

1.112.897



PATENT SPECIFICATION

NO DRAWINGS

1.112.897

Date of Application and filing Complete Specification: 13 May, 1965.
No. 20146/65.

Application made in Japan (No. 27137) on 15 May, 1964.

Application made in Japan (No. 39319) on 9 July, 1964.

Complete Specification Published: 8 May, 1968.

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Index at acceptance:—C2 C(2B2A2, 2B2F, 2B2G2, 2B2G6, 2B46C1, 2B46G1)

Int. Cl.:—C 07 c 101/04

COMPLETE SPECIFICATION

Process for the production of *Trans*-4-Aminomethylcyclohexane-1-Carboxylic Acid

We, DAIICHI SEIYAKU COMPANY LIMITED of 2, No. 1 3-chome, Edobashi, Nihonbashi, Tokyo, Japan; and MITSUBISHI CHEMICAL INDUSTRIES LIMITED of No. 4, 2-chome, Marunouchi, Chiyoda-ku, Tokyo, Japan, both Japanese Companies, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

The present invention relates to a process for the production of *trans*-4-aminomethylcyclohexane-1-carboxylic acid.

An object of the present invention is to provide an improved and economical process for producing *trans*-4-aminomethylcyclohexane-1-carboxylic acid which has significant value as an antiplasmic agent.

So far, 4-aminomethylcyclohexane-1-carboxylic acid has been known as a valuable substance for pharmaceutical use, and it is specifically pointed out in the Specification of British Patent No. 949512 that the compound has an antiplasmic activity and an excellent therapeutic effect on disorders caused by activated plasmin in vivo. Two stereo isomers of the compound exist and the *trans*-isomer has a far stronger antiplasmic activity than the *cis*-isomer.

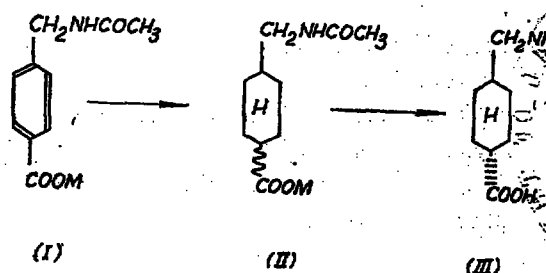
In the reaction of preparing 4-aminomethylcyclohexane-1-carboxylic acid by reducing the benzene nucleus of 4-aminomethylbenzoic acid, Raney-nickel such as any Raney-nickel of W-1 to W-7 (cited in the following references: The Journal of the American Chemical Society, vol. 68, p.1471 (1946), vol. 69, p.3040 (1947) and vol. 70, p.695 (1948) and Organic Syntheses, vol 21, p.15 (1941) is far more convenient than platinum as a catalyst to be utilized industrially. It was recognized, however, that if the reduction is carried out using Raney-nickel upon 4-aminomethylbenzoic acid with its amino group and carboxyl group unprotected, the reaction gives only a small amount of the desired product.

We have further executed numerous experiments and studies and have now developed a profitable process of the present invention for producing *trans*-4-aminomethylcyclohexane-1-carboxylic acid.

In the process of the present invention, the amino group of 4-aminomethylbenzoic acid is protected with an acetyl group and the carboxyl group thereof is in the form of an alkali or alkaline earth metal salt, that is, an alkali or alkaline earth metal salt of 4-acetamidomethylbenzoic acid is used as the starting material.

The process of the present invention may be represented by the following reaction formula:

SEE ERRATA SLIP ATTACHED



wherein M stands for an alkali metal such as sodium or potassium, or one equivalent of an alkaline earth metal such as calcium or barium.

The process comprises reducing an alkali or alkaline earth metal salt (I) of 4-acetamidomethylbenzoic acid by heating it under pressure in the presence of a hydrogenation catalyst and in an atmosphere of hydrogen to produce an alkali or alkaline earth metal salt (II) of 4-acetamidomethylcyclohexane-1-carboxylic acid, and subjecting such salt to a hydrolysis-conversion reaction by heating it under pressure with an aqueous alkali or alkaline earth metal hydroxide, so that both the deacetylation and the transformation of the stereo conformation are effected simultaneously to produce the desired *trans*-4-aminomethylcyclohexane-1-carboxylic acid (III).

