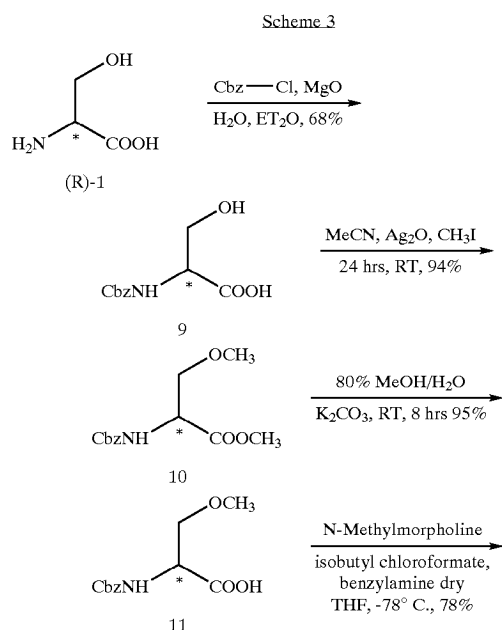


For example, beginning with D-serine (1), treatment with an acylating derivative of acetic acid such as acetic anhydride in acetic acid, gives the corresponding amide 6 which is then reacted with ArCH_2NH_2 under mixed anhydride coupling reaction conditions, as described by Anderson, et al., in JACS, 1967, 89, 5012-5017, the contents of which are incorporated herein by reference, to give the corresponding compound of the formula:



e.g., 7. Alkylation of this R-product in the presence of base under Williamson conditions, such as methyl iodide in Ag_2O , provides a product of Formula I (8).

An alternative route is depicted in Scheme 3.



D Serine (1) is protected with a N-protecting group known in the art, by standard techniques. Thus, for example, it is reacted with carbobenzyloxy chloride (CBZ-cl, benzyl chloroformate) generating the N-protected CBZ-D-serine adduct 9. The product serine adduct is converted to the corresponding ether under Williamson conditions by reacting it with QX wherein Q and X are defined hereinabove (e.g., CH_3I) in the presence of base (e.g., Ag_2O) to form an ether 10. Under these conditions, the acid is also esterified. Subsequent hydrolysis of the ester group in 10 permits amide coupling with ArCH_2NH_2 using amide coupling methodology (e.g., mixed anhydride 1,1' Carbonyldiimidazole) to give the amide 12. Deprotection of the N-protecting group provide the free amine 13 which is then reacted with an acylating agent such as acetic anhydride in base, (e.g., pyridine) to provide the product (R)-8.

If necessary, in any of the procedures described hereinabove, the optical purity of the product may be enhanced by further separation of the S enantiomer from the R enantiomer, by standard techniques known in the art, such as chiral chromatography using a standard chiral support known in the art.

Alternatively, in any of the procedures provided hereinabove, a racemic D serine may be utilized as the starting material. Following the procedures in any of the schemes outlined hereinabove would provide the racemic mixture, which can be resolved into the R isomer by standard techniques known in the art such as chiral chromatography.

The active ingredients of the therapeutic compositions and the compounds of the present invention exhibit excellent anticonvulsant activity when administered in amounts ranging from about 1 mg to about 100 mg per kilogram of body weight per day. This dosage regimen may be adjusted by the physician to provide the optimum therapeutic response. For

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