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(54) Title: NOVEL PROCESS FOR THE PREPARATION OF CISATRACURIUM BESYLATE

(57) Abstract: The present invention is related to a novel process for the preparation of cisatracurium besylate, more particularly optically and geometrically pure cisatracurium besylate in large scale.

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NOVEL PROCESS FOR THE PREPARATION OF CISATRACURIUM BESYLATE

FIELD OF INVENTION

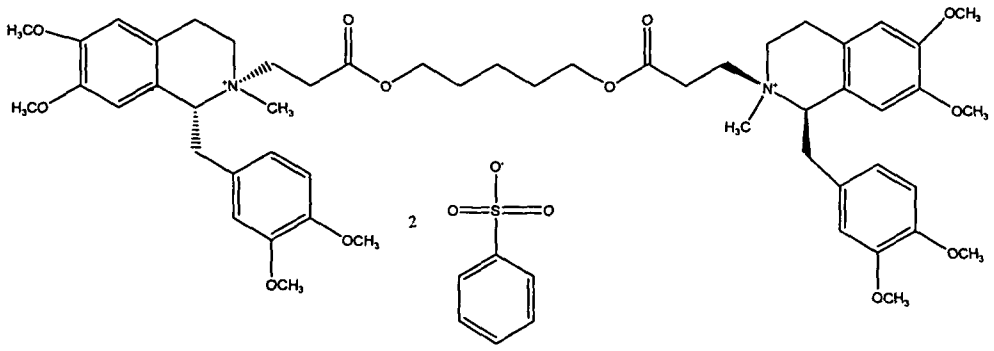
The present invention is related to a novel process for the preparation of cisatracurium besylate, more particularly optically and geometrically pure cisatracurium besylate in large scale.

BACKGROUND OF THE INVENTION

Atracurium besylate , 2,2'-[l,5-pentanediylbis[oxy(3-oxo-3,l-propanediyl)]]bis[l-[(3,4-dimethoxyphenyl) methyl]- 1,2,3,4-tetrahydro-6,7-dimethoxy-2- methylisoquinolinium] dibenzenesulfonate is a non polarizing neuromuscular blocking agent was first approved in 1982.

Atracurium besylate is a mixture of Cis-Cis, Cis-Trans and Trans-Trans isomer and also optically inactive. Cisatracurium besylate is lR-Cis-l'R-Cis-2,2'-[l,5 pentanediylbis -[oxy(3-oxo-3, 1-propanediyl)]]bis[1-[(3,4- dimethoxyphenyl) methyl]- 1,2,3,4-tetrahydro-6,7-dimethoxy-2- methylisoquinolinium]dibenzenesulfonate the Cis-Cis isomer of R-Atracurium besylate.

Cisatracurium besylate has the below structural formula as follows



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Derek A.Hill, et.al, in their patents US 5,453,510 and 5,556,987, described the preparation of cisatracurium besylate.This process involves : condensation of 1, 5-pentanediol with 3-bromopropionic acid in the presence of para-toluenesulfonic acid followed by dehydrobromination using triethylamine to yield 1, 5-pentamethylene diacrylate; resolution of tetrahydropapaverine was reported using N-acetyl-L-leucine in methanol/ether mixture. This resolution method, however, gave poor yields and the product contained 3% of enantiomeric impurity; the condensation of R-tetrahydropapaverine-N-acetyl-L-leucine salt with 1,5-pentamethylene diacrylate in the presence of acetic acid , followed by conversion to oxalate using oxalic acid in acetone yields (lR,l'R)-2,2'-(3,l l-dioxo-4,10-dioxotridecylene)-bis-(l, 2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-l-veratryliso-quinolium dioxalate. This process, however, did not describe a method for removal of unchanged tetrahydropapaverine; the product obtained was converted into IR, l'R-Atracurium besylate by quaternization with methyl benzenesulfonate to yield geometrical isomers. The final product was obtained by lyophilization which is commercially expensive; from the isomeric mixture the Cis-Cis isomer was separated by column chromatography using Silica Gel as stationary phase and dichloromethane, methanol mixture containing benzene sulfonic acid as an eluent. This process employs single mobile phase to elute the product and gives poor yields.

