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(54) Title: A PROCESS FOR PREPARATION OF MIVACURIUM CHLORIDE

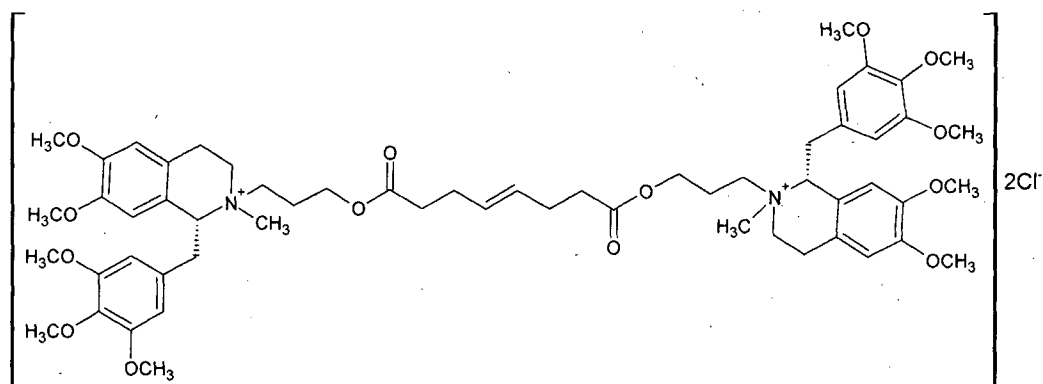
(57) Abstract: The present invention discloses a novel, cost-effective process for preparation of [R-[R*,R*-(E)]]-2,2'-(1,8-dioxo-4-octene-1,8-diyl) bis(oxy- 3, 1-propanediyl) bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-[(3,4,5- trimethoxyphenyl)- methyl] isoquinolinium) dichloride, commonly known as mivacurium chloride, which avoids the conversion of (E)-4-octene-1,8-dioic acid to its acid chloride and use of non-ionic polymeric adsorbent resin to get a highly pure product.



A Process for Preparation of Mivacurium Chloride

Field of Invention

The present invention relates to a process for preparing the [R-[R*,R*-(E)]]-2,2'-(1,8-dioxo-4-octene-1,8-diyl) bis(oxy-3,1-propanediyl) bis(1,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-1-[(3,4,5-trimethoxyphenyl)-methyl]isoquinolinium) dichloride, commonly known as mivacurium chloride, having the formula I:



Background of the Invention

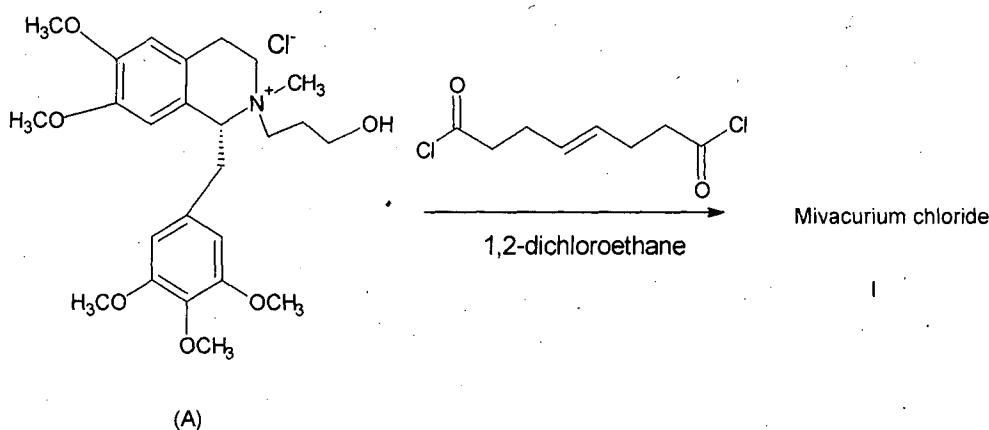
Mivacurium chloride is a rapid, non-depolarising, neuromuscular blocking agent of short duration, used therefore as anaesthetic, to provide skeletal muscle relaxation in minor surgical operations, in emergency surgical procedures of short to intermediate duration and during intubation of the trachea.

As it is evident from the above formula, mivacurium chloride contains two chiral centres, at each centre, may therefore exist either the R or the S configuration. Moreover, the methyl substituent on each of the two quaternary nitrogen atoms may exist in either the R or the S configuration.

The compound having the R configuration at both chiral centres is known to be free from significant side effects at the normal dosages. In view of what explained above, this compound may exist in three distereoisomers: the trans-

trans (1R, 1'R; 2S, 2'S); the cis-trans (1R, 1'R; 2R, 2'S), and the cis-cis distereoisomer (1R, 1'R; 2R, 2'R). The trans-trans and the cis-trans distereoisomers have neuromuscular blocking potencies not significantly different from each other, whereas the cis-cis distereoisomer has been estimated to have approximately one tenth the neuromuscular blocking potency of the other two distereoisomers.

