Title: PROCESS FOR PREPARING GABAPENTIN

Abstract: A one pot process for preparing l-(aminomethyl)-cyclohexanecarboxylic acid or pharmaceutically acceptable salts thereof comprises the steps of: hydrolysing 1-cyanocyclohexanecarboxylic acid ethyl ester with a potassium, sodium or lithium hydroxide to form a salt of 1-cyanocyclohexanecarboxylic acid; in-situ hydrogenating the salt of 1-cyanocyclohexanecarboxylic acid in the presence of a catalyst to form the salt of l-(aminomethyl)-cyclohexanecarboxylic acid; and isolating l-(aminomethyl)-cyclohexanecarboxylic acid.
"Improved process for preparing gabapentin"

The invention relates to an improved process for preparing gabapentin.

United States Patent Numbers 4,024,175 and 4,087,544 disclose novel cyclic amino acids of Formula A

\[
\begin{align*}
\text{H}_2\text{N} & \quad \text{CH}_2 \\
\text{C} & \quad \text{CH}_2 \\
\text{CO}_2\text{R}_1 & \quad A
\end{align*}
\]

wherein \( R_1 \) is a hydrogen atom or a lower alkyl radical, and \( n \) is 4, 5 or 6 and the pharmacologically compatible salts thereof.

The compounds disclosed in the above United States patents are useful for the therapy of certain cerebral diseases, for example, they can be used for the treatment of certain forms of epilepsy, faintness attacks, hypokinesia, and cranial traumas. Additionally, they bring about an improvement of cerebral functions, and thus are useful in treating geriatric patients. Particularly valuable is 1-(aminomethyl)-cyclohexaneacetic acid (gabapentin).

Gamma-aminobutyric acid (GABA) is an inhibitory amino acid found in the mammalian central nervous system (CNS). It has been reported that dysfunction with GABA neurotransmission in the CNS may contribute or even cause psychiatric and neurological diseases such as epilepsy, schizophrenia, Parkinson's disease, Huntington's Chorea, and dyskinesia (Saletu B., et al., *International Journal of Clinical Pharmacology, Therapy and Toxicology*. 1986;24:362-373). Gabapentin was designed as a GABA analog that would cross the blood-brain barrier. Gabapentin was found to have anticonvulsant and antispastic activity with extremely low toxicity in man.

5,693,845 disclose additional processes and intermediates for preparing gabapentin. These processes require a number of steps and in some cases utilise large uneconomic quantities of reagents and hazardous solvents.

There is a need for an improved process for preparing gabapentin more efficiently on a large scale.

Statements of Invention

According to the invention there is provided a one pot process for preparing 1- (aminomethyl)-cyclohexaneacetic acid or pharmaceutically acceptable salts thereof comprising the steps of:

- hydrolysing 1-cyanocyclohexaneacetic acid ethyl ester with a potassium, sodium or lithium hydroxide to form a salt of 1-cyanocyclohexaneacetic acid;

- in-situ hydrogenating the salt of 1-cyanocyclohexaneacetic acid in the presence of a catalyst to form the salt of 1-(aminomethyl)-cyclohexaneacetic acid; and

- isolating 1-(aminomethyl)-cyclohexaneacetic acid.

In one embodiment of the invention the process is carried out in an aqueous environment.

In one embodiment of the invention after hydrolysis the solution is washed with a water immiscible solvent. Preferably the water immiscible solvent is toluene or MTBE.

In one embodiment of the invention hydrolysis is carried out at a temperature of about 80°C for approximately 3 hours.
Hydrolysis may be carried out at room temperature.

In one embodiment of the invention hydrogenation is carried out at approximately 30°C for up to 20 hours. Preferably hydrogenation is carried out for approximately 14 hours.

In one embodiment of the invention the catalyst is Raney nickel.

In another embodiment of the invention the solution is filtered to remove the catalyst.

In another embodiment of the invention the filtered catalyst is re-used.

In one embodiment of the invention the product is isolated by:

- adding a weak acid; and

- isolating l-(aminomethyl)-cyclohexaneacetic acid.

Preferably the weak acid is acetic acid.

In one embodiment of the invention after addition of the acid, the solution is seeded with gabapentin.

 Preferably the process includes the step of stirring the product at 0 °C for approximately 4 hours.

In one embodiment of the invention the isolated l-(aminomethyl)-cyclohexaneacetic acid is washed with an alcohol. Preferably the alcohol is isopropyl alcohol (IPA).

In one embodiment of the invention the l-(aminomethyl)-cyclohexaneacetic acid is recrystallised.
In one embodiment of the invention the l-(aminomethyl)-cyclohexaneacetic acid is dissolved in methanol and water.