John.B.Stealake, et.al, in their patent, US 4,179,507, disclosed a process for the preparation of quaternary ammonium compounds such as Atracurium besylate, Atracurium mesylate, R-atracurium besylate etc, however, the patent does not describe process for getting cisatracurium besylate.

Naddaka et.al, in their patents WO 2008/132748 and WO 2008/132746, revealed a process for producing isoquinolium compounds and for converting them into cisatracurium besylate.However the purity of the product reported was not satisfactory.

ARAD, Oded et.al, WO 2008/107887, reported a method for chromatographically separating the isomers of (IR, l'R) atracurium besylate by HPLC in the absence of strong acid using silica gel HPLC column and eluting the compound containing, an polar aprotic co solvent and a week acid.However,this is commercially expensive .

Ostrovsky et.al, WO 2008/1 1721, described a method for separating cisatracurium besylate from the mixture of atracurium isomers using a reverse phase HPLC with a mobile phase in which the isomers are claimed to be stable. However, this is not an industrially viable process.

Therefore it is an object of the present invention to provide a novel process for the preparation of cis artacurium besylate.

Another object of the present invention to provide a novel process for the preparation of cis artacurium besylate which is enatiometrically and isomerically pure.

Yet another object of the present invention provides a method which is industrially viable and economical process for the production of cisatracurium besylate.

BRIEF SUMMARY OF THE INVENTION

According to the present invention a novel process for the preparation of cisatracurium besylate comprising:

a) condensing 1, 5-pentane diol with methylacrylate in the presence of para-toluenesufonic acid to obtain 1, 5-pentamethylenediacrylate;
b) resolution of tetrahydropapaverine using N-acetyl-D-leucine in isopropyl alcohol to yield R-tetrahydropapaverine with enantiomeric purity greater than 99.5%;
c) condensing R-tetrahydropapverine with 1,5-Pentamethylenediacrylate in acetic acid medium to yield lR,l'R)-2,2'-(3,l l-dioxo-4,10-dioxotridecylene)-bis-(l,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-l-veratryliso-quinolium dioxalate and excess of R-tetrahydropapaverine present in the reaction mixture by treating

the said reaction mixture with acetic anhydride in toluene to form an amide wherein the said amide formed is dissolved in acetone and removed from the product;

d) treating the product obtained from step (c) with methyl benzenesulfonate in acetonitrile in the presence of inorganic base yielded IR, l'R-Atracurium besylate;
e) separating pure cisatracurium besylate from the product obtained in step (d) by flash chromatography using silica gel (30 to 50μ) in the ratio of l(substrate): 40 and solvent system comprising dichloromethane, methanol mixture containing benzene sulfonic acid;
f) washing the eluted fractions with water and then with sodium benzenesulfonate and/or 10% sodium chloride solution to remove excess methanol and benzene sulfonicacid;
g) evaporating the solvent and precipitating the product with ether to yield fairly pure cisatracurium besylate;
h) cisatracurium besylate was further purified by dissolving the product from step (g) in a mixture of acetonitrile, isopropyl alcohol (IPA) and precipitating in ethyl acetate to yield pure cisatracurium besylate.

Another embodiment of the present invention to provide a industrially viable and economical process for the production of cisatracurium besylate.

Yet another embodiment of the present invention to provide a novel process for the preparation of cis artacurium besylate, which is enatiometrically and isomerically pure.

Still another embodiment of the present invention to provide a industrially viable separation process to separate the cis-cis isomer from other isomer atracurium besylate.

