(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
3 December 2009 (03.12.2009)

PCT

(10) International Publication Number
WO 2009/144225 A1

(51) International Patent Classification:
C07C 241/02 (2006.01) *C07C 243/40* (2006.01)

(21) International Application Number:
PCT/EP2009/056379

(22) International Filing Date:
26 May 2009 (26.05.2009)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
08156903.0 26 May 2008 (26.05.2008) EP
08164564.0 18 September 2008 (18.09.2008) EP

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

WO 2009/144225 A1

(54) Title: NEW PROCESS FOR THE PREPARATION OF 3-(2,2,2- TRIMETHYLHYDRAZINIUM) PROPIONATE DIHYDRATE

(57) Abstract: The invention provides an improved, efficient method for preparing 3- (2,2,2- trimethylhydrazinium) propionate dihydrate from 3- (2,2, 2-trimethylhydrazinium) propionate methylsulphate.

Description

NEW PROCESS FOR THE PREPARATION OF 3-(2,2,2-TRIMETHYLHYDRAZINIUM) PROPIONATE DIHYDRATE

Technical Field

The present invention relates to an improved process for preparation of 3-(2,2,2-trimethylhydrazinium)propionate dihydrate (international non-proprietary name–"Meldonium").

Background Art

A number of processes for the preparation of 3-(2,2,2-trimethylhydrazinium)propionate dihydrate is known.

The first process for preparation 3-(2,2,2-trimethylhydrazinium)propionate dihydrate is disclosed in WO 80/01068 A (INST ORGANICHESKOGO SINTEZA) 1980.05.29. . The process starts with methyl 3-(2,2-dimethylhydrazino)propionate is treated with a methyl halide or dimethylsulphate to give the appropriate trimethylhydrazinium salt, which is transferred to 3-(2,2,2-trimethylhydrazinium)propionate by Amberlite IRA-400 (OH form). After crystallization from ethanol the inner salt is obtained as a dihydrate.

This process disclosed in above patent can be considered as a common process for 3-(2,2,2-trimethylhydrazinium)propionate dihydrate preparation. The method has many disadvantages: strongly basic ion exchangers are unstable and undergo decomposition and oxidation during processing; they withstand only a limited number of regeneration cycles; large quantities or solvents, acids and bases as well as deionised water are needed to regenerate the resins; low ion exchange capacity and therefore high production costs of 3-(2,2,2-trimethylhydrazinium)propionate dihydrate by this process are typical. This process is not convenient for large scale production of 3-(2,2,2-trimethylhydrazinium)propionate dihydrate.

A standard method of alkaline hydrolysis of carbonic acid ester in case of an 3-(2,2,2-trimethylhydrazinium)propionate salt could not be successfully realised because of the problems of separation of 3-(2,2,2-

trimethylhydrazinium)propionate dihydrate and the resulting inorganic salts. It is known that 3-(2,2,2-trimethylhydrazinium)propionate forms various double salts, some of them as well is disclosed in SU 978808 (INST ORGANICHESKOGO SINTEZA) 07.12.1982.

The above mentioned technical problem was tried to solve in WO 2008/028514 A (SILVA JORGE) 2008.03.13. , which disclosed a method for producing 3-(2,2,2-trimethylhydrazinium)propionate dihydrate by hydrolyzed under acidic conditions with catalysis by HCl, sulphuric acid, phosphoric acid etc., esters of 3-(2,2,2-trimethylhydrazinium)propionate halide or methyl sulphate followed by neutralisation by an appropriate inorganic base (for example-sodium, potassium, calcium or magnesium hydroxide or another appropriate base, for example sodium, potassium, lithium or caesium carbonate or bicarbonate etc.) and the double salts thus obtained can be separated by the invented process using saturation the solution with carbon dioxide or sulphur dioxide.

Nevertheless method disclosed in WO 2008/028514 A (SILVA JORGE) 2008.03.13. allow to avoid use of electrodyalysis in preparation 3-(2,2,2-trimethylhydrazinium)propionate dihydrate, but at the same time double salts are formed and then have to follow process step for separation of double salts, in this case it is saturation the solution with carbon dioxide or sulphur dioxide.

Disclosure of Invention

The above objective is achieved according to present invention by hydrolysis of methyl-3-(2,2,2-trimethylhydrazinium)propionate methylsulphate to yield crude 3-(2,2,2-trimethylhydrazinium)propionate dihydrate; crystalization of crude 3-(2,2,2-trimethylhydrazinium)propionate dihydrate with mixture of ethanol/water solution or isopropanol/water.

