A process for the production of atropine is provided. The process provides for a new, efficient and commercially feasible synthetic process for the preparation of atropine and atropine salts. In one aspect, a one pot process for the synthesis of atropine is provided. The process provides excellent yield and can be used to prepare commercial 5 scale batches of atropine or atropine salts. The process avoids the additional steps of having to isolate intermediates to complete the process and has the advantage of proceeding efficiently at ambient temperature for many of the steps. The process includes providing acetyltropoyl chloride and reacting the acetyltropoyl chloride with tropine followed by a contact with an acid to form atropine.
PROCESS FOR PREPARATION OF ATROPINE

TECHNICAL FIELD

The present invention relates to atropine. More particularly, the present invention relates to processes for preparing atropine and its related salts and hydrates.

BACKGROUND

Atropine is a naturally occurring compound extracted from plants such as Atropa belladonna, Datura stramonium and Duboisia myoporoides. Atropine competitively blocks acetylcholine, a neurotransmitter, from acting on the muscarinic receptors in the body. As a result, atropine dilates the pupils, increases heart rate, and reduces salivation and other secretions. Atropine is used for many medicinal purposes. More common uses include administration before anesthesia to decrease mucus secretions, such as saliva. During anesthesia and surgery, atropine is used to maintain a normal heart rate in certain circumstances. Atropine sulfate, a salt of atropine, is also used to block or reverse the adverse effects caused by some medicines and certain types of pesticides. Atropine is also used in ophthalmology. In this regard, atropine is administered prior to eye examinations to dilate the pupil, and to relieve pain caused by swelling and inflammation of the eye.

Atropine used for medical purposes is most commonly administered as atropine or as a pharmaceutically acceptable salt, such as atropine sulfate. Although synthetic methods for preparing atropine are known, commercial production of atropine is typically accomplished by the extraction of atropine from plants. Currently known processes for synthetically producing atropine or atropine sulfate suffer from a number of disadvantages that make the synthesis impractical on a commercial scale. This is primarily due to the inefficiency of the reactions involved. Known methods require, for example, the isolation of intermediates, a large excess of reagents, and/or uncertain quality of the synthesized atropine.

Accordingly, there is a need for an improved synthetic process for atropine and its salts. There is a need for a synthetic process for commercial scale production of atropine and atropine salts.
SUMMARY

The present invention provides for a new, efficient and commercially feasible process for the preparation of atropine and atropine salts. In one aspect, a one pot process for the synthesis of atropine is provided. The process provides a high yield and can be used to prepare commercial scale batches of atropine or atropine salts. The process avoids the additional steps of having to isolate intermediates to complete the process. In addition, the process has the advantage of proceeding efficiently, for many of the steps, at ambient temperature.

Accordingly, in one aspect a process for the production of atropine and atropine salts is provided. The process includes:

(a) providing acetyltropoyl chloride; and

(b) reacting the acetyltropoyl chloride with tropine other necessary reagent or reagents to form atropine.

According to another aspect of the application, there are provided processes for preparing the atropine and salts of atropine, embodiments comprising one or a combination of the following steps or features. In one aspect the acetyltropoyl chloride is prepared by reacting tropic acid (3-hydroxy-2-phenylpropanoic acid) with acetyl chloride and a chlorinating agent in the presence of a catalyst to produce acetyltropoyl chloride. The catalyst used may be dimethylformamide (DMF). In another aspect the chlorinating agent is oxalyl chloride.

In another aspect of the invention the tropine is first reacted with methanesulfonic acid to form tropine methanesulfonate prior to step (b). In another aspect, the tropic acid, acetyl chloride and catalyst are in solution prior to the addition of the chlorinating agent to form an acetyltropoyl chloride solution. In yet another aspect the tropine is first reacted with methanesulfonic acid to form tropine methanesulfonate prior to step (b) and the acetyltropoyl chloride solution is contacted with the tropine methanesulfonate.

In another aspect, the atropine sulfate is converted back to the base form.

The process of the invention provides many advantages over known techniques to synthesize atropine or its salts. The process of the invention requires only stoichiometric amounts of the reagents, so excess reagents are not required and the yields of the reaction are high. Moreover, significant steps in the reaction can be performed at ambient temperature. Finally, the process of the invention is efficient even for kilogram sized
batches, making the process ideal for the commercial production of atropine and atropine salts.

