Description

Field of the invention

The present invention is directed to a new optically pure compound, a process for its preparation and its use in the manufacture of pharmaceutical preparations.

Background of the invention

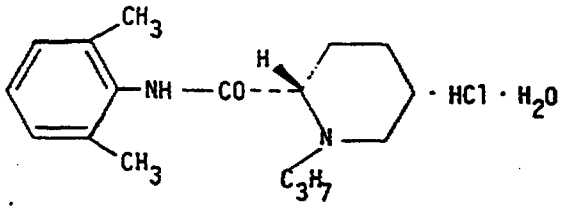
A new local anesthetic namely (S)-(-)-l-propyl-2',6'-pipecoloxylidide hydrochloride is described in WO 85/00599. The new compound has an unexpected long duration compared to the racemate and the corresponding R-(+)-enantiomer. The preparation method described in WO 85/00599 gives however a product which contains about 10 % of the (R)-(+)-enantiomer. This means that the product from a physical chemical point of view, contains only about 80 % of the (S)-(-)-enantiomer, while the residual about 20 % constitutes the racemic form. In addition the product obtained is hygroscopic and thus not stable and contains about 2 % of water. One mole of water of crystallization implies a water content of 5,5 %.A product having a varying content of water has the drawback that the percentage of water must be analyzed each time a pharmaceutical formulation shall be prepared. As the (S)-(-)-enantiomer is the most potent enantiomer a product containing less (R)-(+)-enantiomer was wanted. One object of this invention is thus to produce the compound in a form, which is stable and which does not change by storing at ordinary room temperature and humidity. A second object of this invention is to obtain a product consisting of the substantially pure (S)-(-)-enantiomer.

Outline of the invention

The present invention is related to the monohydrate of (S)-(-)-l-propyl-2',6'-pipecoloxylidide hydrochloride. By means of a specific method of preparing the named hydrate, the (S)-(-)-enantiomer is obtained in high optical purity, namely ≥99.5 %, even from an optically highly contaminated preparation. This specific method is a further aspect of this invention. The monohydrate of (S)-(-)-l-propyl-2',6'-pipecoloxylidide hydrochloride has the further advantage that it is very stable and hardly affected by drying in a desiccator over calcium chloride at room temperature and 0.5 mm Hg. Only when the compound was heated at 75°C for 16 hours, other conditions being equal, the water of crystallization was removed. No further change of the compound was noticed.

Preparation

The monohydrate of (S)-(-)-l-propyl-2',6'-pipecoloxylidide hydrochloride with the structural formula



is prepared according to the invention by dissolving S-(-)-l-propyl-2',6'-pipecoloxylidide hydrochloride in water, whereupon hot acetone is added. The solution is then filtered as hot as possible and left for crystallization. At the preparation the starting compound is dissolved in an amount of water, which corresponds to about 1-3 times of the weight of the added compound and the volume of acetone added is 5-15 times of the water volume. If more water is added, that is an amount of water, which corresponds to up to 4 times of the weight of the added compound, the volume of the acetone added is 15-20 times of the water volume. It is especially preferred to make the preparation in the following way: The starting compound is heated with an amount of water equal to the weight of the starting compound. Hot acetone in such an amount that the compound is completely dissolved is added. Additional acetone to a volume of ten times of the volume of the added water is then poured into the solution, whereafter the solution is filtered and left for crystallization.The proportion between water and acetone is important. If too much acetone is added the product obtained is less pure and more recrystallizations are needed. When acetone less than 10 times the volume of water is added on the other hand the yield diminishes. The acetone added is hot preferably boiling (b. p. 56°C). Acetone having a temperature between 45-56°C can be used according to the invention.

The invention also relates to pharmaceutical preparations containing the new pure compound as active ingredient: to the use of the new compound in therapy, especially for obtaining local anesthesia in mammals including man; to a method for obtaining local anesthesia in mammals including man by administering the new compound; and to the use of the new compound in the manufacture of pharmaceutical preparations having local anesthetic effect.

For the preparation of pharmaceutical preparations the new compound is dissolved in a liquid diluent, which is suitable for injection. The preparations used are aqueous solutions which contain between 1.25 and 15.0 mg/ml of the active compound calculated as the hydrochloride salt. In some applications a vasoconstrictor, epinephrine, is included in concentrations between 2.0 and 20.0 µg/ml calculated as the base. The solutions are made isoosmotic with physiologic saline by the addition of an appropriate amount of sodium chloride. Solutions containing epinephrine will also contain sodium metabisulphite in order to protect epinephrine from oxidation. pH of solutions without epinephrine is adjusted to approximately 5.5 wheras pH in solutions containing epinephrine is adjusted to approximately 3.6.