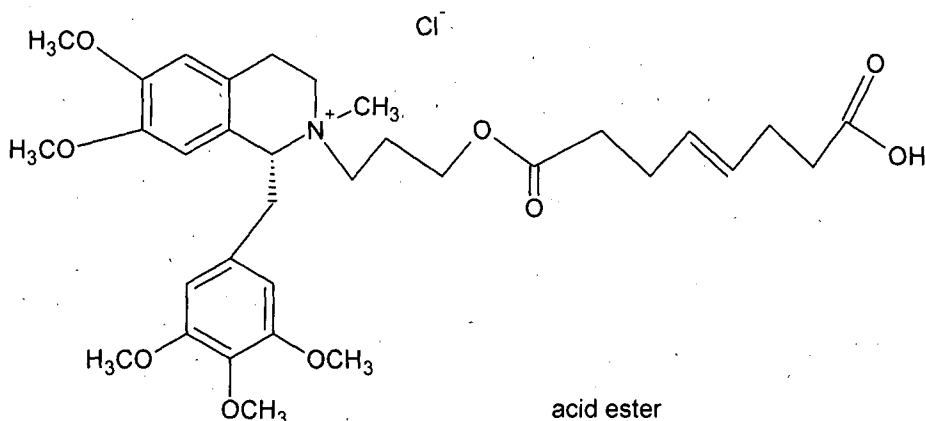
Mivacurium chloride has been disclosed for the first time in US patent 4,761,418. This patent describes a process for the preparation of mivacurium chloride by coupling of (E)-4-octene-1,8-dioic acid dichloride with N-3-hydroxypropyl-1-(R)-5'-methoxyaudanosinium chloride of formula (A), in warm 1,2-dichloroethane:



According to US patent 4,761,418, once the coupling reaction is complete, the solvent is removed by distillation under vacuum and replaced by chloroform. The so obtained chloroform solution is then washed with diluted aqueous solutions of sodium chloride to eliminate the isochinolinic compound (A) in excess, and the organic solvent is removed by distillation under vacuum, thus obtaining an amorphous solid. This solid product is then purified from impurities by washings with warm 2-butanone, removing the residual organic solvent by distillation under vacuum. Finally, the amorphous solid product is dissolved in methanol, filtered and freeze-dried, thus yielding the mivacurium chloride.

A similar synthesis is disclosed in *Current Medicinal Chemistry*, vol. 9, Nov. 16, 2002 also.

The primary drawback of this process is that the raw product obtained contains a high amount of various impurities, mainly represented by the compound A used as starting material both as cis and trans diastereoisomer, and an "acid ester", both as cis and trans diastereoisomer represented by following formula:



Another patent US7,872,137 describes a process in which (E)-4-octene-1,8-dioic acid is reacted with thionyl chloride to make (E)-4-octene-1,8-dioic acid dichloride which is further coupled with N-3-hydroxypropyl-1-(R)-5'-methoxylauidanosinium chloride to obtain crude Mivacurium chloride. This crude Mivacurium chloride is further extracted with water, treated with a suitable non-ionic polymeric adsorbent resin insoluble in water to recover pure mivacurium chloride. Thus this process involves first conversion of (E)-4-octene-1,8-dioic acid to its acid chloride and involves an essential purification of crude Mivacurium chloride using non-ionic polymeric adsorbent resin, which is very costly and used in huge quantities. Moreover, the maximum yield reported after the resin treatment is 32%. The maximum purity reported for the resin purified mivacurium chloride is 99.1% (trans-trans 56.3%, trans-cis 36.1% and cis-cis 6.7%).

The prior art process involves handling of thionyl chloride, a hazardous reagent and usage of ethylene dichloride, a class two solvent which is not recommended for the synthesis of final API. Moreover the purification of the product to remove acid ester impurities is done by washing the residue with hot

2-butanone. The 2-butanone is removed by decanting from the slurry, which is not practicable during scale up. The product is further subjected to lyophilization to obtain amorphous solid. The isolation of product by lyophilization method is not normally recommended for scale up. The HPLC assay reported for mivacurium chloride is 94.5% (trans-trans 44.6%, trans-cis 42.4% and cis-cis 7.5%) and impurities trans (RS) acid ester 4.0%, cis (RR) acid ester 1.5%. The process failed to meet the percentage of trans-trans and cis-trans stereoisomers. The sum of HPLC assays of trans-trans and cis-trans stereoisomers were 87.0%, it should be 92-96% of Mivacurium chloride.