These and further aspects and preferred embodiments of the invention are described in the following sections and in the appended claims.

DETAILED DESCRIPTION

In an aspect of the invention, there is provided processes for the preparation of atropine (Formula I), including derivatives thereof such as salts and hydrate forms. The processes can be completed without the isolation of any intermediates. A general preparation of atropine according to embodiments of the present invention proceeds as shown in reaction Scheme 1.

Scheme 1 illustrates the synthetic route leading to atropine, the compound shown in Formula I. The synthetic route involves reacting tropic acid under appropriate conditions to obtain acetyltropoyl chloride, the compound Formula II. From there, the acetyltropoyl chloride is coupled with tropine (also known as tropanol) to produce atropine (Formula I). The resulting atropine can optionally be converted to a salt or hydrate form, such as for example, atropine hemisulfate hemihydrate, shown below in Formula III.
The reactions of the synthetic processes claimed herein are preferably carried out in suitable solvents which may be readily selected by one of ordinary skill in the art. A given reaction may be carried out in one solvent or a mixture of more than one solvent. Depending on the particular reaction step, suitable solvents for a particular reaction step may be selected. Preferred solvents for specific steps are discussed in more detail below. The reaction of tropic acid to produce atropine is preferably carried out according to Scheme II.

In the first step of the process of Scheme II, tropic acid is added to a reaction vessel with a solvent, preferably dichloromethane, to form a suspension. A stoichiometric amount (approximately) of acetyl chloride is added to the reaction vessel in the presence of a catalyst. For the purposes of the invention, reference to a stoichiometric amount means at least a stoichiometric amount. Unless noted otherwise, reagents identified as a being present in a stoichiometric amount include an amount in excess of the stoichiometric amount, such as up to 120% of the stoichiometric amount. However, the use of too great an excess of that amount is generally undesirable. In theory, less than a stoichiometric amount may be used but that will have an impact on the yield.
Preferably the catalyst is DMF (Dimethylformamide) in a substoichiometric amount. More preferably the DMF is present in amount of 0.1 Eq. Oxalyl chloride is subsequently added to the reaction vessel to produce acetyltropoyl chloride. A preferred method for the process of producing acetylpropoyl chloride (Formula II) is shown in more detail in Scheme III below.

Returning to Scheme II, the acetylpropoyl chloride is coupled with tropine to form atropine. The tropine is first reacted with methanesulfonic acid in a solvent (preferably dichloromethane) to form atropine methanesulfonate solution. The tropine methanesulfonate is reacted with the acetyltropoyl chloride and then hydrolyzed with an acid, preferably a strong acid and more preferably HCl, to produce atropine.

Scheme III shows in detail a preferred method for producing acetylpropoyl chloride in accordance with the invention. Although, Scheme III shows the preferred method, acetylpropoyl, available under a variety of names, can be obtained through other means or synthetic processes. Times shown are approximate. The entire reaction can be performed in a single reaction vessel. Throughout the reaction, dichloromethane ("DCM") is used as the solvent as it allows the reaction to process at a single condition. The concentrations described are approximate and chosen to achieve a high rate of reaction while allowing the reaction to proceed to completion or near completion. Dichloromethane is preferred but other solvents can be used; non-limiting examples include chloroform or 1,2-dichloroethane.

The reaction proceeds in two steps. The tropic acid is first reacted with acetyl chloride, preferably in an amount of 1.2 Eq., in a solvent of dichloromethane (preferably about 3 parts). While acetyl chloride is preferred, the acetyl chloride may be replaced by other O-protective groups such as other esters and carbonates for example. To the reaction medium, approximately 0.1 Eq. of DMF is also added and functions as a catalyst.
The reaction proceeds at ambient temperature to produce an intermediate. The intermediate is not, and need not be isolated from the reaction medium before proceeding to the next step of the reaction, and is shown in Scheme III for illustrative purposes only. The inventors have surprisingly found that the reaction proceeds effectively to completion or near completion at ambient temperature. Therefore, heating the reaction medium is not necessary and, it has been found to that heating may prevent the reaction from completion.