DETAILED DESCRIPTION OF PRESENT INVENTION:

The present invention pertains to a novel process for the preparation of cisatracurium besylate involving the followings steps:

According to the present invention a novel process for the preparation of cisatracurium besylate comprising:

a. condensing 1, 5-pentane diol with methylacrylate in the presence of para-toluenesufonic acid to obtain 1, 5-pentamethylenediacrylate;
b. resolution of tetrahydropapaverine using N-acetyl-D-leucine in isopropyl alcohol to yield R-tetrahydropapaverine with enantiomeric purity greater than 99.5%;
c. condensing R-tetrahydropapverine with 1,5-Pentamethylenediacrylate in acetic acid medium to yield lR,l'R)-2,2'-(3,l l-dioxo-4,10-dioxotridecylene)-bis-(l,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-l-veratryliso-quinolium dioxalate and excess of R-tetrahydropapaverine present in the reaction mixture by treating the said reaction mixture with acetic anhydride in toluene to form an amide wherein the said amide formed is dissolved in acetone and removed from the product;
d. treating the product obtained from step (c) with methyl benzenesulfonate in acetonitrile in the presence of inorganic base yielded IR, l'R-Atracurium besylate;
e. separating pure cisatracurium besylate from the product obtained in step (d) by flash chromatography using silica gel (30 to 50μ) in the ratio of 1(substrate): 40 and solvent system comprising dichloromethane, methanol mixture containing benzene sulfonic acid;
f. washing the eluted fractions with water and then with sodium benzenesulfonate and/or 10% sodium chloride solution to remove excess methanol and benzene sulfonicacid;
g. evaporating the solvent and precipitating the product with ether to yield fairly pure cisatracurium besylate;
h. cisatracurium besylate was further purified by dissolving the product from step (g) in a mixture of acetonitrile, isopropyl alcohol (IPA) and precipitating in ethyl acetate to yield pure cisatracurium besylate.

The acrylate used in the step a) of the present invention is preferably methylacrylate, ethyl acrylate, propyl acrylate and the like most preferably methyl acrylate.

The acid catalyst used in the step a) according to the present invention is benzenesulfonic acid, p-toluenesulfonic acid, methanesulfonic acid and the like, most preferably p-toluenesulfonic acid.

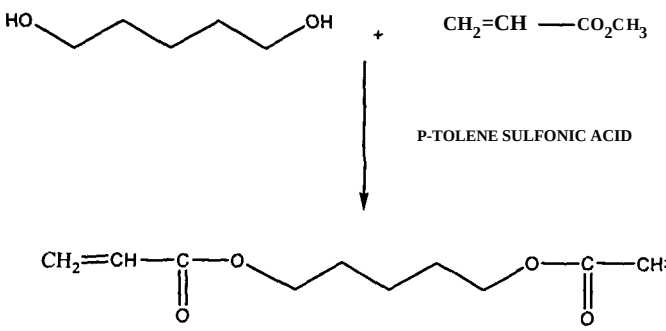
The chiral compound used for the resolution in the step b) of present invention is N-acetyl-L-leucine, N-acetyl-D-leucine and, the like preferably N-acetyl-D-leucine. The solvent used for the resolution in the step b) of this novel process is methanol, ethanol, isopropanaol and the like, most preferably isopropanol.

The preferred temperature for the reaction step (c) is 65-75°C, most preferably 70-75°C.The acid used is acetic acid, formic acid, propionic acid and the like, most preferably acetic acid. The product isolated was besylate, oxalate, and mesylate and the like, most preferably oxalate.

