Title: PROCESS FOR THE PREPARATION OF 1,1-CYCLOHEXANEDIACETIC ACID

Abstract: Process for the preparation of 1,1-cyclohexane-diacetic acid (CHDAA) from 1,5-dicarbonitrile-2,4-dioxo-3-aza-spiro[5,5]undecane (the imide), by reacting it with sulfuric acid in two steps. The first step at a temperature lower than 100°C and the second step at a reaction temperature from 160 to 190°C. The first step is carried out by dissolving the imide in aqueous sulfuric acid at temperatures from about 65°C to about 85°C and then cooling the solution thus obtained to room temperature. The second step is carried out by reacting said solution with aqueous sulfuric acid at temperatures of about 170°C.
PROCESS FOR THE PREPARATION OF
1,1-CYCLOHEXANEDICETIC ACID

Field of the Invention
This invention relates to an improved process for the preparation of 1,1-Cyclohexanedicetic acid.

Background of the Invention
1,1-Cyclohexanedicetic acid – hereinafter, briefly, CHDAA – is an intermediate for the preparation of 1,1-cyclohexanedicetic acid monoamide – hereinafter, briefly, CHDAAM – which is an essential starting material for the preparation of a medicament known as Gabapentin, 1-(aminomethyl)cyclohexaneacetic acid. The preparation of CHDAA, however, is fraught with technical difficulties which reflect on the whole process for the preparation of Gabapentin.

USP 2,960,441 and BP 898,692 to Lambert disclose the preparation of cyclohexanedicetic acid from the ammonium salt of 4,4-pentamethylene-3,5-dicyan-glutarimide. Said ammonium salt has the formula:

![Chemical Structure]

The preparation of said ammonium salt from cyclohexanone in a high yield is also described in the aforesaid patents.
However, the preparation of cyclohexanediacetic acid (CHDAA) from the said ammonium salt is difficult and inefficient as taught in the prior art. According to the aforesaid USP 2,960,441, CHDAA is obtained with a yield of 65%, but this applicant believes that in fact this is a maximum yield and that in actual practice the yield is perhaps 60%. BP 898,692 claims an improvement in the yield to 75%. Additionally, the reaction carried out as described in the aforesaid patents, and as generally known in the prior art, is accompanied by a foaming of the reaction mass to a very great extent, and this constitutes a process problem of the first magnitude, causing inefficient use of the process apparatus and limiting the amount of product that can be obtained in a batch. Generally, CHDAA, obtained as a precipitate in the said prior art process and filtered off the reaction mass, must be redissolved and subjected to filtration four more times, resulting in a very inefficient process.

It is therefore a purpose of this invention to provide a process for the preparation of CHDAA that is free from the drawbacks of the prior art process and is therefore adapted to efficient industrial operation.

It is another purpose of this invention to provide such a process in which foaming of the reaction mass is avoided.

It is a further purpose of this invention to provide such a process which has a high yield, e.g., about 90%.

It is a still further purpose of this invention to provide such a process which involves a single filtration only.
It is a still further purpose of this invention to provide such a process which yields a pure CHDAA, e.g., having a purity of more than 99% by HPLC.

It is a still further purpose of this invention to provide such a process that reduces the amount of sulfur dioxide that is given off in the production of CHDAA.

Other purposes and advantages of this invention will appear as the description proceeds.

**Summary of the Invention**

The process of the invention involves hydrolysis of 1,5-dicarbonitrile-2,4-dioxo-3-azaspiro[5,5]undecane, hereinafter briefly called "the imide", by reacting it with sulfuric acid in two steps. In the first step, the imide is dissolved in aqueous concentrated sulfuric acid at temperatures lower than 100°C, e.g. from about 65° to about 85°C. The concentration of the sulfuric acid is from 75 to 90% and the imide is in an amount of 400 to 600 grams per liter of the sulfuric acid. The imide reacts with the sulfuric acid to produce a clear solution of 1,5-dicarbamoyl-2,4-dioxo-3-azaspiro[5,5]undecane, which will be called hereinafter “the first intermediate”. The clear solution of the first intermediate is then preferably cooled to room temperature. In the next step, the said clear solution is added to aqueous 70% sulfuric acid preheated to a reaction temperature from about 160 to about 190°C, e.g., about 170°C, preferably at a constant rate, during a time period of a few
hours, e.g. 3-4 hours. CHDAA is formed and carbon dioxide (CO₂) evolves. Thereafter the reaction mass is preferably kept at the reaction temperature until the evolution of CO₂ ceases, this indicating that the reaction has been completed, and generally occurring in about 1-2 hours. The reaction mixture is then worked up to obtain the pure CHDAA, in a manner, a preferred embodiment of which, will be described hereinafter. It is believed that the formation of CHDAA from the imide occurs in a number of stages which will be described hereinafter, but this opinion is not part of the invention and does not bind the inventor.

