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Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(H))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(in))*

— *of inventorship (Rule 4.17(iv))*

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(54) Title: PROCESS FOR PREPARATION OF SUCCINYLCHOLINE CHLORIDE

(57) Abstract: The invention discloses a novel process for preparation of succinylcholine chloride via transesteriiication of succinic acid diester with choline chloride.

PROCESS FOR PREPARATION OF SUCCINYLCHOLINE CHLORIDE

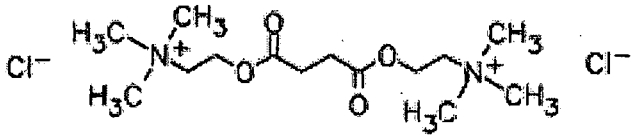
Technical Field:

The present invention relates to a novel process for preparation of succinylcholine chloride via transesterification of succinic acid diester with choline chloride.

Background and Prior art:

Succinylcholine chloride also known as suxamethonium chloride is a paralytic drug used to induce muscle relaxation and short-term paralysis, usually to facilitate tracheal intubation. Suxamethonium chloride is sold under the trade names Anectine, Quelicin, and Scoline.

Succinylcholine chloride, chemically 2,2'-((l,4-dioxo-l,4-butanediyl)bis(oxy))bis(N,N,N-trimethylethanaminium)dichloride has following structure:



The article published in Acad. Rep. Populare Romine Inst. Biochimie, studii ceetari biochimie, 1, (1958), 167 - 170 describes reaction of bis(2-chloroethyl)succinate with trimethylamine in presence of benzene to provide succinylcholine chloride in 46% yield. However, trimethyl amine is a gas and hence difficult to handle. The reaction is carried out by bubbling of trimethylamine through the reaction mixture. Therefore the method is not feasible on plant level. Another disadvantage of the process is the use of. benzene which is well known carcinogen. Further the process requires cumbersome method of purification.

Farmatsiya (Sofia) 11(6), 29 - 32 (1961) discloses the above mentioned process in presence of absolute ethanol. However yield and purity of the product is not mentioned in the article.

It is reported in Bulletin of the Institute of Chemistry, Academia Sinica, 26 (1979), 47-54, that the method mentioned in Farmatsiya yields only choline chloride instead of succinylcholine chloride.

Institute of Chemistry, Academia Sinica, 26 (1979), 47-54 discloses five methods for preparing succinylcholine chloride:

In the method (I) succinic acid is reacted with dimethylaminoethanol to give bis(2-dimethylaminoethyl)succinate, which is then reacted with methyl chloride to give succinylcholine chloride. However methyl chloride is a gas which is difficult to handle on industrial scale.

In the method (II) bis(2-chloroethyl)succinate is reacted with dimethylamine to obtain bis(2-dimethylaminoethyl) succinate, which is then reacted with methyl chloride to give succinylcholine chloride. The method also requires methyl chloride which is difficult to handle.

The method (III) describes the reaction of succinic acid with ethylene chlorohydrin to give bis(2-chloroethyl) succinate, followed by alkylation with trimethylamine to provide succinylcholine chloride.

The yield is relatively low in the methods (I) to (III).
In the method (IV) succinylcholine chloride is obtained by reacting succinyl dichloride with choline chloride. However, this method has the disadvantage that succinyl dichloride is hygroscopic and hence difficult to handle. Thionyl chloride which is required for preparing succinyl dichloride is a toxic reagent.

In the method (V) succinic anhydride is reacted with choline chloride in presence of dry HC1 as a catalyst. The reaction is carried out in benzene which is classified as human carcinogen.

A modified procedure was described in Organic Preparations and Procedures Int. 11(2), 93 - 103 (1979). The method discloses reaction of succinic anhydride and choline chloride in presence of catalytic amount of dry hydrogen chloride gas; followed by azeotrpic removal of water using benzene as a solvent. The disadvantage of this process is the use of hydrogen chloride gas which is difficult to handle and use of benzene which is a carcinogen.

The U.S. Patent Number 5206420 discloses preparation of succinylcholine chloride. The method involves reaction of diakyl succinate with large excess of dimethylaminoethanol in presence of an alkali metal alcoholate or amide as a catalyst; followed by reaction of resulting bis(2-dimethylaminoethyl)succinate with methyl chloride in an inert solvent to provide succinylcholine chloride. The process requires recovery of excess dimethylaminoethanol by distillation which is a tedious operation. Further it involves use of methyl chloride gas which is difficult to handle on industrial scale.