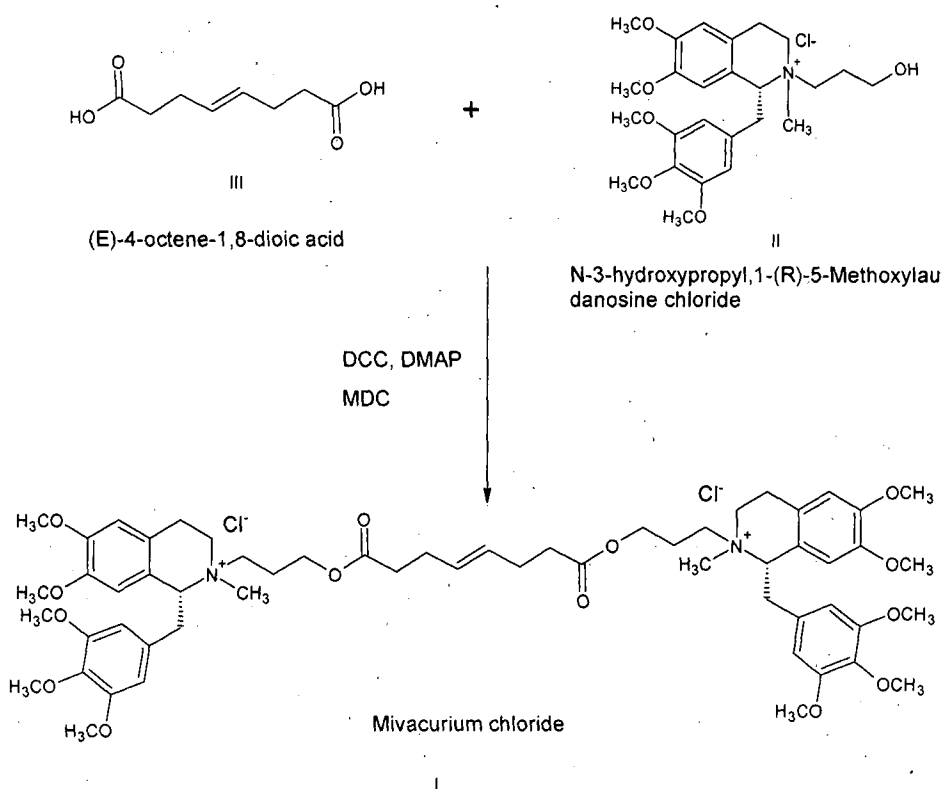
Thus there is a need to develop a process for the preparation of mivacurium chloride, which avoids the conversion of (E)-4-octene-1,8-dioic acid to its acid chloride and use of non-ionic polymeric adsorbent resin for the purification of crude mivacurium chloride. The present inventors have developed a novel process for the preparation of mivacurium chloride, which avoids the above conversion of (E)-4-octene-1,8-dioic acid to its acid chloride and use of non-ionic polymeric adsorbent resin to get a highly pure product.

Summary of the Invention

The principal aspect of the present invention is to provide a process for the preparation of mivacurium chloride of formula I having purity more than 99.5%, which comprises;

- a) condensation of (E)-4-octene-1,8-dioic acid of formula (III) with N-3-hydroxypropyl-1-(R)-5'-methoxylaunosinium chloride of formula (II) in presence of a coupling agent and a catalyst in a suitable organic solvent;
- b) extraction of crude mivacurium chloride with water; and
- c) recovery of mivacurium chloride having purity more than 99.5% from the obtained aqueous solution in step (b).

The process of the present invention may be illustrated by the below scheme:



Detail Description of the Invention

Accordingly in an embodiment of the invention, the starting N-3-hydroxypropyl-1-(R)-5'-methoxylaundanosinium chloride of formula (II) in step (a) may be for example in the form of trans diastereomers, or in the form of a diastereomeric mixture wherein trans:cis ratio is higher than 2.3:1, and preferably equal to 3:1.

In another embodiment of the invention, the coupling agent for the condensation of (E)-4-octene-1,8-dioic acid of formula (III) with N-3-hydroxypropyl-1-(R)-5'-methoxylaundanosinium chloride of formula (II) is selected from dicyclohexylcarbodiimide (DCC), N-Hydroxybenzotriazole (HOBT) and 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride (EDAC), preferably dicyclohexylcarbodiimide. The suitable organic solvent for the above condensation is selected from chlorinated solvents preferably methylenedichloride (MDC), ethylenedichloride (EDC), chloroform etc. The

solvent is most preferably methylenedichloride. The catalyst is preferably basic in nature selected from a pyridine derivatives preferably N,N-dimethylamino pyridine (DMAP).

In yet another embodiment of the invention, the extraction of crude Mivacurium chloride in step (b) may be carried out directly by adding water to the solution in organic solvent coming from step (a).