The sulfuric acid used to prepare CHDAA from the first intermediate (1,5-dicarbamoyl-2,4-dioxo-3-azaspiro[5,5]undecane) has a concentration from 60 to 80%, and the molar ratio of sulfuric acid to the first intermediate is from 6 to 9.

The imide - 1,5-dicarbonitrile-2,4-dioxo-3-azaspiro[5,5]undecane- that is the starting compound of the present process, can be prepared in a known way, described in publications mentioned hereinafter.

In a preferred form of the invention, the transformation of the imide - 1,5-dicarbonitrile-2,4-dioxo-3-azaspiro[5,5]undecane- to CHDAA is carried out through the following steps:

a) forming the solution of the first intermediate by dissolving the imide in aqueous sulfuric acid, as hereinbefore described;

b) reacting the first intermediate with aqueous sulfuric acid to form CHDAA until completion of the reaction, as hereinbefore described;
c) cooling the mixture obtained from said reaction to about 100°C, to obtain a slurry;
d) diluting the reaction mixture with water;
e) extracting the reaction product with MIBK (methylisobutyl ketone), e.g. at a temperature of 70-80 °C, whereby an organic phase and an aqueous phase are formed;
f) separating the organic phase from the aqueous phase and washing it with water, e.g. at a temperature of 70-80 °C, to reduce the sulfuric acid content;
g) distilling off the MIBK until a concentration of 30-35 wt% of CHDAAn is reached;
h) filtering the resulting slurry, washing once again with MIBK and drying.

It is believed by the applicant, although this belief is not essential to this invention and is not part of the invention, that the formation of CHDAAn from the imide occurs through the reaction chain shown in Fig. 2, in the first stage of which 1,5-dicarbamoyl-2,4-dioxo-3-azaspiro[5,5]undecane, then spiro(cyclohexane-1,9-[3,7]-diaza-bicyclo[3.3.1]nonane-2,4,6,8-tetraone is formed.

**Brief Description of the Drawings**

In the drawing:

- Fig. 1 is a flow scheme for the preparation of CHDAAn from imide, according to an embodiment of the invention; and
Fig. 2 is a reaction chain which the applicant believes to be the one that leads to the formation of CHDAA from the imide.

**Detailed Description of Preferred Embodiments**

The preparation of the imide, which is the starting product of the process of this invention, is known in the literature. It can be prepared from the ammonium salt by acidification with aq. HCl or H₂SO₄.

A preferred embodiment of the process of the invention is illustrated in Fig. 1. In said embodiment, the starting product is crude, wet imide, containing about 72 wt% of imide, 20.5 wt% of water and 7.5 wt% of (NH₄)₂SO₄. The process preferably involves the following steps:

**First step**

A solution of 1,5-dicarbamoyl-2,4-dioxo-3-azaspiro[5,5]undecane (first intermediate) is prepared by adding wet, crude 1,5-dicarbonitrile-2,4-dioxo-3-azaspiro[5,5]undecane (the imide) to conc. H₂SO₄ at 65-85°C. A preferred initial weight ratio between the reactants is:

\[
\text{H}_2\text{SO}_4 : \text{imide} \quad \sim 2.8 \pm 0.2 \\
\text{Imide} : \text{water} \quad \sim 2.5 \pm 0.5.
\]

Care should be taken that the addition of the wet crude imide should take 2-4 hours and that the temperature of the solution should be maintained between 65 and 85°C. After a clear solution is obtained, the reaction mixture is cooled to room temperature for continuation to the second step.
Second step
The solution of the first intermediate in aqueous H₂SO₄ at room temperature, thus obtained, is added to aqueous 70% H₂SO₄ heated to ~170°C, at a constant rate, over ~3-4 hours. During the addition, the reactions illustrated in Fig. 2 are believed to take place, and 1,1-cyclohexanediacetic acid (CHDAA) is obtained. CO₂ is formed during the reaction, which evolves from the mixture without foaming.