The Indian patent publication No.IN2005CHO1794 discloses preparation of succinylcholine chloride by reacting bis(2-chloroethyl)succinate with trimethylamine using C1 - C4 alcohols (preferably isopropanol) as a solvent. It is also disclosed in the publication that by using alcohol solvent in the reaction, all tedious work-up procedures, recoveries of extra reactants, use of difficult to handle reagents etc. were eliminated and succinylcholine chloride was isolated by simple filtration process. However the method requires trimethylamine as a reactant, which is a gas.

Apparently use of gaseous, toxic and carcinogenic raw materials is the major difficulty in preparation of succinylcholine chloride. Needless to say it is advantageous to develop a process which eliminates the necessity of toxic raw materials thus making the overall process safe, industrially applicable, simple and short.

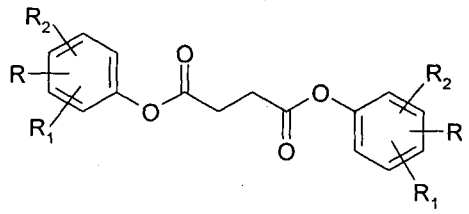
Object of the invention:

An object of the invention is to overcome or ameliorate atleast one disadvantage of the prior art or to provide a useful alternative.

Another object of the invention is to provide a novel, commercially viable and industrially applicable process for preparing succinylcholine chloride which eliminates the necessity of gaseous, toxic and carcinogenic substances.

Summary of the invention:

In accordance with the above objectives, the present invention provides a process for preparation of succinylcholine chloride comprising transesterification of succinic acid diester of formula (I) with choline chloride.



Formula (I)

Wherein **R** is an electron withdrawing group; and **Ri** and R_2 are independently hydrogen, electron withdrawing group, alkyl containing 1 to 7 carbon atoms, alkoxy containing 1 to 7 carbon atoms, halogen, **NR3R4,** mercapto, thioalkyl containing 1 to 7 carbon atoms, or **Ri** and R_2 when placed ortho to each other form benzene ring; R_3 and R4 are independently hydrogen, alkyl containing 1 to 7 carbons atoms, substituted or unsubstituted phenyl, or R_3 and **R4** together with nitrogen form 3 to 7 membered heterocyclic ring.

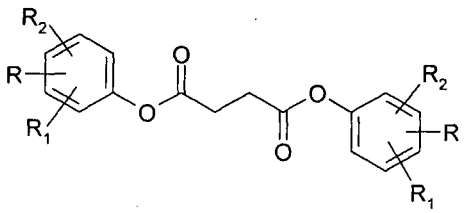
Detailed description of the invention:

Unless specified otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art, to which this invention belongs. Although any method and material or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described. To describe the invention, certain terms are defined herein specified as follows:

Unless stated to the contrary, any of the words 'having', 'including', 'includes', 'comprising' and 'comprises' mean 'including without limitations' and shall not be

construed to limit any general statement that it follows to the specific or similar items or matters immediately following it. Embodiments of the invention are not mutually exclusive, but may be implemented in various combinations. The described embodiments of the invention and the disclosed examples are given for the purpose illustration rather than limitation of the invention as set forth the appended claims.

Accordingly, the present invention provides a novel method for preparation of succinylcholine chloride comprising transesterification of succinic acid diester of formula **(i);**



Formula (I)

wherein **R** is an electron withdrawing group; and **Ri** and R_2 are independently hydrogen, electron withdrawing group, alkyl containing 1 to 7 carbon atoms, alkoxy containing 1 to 7 carbon atoms, halogen, **NR3R4,** mercapto, thioalkyl containing 1 to 7 carbon atoms, or R_1 and R_2 when placed ortho to each other form benzene ring; R_3 and **R4** are independently hydrogen, alkyl containing 1 to 7 carbons atoms, substituted or unsubstituted phenyl, or R_3 and **R4** together with nitrogen form 3 to 7 membered heterocyclic ring; with choline chloride.

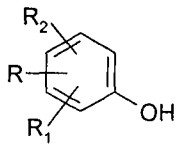
In a preferred embodiment **Ri** is an electron withdrawing group selected from $N0_2$ or CN; R_2 is hydrogen or electron withdrawing group selected from $N0_2$ or CN; and R_3 is hydrogen.

Choline chloride is conveniently used in an amount, relative to succinic acid diester of formula (I) in a range between 2.0 to 4.0 equivalents. The preferred amount of Choline chloride is 2.0 to 2.5 equivalents.

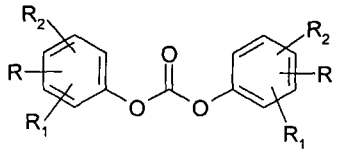
The process of the present invention may be carried out at suitable temperature. To minimize the decomposition of products and impurity formation the reaction is carried out at 50 to 150°C, more preferably at 60 to 100°C. The most preferred temperature for transesterification is 70 to 80°C.