After completion of the acetylation reaction, the intermediate is reacted with oxalyl chloride. The oxalyl chloride is added directly to the medium, preferably in an amount of about 1.2 Eq. The reaction to acetylpropoyl chloride proceeds at ambient temperature and again, heating is not necessary, as the reaction will proceed to completion or near completion without heat. While oxalyl chloride is preferred, other chlorinating agents may be used as a substitute or in combination, such as thionyl chloride or phosphoryl chloride for example, or phosgene and derivatives for additional examples.

Scheme IV shows in detail a preferred method for coupling the acetylpropoyl chloride (Formula II) with tropine to produce atropine (Formula I) in accordance with the invention.

In a reactor tropine is mixed with about 3 parts of dichloromethane and heated to about 40 °C. About 1 Eq. of methanesulfonic acid is added to the medium. While methanesulfonic acid is preferred, other sulfonic acids may be substituted or used in combination such as toluenesulfonic acid. Other acids may also be used such as
hydrochloric acid or hydrobromic acid, for example, but sulfonic acids are preferred. A solution of tropine methanesulfonate is produced.

The tropine methanesulfonate need not be isolated from the medium. The tropine methanesulfonate medium (about 1.2 Eq.) is mixed with the acetylpropoyl chloride medium, and then hydrolyzed with a strong acid, preferably HCl, to produce atropine. (Formula I). Preferably the HCl is 1M and added at a concentration of about 6 parts. The reaction medium is preferably heated to about 35°C.

The atropine can optionally be purified by techniques known in the art. In one embodiment, the crude atropine is recrystallized in a solvent mixture of heptane and dichloromethane. The atropine can optionally be converted to a salt or hydrate. In one embodiment, the atropine is converted to the sulfate hemihydrate salt.

Scheme V shows in detail a preferred method for converting atropine to atropine hemisulfate hemihydrate (Formula III).

![Scheme V](image)

Preferably, purified atropine is dissolved in a solvent system comprising an organic solvent, water or a mixture thereof. Preferably the solvent system is a water/acetone mixture. The atropine solution is mixed in a solution of Sulfuric acid and pH adjusted to between 5.0 and 6.0 to produce the atropine hemisulfate hemihydrate (Formula III).

Optionally, the atropine atropine hemisulfate hemihydrate can be converted back to the base form if desired. In one embodiment, 4M NaOH is slowly added until pH > 13 at T <20°C. The precipitate is filtered and washed with water then dried to provide atropine base. Other methods known in the art may also be used.

EXAMPLES

Certain specific aspects and embodiments of the present disclosure will be explained in more detail with reference to the following examples, which are provided solely for purposes of illustration and are not to be construed as limiting the scope of the disclosure in any manner.
A batch size of about 2 kg of atropine sulfate was manufactured from 2.0 kg of tropic acid and 2.0 kg of tropanol.

**Synthesis crude atropine**

In a reactor 2.0 kg of tropic acid was added to 6 L of dichloromethane and a suspension was formed. The suspension was stirred at 40 Hz at 25 °C. To the suspension 0.1 Eq. of DMF was added. Acetyl chloride was slowly added over the course of at least 30 minutes. The medium was stirred at 25 °C for 3 hours. 1.2 Eq. of oxaryl chloride (1.84 kg) was then added to the medium over the course of at least 1 hour. The medium was stirred for 2 hours at 25 °C.

The medium, containing acetyltropanoyl chloride solution, was transferred to a clean container and stored at room temperature.

In a reactor 2.0 kg of tropine was added to 6 L of dichloromethane to form a solution. The solution was stirred until it reached 35 °C. 1.0 Eq. of methane sulfonic acid (1.39 kg) was added over the course of at least 30 minutes. The medium was stirred for 10 min at 35 °C to form a tropine methanesulfonate solution.

The acetyltropanoyl chloride solution was then transferred to the tropine methanesulfonate solution and the resulting solution was stirred at reflux for at least 18 hours. The reaction medium was then cooled down to 35 °C. 12 L of a 1 M solution of hydrochloric acid was added producing a biphasic mixture. The biphasic mixture was stirred for at least 24 hours at 35 °C resulting in an aqueous layer containing tropine.