The catalytic reduction step of the present invention may be carried out by shaking in an autoclave the compound (I) and a Raney-nickel catalyst such as any Raney-nickel of W-1 to W-7 in a solvent consisting of water, methanol, ethanol or a mixture of two or all three thereof at 120 to 200°C (preferably 160 to 180°C) for 1—5 hours in an atmosphere of hydrogen, the initial pressure of which is 40—100 atmospheres gauge, so that the theoretical amount of hydrogen is absorbed. The resultant alkali or alkaline earth metal salt of 4-acetamidomethylcyclohexane-1-carboxylic acid (II), with or without being isolated from the reaction mixture, is then subjected to the second step of the process, which conveniently involves heating the isolated salt or the reaction mixture aforesaid at 180—250°C in an autoclave for 8—18 hours with an aqueous solution of an alkali metal hydroxide such as sodium or potassium hydroxide or an alkaline earth metal hydroxide such as calcium hydroxide or barium hydroxide. The amount of alkali or alkaline earth metal hydroxide should be sufficient to hydrolyze the acetyl group, for example, about 1—1.2 mol equivalent of the amount of the compound (II).

Thereafter, the treatment may be continued as follows in order to remove inorganic ions:

(1) When an alkali metal salt of 4-acetamidomethylbenzoic acid is used as the starting material and/or an alkali metal hydroxide is used as the hydrolyzing-transforming agent:

The reaction mixture containing the salt of *trans*-4-aminomethylcyclohexane-1-carboxylic acid is passed through a column of a strong cation-exchange resin, for example Diaion KS #1 (H type) (trade name of Mitsubishi Chemical Industries Limited, Japan) into which 5% aqueous ammonia is then poured to elute the ammonium salt of *trans*-4-aminomethylcyclohexane-1-carboxylic acid. This procedure may be simplified when the potassium salt of 4-acetamidomethylbenzoic acid is used as the starting material and potassium hydroxide is used as the hydrolyzing-transforming agent, since the difference in solubility between the potassium acetate produced by deacetylation of the 4-acetamidomethylbenzoic acid and the potassium salt of the desired product can then be utilized, and the potassium acetate removed by dissolution in methanol without recourse to the aforesaid treatment with a cation-exchange resin.

(2) When an alkaline earth metal salt of 4-acetamidomethylbenzoic acid is used as the starting material and/or an alkaline earth metal hydroxide is used as the hydrolyzing-transforming agent:

An equivalent amount of an acid (for example, sulphuric acid or oxalic acid) capable of forming a sparingly soluble alkaline earth metal salt must be added to the reaction mixture before the treatment with a cation-exchange resin, to remove the alkaline earth metal ion contained therein, as, for example, barium sulphate or calcium oxalate. Treatment with a cation-exchange resin can, however, be omitted when an alkaline earth metal salt of 4-acetamidomethylbenzoic acid and an alkaline earth metal hydroxide are used.

The final filtrate is concentrated and the residue recrystallized from water-acetone

cation

or water-acetone-methanol to give crystals of the required *trans*-4-aminomethylcyclohexane-1-carboxylic acid.

The product of the present invention has a potent inhibitory action on the plasmin system, and also an excellent therapeutic effect on disorders associated with and/or caused by activated plasmin in vivo, without any accompanying noticeable toxicity.

Some preferred embodiments of the present invention will now be described in detail, the examples given being for the purpose of illustrating preferred embodiments only.

EXAMPLE 1

In an aqueous solution prepared by dissolving 0.8 g (0.02 mol) of sodium hydroxide in 20 ml of water, 3.9 g (0.02 mol) of 4-acetamidomethylbenzoic acid was dissolved to make a neutral solution. In this solution, 1 g of Raney-nickel catalyst was suspended, and the suspension was shaken in an autoclave at 170°C for two hours in an atmosphere of hydrogen, the initial pressure of which was 82 atmospheres gauge (at room temperature), so that the theoretical amount of hydrogen was absorbed. After cooling, the catalyst was removed by filtration. To the filtrate, 0.96 g (0.024 mol) of sodium hydroxide was added, and in an autoclave the solution was heated at 190–200°C for 16 hours. The reaction solution was poured into a column of 150 ml of a strong cation exchange resin, Diaion SK#. The column was washed with water, and then *trans*-4-aminomethylcyclohexane-1-carboxylic acid was eluted with 5% aqueous ammonia. This ammoniacal eluate (positive in the Ninhydrin Reaction) was concentrated to dryness, and the residue was recrystallized from water-acetone or water-alcohol to give 2.25 g (yield: 71%) of crystals of *trans*-4-aminomethylcyclohexane-1-carboxylic acid which melt at 380–390°C (decomp.).

