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(54) **Title:** PROCESSES FOR THE PREPARATION OF LEVETIRACETAM, ITS INTERMEDIATE AND THE USE OF LEVETIRACETAM IN PHARMACEUTICAL COMPOSITIONS

(57) **Abstract:** The invention relates to processes for the preparation of (S)-2-aminobutanamide of Formula I, and to the use of the compound of Formula I as intermediate for the preparation of levetiracetam of Formula (II).The invention also relates to a process for the preparation of levetiracetam and pharmaceutical compositions that include the levetiracetam.

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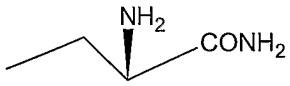
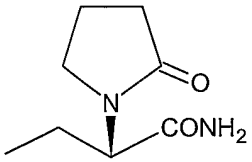
PROCESSES FOR THE PREPARATION OF LEVETIRACETAM, ITS INTERMEDIATE AND THE USE OF LEVETIRACETAM IN PHARMACEUTICAL COMPOSITIONS

Field of the Invention

The field of the invention relates to processes for the preparation of (S)-2-aminobutanamide of Formula I, and to the use of the compound of Formula I as intermediate for the preparation of levetiracetam of Formula II.



Formula I



Formula II

The invention also relates to a process for the preparation of levetiracetam and pharmaceutical compositions that include the levetiracetam.

Background of the Invention

Levetiracetam is an antiepileptic drug indicated as adjunctive therapy in the treatment of partial onset seizures in adults with epilepsy. Levetiracetam is a single enantiomer and the chemical name for levetiracetam is (S)-α-ethyl-2-oxo-1-pyrrolidineacetamide. Several processes have been reported for the preparation of (S)-2-aminobutanamide and levetiracetam. British Patent No. 1,309,692 discloses the compound α-ethyl-2-oxo-1-pyrrolidineacetamide (melting point 112°C) and states that the compounds of this type can be used for therapeutic purposes, for example for the treatment of motion sickness, hyperkinesia, hypertonia and epilepsy.

U.S. Patent No. 4,969,943 discloses the levorotatory isomer of α-ethyl-2-oxo-1-pyrrolidineacetamide, which has the absolute S configuration. The patent discloses the preparation of levetiracetam by reacting (S)-α-ethyl-2-oxopyrrolidineacetic acid

successively with alkylhaloformate and with ammonia. It also discloses the preparation of levitiracetam by cyclizing an (S)-2-aminobutanamide.

U.S. Patent Publication Nos. 2004/0192757 and 2004/0092576 disclose a process for the preparation of levetiracetam from corresponding unsaturated 2-oxo-1-pyrrolidine derivative by asymmetric hydrogenation using a chiral catalyst.

International (PCT) Publication No. WO 04/069796 discloses a process for preparing levetiracetam from (S)-2-aminobutanamide without using a catalyst.

U.S. Patent Publication No. 2004/0204476 discloses a method of preparing levetiracetam by ammonolysis. U.S. Patent No. 6,124,473 and U.S. Patent Publication No. 2004/0204476 disclose the methods of separating optical isomers of levetiracetam by chromatographic techniques.

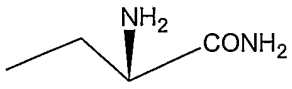
Journal of American Chemical Society, 1952, 74, 1580, discloses a process for the preparation of 2-aminobutyramide by passing ammonia gas to ethyl-α-bromobutyrate at 0°C and keeping it at -5°C for 10 days for completion of reaction.

Journal of American Chemical Society, 1955, 77, 1522 discloses the preparation of amino acid amides by contacting the corresponding freebase with ammonia at 0°C and keeping for three days.

The present inventors have observed that the methods known in the art require the maintenance at low temperature for considerable number of days which leads to the formation of large quantity of byproducts and impurities including dimeric impurity. Further, the levetiracetam gets racemized due to the alkaline conditions of the reaction mixture during the cyclization step.

Summary of the Invention

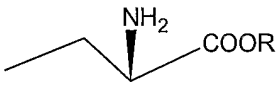
In one general aspect there is provided a process for the preparation of (S)-2-aminobutanamide of Formula I.