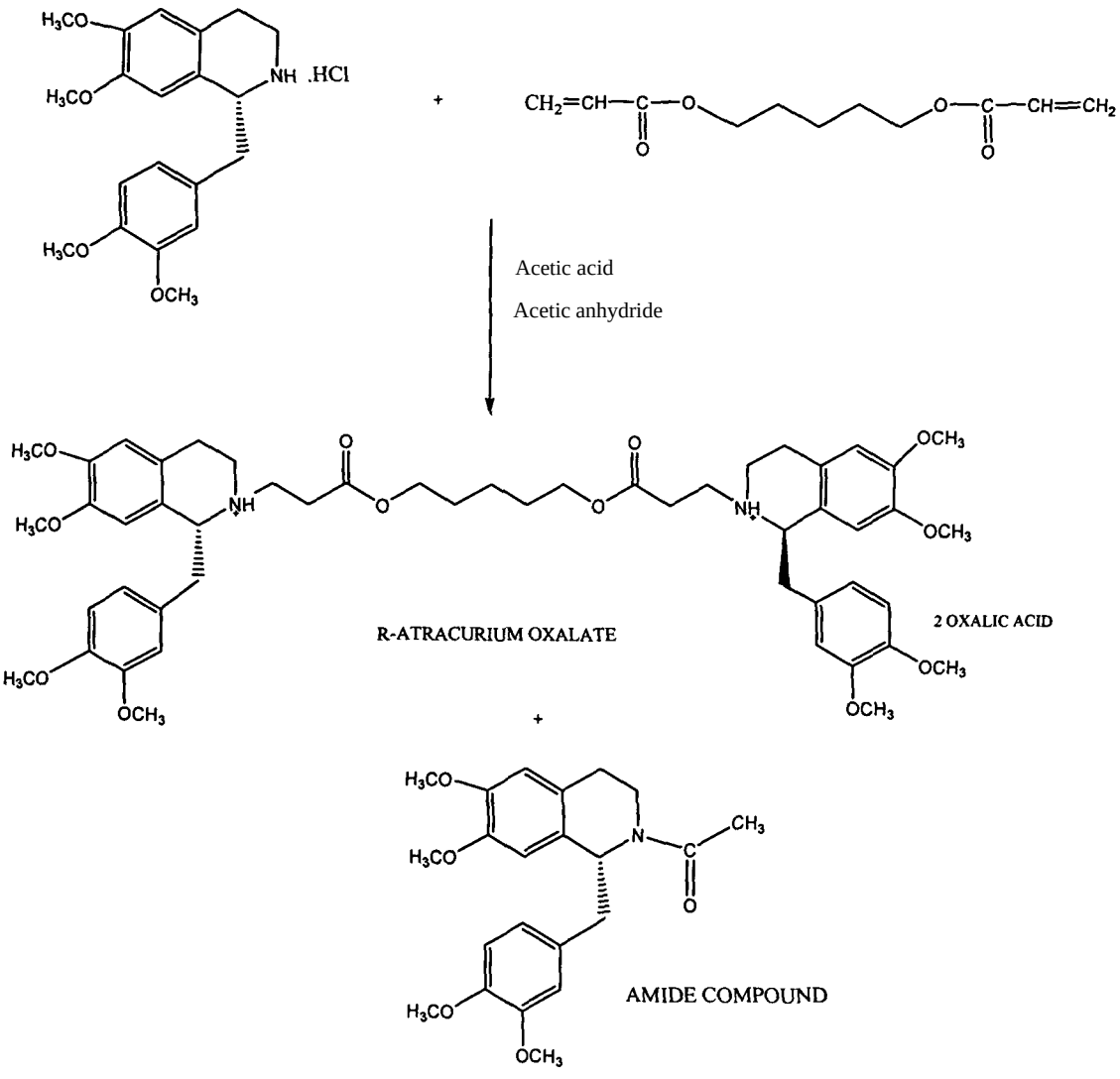
Separation of side products are cumbersome, which is controlled before forming by using molar excess of R-tertrahydropaverine in step (c) that prevents forming the said side products. Excess of the said R-tertrahydropaverine present in the reaction mixture after completion of reaction is removed by amide formation.

The reaction temperature in step (d) of the present invention is at 15-30^{0}C, most preferably 20-25^{0}C and the inorganic base used was sodium carbonate, potassium carbonate, sodium bicarbonate and the like, and most preferably sodium bicarbonate. The organic solvent used for the reaction was actonitrile or dichloromethane, dichloroethane, and most preferably acetonitrile. Removal of the excess methyl benzenesulfonate after the completion of reaction by extraction with methyl t-butyl ether (MTBE) and the isolation of product by extraction with dichloromethane from the aqueous solution and precipitation with MTBE to yield 1R,1'R-atracurium besylate.