The reaction normally completes in a span of 0.25 to 6.0 hours, more preferably 0.5 to 4.0 hours and most preferably 1.0 to 3.0 hours.

The process of the present further comprises a method for preparation of succinic acid diester of formula (I) via esterification of succinic anhydride with phenol derivative of formula (II); and reacting the resulting product with carbonate of formula (III) or triphosgene.



Formula (II)



Formula (III)

Wherein **R** is electron withdrawing group; and R_1 and $\mathbf{R_2}$ are independently hydrogen, electron withdrawing group, alkyl containing 1 to 7 carbon atoms, alkoxy containing 1 to 7 carbon atoms, halogen, **NR3R4,** mercapto, thioalkyl containing 1 to 7 carbon atoms, or $\mathbf{R_1}$ and $\mathbf{R_2}$ when placed ortho to each other form benzene ring; $\mathbf{R_3}$ and **R4** are independently hydrogen, alkyl containing 1 to 7 carbons atoms, substituted or unsubstituted phenyl, or $\mathbf{R_3}$ and **R4** together with nitrogen form 3 to 7 membered heterocyclic ring.

Succinic acid diester of formula (I) can also be prepared by esterification of succinic acid with carbonate of formula (III).

Alternatively, succinic acid diester of formula (I) can be prepared by esterification of succinic acid with phenol derivative of formula (II) and triphosgene.

Preferably esterification and transesterification are carried out in presence of a base and a solvent.

The base is organic base or inorganic base. Examples of organic base include tertiary amines such as trialkyl amine. Examples of inorganic base include alkali metal carbonate, alkaline earth metal carbonate, alkali metal bicarbonate, alkaline earth metal bicarbonate and mixture thereof. Examples of alkali metal carbonate include sodium carbonate and potassium carbonate. Examples of alkali metal bicarbonate include sodium bicarbonate and potassium bicarbonate. Examples of alkaline earth metal carbonate include calcium carbonate and magnesium carbonate. Examples of alkaline earth metal bicarbonate include calcium bicarbonate and magnesium bicarbonate. The most preferred base is triethylamine.

The solvent for esterification and transesterification is selected from aprotic solvents. Preferably the solvent is acetonitrile, dimethylformamide or tetrahydrofuran. The most preferred solvent for esterification and transesterification is acetonitrile.

The resulting succinylcholine chloride is recrystallized using water and isopropanol and isolated as dihydrate with HPLC purity greater than 99%.

As both the steps of preparation of succinylcholine chloride are carried out in a single solvent and a single base which are inexpensive, the process is highly economical. Also the process of the present invention eliminates the necessity of gaseous, toxic and carcinogenic substances.

The pure succinylcholine chloride obtained according to the present invention may be formulated into a dosage form by combining with one or more pharmaceutically acceptable excipients using known techniques.

Further details of the process of the present invention will be apparent from the examples presented below. Examples presented are purely illustrative and should not be construed as limiting the scope of the invention in any manner.

Examples

Example 1

A clean and dry four neck round bottom flask was charged with bis(4-nitrophenyl)succinate (100 gm), choline chloride (81.45 gm), triethylamine (81.98 ml) and acetonitrile (2000 ml). The reaction mass was refluxed at 70 -75°C for 2 hours. The reaction mass was cooled to room temperature, acidified with dilute hydrochloric acid to obtain a precipitate. The resulting precipitate was collected by Alteration and dried to obtain succinylcholine chloride. The crude product was purified in water/IPA to obtain pure product as succinylcholine chloride dihydrate.

Yield - 95 gm (86.0%)

HPLC Purity - 99.44%

Example 2

Succinylcholine chloride was prepared according to the example 1 using bis(2-nitrophenyl)succinate (100 gm) instead of bis(4-nitrophenyl)succinate. The crude product was purified in water/IPA to obtain pure product as succinylcholine chloride dihydrate.

Yield - 97.4 gm (88.5%)

HPLC Purity - 99.2%

Example 3

A clean and dry four neck round bottom flask was charged with succinic acid (100 gm), triethylamine (250 ml), bis(4-nitrophenyl)carbonate (540.5 gm) and acetonitrile (600 ml). The reaction mixture was stirred overnight at room temperature. The reaction mixture was quenched with water, the resulting solid was filtered, washed with water, dried and recrystallized with dichloroethane to obtain bis(4-nitrophenyl)succinate.