Analysis for $C_9H_{14}O_2N$

Calculated (%)	C 61.12,	H 9.62,	N 8.91.
Found (%)	C 61.10,	H 9.52,	N 8.58.

EXAMPLE 2

In an aqueous solution prepared by dissolving 1.1 g (0.02 mol) of potassium hydroxide in 30 ml of water, 3.9 g (0.02 mol) of 4-acetamidomethylbenzoic acid was dissolved to make a neutral solution. In this aqueous solution, 1 g of Raney-nickel catalyst was suspended, and the suspension was shaken in an autoclave at 170–180°C for about 2 hours in an atmosphere of hydrogen, the initial pressure of which was 90 atmospheres gauge, so that the theoretical amount of hydrogen was absorbed. After cooling, the catalyst was removed by filtration. To the filtrate, 1.35 g (0.024 mol) of potassium hydroxide was added, and in an autoclave the solution was heated at 190–200°C for 18 hours. After cooling, 1.45 g (0.024 mol) of glacial acetic acid was added to the reaction solution to neutralize it, and the solution was then concentrated under reduced pressure. To the residue, 15 ml of methanol was added to remove potassium acetate by dissolution. The residue was further treated twice with methanol to give a crystalline powder. This powder gave, upon recrystallization from water-acetone, 2.36 g (yield: 75%) of colourless crystals of *trans*-4-aminomethylcyclohexane-1-carboxylic acid which melt at 380–390°C (decomp.). This product agreed well with an authentic sample in respect of both infra-red spectrum and melting point.

EXAMPLE 3

In 30 ml of water, 3.9 g (0.02 mol) of 4-acetamidomethylbenzoic acid and 3.15 g (0.01 mol) of barium hydroxide were suspended, 1 g of Raney-nickel catalyst was added to this suspension, and the reduction was carried out by heating in a hydrogen atmosphere under superatmospheric pressure. The catalyst was removed by filtration from the reaction mixture and the filtrate was concentrated to dryness. To the residue, 1.2 ml of water and 0.96 g (0.024 mol) of sodium hydroxide were added, and the mixture was heated in an autoclave at 190–200°C for 16 hours. To the reaction solution, 100 ml of water was added, and, while warm, the theoretical amount of dilute sulphuric acid was added to precipitate barium sulphate. After cooling, the barium sulphate was filtered, and the filtrate was treated with a strong cation exchange resin in the same manner as in Example 1 to give 2.55 g (yield: 81%) of colourless crystals of *trans*-4-aminomethylcyclohexane-1-carboxylic acid which melt at 380–390°C (decomp.).

EXAMPLE 4

In 50 ml of water, 3.9 g (0.02 mol) of 4-acetamidomethylbenzoic acid and 0.74 g of calcium hydroxide were suspended, and 1 g of Raney-nickel catalyst was added



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thereto. The mixture was shaken in an autoclave at 180°C for an hour in an atmosphere of hydrogen, the initial pressure of which was 99 atmospheres gauge. The reaction solution was concentrated under reduced pressure, 1.35 g (0.024 mol) of potassium hydroxide was added thereto and in an autoclave the mixture was heated at 190–200°C for 18 hours. To the reaction solution, 50 ml of water was added, and then the theoretical amount of oxalic acid was added to precipitate calcium oxalate. The precipitate was removed by filtration and the filtrate was treated with a strong ion-exchange resin in the same manner as in Example 1 to give 2.08 g (yield: 66%) of colourless crystals of *trans*-4-aminomethylcyclohexane-1-carboxylic acid which melt at 380–390°C (decomp.).