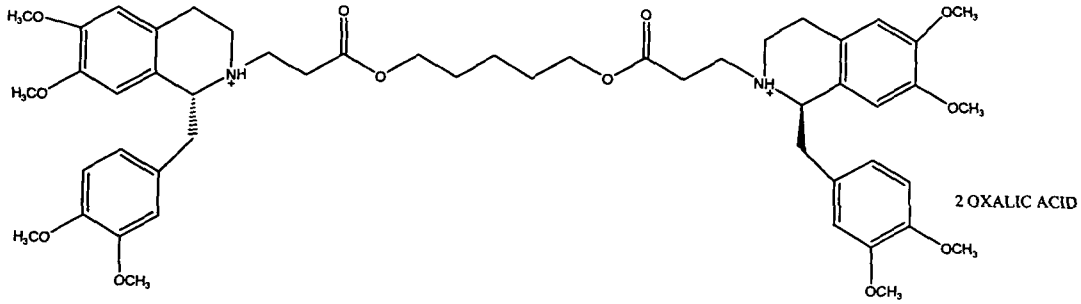
STEP I



STEPII

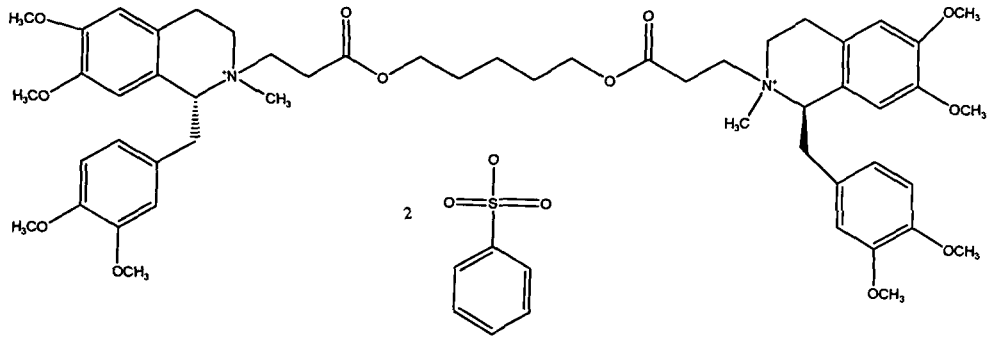


STEP HI



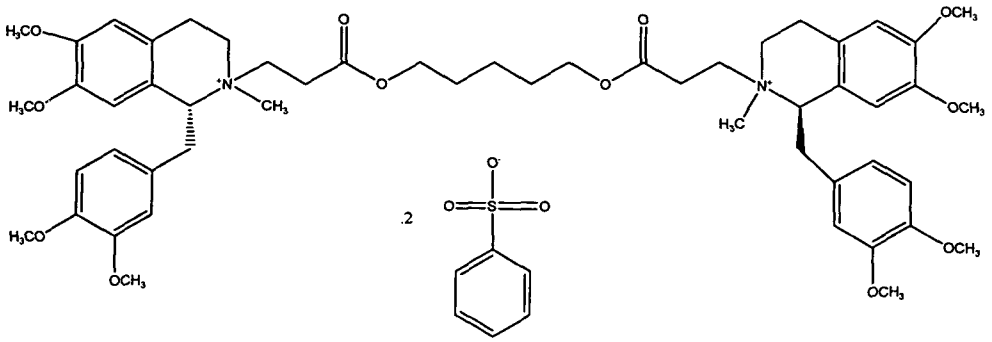
METHYLBENZENE SULFONATE

STEP IV



IR I'R-ATRACURIUM BESYLATE

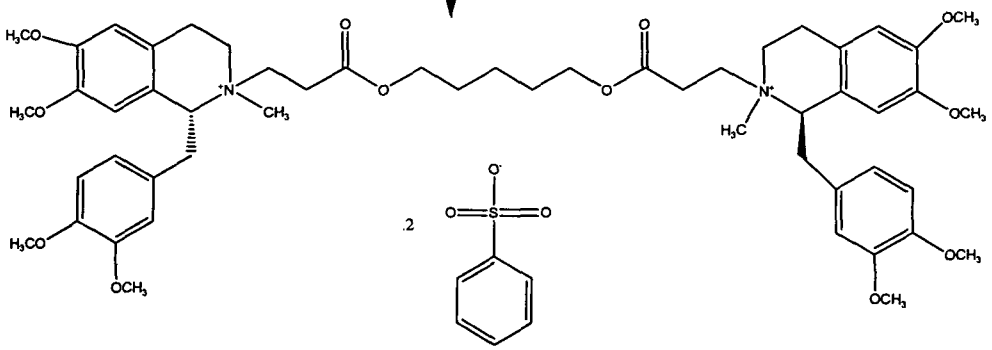
STEP III



1R.1'R-ATRACURIUM BESYLATE

FLASH CHROMATOGRAPHY

ISOMER SEPARATION



CISATRACURIUM BESYLATE

Using sodium bicarbonate in step(d) facilitate *in situ* isolation of base from the reaction mixture. Since sodium carbonate is a strong base compare with sodium bicarbonate, it is not suitable to use as a base in the reaction because the product formed during the reaction becomes unstable in such a high pH and also gives some side products.

Separating the cis-cis isomer from cis-trans, trans-trans reaction mixture, using silica gel (30 to 50μ) wherein the ratio of the said reaction mixture with respect to silica gel isl: 80 to 1:20, most preferably 1:40.

The solvent system used to separate the cis-cis isomer according to the present invention is a mixture of dichloromethane: methanol: benzenesulfonic acid in the ratio of 6 to 10% of methanol in dichloromethane containing 0.05% benzenesulfonic acid, which results in high yield, better resolution and improved purity

A process for the removal of unchanged R-tetrahydropapaverine by converting it into amide using acetic anhydride. A process for the preparation of 1R,1'R-Atracurium besylate from IR, I'R -2,2'-(3,l l-dioxo-4,10-dioxotridecylene)-bis-(l,2,3,4-tetrahydro-6,7-dimethoxy-2-methyl-l-veratryliso-quinolium dioxalate in the claim 1 in step d),wherein, the inorganic base used is sodium bicarbonate, sodium carbonate or potassium carbonate and most preferably sodium bicarbonate.

Lyophilisation is not a recommended process for this drug, because it this drug is unstable in basic medium and also not a industrially viable method.

The removal of excess methylbenzene sulfonate was effected by extraction with solvents like toluene, ethyl acetate, methyl tertiary butyl ether or diethyl ether and most preferably methyl tertiary butyl ether.