The medium was then cooled down to 20 °C. The agitation was stopped for a 30 minute decantation and the organic layer was discarded. 2 L of new dichloromethane was added and the medium was stirred for 10 minutes. A second 30 minute decantation was performed and again the organic layer was discarded.

The aqueous layer was cooled down to 5 °C and a 4 M aqueous solution of sodium hydroxide was added over the course of at least 1 hour until the pH of the solution reached at least 13. A solid precipitate formed while the medium was stirred at 5 °C. The solid was collected by filtration after 2 hours of stirring and then washed with 4 L of distilled water resulting in solid atropine (Formula I)(referred to as crude atropine).

In a reactor the crude atropine was added to 14 L of distilled water to form a suspension. The suspension was stirred at 20 °C for at least 1 hour. The solid atropine was collected by filtration and washed with 5 L of distilled water.

The crude atropine was dried under vacuum at 60 °C until water content was below 1.0% as measured by Karl Fischer titration. The yield was about 75%. 
Crystallization of crude atropine

In a reactor the crude atropine (about 2.9 kg) was added to dichloromethane (about 5.8 L) (2 L for every kg of crude atropine) to form a suspension. The suspension was stirred until it reached 30 °C. To the suspension, heptane (about 20 L) (7 L of heptane for every L of dichloromethane) was added over the course of at least 1 hour. The medium was cooled to 5 °C and stirred at this temperature for 1 hour allowing the atropine to crystallize. The crystallized atropine was collected by filtration and washed with heptane (2 L of heptane for every L of dichloromethane). The crystallized atropine was dried under vacuum at 60 °C until it measured below 2.0% by loss on drying. The yield of this process was about 90%.

Preparation of the sulfate hemihydrate salt of atropine

In a reactor 2 kg of crystallized atropine was added to 20 L of acetone and 60 mL of microbio water (bacteria free water) to form a solution. The solution was stirred and heated to 50 °C. The medium was then filtered on a clarification membrane. The medium was then cooled to 30 °C. Separately, a sulfuric acid solution was prepared by adding 372 mL of H2SO4 (95%) to 1680 mL of microbio water. The sulfuric acid solution was added over the course of 1 hour so that the pH was adjusted to between 5.0 and 6.0. The medium was then cooled down to 15 °C and the solid (atropine hemisulfate hemihydrate, (Formula III)) was collected by filtration. The white solid was washed with another 4 L of acetone. The final atropine hemisulfate hemihydrate was dried at 20 °C under vacuum until the acetone content was less than or equal to 5000 ppm. The final batch size was about 2 kg and the yield on the conversion to the salt was about 95%.

The atropine sulfate can be converted back to the base form if desired. In one embodiment, 4 M NaOH is slowly added until pH > 13 at T < 20°C. The precipitate is filtered and washed with water then dried to provide atropine base.

Unless defined otherwise, all technical terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Any methods and materials similar or equivalent to those described herein also can be used in the practice or testing of the present disclosure.

It must be noted that as used herein and in the appended claims, the singular forms "a", "and", and "the" include plural references unless the context clearly dictates otherwise.

While the present disclosure has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various
changes may be made and equivalents may be substituted without departing from the true spirit and scope of the invention. In addition, many modifications may be made to adapt a particular situation, material, composition of matter, process, process step or steps, to the objective spirit and scope of the present disclosure. All such modifications are intended to be within the scope of the claims appended hereto.
CLAIMS

1. A process for the preparation of atropine (Formula I), comprising the steps of:
   (a) reacting tropic acid (3-hydroxy-2-phenylpropanoic acid) with acetyl chloride and a chlorinating agent in the presence of a catalyst to produce acetyltropoyl chloride (Formula II);
   (b) reacting the acetyltropoyl chloride with tropine, followed by a contact with an acid to produce atropine.

2. A process according to claim 1, wherein the catalyst used in step (a) is dimethylformamide (DMF).

3. A process according to claim 1, wherein the chlorinating agent is oxalyl chloride.

4. A process according to claim 1, wherein the tropine is first reacted with methanesulfonic acid to form tropine methanesulfonate prior to step (b).