Formula I

The process includes:

a) reacting a compound of Formula III,



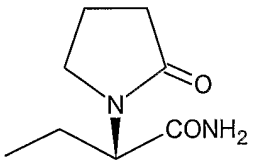
Formula III

wherein R represents C_1-C_5 alkyl, haloalkyl, aryl, arylalkyl or heteroaryl , or an acid addition salt thereof, with ammonia in the presence of an ammonium salt; and

b) isolating the (S)-2-aminobutanamide of Formula I.

The process may include further drying of the product obtained. The process may include further converting the product obtained into levetiracetam. The levetiracetam may be made into a finished dosage form with one or more pharmaceutically acceptable excipients.

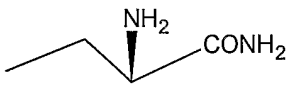
In another general aspect there is provided a process for the preparation of levetiracetam of Formula II.



Formula II

The process includes:

a) reacting (S)-2-aminobutanamide of Formula I,



Formula I

with 4-chlorobutyryl chloride to get (S)-N-[1-(aminocarbony)propyl]-4-chlorobutyramide;

b) cyclizing the (S)-N-[1-(aminocarbony)propyl]-4-chlorobutyramide in the presence of an alkali;

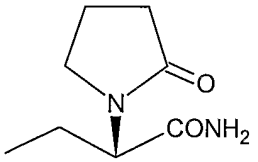
c) adjusting pH of reaction mixture obtained in step b); and

d) isolating the levetiracetam of Formula II from the reaction mixture thereof.

The process may include further drying of the product obtained.

The process may produce the levetiracetam having optical purity more than 99.5%. In particular, it may produce the levetiracetam having optical purity more than 99.8%.

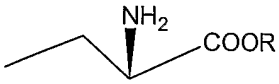
In another aspect there is provided a process for the preparation of levetiracetam of Formula II.



Formula II

The process includes:

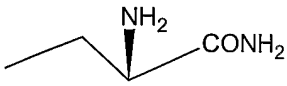
a) reacting a compound of Formula III,



Formula III

wherein R represents C_1-C_5 alkyl, haloalkyl, aryl, arylalkyl or heteroaryl, or an acid addition salt thereof, with ammonia in the presence of an ammonium salt;

b) isolating (S)-2-aminobutanamide of Formula I from reaction mixture obtained in step a);



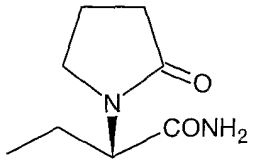
Formula I

c) reacting the (S)-2-aminobutanamide of Formula I obtained in step b) with 4-chlorobutyryl chloride to get (S)-N-[1-(aminocarbony)propyl]-4-chlorobutyramide;

d) cyclizing the (S)-N-[1-(aminocarbony)propyl]-4-chlorobutyramide in the presence of an alkali; and

e) isolating the levetiracetam of Formula II.

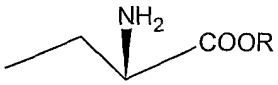
In another general aspect there is provided a process for the preparation of levetiracetam of Formula II.



Formula II

The process includes:

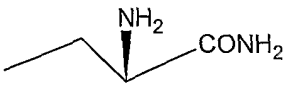
a) reacting a compound of Formula III,



Formula III

wherein R represents C_1-C_5 alkyl, haloalkyl, aryl, arylalkyl or heteroaryl or an acid addition salt thereof, with ammonia;

b) isolating (S)-2-aminobutanamide of Formula I from reaction mixture obtained in step a);



Formula I

c) reacting the (S)-2-aminobutanamide of Formula I obtained in step b) with 4-chlorobutyryl chloride to get (S)-N-[1-(aminocarbony)propyl]-4-chlorobutyramide;

d) cyclizing the (S)-N-[1-(aminocarbony)propyl]-4-chlorobutyramide in the presence of an alkali;

e) adjusting pH of reaction mixture obtained at step d); and

f) isolating the levetiracetam of Formula II from the reaction mixture thereof.

The process may include further drying of the product obtained.

The process may produce the levetiracetam having optical purity more than 99.5%. In particular, it may produce the levetiracetam having optical purity more than 99.8%.

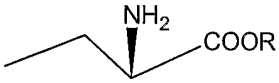
In another aspect there is provided a pharmaceutical composition that includes a therapeutically effective amount of levetiracetam having optical purity more than 99.5%; and one or more pharmaceutically acceptable carriers, excipients or diluents.

The details of one or more embodiments of the invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the description and claims.