In yet another embodiment of the invention, the recovery of mivacurium chloride from aqueous solution is done by saturating with an inorganic salt preferably with sodium chloride and treated with a chlorinated organic solvent preferably with methylenedichloride. The solvent is evaporated to obtain pure mivacurium chloride of purity 99.5% or more.

The process of the present invention has following advantages:

1. In the present process directly diacid is coupled without converting it to an acid chloride which obviates the use of hazardous thionyl chloride.
2. The present process also avoids the use of class -2 solvent ethylene dichloride making the process scale up and eco-friendly.
3. The present process is an improved, efficient, cost-effective, and provides impurity-free synthesis of mivacurium chloride with a yield of 76%.
4. The addition of coupling agent in the present process reduces the reaction time significantly up to 8 hours.
5. In the present process, the impurities are removed by simple washing the product layer with 7% aq. sodium chloride solution whereas the prior art process uses non-ionic resin for the same.
6. The present process provides highly pure mivacurium chloride having purity more than 99.5%.

Example-1: Preparation of mivacurium chloride :

To the suspension of (4E)-octene-1,8-dioic acid (4.3g, 0.0248 mol) in MDC was charged DCC(11.12g, 0.0539 mol) and DMAP (0.02g) under stirring at 25-30°C. After 30minutes stirring, a solution of N-3-hydroxypropyl-1-(R)-5'-

methoxylauidanosinium chloride (20.0g, 0.0415 mol) in MDC (60.0mL) was added under nitrogen atmosphere. The whole mass was stirred for 8hrs at 25-30°C under nitrogen atmosphere; the progress of the reaction was monitored by TLC (mobile phase acetonitrile: trifluoroacetic acid 4.8:0.2). The DCU precipitated during the reaction was filtered off; the filtrate was taken in the separating funnel washed with 40.0mL of 7% sodium chloride solution. The MDC layer was charged into RBF containing water (80.0mL) and stirred well. After complete extraction of the product in water, it was further washed with MDC (40.0mL) to remove impurities. To the aq. Layer containing product was charged 16.0g of sodium chloride and 100.0mL of MDC, the contents were stirred well for 30minutes at 25-30°C. Separated layers, the MDC layer was dried over anhydrous sodium sulphate and distilled out completely under reduced pressure to obtain colourless foamy solid. The product was further dried using high vacuum to give 17.5g (76.75%) of (I) as a colourless solid which was assayed by HPLC as 56.99% (RS-RS) (trans-trans) diester, 36.77% (RR-RS) (trans-cis) diester, 5.94% (RR-RR) (cis-cis) acid ester, 0.16% (RS) (trans) acid ester and 0.05% (RR) (cis) acid ester and quaternary amino alcohol was nil. $[\alpha]_D^{20} = -62.5^\circ$ (1.9% water) (Lit: $[\alpha]_D^{20} = -62.7^\circ$). IR: 2941.88, 2838.70, 1592.91, 1730.80, 1122.37 cm^{-1} . MS 515.9 ($\text{M}^+ \text{H}$).

We claim:

1. A process for the preparation of mivacurium chloride, which comprises;
 - a) condensation of (E)-4-octene-1,8-dioic acid with N-3-hydroxypropyl-1-(R)-5'-methoxyaudanosinium chloride in presence of a coupling agent and a catalyst in a suitable organic solvent;
 - b) extraction of crude mivacurium chloride with water; and
 - c) recovery of mivacurium chloride from the obtained aqueous solution in step (b).
2. A process according to claim 1, wherein the recovered mivacurium chloride is more than 99.5% pure.
3. A process according to claim 1, wherein the coupling agent in step (a) is selected from dicyclohexylcarbodiimide, N-Hydroxybenzotriazole and 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride.
4. A process according to claim 1, wherein the catalyst in step (a) is N,N-dimethylamino pyridine.
5. A process according to claim 1, wherein the suitable organic solvent in step (a) is methylenedichloride.
6. A process according to claim 1, wherein said extraction of crude mivacurium chloride in step (b) is carried out by adding water directly to the solution in said organic solvent coming from step (a).
7. A process according to claim 1, wherein said N-3-hydroxypropyl-1-(R)-5'-methoxyaudanosinium chloride in step (a) is in the form of trans diastereoisomer.
8. A process according to claim 1, wherein said N-3-hydroxypropyl-1-(R)-5'-methoxyaudanosinium chloride in step (a) is in the form of diastereoisomeric mixture wherein the trans:cis ratio is higher than 2.3:1 .
9. A process according to claim 1, wherein said N-3-hydroxypropyl-1-(R)-5'-methoxyaudanosinium chloride in step (a) is in the form of diastereoisomeric mixture having the trans:cis ratio equal to 3:1.