EXAMPLE 5

In 30 ml of water, 3.9 g (0.02 mol) of 4-acetamidomethylbenzoic acid and 3.15 g (0.01 mol) of barium hydroxide were suspended. In an autoclave, 1 g of Raney-nickel catalyst was added thereto, and the mixture was shaken at 170–180°C for an hour in an atmosphere of hydrogen, the initial pressure of which was 98 atmospheres gauge, so that the theoretical amount of hydrogen was absorbed. The catalyst was removed by filtration, and the filtrate was concentrated under reduced pressure to dryness. To the residue, 12 ml of water and 4.7 g (0.015 mol) of barium hydroxide was added, and the mixture was heated in an autoclave at 200°C for 15 hours. To the reaction solution 100 ml of water was added and, while warm, the theoretical amount of dilute sulphuric acid was added to precipitate barium sulphate. After cooling, the precipitate was removed by filtration. The filtrate was evaporated and the precipitated crystals were recrystallized from water-acetone. They were again recrystallized from water-methanol-acetone to give 2.55 g (yield: 81%) of *trans*-4-aminomethylcyclohexane-1-carboxylic acid which melts at 380–390°C (decomp.). The product agreed well with an authentic sample in respect of infra-red spectrum, melting point and the characteristics of its derivatives.

EXAMPLE 6

In 50 ml of water, 3.9 g (0.02 mol) of 4-acetamidomethylbenzoic acid and 0.74 g of calcium hydroxide were suspended. In an autoclave, 1 g of Raney-nickel was added thereto, and the mixture was shaken at 180°C for an hour in an atmosphere of hydrogen, the initial pressure of which was 99 atmospheres gauge. The reaction mixture was concentrated to 20 ml, 0.85 g (0.015 mol) of calcium oxide was added with resultant hydration and the mixture was heated in an autoclave at 200°C for 15 hours. To the reaction solution, 50 ml of water was added, and then the theoretical amount of oxalic acid was added to precipitate calcium oxalate. The precipitate was removed by filtration, and the filtrate was treated in the same manner as in Example 5 to give 1.6 g (yield: 51%) of *trans*-4-aminomethylcyclohexane-1-carboxylic acid which melts at 380–390°C (decomp.).

Having regard to the provisions of Section 9 of the Patents Act, attention is directed to the Claims of Specification No. 1086952.

WHAT WE CLAIM IS:—

1. A process for producing *trans*-4-aminomethylcyclohexane-1-carboxylic acid, which comprises reducing an alkali or alkaline earth metal salt of 4-acetamidomethylbenzoic acid by heating it under pressure in the presence of a hydrogenation catalyst and in an atmosphere of hydrogen to produce an alkali or alkaline earth metal salt of 4-acetamidomethylcyclohexane-1-carboxylic acid, and subjecting such salt to a hydrolysis-conversion reaction by heating it under pressure with an aqueous alkali or alkaline earth metal hydroxide.

2. A process according to Claim 1 in which the initial pressure in the first step is 40 to 100 atmospheres gauge.

3. A process according to Claim 1 or Claim 2 in which the catalyst is Raney-nickel.

4. A process according to any one of Claims 1 to 3 in which the temperature in the first step is 120 to 200°C.

5. A process according to any one of Claims 1 to 4 in which the temperature in the second step is 180 to 250°C.

6. A process according to any one of Claims 1 to 5 in which the time of heating in the second step is 8 to 18 hours.

7. A process according to any one of the preceding Claims including the step of recovering *trans*-4-aminomethylcyclohexane-1-carboxylic acid from the reaction mixture.

thereto. The mixture was shaken in an autoclave at 180°C for an hour in an atmosphere of hydrogen, the initial pressure of which was 99 atmospheres gauge. The reaction solution was concentrated under reduced pressure, 1.35 g (0.024 mol) of potassium hydroxide was added thereto and in an autoclave the mixture was heated at 190—200°C for 18 hours. To the reaction solution, 50 ml of water was added, and then the theoretical amount of oxalic acid was added to precipitate calcium oxalate. The precipitate was removed by filtration and the filtrate was treated with a strong ion-exchange resin in the same manner as in Example 1 to give 2.08 g (yield: 66%) of colourless crystals of *trans*-4-aminomethylcyclohexane-1-carboxylic acid which melt at 380—390°C (decomp.).

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