Detailed Description of the Invention

The inventors have found that the (S)-2-aminobutanamide can be prepared by an ammonolysis of (S)-2-aminobutyric acid ester, and the reaction can be carried out at room temperature. The inventors have found that the use of ammonium salts along with ammonia gas helps in reducing the reaction time and also retards the impurity formation. The inventors have also found that undesired racemization of the levetiracetam can be avoided if pH of the reaction mixture is adjusted before isolating the levetiracetam. The process also enables the production of crude levetiracetam having a high chemical purity.

The inventors have developed a process for the preparation of (S)-2-aminobutanamide of Formula I. The process involves reacting (S)-2-aminobutanoic acid ester of Formula III,



Formula III

wherein R represents C_1-C_5 alkyl, haloalkyl, aryl, arylalkyl or heteroaryl , or an acid addition salt thereof, with ammonia in the presence of an ammonium salt.

In general, the (S)-2-aminobutanoic acid ester of Formula III may be dissolved in a solvent and ammonia gas may be passed through the reaction mixture at a temperature less than about 0°C, followed by the addition of an ammonium salt. The temperature may be raised and maintained between about 10° to 60°C until the completion of the reaction.

The term "solvent" includes any solvent or solvent mixture in which (S)-2-aminobutanoic acid ester is soluble, including, for example primary alcohols.

Examples of ammonium salts include ammonium sulfate, ammonium chloride, ammonium formate, ammonium acetate, ammonium propionate, ammonium persulfate, ammonium sulfide, ammonium phosphate, ammonium nitrite, ammonium nitrate, ammonium carbonate, ammonium bicarbonate, ammonium chlorate, ammonium bromide, ammonium iodide and ammonium fluoride.

The product may be isolated from the reaction mixture by a technique which includes, for example, distillation, distillation under vacuum, filtration, filtration under vacuum, evaporation, decantation, and centrifugation.

The product thus isolated may be further purified or additionally purified, by employing commonly practiced recrystallization techniques using solvent/antisolvent mixture to obtain pure (S)-2-aminobutanamide.

The inventors also have developed a process for the preparation of levetiracetam by reacting (S)-2-aminobutanamide of Formula I with 4-chlorobutyryl chloride to get (S)-N-[1-(aminocarbony)propyl]-4-chlorobutyramide; cyclizing the (S)-N-[1-(aminocarbony)propyl]-4-chlorobutyramide in the presence of an alkali; adjusting pH of the reaction mixture; and isolating the levetiracetam from the reaction mass.

(S)-2-aminobutanamide may be reacted with 4-chlorobutyryl chloride in the presence of an organic solvent to get (S)-N-[1-(aminocarbony)propyl]-4-chlorobutyramide, which may be further cyclized in the presence of an alkali.

The organic solvent and alkali which can be used in the reaction are known to a person of ordinary skill in the art. Any organic solvents can be used which are inert and do not change under the reaction conditions. Examples of alkali include salts of lithium, sodium, or potassium. The pH of the reaction mixture may be adjusted in the range from about 7 to about 8.5 before isolating the levetiracetam.

The levetiracetam may be isolated from the reaction mixture by a technique which includes, for example, distillation, distillation under vacuum, filtration, filtration under vacuum, evaporation, decantation, and centrifugation.

The levetiracetam thus isolated may be further purified or additionally purified, by employing commonly practiced recrystallization techniques using solvent/antisolvent mixture to obtain pure levetiracetam.

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the invention and do not limit the scope of the invention.

Example 1: Preparation of (S)-2-aminobutanamide

Methyl (S)-2-aminobutyric acid ester (220 g) was dissolved in methanol (1200 ml). The reaction mixture was cooled to -5° to -10°C and ammonia gas was passed for about 4 hours. The temperature was slowly raised to 20°C in about 2 to 3 hours and ammonium sulfate (120 g) was added at 20° to 25°C. The reaction mixture was stirred at 20° to 25°C for 2 to 3 days. The reaction mixture was filtered through celite bed and washed with methanol (100 ml). The combined filtrate was concentrated to get crude product, which was recrystallized from methanol-ethyl acetate to get the title compound.