Yield - 261 gm (85.7%)

HPLC Purity - 99.8%

Example 4

A clean and dry four neck round bottom flask was charged with succinic anhydride (15.0 gm), 4-nitrophenol (24.9 gm), triethylamine (23.13 ml) and ethylene dichloride (150 ml).

The reaction mixture was refluxed at 70 - 75°C for 3 hours and cooled to room temperature. Bis(4-nitrophenyI)carbonate (68.3 gm) and triethylamine (32 ml) were added to the reaction mixture and refluxed at 70 - 75°C for 3 hours. The reaction mixture was cooled; followed by conventional work-up to obtain crude bis(4-nitrophenyl)succinate; which was crystallized from dichloroethane to obtain purified product.

Yield - 40 gm (74%)

HPLC Purity - 99.45%

Example 5

Bis(2-nitrophenyl)succinate was prepared according to the example 3 using bis(2-nitrophenyl)carbonate instead of bis(4-nitrophenyl)carbonate. The reaction mixture was quenched in water; followed by conventional work-up to obtain crude bis(2-nitrophenyl)succinate; which was crystallized from dichloroethane to obtain purified product.

Yield - 260.0 gm (85.3%)

HPLC Purity - 99.3%

Example 6

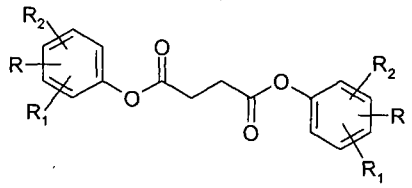
Bis(2-nitrophenyl)succinate was prepared according to the example 4 using 2-nitrophenol instead of 4-nitfophenol and bis(2-nitrophenyl)carbonate instead of bis(4-nitrophenyl)carbonate. The reaction mixture was cooled; followed by conventional work¬up to obtain crude bis(2-nitrophenyl)succinate; which was crystallized from dichloroethane to obtain purified product.

Yield - 45.0 gm (83.3%)

HPLC Purity - 99.5%

We claim,

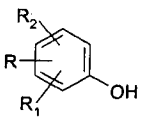
1. A process for preparing succinylcholine chloride comprising transesterification of succinic acid diester of formula (I);



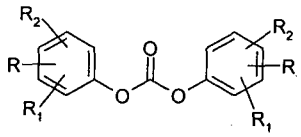
Formula (I)

wherein **R** is electron withdrawing group; and **Ri** and $\mathbf{R_2}$ are independently hydrogen, electron withdrawing group, alkyl containing 1 to 7 carbon atoms, alkoxy containing 1 to 7 carbon atoms, halogen, **NR3R4,** mercapto, thioalkyl containing 1 to 7 carbon atoms, or **Ri** and $\mathbf{R_2}$ when placed ortho to each other form benzene ring; $\mathbf{R_3}$ and $\mathbf{R_4}$ are independently hydrogen, alkyl containing 1 to 7 carbons atoms, substituted or unsubstituted phenyl, or $\mathbf{R_3}$ and $\mathbf{R_4}$ together with nitrogen form 3 to 7 membered heterocyclic ring; with choline chloride.

2. The process as claimed in claim 1, optionally comprising preparation of succinic acid diester of formula (I) via esterification of succinic anhydride with phenol derivative of formula (II); and reacting the resulting product with carbonate of formula (III) or triphosgene;



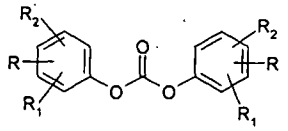
Formula (II)



Formula (III)

wherein **R** is electron withdrawing group; and **Ri** and $\mathbf{R_2}$ are independently hydrogen, electron withdrawing group, alkyl containing 1 to 7 carbon atoms, alkoxy containing 1 to 7 carbon atoms, halogen, **NR^,** mercapto, thioalkyl containing 1 to 7 carbon atoms, or R_1 and $\mathbf{R_2}$ when placed ortho to each other form benzene ring; $\mathbf{R_3}$ and R_4 are independently hydrogen, alkyl containing 1 to 7 carbons atoms, substituted or unsubstituted phenyl, or $\mathbf{R_3}$ and **R4** together with nitrogen form 3 to 7 membered heterocyclic ring.