5. A process according to claim 1, wherein the tropic acid, acetyl chloride and catalyst are in solution prior to the addition of the chlorinating agent to form an acetyltropoyl chloride solution.

6. A process according to claim 4, wherein the acetyl chloride is added in a stoichiometric amount.

7. A process according to claim 5, wherein the tropine is first reacted with methanesulfonic acid to form tropine methanesulfonate prior to step (b) and the acetyltropoyl chloride solution is contacted with the tropine methanesulfonate.
8. A process according to claim 2, wherein the reaction to form acetyltropoyl chloride is performed at ambient temperature.

9. A process according to claim 1 further comprising the step of converting the atropine to atropine hemisulfate hemihydrate.

10. A process for the preparation of atropine sulfate (Formula III) comprising the steps of:

\[ \text{Formula III} \]

(a) providing acetyltropoyl chloride, Formula II; and

\[ \text{Formula II} \]

(b) reacting the acetyltropoyl chloride with tropine, followed by a contact with an acid to form atropine; and

(c) converting the atropine to atropine sulfate.

11. A process according to claim 1, wherein the acetyltropoyl chloride is provided by reacting tropic acid (3-hydroxy-2-phenylpropanoic acid) with acetyl chloride and a chlorinating agent in the presence of a catalyst.

12. A process according to claim 11, wherein the catalyst used is dimethylformamide (DMF).

13. A process according to claim 11, wherein the chlorinating agent is oxaly chloride.

14. A process according to claim 11, wherein the tropine is first reacted with methanesulfonic acid to form tropine methanesulfonate prior to step (b).

15. A process according to claim 11, wherein the tropic acid, acetyl chloride and catalyst are in solution prior to the addition of the chlorinating agent to form an acetyltropoyl chloride solution.
16. A process according to claim 15, wherein the acetyl chloride is added in a stoichiometric amount of the tropic acid.

17. A process according to claim 15, wherein the tropine is first reacted with methanesulfonic acid to form tropine methanesulfonate prior to step (b) and the acetyltropoyl chloride solution is contacted with the tropine methanesulfonate.

18. A process according to claim 12, wherein the reaction to form acetyltropoyl chloride is performed at ambient temperature.

19. A process for the preparation of atropine (Formula I), comprising the steps of:

(a) reacting tropic acid (3-hydroxy-2-phenylpropanoic acid) with acetyl chloride and a chlorinating agent in the presence of a catalyst to produce acetyltropoyl chloride (Formula II);

(c) reacting the acetyltropoyl chloride with tropine, and contact with an acid to form atropine.
**A. CLASSIFICATION OF SUBJECT MATTER**

INV. C07D451/10

ADD.

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)

C07D

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 practicable, search terms used)

EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEM ABS Data

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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<td>SCHMIDT G C; ELING T E; DRACH J C: &quot;Synthesis of tropi ne-l abel ed atropi ne. I. Mi cro methods for the synthesis of tropi ne and for i ts esteri f icati on wi th tropi c aci d.&quot;, JOURNAL OF PHARMACEUTICAL SCIENCES, vol. 56, no. 2, 1 February 1967 (1967-02-01), pages 215-221, XP055158885, WASHINGTON, US ISSN: 0022-3549 the whole document in particular Scheme 1 ----- -/- -</td>
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Further documents are listed in the continuation of Box C. See patent family annex.

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Date of the actual completion of the international search: 17 December 2014

Date of mailing of the international search report: 15/01/2015

Authorized officer: Papathoma, Sofia

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<td>ATKINSON E R; MCRITCHI E TICKNOR D D; HARRIS L S; ET AL.: &quot;Parasympatholytic c (anti cholinergic c) esters of the isomeric 2-tropanol s. 2. Non-glycol ates&quot;, JOURNAL OF MEDICINAL CHEMISTRY, vol. 26, no. 12, 1983, pages 1772-1775, ISSN: 0022-2623 the whole document in particular synthesis on page 1775</td>
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<td>WO 2014/102829 A1 (MYLAN LAB LTD [IN]; GORE VINAYAK [IN]; JOSHI RAJESH [IN]; TRI PATHI ANI) 3 July 2014 (2014-07-03) the whole document in particular examples 3-6</td>
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