Advantageous Effects of the Invention

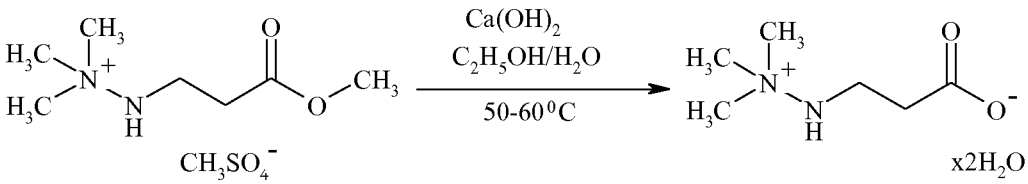
The following Reaction Scheme 1 outlines the present method of preparation 3-(2,2,2-trimethylhydrazinium)propionate dihydrate. The method includes the following advantages:

The main effort of present invention disclosed in when methyl-3-(2,2,2-trimethylhydrazinium)propionate methylsulphate was hydrolyzed with calcium hydroxide in ethanolic mixture, by obtaining calcium sulphate dihydrate residue, which is poorly soluble in water/ethanol and fall quantitative into the residue. Thereby not formed complexes or double salts with methyl-3-(2,2,2-trimethylhydrazinium)propionate, what is the main problem by using correspond halides of compound methyl-3-(2,2,2-trimethylhydrazinium)propionate. Residue of calcium sulphate dihydrate is easily remove by filtration and filtrate contains crude product of 3-(2,2,2-trimethylhydrazinium)propionate dihydrate. No further electrodialysis is necessary.

Calcium hydroxide as such for preparation 3-(2,2,2-trimethylhydrazinium)propionate dihydrate is mentioned in WO 2008/028514 A (SILVA JORGE) 2008.03.13, but it is just mentioned in description and in the claims, and expected result is what forms double salts, which thereafter will be can be separated by using saturation the solution with carbon dioxide or sulphur dioxide, person skilled in the art can't expect what no double salt is formed and no further saturation the solution with carbon dioxide or sulphur dioxide is not necessary.

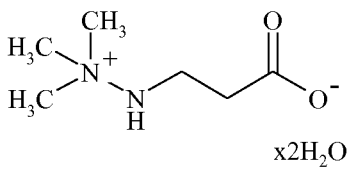
This process is amenable to large scale production which does not require specialized equipment.

Reaction Scheme 1



I II

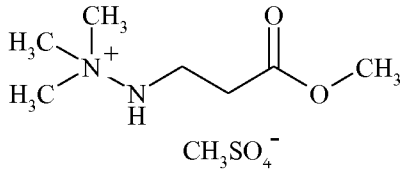
Thus, the subject matter of the present invention is a process for preparing a compound of formula II:



II

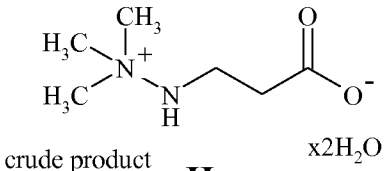
The process comprising the following:

hydrolysis compound of formula I



I

with calcium hydroxide to form crude 3-(2,2,2-trimethylhydrazinium)propionate dihydrate of formula II; and



crude product

II

crystallization crude product from water/ethanol solution or water/isopropanol for obtaining the desired compound 3-(2,2,2-trimethylhydrazinium)propionate dihydrate.

Best Mode for Carrying Out the Invention

The present invention will be described in more detail by referring to the following non-limiting examples.

Example

The crude emulsive methyl-3-(2,2,2-trimethylhydrazinium) propionate methylsulphate was dissolved in distilled water (500 mL) and ethanol (200mL, 96%). Alkaline agent was added to stirred reaction mixture.

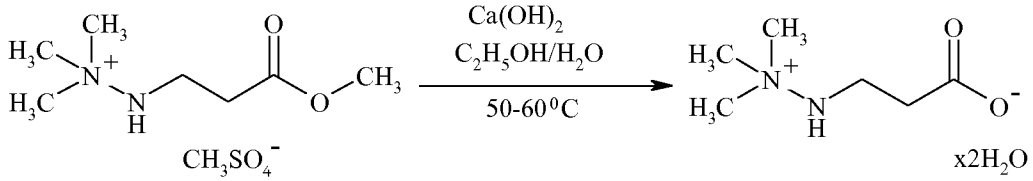
Great list of alkaline agents were used, almost all of them formed double salts, surprisingly just only calcium hydroxide didn't form any double salt.