In another embodiment of the invention the l-(aminomethyl)-cyclohexaneacetic acid is dissolved in methanol and water, isopropyl alcohol is added and the solution distilled under vacuum.

In a further embodiment of the invention the product is washed with isopropyl alcohol and dried under vacuum.

The invention also provides the compound l-(aminomethyl)-cyclohexaneacetic acid potassium salt.

The invention further provides l-(aminomethyl)-cyclohexaneacetic acid containing less than 0.01% by weight of potassium acetate.

Detailed description

We have developed an improved process for the preparation of gabapentin. The process comprises a one pot reaction involving fewer unit operations than previous preparation methods. The reaction takes place in water resulting in an environmentally friendly process with a high product yield. The process is illustrated in scheme 1 below.

Scheme 1
The process of the invention has a number of advantages over known processes for preparing gabapentin as follows:

The isolation of the intermediate cyano acid (1-cyanocyclohexaneacetic acid) is not required. This offers major advantages over existing routes as this material is labile and requires refrigerated storage. The hydrogenation step is conducted in a purely aqueous medium with concomitant reduction in costs of solvents and environmental burden. In addition the Raney Nickel catalyst may be removed at the end of the process and directly reused in a subsequent process.

The process doubles the throughput in comparison to current known processes for preparing gabapentin.

The 1-cyanocyclohexaneacetic acid ethyl ester is heated to high temperatures (about 80°C) with potassium hydroxide during the hydrolysis step (approximately 3 hours). This has been found to result in very reproducible hydrogenations and provides a very efficient process overall. Reproducibility is a very important factor when preparing gabapentin on a large plant scale. The process may however also be carried out at room temperature.

Because the cyano acid potassium salt is hydrogenated (in comparison to the free cyano acid as used in other processes), at least 50% less Raney Nickel is used in comparison to other processes for preparing gabapentin. In some instances approximately 60% less Raney Nickel may be used in comparison to other processes. This results in a safer process which is more environmentally friendly.

A major problem encountered in current processes for preparing gabapentin is the generation of impurities in the form of secondary amines. Typically ammonia is added to suppress these impurities. The use of the potassium salt as in the process of the invention appears to inhibit the formation of secondary amine impurities and therefore no ammonia is required to be added to suppress such impurities; a significant environmental advantage.
The absence of ammonia also appears to prevent the leaching of nickel by complexation with ammonia. As a result there is no longer a requirement for ion exchange resins post hydrogenation to remove solubilised nickel resulting in a significantly streamlined batch process.

The process of the invention provides an improved process for the production of Gabapentin which is substantially free of chloride ions. Chloride ions affect the stability of gabapentin drug substance, increasing the propensity towards lactam formation.

Overall the process of the invention is a more environmentally friendly process as all reactions take place in water. Reaction concentrations are high, thus maximising energy consumption and minimising waste processing. Only one hydrocarbon (toluene) is used in impurity extraction. The toluene used is fully recyclable.

The invention will be more clearly understood by the following examples.

**Example 1 - Preparation of 1-(aminomethyl)-cyclohexaneacetic acid**

1-cyanocyclohexaneacetic acid ethyl ester (1) is prepared as described in US5693845, the entire contents of which are herein incorporated by reference.

**Preparation of Ethyl 1-cyanocyclohexaneacetate (1) (or 1-cyanocyclohexaneacetic acid ethyl ester)**

A 1-L pressure flask is charged with 148 g (1 mol) of 1-cyanocyclohexaneacetonitrile, 206 mL of ethanol, and 100 mL of toluene. The mixture is cooled to 50°C and evacuated. Anhydrous hydrogen chloride (148 g, 4.05 mol) is added to the evacuated flask, causing the pressure to rise to 10 pounds per square inch gauge (psig) while allowing the temperature to rise to 350°C. This temperature is maintained for 7 hours, during which time additional hydrogen chloride (25 g, 0.68 mol) is added to maintain a pressure of 5 pounds per square inch gauge (psig.). At the end of the 7-hour period, the excess
hydrogen chloride and ethanol are removed by vacuum distillation, maintaining the mixture at below 250°C. To the resulting slurry is added 200 mL of toluene, which is then removed by vacuum distillation. This procedure is repeated two more times with 150 mL of toluene. After the final distillation, 150 mL of toluene and 500 mL of ice water are added and the pH adjusted to four with aqueous sodium hydroxide solution. After stirring for 18 hours, the mixture is filtered, the filtrate layers separated, the aqueous layer washed with 100 mL of toluene, and then the combined toluene layers washed with 100 mL of 1N aqueous sodium hydroxide solution, followed by two water washes of 50 mL each. The toluene solution is then dried by azeotropic distillation, which is followed by vacuum distillation to remove the toluene. The residual yellow oil (166 g) is 91% ethyl 1-cyanocyclohexaneacetate. Further purification can be effected by vacuum distillation, collecting distillate with by 85°C to 95°C at 0.2 to 0.3 mm of Hg.