Yield: 138 g

Purity (HPLC): 91.36%

Example 2: Preparation of Levetiracetam

a) Preparation of (S)-N-[1-(aminocarbony)propyl]-4-chlorobutyramide

Acetonitrile (1800 ml) and (S)-2-aminobutyramide (100 g) were mixed at about 25°C and stirred under nitrogen atmosphere. Pulverized potassium carbonate (203 g) was added to the reaction mixture and cooled to –5°C. A solution of 4-chlorobutyryl chloride (138.25 g) in acetonitrile (100 ml) was added slowly to the reaction mixture at a temperature of –5°C to 0°C for about 60 minutes. The reaction mixture was stirred at the same temperature until the completion of the reaction. The mixture was filtered through celite bed and washed with acetonitrile (200 ml). The combined filtrate was concentrated under vacuum at 40°C to 45° C to get the residue which was subsequently mixed with toluene (200 ml)

and the resultant mass was stirred for 30 minutes at about 25°C. Toluene was recovered under vacuum at 40° to 45°C to get the title compound as a residue.

b) Preparation of Crude Levetiracetam

Methylene chloride (2200 ml) was added at 25°C to the residue obtained from step a) and stirred for 30 minutes. Anhydrous sodium sulphate (218 g) was added to the reaction mixture, stirred for 15 minutes and cooled to 0°C. A solution of tetrabutylammonium bromide (14.2 g) in methylene chloride (100 ml) was added to the reaction mixture, followed by the addition of pulverized sodium hydroxide in three lots (42.25 g, 10.6 g and 8.8 g) at –5° to 0°C with stirring until the completion of the reaction. The pH of the resultant mixture was adjusted to the range of 7.5 to 8.0 with acetic acid (31 g) and stirred for 15 minutes. The temperature of the reaction mixture was raised to 20°C and stirred for 15 minutes at 20° to 25°C. The reaction mixture was filtered through celite bed, washed with methylene chloride (300 ml), and concentrated under vacuum at 40° to 45°C. Toluene (100 ml) was added to the residue and recovered under vacuum at 40° to 45°C. Ethyl acetate (300 ml) was added to the residue, cooled slowly to 10° to 15° C, stirred for 3 hours, filtered and washed. The product obtained was dried under vacuum at 40° to 45°C for 16 hours to obtain the title compound.

Yield: 76 g

Purity (HPLC): 99.79%

Chiral Purity: 99.89%

c) Preparation of Pure Levetiracetam

Crude levetiracetam (60 g) was dissolved in acetone (1380 ml). The mixture was filtered and washed with acetone (120 ml). The filtrate was concentrated to about 150 ml of the volume, followed by the addition of ethyl acetate (180 ml). The resultant mixture was stirred for 2 hours at 15°C, filtered and washed with cold ethyl acetate (60 ml). The product obtained was dried under vacuum at 40° to 45°C for 8 hours to get the title compound.

Yield: 50 g

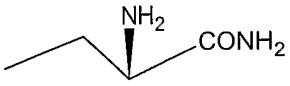
Purity (HPLC): 99.9%

Chiral Purity: 100%

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

We Claim:

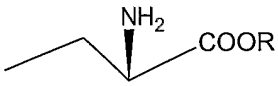
1. A process for the preparation of (S)-2-aminobutanamide of Formula I,



Formula I

the process comprising:

a) reacting a compound of Formula III,



Formula III

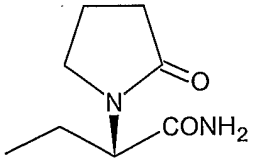
wherein R represents C_1-C_5 alkyl, haloalkyl, aryl, arylalkyl or heteroaryl, or an acid addition salt thereof, with ammonia in the presence of an ammonium salt; and

b) isolating the (S)-2-aminobutanamide of Formula I.

2. The process of claim 1, wherein the step a) is carried out from about 10°C to about 60°C.

3. The process of claim 1, wherein the ammonium salt comprises one or more of ammonium sulfate, ammonium chloride, ammonium formate, ammonium acetate, ammonium propionate, ammonium persulfate, ammonium sulfide, ammonium phosphate, ammonium nitrite, ammonium nitrate, ammonium carbonate, ammonium bicarbonate, ammonium chlorate, ammonium bromide, ammonium iodide, and ammonium fluoride.

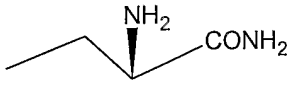
4. A process for the preparation of levetiracetam of Formula II,



Formula II

the process comprising:

a) reacting (S)-2-aminobutanamide of Formula I,



Formula I

with 4-chlorobutyryl chloride to get (S)-N-[1-(aminocarbony)propyl]-4-chlorobutyramide;

b) cyclizing the (S)-N-[1-(aminocarbony)propyl]-4-chlorobutyramide in the presence of an alkali;

c) adjusting pH of reaction mixture obtained in step b); and

d) isolating the levetiracetam of Formula II from the reaction mixture thereof.