Third step
After completing the addition of the said solution of the first intermediate, the reaction mixture is kept at 170°C for 1-2 hours to complete the reaction. Completion is determined by cessation of the evolution of gases and confirmed by HPLC analysis of the reaction mixture.

Fourth step
After completion of the aforesaid reaction, the reaction mixture is cooled to ~100°C and diluted with water. At the end of the addition of the water, the temperature stabilizes at 70-80°C and a slurry with a density of ~1.3 g/ml is obtained. A preferred weight ratio is: reaction mixture : water ~1.2 ±0.2.

Fifth step
The product is completely extracted from the diluted reaction mixture with methylisobutylketone (MIBK) under stirring. The weight of the MIBK required for the reaction is ~12 times the theoretical amount of the CHDAA obtained in the reaction. A preferred extraction temperature is
70-80°C. After stopping the stirring, two liquid phases are obtained, an organic one (d ~0.85 g/ml) and an aqueous one (d ~1.3 g/ml).

Sixth step
After separation of the aqueous phase, the remaining organic phase is washed with water at 70-80°C to reduce the H₂SO₄ content. A preferred amount of water for the wash is 20% of the organic phase. The washings are combined with the aqueous phase as aqueous waste.

Seventh step
The MIBK is distilled off at a vacuum of 100-200 mm Hg and the remaining slurry is concentrated to 30-35 wt% CHDAA. The distillation fractions containing a mixture of MIBK/H₂O can be used in the extraction of the next batch. The distillation residues are cooled to room temperature for crystallization of pure CHDAA.

Eighth step
Pure CHDAA is obtained by filtration of the slurry, washing with MIBK and drying. A preferred weight of MIBK for the washing is equal to that of the product. Pure CHDAA (>99% by HPLC) is obtained in a yield of ~90%. The product obtained is suitable for the preparation of CHDAAM. A part of the filtrate can be recycled to the fifth step of the next batch – extraction with MIBK.

The preparation of 1,5-dicarbonitrile-2,4-dioxo-3-azaspiro[5,5]undecane (the imide) is described in A. I. Vogel, Physical properties and chemical constitution, Part II: Esters of ββ-disubstituted glutaric acids, J. Chem.

While embodiments of the invention have been described for purposes of illustration, it will be understood that the invention can be carried out with many modifications, variations and adaptations, without departing from its spirit or exceeding the scope of the claims.
CLAIMS

1. Process for the preparation of 1,1-cyclohexane-diacetic acid (CHDAA) from 1,5-dicarbonitrile-2,4-dioxo-3-azaspiro[5,5]undecane (the imide), which comprises reacting it with sulfuric acid in two steps, the first step at a temperature lower than 100°C and the second step at a reaction temperature from 160 to 190°C.

2. Process according to claim 1, wherein the first step is carried out by dissolving the imide in aqueous sulfuric acid at temperatures from about 65°C to about 85°C and then cooling the solution thus obtained to room temperature and the second step is carried out by reacting said solution with aqueous sulfuric acid at temperatures of about 170°C.

3. Process according to claim 1, wherein the first step comprises mixing the imide with aqueous 75-90% H₂SO₄, in an amount of 400-600 grams of imide per liter of aqueous H₂SO₄ whereby a clear solution of 1,5-dicarbamoyl-2,4-dioxo-3-azaspiro[5,5]undecane is formed.

4. Process according to claim 1, wherein the second step is continued until the reaction is completed.

5. Process according to claim 1, wherein the second step comprises mixing a solution of 1,5-dicarbamoyl-2,4-dioxo-3-azaspiro[5,5]undecane in aqueous H₂SO₄ with sulfuric acid having a concentration from 60 to 80%,
the molar ratio of sulfuric acid to 1,5-dicarbamoyl-2,4-dioxo-3-azaspiro[5,5]undecane being from 6 to 9.