The product was isolated from aqueous solution by extraction with dichloromethane and the precipitation of the product with diethyl ether. The step f) the particle size of silica gel used for the separation of Cis-Cis isomer is 30-50µ.

Examples I:

Synthesis of 1, 5-Pentanediol diacrylate:

A mixture of 1, 5-Pentane diol (1 kg), methyl acrylate (lOLit) and p-toluenesulfonic acid in a 20 lit reactor was heated to 90-100^{0}C with stirring under nitrogen atmosphere. Further methyl acrylate (7 lit) was added drop by drop while a mixture of methyl acrylate and methanol are distilled at the same temperature for 6 to 8 hrs. Progress of the reaction

is monitored by TLC.After completion of the reaction, the excess methyl acrylate was distilled out completely under vacuum. The reaction mixture was cooled to room temperature, diluted with pet ether (1OLit), and the mixture washed once with aqueous 5% sodium bi carbonate followed by brine. The pet ether from the extract was distilled out, followed by high vacuum distillation of the product at less than lmm of Hg at 130-140^{0}C to yield pure 1, 5-Penatanediol diacrylate (1 kg)

Examples II:

Resolution of Tetrahydropapverine:

The racemic tetrahydropaverine (THP) hydrochloride (2kg) was dissolved in water (20Lit) and basified with ammonia solution (900 ml) with stirring. The THP base was extracted with dichloromethane (2xlOLit), and the organic layer washed with water and brine. Dichloromethane from the extract was distilled out completely and the gummy material obtained dissolved in IPA (15 Lit) and added to N-acetyl-D-leucine with stirring. The mixture was heated under reflux for 30 minutes to get a clear solution, cooled to RT and the solution kept aside overnight. The crystallized material was filtered, dried under vacuum and again recrystallised from IPA, to yield pure R-teterahydropapaverine salt (greater than 99.5% enantiomeric pure).