5. The process of claim 4, wherein the reaction mixture at step c) is adjusted to a pH of about 7.0 to about 8.5.

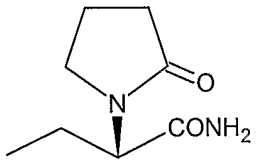
6. The process of claim 4, further comprising drying of the product obtained.

7. The process of claim 4, further comprising forming the product obtained into a finished dosage form.

8. The process of claim 4, wherein the levetiracetam has an optical purity greater than 99.5%.

9. The process of claim 4, wherein the levetiracetam has an optical purity greater than 99.8%.

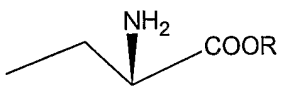
10. A process for the preparation of levetiracetam of Formula II,



Formula II

the process comprising:

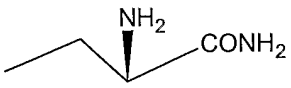
a) reacting a compound of Formula III,



Formula III

wherein R represents C_1-C_5 alkyl, haloalkyl, aryl, arylalkyl or heteroaryl, or an acid addition salt thereof, with ammonia in the presence of an ammonium salt;

b) isolating (S)-2-aminobutanamide of Formula I from reaction mixture obtained in step a);



Formula I

c) reacting the (S)-2-aminobutanamide of Formula I obtained in step b) with 4-chlorobutyryl chloride to get (S)-N-[1-(aminocarbony)propyl]-4-chlorobutyramide;

d) cyclizing the (S)-N-[1-(aminocarbony)propyl]-4-chlorobutyramide in the presence of an alkali; and

e) isolating the levetiracetam of Formula II.

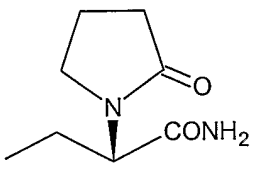
11. The process of claim 10, wherein the step a) is carried out from about 10°C to about 60°C.

12. The process of claim 10, wherein the ammonium salt comprises one or more of ammonium sulfate, ammonium chloride, ammonium formate, ammonium acetate, ammonium propionate, ammonium persulfate, ammonium sulfide, ammonium phosphate, ammonium nitrite, ammonium nitrate, ammonium carbonate, ammonium bicarbonate, ammonium chlorate, ammonium bromide, ammonium iodide, and ammonium fluoride.

13. The process of claim 10, further comprising drying of the product obtained.

14. The process of claim 10, further comprising forming the product obtained into a finished dosage form.

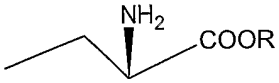
15. A process for the preparation of levetiracetam of Formula II,



Formula II

the process comprising:

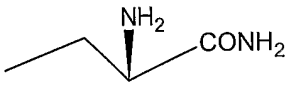
a) reacting a compound of Formula III,



Formula III

wherein R represents C_1-C_5 alkyl, haloalkyl, aryl, arylalkyl or heteroaryl or an acid addition salt thereof, with ammonia;

b) isolating (S)-2-aminobutanamide of Formula I from reaction mixture obtained in step a);



Formula I

c) reacting the (S)-2-aminobutanamide of Formula I obtained in step b) with 4-chlorobutyryl chloride to get (S)-N-[1-(aminocarbony)propyl]-4-chlorobutyramide;

d) cyclizing the (S)-N-[1-(aminocarbony)propyl]-4-chlorobutyramide in the presence of an alkali; and

e) adjusting pH of reaction mixture obtained at step d); and

f) isolating the levetiracetam of Formula II from the reaction mixture.

16. The process of claim 15, wherein the reaction mixture at step e) is adjusted to a pH of about 7.0 to about 8.5.

17. The process of claim 15, further comprising forming the product obtained into a finished dosage form.

18. The process of claim 15, wherein the levetiracetam has an optical purity greater than 99.5%.

19. The process of claim 15, wherein the levetiracetam has an optical purity greater than 99.8%.

20. The process of claim 15, further comprising using the levetiracetam to form a pharmaceutical composition comprising a therapeutically effective amount of the levetiracetam and one or more pharmaceutically acceptable carriers, excipients or diluents.