**Preparation of 1-(aminomethyD-cyclohexaneacetic acid**

1-cyanocyclohexaneacetic acid ethyl ester (1) is mixed with 34% w/w KOH (1.05 kg/kg 1) over 1h. On complete addition the batch is heated to about 80°C and stirred for 3h. The solution is cooled to 20-25°C then washed with toluene (0.70 kg/kg 1). After separating the layers, the product rich aqueous stream comprising 1-cyanocyclohexaneacetic acid potassium salt (2) is forward processed to the hydrogenation reaction.

1-Cyanocyclohexaneacetic acid potassium salt (2) is hydrogenated over sponge Nickel catalyst (12% active Nickel loading vs. 1) at 3.5 barg and 30°C for 14-16 hrs. The batch is cooled to ambient temperature and filtered to remove catalyst. The catalyst bed is washed with water (0.4kg/kg 1) and the solution stored at 0-5°C. The catalyst bed is then washed with potassium hydroxide solution in preparation for re-use. This wash is disposed and the Raney Nickel stored under caustic solution.

The solution of 1-(aminomethyl)cyclohexaneacetic acid potassium salt (3) (pH 13-14) is heated to about 40°C before pH adjustment to 7.1 (isoelectric point) by
addition of 80% acetic acid - (ca. 0.53kg/kg vs. 1). The 80% acetic acid is added at such a rate to maintain the temperature <55°C. The batch is cooled to 40°C and seeded by addition of gabapentin to the batch. The batch is then cooled to 0°C and stirred for a minimum of 4h. The batch is isolated, and washed with isopropyl alcohol (IPA) (1.56kg/kg 1). The IPA wet, 1-(aminomethyl)-cyclohexanecarboxylic acid (4) may be recrystallised using either of the crystallisation steps described in examples 2 or 3. Yield = 68-73% from active 1-cyanocyclohexaneacetic ethyl ester.

Example 2 - Recrystallisation HaminomethylVcyclohexanecarboxylic acid (4)
1-(Aminomethyl)-cyclohexanecarboxylic acid (4) as prepared in Example 1 is dissolved (ca. 65-67°C) in methanol (2.5 vol) and water (ca. 0.6 vol). Water is added in small portions until solution is achieved. Preheated IPA (5.0 vol) is added to the solution and the batch cooled to 0°C for isolation. The batch is washed with IPA (1.0 vol) and dried under vacuo at 50°C. Recovery: 88 to 92%.

Example 3 - Recrystallisation of 1-(aminomethyl)-cyclohexanecarboxylic acid (4)
1-(Aminomethyl)-cyclohexanecarboxylic acid (4) as prepared in Example 1 is dissolved (ca. 65-67°C) in methanol (2.5 vol) and water (ca. 0.6 vol). The solution is added to preheated IPA (5.0 vol). The solution is then distilled to remove up to 70% of the batch volume. The batch is cooled to 0°C for isolation. The batch is washed with IPA (1.0 vol) and dried under vacuo at 50°C. Recovery: 88 to 95%.

Example 4 - Preparation of 1-(aminomethyl)Vcyclohexanecarboxylic acid (4) using recovered Nickel catalyst

1-cyanocyclohexanecarboxylic acid ethyl ester (1) is mixed with 34% w/w KOH (1.05 kg/kg 1) over 1h. On complete addition the batch is heated to about 80°C and stirred for 3h. The solution is cooled to 20-25°C then washed with toluene (0.70 kg/kg 1). After separating the layers the product rich aqueous stream comprising 1-cyanocyclohexanecarboxylic acid potassium salt (2) is forward processed to the hydrogenation reaction.
1-Cyanocyclohexaneacetic acid potassium salt (2) is hydrogenated over the recovered sponge Nickel catalyst from Example 1 (12% active Nickel loading vs. 1) at 3.5 barg and 30°C for 14-16 hrs. The batch is cooled to ambient temperature and filtered to remove catalyst. The catalyst bed is washed with water (0.4 kg/kg vs. 1) and the solution stored at 0-5°C.

The solution of l-(aminomethyl)cyclohexaneacetic acid potassium salt (3) (pH 13-14) is heated to about 40°C before pH adjustment to 7.1 (isoelectric point) by addition of 80% acetic acid —(ca. 0.53 kg/kg vs. 1). The 80% acetic acid is added at such a rate to maintain the temperature <55°C. The batch is cooled to 40°C and seeded by addition of gabapentin to the batch. The batch is then cooled to 0°C and stirred for a minimum of 4h. The batch is isolated, and washed with isopropyl alcohol (IPA) (1.56 kg/kg vs. 1). The IPA wet, l-(aminomethyl)-cyclohexaneacetic acid (4) can be recrystallised using either of the crystallisation steps described in examples 2 or 3. Yield = 68-73% from active 1-cyanocyclohexaneacetic ethyl ester.