Examples III:

Preparation of **R-Atracurium oxalate:**

R-Tetrahydropapaverine-N-Acetyl-L-Leucine salt (1 kg) was dissolved in water (lOLit) and basified with ammonia solution (375 ml) with stirring. The base was extracted with dichloromethane (2x5Lit).The organic layer was washed with water and brine. The dichloromethane was distilled out and to the gummy material was added 1, 5-pentanediol diacrylate (162 ml) and acetic acid (51ml) and the mixture stirred at 70-75^{0}C under nitrogen atmosphere for 5 to 6 hrs. The reaction mixture in toluene (1 lit) was stirred with

acetic anhydride (80 ml) at 70-75°C for 30 minutes, cooled and diluted with acetone (5 Lit). To the mixture oxalic acid (380 g) in acetone (5 lit) was added and kept at 2 to 8°C overnight. The solid formed was filtered and dried to yield R-Atracurium oxalate (50Og).

Examples III:

Preparation of IR, l'R -Atracurium beyslate:

To a suspension of R-atracurium oxalate (50Og) in acetonitrile (1.25 Lit), were added methyl benzenesulfonate (750ml) and sodium bicarbonate (235g). The reaction mixture stirred at 20-25°C for 48 hrs, filtered and the filtrate was diluted with water and extracted with methyl t- butyl ether.The aqueous layer was then extracted with dichloromethane. The extract was concentrated and the product from concentrate precipitated by pouring into methyl t- butyl ether .The material was filtered and dried under vacuum to yield IR, 1'R -Atracurium beyslate (500g)

Examples IV:

Separation of Cis-Cis isomer from **IR, l'R -Atracurium** beyslate

Silica Gel (30-50 μ) (8 kg) was stirred with dichloromethane in methanol (8%) containing benzene sulfonic acid and the slurry loaded into the SS column 15 cm Dia x 150 cm length. The solvent was eluted under pressure (0.5 to 1 kg/cm^2). IR, 1'R -Atracurium beyslate(geometrical mixture) was dissolved in dichloromethane and loaded into the column and eluted with dichloromethane in methanol(8%) containing benzenesulfonic acid (.05 to .1%) followed by dichloromethane in methanol(10%) containing benzenesulfonic acid. The fractions containing pure Cis-Cis isomer as monitored by HPLC was collected and washed once with water followed by 10%sodium benzene sulfonate and or 10% sodium chloride solution. The dichloromethane solution was concentrated and the product precipitated with MTBE to yield fairly pure cistatracurium besylate. (7Og)

Examples V:

Purification of Cis-Cis isomer from IR, l'R -Atracurium beyslate

The crude cistaracurium besylate (10Og), obtained in example IV, was dissolved in a mixture of acetonitrile-IPA mixture (5 lit) and the product was precipitated with ethyl acetate at 0-5^{0}C with stirring. The supernatant liquid was siphoned out and the gummy material dissolved in dichloromethane and poured into diethyl ether to yield pure cisatracurium besylate. (7Og)

We claim;