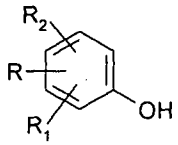
3. The process as claimed in claim 1, optionally comprising preparation of succinic acid diester of formula (I) via esterification of succinic acid with carbonate of formula (III);



Formula (III)

wherein R is electron withdrawing group; and R_1 and R_2 are independently hydrogen, electron withdrawing group, alkyl containing 1 to 7 carbon atoms, alkoxy containing 1 to 7 carbon atoms, halogen, **NR3R4,** mercapto, thioalkyl containing 1 to 7 carbon atoms, or R_1 and R_2 when placed ortho to each other form benzene ring; R_3 and R_4 are independently hydrogen, alkyl containing 1 to 7 carbons atoms, substituted or unsubstituted phenyl, or R_3 and R_4 together with nitrogen form 3 to 7 membered heterocyclic ring.

4. The process as claimed in claim 1, optionally comprising preparation of succinic acid diester of formula (I) via esterification of succinic acid with phenol derivative of formula (II) and triphosgene;



Formula (II)

wherein R is electron withdrawing group; and R_1 and R_2 are independently hydrogen, electron withdrawing group, alkyl containing 1 to 7 carbon atoms, alkoxy containing 1 to 7 carbon atoms, halogen, **NR_3R_4,** mercapto, thioalkyl containing 1 to 7 carbon atoms, or R_1 and R_2 when placed ortho to each other form benzene ring; R_3 and R_4 are independently hydrogen, alkyl containing 1 to 7 carbons atoms, substituted or unsubstituted phenyl, or R_3 and R_4 together with nitrogen form 3 to 7 membered heterocyclic ring.

5. The process as claimed in claims 1, 2, 3 and 4, wherein R is nitro or cyano; R1 is hydrogen, nitro or cyano; and R_2 is hydrogen.

6. The process as claimed in claim 5, wherein R is nitro; R_1 is nitro or hydrogen; and R_2 is hydrogen.

7. The process as claimed in any one of the preceding claims, wherein the process is carried out in presence of a base and a solvent.

8. The process as claimed in claim 7, wherein the base is selected from organic base or inorganic base.

9. The process as claimed in claim 8, wherein the base is selected from tertiary amines, alkali metal carbonate, alkaline earth metal carbonate, alkali metal bicarbonate or alkaline earth metal bicarbonate.

10. The process as claimed in claim 9, wherein the base is triethylamine.

11. The process as claimed in claim 7, wherein the solvent is selected from aprotic solvents.

12. The process as claimed in claim 11, wherein the solvent is selected from acetonitrile, ethylene dichloride, tetrahydrofuran or dimethylformamide.

13. The process as claimed in claim 12, wherein the solvent is acetonitrile.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2013/000225

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07C213/06 C07C219/06
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)
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 practicable, search terms used)
EPO-Internal , WPI 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.
Y	CN 1 062 346 A (SHAANXI PROV INST OF MEDICAL I [CN]) 1 July 1992 (1992-07-01) abstract *schemes * ; page 3 example 1 claims 1-3	1-13

Y	DE 41 29 323 Al (CHEMI E LINZ DEUTSCHLAND [DE]) 11 March 1993 (1993-03-11) abstract example 1 claims 1-7	1-13

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[X] Further documents are listed in the continuation of Box C.

[X] 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 application or patent but published on or after the international filing date

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"P" document published prior to the international filing date but later than the priority date claimed

"T" 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

"X" 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

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

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Date of the actual completion of the international search	Date of mailing of the international search report
18 November 2013	25/11/2013

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Dunet, Guillaume

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Form PCT/ISA/210 (second sheet) (April 2005)

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 206 420 A (RAML WALTER [AT] ET AL) 27 Apri l 1993 (1993-04-27) ci ted i n the appl i cati on abstract exampl es 1, 2 cl aims 1-7	1-13
Y	UTA KUEPPER ET AL: "Synthesi s and characteri zati on of succi nyl chol i ne-dl8 and succi nylmonochol i ne-d3 desi gned for simul taneous use as i nternal standards i n mass spectrometri c analyses" , JOURNAL OF MASS SPECTROMETRY, vol . 42, no. 7, July 2007 (2007-07) , pages 929-939 , XP55079385 , ISSN: 1076-5174, D0I: 10. 1002/jms . 1230 * preparati on of SUX-dl8 * ; page 931 - page 932	1-13
A	US 2 858 329 A (BRAATEN WI LLARD C ET AL) 28 October 1958 (1958-10-28) * scheme * ; col umn 1 exampl es I - 111 cl aims 1-9	1-13
Y	ARTHUR P. PHI LLI PS' JOURNAL OF THE AMERICAN CHEMICAL SOCI ETY, vol . 71, no. 9, 19 September 1949 (1949-09-19) , pages 3264-3264, XP55079383 , ISSN: 0002-7863 , D0I: 10. 1021/ja01177a535 page 3264, l eft-hand col umn	1-13
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