The invention is not limited to the embodiments hereinbefore described which may be varied in detail.
Claims

1. A one pot process for preparing 1-(aminomethyl)-cyclohexaneacetic acid or pharmaceutically acceptable salts thereof comprising the steps of:-

   hydrolysing 1-cyanocyclohexaneacetic acid ethyl ester with a potassium, sodium or lithium hydroxide to form a salt of 1-cyanocyclohexaneacetic acid;

   in-situ hydrogenating the salt of 1-cyanocyclohexaneacetic acid in the presence of a catalyst to form the salt of 1-(aminomethyl)-cyclohexaneacetic acid; and

   isolating 1-(aminomethyl)-cyclohexaneacetic acid.

2. A process as claimed in claim 1 wherein the process is carried out in an aqueous environment.

3. A process as claimed in claim 1 or 2 wherein after hydrolysis the solution is washed with a water immiscible solvent.

4. A process as claimed in claim 3 wherein the water immiscible solvent is toluene or MTBE.

5. A process as claimed in any of claims 1 to 4 wherein hydrolysis is carried out at a temperature of about 80°C for approximately 3 hours.

6. A process as claimed in any of claims 1 to 4 wherein hydrolysis is carried out at room temperature.

7. A process as claimed in any of claims 1 to 6 wherein hydrogenation is carried out at approximately 30°C for up to 20 hours.
8. A process as claimed in claim 7 wherein hydrogenation is carried out for approximately 14 hours.

9. A process as claimed in any of claims 1 to 8 wherein the catalyst is Raney nickel.

10. A process as claimed in any of claims 1 to 9 wherein the solution is filtered to remove the catalyst.

11. A process as claimed in claim 10 wherein the filtered catalyst is re-used-.

12. A process as claimed in any of claims 1 to 11 wherein the product is isolated by:-

   adding a weak acid; and

   isolating l-(aminomethyl)-cyclohexanecetic acid.

13. A process as claimed in claim 12 wherein the weak acid is acetic acid.

14. A process as claimed in claim 12 or 13 wherein, after addition of the acid, the solution is seeded with gabapentin.

15. A process as claimed in any of claims 12 to 14 including the step of stirring the product at 0°C for approximately 4 hours.

16. A process as claimed in any of claims 12 to 15 wherein the isolated l-(aminomethyl)-cyclohexanecetic acid is washed with an alcohol.

17. A process as claimed in claim 16 wherein the alcohol is isopropyl alcohol (IPA).
18. A process as claimed in any of claims 1 to 17 wherein the \( \text{l-(aminomethyl)-cyclohexaneacetic acid} \) is recrystallised.

19. A process as claimed in claim 18 wherein the \( \text{l-(aminomethyl)-cyclohexaneacetic acid} \) is dissolved in methanol and water.

20. A process as claimed in claim 18 wherein the \( \text{l-(aminomethyl)-cyclohexaneacetic acid} \) is dissolved in methanol and water, isopropyl alcohol is added and the solution distilled under vacuum.

21. A process as claimed in claim 19 or 20 wherein the product is washed with isopropyl alcohol and dried under vacuum.

22. A process substantially as hereinbefore described with reference to the examples.

23. \( \text{l-(aminomethyl)-cyclohexaneacetic acid potassium salt} \).

24. \( \text{l-(aminomethyl)-cyclohexaneacetic acid containing less than 0.01\% by weight of potassium acetate} \).
# INTERNATIONAL SEARCH REPORT

## A. CLASSIFICATION OF SUBJECT MATTER

INV. C07C227/18 C07C227/06 C07C229/28

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BEILSTEIN Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Further documents are listed in the continuation of Box C

See patent family annex

* Special categories of cited documents

IA1 document defining the general state of the art which is not considered to be of particular relevance

IE earlier document, but published on or after the international filing date

IL document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or to establish a date other than the priority date claimed

IO1 document referring to an oral disclosure, use, exhibition or other means

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"X" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"Y" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

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* A document member of the same patent family

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<td>A</td>
<td>ZOIDIS G ET AL: &quot;The novel GABA adamantane derivative (AdGABA): design, synthesis, and activity relationship with gabapentin&quot; BIOORGANIC &amp; MEDICINAL CHEMISTRY, ELSEVIER SCIENCE LTD, GB, vol. 13, no. 8, 15 April 2005 (2005-04-15), pages 2791-2798, XP004802818 ISSN: 0968-0896 page 2793, Scheme 2 and Scheme 3</td>
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