6. Process according to claim 1, which comprises the following steps:
   a) forming the solution of 1,5-dicarbamoyl-2,4-dioxo-3-azaspiro[5,5]undecane by dissolving 1,5-dicarbonitrile-2,4-dioxo-3-azaspiro[5,5]undecane in aqueous sulfuric acid;
   b) reacting the 1,5-dicarbamoyl-2,4-dioxo-3-azaspiro[5,5]undecane with aqueous sulfuric acid to form CHDAA;
   c) cooling the mixture obtained from said reaction to about 100°C, to obtain a slurry;
   d) diluting the reaction mixture with water;
   e) extracting the reaction product with methylisobutyl ketone, whereby an organic phase and an aqueous phase, separate from one another, are formed;
   f) separating the organic phase from the aqueous phase and washing it with water;
   g) distilling off the methylisobutyl ketone until a slurry having a concentration of 30-35 wt% of CHDAA is obtained;
   h) filtering said slurry, washing once again with methylisobutyl ketone and drying.

7. Process according to claim 1, further comprising preparing 1,5-dicarbamoyl-2,4-dioxo-3-azaspiro[5,5]undecane.
98% H₂SO₄, 460g
*crude, wet "imide", 232g
H₂O, 38g

Preparation of "solution of imide" in aq. H₂SO₄
65 – 85°C
(730g)

H₂SO₄, 69g
H₂O, 28g

Addition of "imide soln." to aq. H₂SO₄
170 – 175°C, 3h

CO₂ to scrubber

CO₂

Reaction continuation
170 – 175°C, 1h
(760g)

H₂O, 645g

Cooling to 110°C, addn. of water and cooling to RT

1390g

**Extraction of product at 70 – 80°C
(1665g)

MIBK, 1500g

aq. waste 1225g

aq. waste 250g

H₂O, 300g

Washing of organic phase
70 – 80°C

1660g

Partial evaporation of solvent, vacuum 20 mmHg

MIBK/H₂O
(1300g)

360g

MIBK, 120g

Cooling to RT, filtration of product and washing

Filtrate
330g
containing 3.2% dissolved materials

Wet CHDAA
135g, (LOD-2%)
Purity > 97% (by HPLC)

Fig. 1
\[
\begin{align*}
\text{NC} & \quad \text{CN} + 2\text{H}_2\text{O} \quad \xrightarrow{\text{H}_2\text{SO}_4} \quad \text{H}_2\text{N} - \text{C} - \text{C} - \text{NH}_2 \\
\text{H}_2\text{N} - \text{C} - \text{C} - \text{NH}_2 + \text{H}_2\text{SO}_4 & \quad \xrightarrow{\text{H}_2\text{SO}_4} \quad \text{NH}_4\text{HSO}_4 + \text{CHDA} \\
\text{CHDA} & \quad + 4\text{H}_2\text{O} + 2\text{H}_2\text{SO}_4 \quad \xrightarrow{} \quad \text{HOOC} - \text{COOH} + 2\text{NH}_4\text{HSO}_4 + 2\text{CO}_2 \\
\text{NC} & \quad \text{CN} + 6\text{H}_2\text{O} + 3\text{H}_2\text{SO}_4 \quad \xrightarrow{\Delta} \quad \text{HOOC} - \text{COOH} + 3\text{NH}_4\text{HSO}_4 + 2\text{CO}_2 \\
\end{align*}
\]
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C55/28 C07C51/08

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)

IPC 7 C07C

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

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

EPO-Internal, WPI Data, CHEM ABS Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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Further documents are listed in the continuation of box C. Patent family members are listed in annex.

* Special categories of cited documents:

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

*E* earlier document but published on or after the international filing date

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Date of the actual completion of the international search: 22 October 2002

Date of mailing of the international search report: 29/10/2002

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<td>RICE L M ET AL: &quot;SIRANS XX SYNTHESIS OF 8,8-DIALKYLAZASPIROU4,5 DECANES AND 9,9-DIALKYLAZASPIROU5,5 UNDECANES&quot; JOURNAL OF HETEROCYCLIC CHEMISTRY, HETEROCORPORATION. PROVO, US, vol. 10, no. 5, 1 October 1973 (1973-10-01), pages 731-735, XP000574828 ISSN: 0022-152X</td>
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