Alkaline agent	Result
Sodium oxide	Form a double salt
Potassium oxide	Form a double salt
Lithium oxide	Form a double salt
Caesium oxide	Form a double salt
Calcium oxide	Form a double salt

Magnesium oxide	Form a double salt
Sodium hydroxidee	Form a double salt
Potassium hydroxide	Form a double salt
Lithium hydroxide	Form a double salt
Caesium hydroxide	Form a double salt
Calcium hydroxide	No double salt was formed
Magnesium hydroxide	Form a double salt
Sodium carbonate	Form a double salt
Potassium carbonate	Form a double salt
Lithium carbonate	Form a double salt
Caesium carbonate	Form a double salt
Calcium carbonate	Form a double salt
Magnesium carbonate	Form a double salt
Sodium bicarbonate	Form a double salt
Potassium bicarbonate	Form a double salt
Lithium bicarbonate	Form a double salt
Caesium bicarbonate	Form a double salt
Calcium bicarbonate	Form a double salt
Magnesium bicarbonate	Form a double salt

Example 1

Preparation of crude 3-(2,2,2-trimethylhydrazinium)propionate dihydrate



I II

The crude emulsive methyl-3-(2,2,2-trimethylhydrazinium) propionate methylsulphate was dissolved in distilled water (500 mL) and ethanol (200mL, 96%). Calcium hydroxide (54.2g, 0.73mol) was added to stirred reaction

mixture. The reaction mixture was stirred and heated to 50–60°C for 2 hours. The reaction process was controlled by TLC.

Thereafter the reaction mixture was filtered to remove calcium sulphate dihydrate. The calcium sulphate dihydrate cake on the filter was washed with ethanol (100mL).

The filtrate of reaction mixture was concentrated in vacuo, then isopropanol (50mL), terc-butylmethylether (20mL) and pure 3-(2,2,2-trimethylhydrazinium)propionate dihydrate as crystallization germ (0.5g) were added to reaction mixture. The obtained crystallization mixture was stirred at -15-(-5) °C. The suspension was filtered; the crude 3-(2,2,2-trimethylhydrazinium)propionate dihydrate was washed with terc-butylmethylether (150mL) on the filter.

Example 2

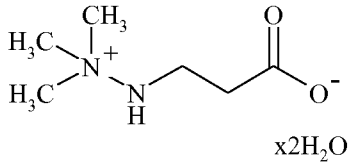
Preparation of 3-(2,2,2-trimethylhydrazinium)propionate dihydrate

The crude 3-(2,2,2-trimethylhydrazinium)propionate dihydrate (162g) was added to stirred in mixture of ethanol (550mL)/water(20mL) or in mixture of isopropanol/water. The reaction mixture was heated to 70°C for 20 minutes till all crude product was dissolved, at which point it was filtered.

The filtrate was cooled to -10°C for 2 hours. The precipitate was separated by filtration. The yield 3-(2,2,2-trimethylhydrazinium)propionate dihydrate was 99.0g (90%) of white crystalline powder.

Claims

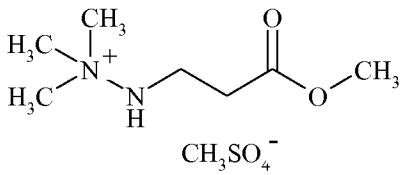
1. A process for preparing 3-(2,2,2-trimethylhydrazinium)propionate dihydrate of formula II



x2H_2O

II

comprising hydrolysis the compound of formula I



$CH_3SO_4^-$

I

carried out with calcium hydroxide;

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/056379

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C241/02 C07C243/40

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2008/028514 A1 (SILVA JORGE [LV]) 13 March 2008 (2008-03-13) cited in the application the whole document	1
A	WO 2005/012233 A1 (GRINDEKS JSC [LV]; KALVINSH IVARS [LV]; BIRMANS ANATOLIJS [LV]) 10 February 2005 (2005-02-10) the whole document	1
A	WO 80/01068 A1 (ORCH SINTEZA I [SU]; EREMEEV A [SU]; LATVIETIS Y [SU]; GILLER S [SU];) 29 May 1980 (1980-05-29) cited in the application the whole document	1

☐ Further documents are listed in the continuation of Box C.

☒ See patent family 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

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 August 2009	18/08/2009

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2009/056379

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