1) A process for the preparation of cistarcurium besylate comprising of:
   a) condensing 1, 5-pentane diol with methylacrylate in the presence of para-toluenesufonic acid to obtain 1, 5-pentamethylenediacrylate;
   b) resolution of tetrahydropapaverine using N-acetyl-D-leucine in isopropyl alcohol to yield R-tetrahydropapaverine with enantiomeric purity greater than 99.5%;
   c) condensing R-tetrahydropapverine with 1,5-Pentamethylenediacrylate in acetic acid medium to yield lR,l'R)-2,2'-(3,l l-dioxo-4,10-dioxotridecylene)-bis-(1,2,3,4-tetrahydro-6,7-dimethoxy-2 -methyl- 1-veratryliso-quinolium dioxalate and excess of R-tetrahydropapaverine present in the reaction mixture by treating the said reaction mixture with acetic anhydride in toluene to form an amide wherein the said amide formed is dissolved in acetone and removed from the product;
   d) treating the product obtained from step (c) with methyl benzenesulfonate in acetonitrile in the presence of inorganic base yielded IR, l'R-Atracurium besylate;
   e) separating pure cisatracurium besylate from the product obtained in step (d) by flash chromatography using silica gel (30 to 50μ) in the ratio of 1(substrate): 40 and solvent system comprising dichloromethane, methanol mixture containing benzene sulfonic acid;
   f) washing the eluted fractions with water and then with sodium benzenesulfonate and/or 10% sodium chloride solution to remove excess methanol and benzene sulfonicacid;
   g) evaporating the solvent and precipitating the product with ether to yield fairly pure cisatracurium besylate;
   h) cisatracurium besylate was further purified by dissolving the product from step (g) in a mixture of acetonitrile, isopropyl alcohol (IPA) and precipitating in ethyl acetate to yield pure cisatracurium besylate.

2. A process of preparing cisatracurium besylate as claimed in claim 1, wherein the acrylate used in the step a) is preferably methylacrylate, ethyl acrylate, propyl acrylate and the like most preferably methyl acrylate and the acid catalyst used is benzenesulfonic acid, p-toluenesulfonic acid, methanesulfonic acid and the like, most preferably p-toluenesulfonic acid.
3. A process of preparing cisatracurium besylate as claimed in claim 1, wherein the chiral compound used for the resolution in the step b) is N-acetyl-L-leucine, N-acetyl-D-leucine and,the like preferably N-acetyl-D-leucine and the solvent used for the resolution is methanol, ethanol, isopropanaol and the like, most preferably isopropanol.
4. A process of preparing cisatracurium besylate as claimed in claim 1, wherein the preferred temperature for the reaction step (c) is 65-75°CC, most preferably 70-75°C.The acid used is acetic acid, formic acid, propionic acid and the like, most preferably acetic acid. The product isolated was besylate, oxalate, and mesylate and the like, most preferably oxalate.
5. A process of preparing cisatracurium besylate as claimed in claim 1, wherein the reaction temperature in step (d) of the present invention is at 15-30^{0}C, most preferably 20-25^{0}C and the inorganic base used was sodium carbonate, potassium carbonate, sodium bicarbonate and the like, and most preferably sodium bicarbonate. The organic solvent used for the reaction was actonitrile or dichloromethane, dichloroethane, and most preferably acetonitrile. Removal of the excess methyl benzenesulfonate after the completion of reaction by extraction with methyl t-butyl ether (MTBE) and the isolation of product by extraction with dichloromethane from the aqueous solution and precipitation with MTBE to yield lR,l'R-atracurium besylate.
6. A process of preparing cisatracurium besylate as claimed in any preceding claim, wherein separating the cis-cis isomer from cis-trans, trans-trans reaction mixture, using silica gel (30 to 50μ) wherein the ratio of the said reaction mixture with respect to silica gel is 1: 80 to 1:20, most preferably 1:40.
7. A process of preparing cisatracurium besylate as claimed in any preceding claim, wherein the solvent system used to separate the cis-cis isomer according to the

present invention is a mixture of dichloromethane: methanol: benzenesulfonic acid in the ratio of 6 to 10% of methanol in dichloromethane containing 0.05% benzenesulfonic acid.

8. A process for the preparation of IR, l'R -2, 2'-(3, 1l-dioxo-4, 10-dioxotridecylene)-bis-(l, 2, 3, 4-tetrahydro-6, 7-dimethoxy-2-methyl-l-veratryliso-quinolium dioxalate with enatiomeric purity greater than 99.5%.

9. A process of preparing cisatracurium besylate as claimed in claim 1, wherein, in the step g) the product was obtained from fractions after washings with water, 10% sodium benzenesulfonate and or 10% sodium chloride, precipitating with diethyl ether.