The invention is illustrated by the following examples.

Example I illustrates a specially preferred way of carrying out the process according to the invention.

Example I

Preparation of the monohydrate of (S)-(-)-I-propyl-2',6'-pipecoloxylidide hydrochloride. 82 g of the hydrochloride of (S)-(-)-I-propyl-2',6'-pipecoloxylidide containing IO % of the (R)-(+)-enantiomer was dissolved in 85 ml of water, whereupon acetone heated to its boiling point was added to a final volume of 85O ml. The solution was filtered and left for crystallization. This first recrystallization yielded 7l,7 g. Another recrystallization was carried out by dissolving the obtained product in 72 ml of H_2O, whereupon boiling acetone to a final volume of 75O ml was added. The solution was filtered and left for crystallization. The final yield was 62.3 g (76 %) of an optically pure (≥ 99.5 %) product containing 5.4-5.6 % of water, being the monohydrate of (S)-(-)-I-propyl-2',6'-pipecoloxylidide hydrochloride, melting interval 266-267.5°C.

Example 2 (S)-(-)-I-propyl-2',6'-pipecoloxylidide hydrochloride monohydrate2.64 mg
Sodium chloride8.53 mg
Sodium hydroxide to pH5.5
Water for injection tol.O ml

2.64 mg of the monohydrate of S-(-)-I-propyl-2',6'-pipecoloxylidide hydrochloride was dissolved in I ml of sterile water. 8.53 mg of sodium chloride was added and the solution was adjusted to pH 5.5 with sodium hydroxide.

Example 3 (S)-(-)-I-propyl-2',6'-pipecoloxylidide hydrochloride monohydrate5.29 mg
Epinephrine hydrogentartrateIO.O µg
Sodium chloride7.89 mg
Hydrochloric acid to pH3.6
Water for injection tol.O ml

The preparation was prepared as described in Example 2

Further attempts to purify the compound

In order to try to purify the product described in WO 85/OO599 further recrystallizations from 2-propanol, the solvent used according to that patent application, were performed. Although water was added it was not possible to obtain an optically more pure or, with respect to the water contents, more well defined product.

Other common solvents such as methanol and ethanol are not suitable because of the too high solubility of the hydrochloride of (S)-(-)-I-propyl-2',6'-pipecoloxylidide in methanol and ethanol. In solvents such as ethyl acetate and dioxan on the other hand the compound is almost insoluble.

Claims for the contracting states: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. (S)–(–)–1-propyl-2',6'-pipecoloxylidide hydrochloride characterized in that the compound is in the form of its monohydrate.

2. Compound according to claim 1 characterized in that it is substantially optically pure.

3. Compound according to claim 1 characterized in that it contains less than 0.5% by weight of the corresponding (R)–(+)–enantiomer.

4. A process for the preparation of substantially optically pure monohydrate of (S)–(–)–1-propyl-2',6'-pipecoloxylidide hydrochloride characterized in that (S)–(–)–1-propyl-2',6'-pipecoloxylidide hydrochloride containing the (R)–(+)–enantiomer is dissolved in water, whereupon acetone heated to a temperature of from 45°C to its boiling point is added and the monohydrate of (S)–(–)–1-propyl-2',6'-pipecoloxylidide hydrochloride is isolated.

5. A process according to claim 4 characterized in that the (S)–(–)–1-propyl-2',6'-pipecoloxylidide hydrochloride is dissolved in an amount of water which corresponds to 1–3 times of its weight, acetone of a volume 5–15 times of the water volume is added, whereupon the solution is filtered and the end product is isolated.

6. A process according to claim 5 characterized in that the weight of the water is equal to the weight of the (S)–(–)–1–propyl-2',6'-pipecoloxylidide hydrochloride and the volume of the acetone is 10 times of the volume of the added water.

7. Pharmaceutical preparation for local anesthesia characterized in that it contains the compound according to claim 1.

8. Compound according to claim 1 for use in inducing local anesthesia.

9. Use of the compound according to claim 1 in the manufacture of pharmaceutical preparations having local anesthetic effect.

Claims for the contracting states: AT, ES, GR

1. A process for the preparation of substantially optically pure monohydrate of (S)–(–)–1-propyl-2',6'-pipecoloxylidide hydrochloride characterized in that (S)–(–)–1-propyl-2',6'-pipecoloxylidide hydrochloride containing the (R)–(+)–enantiomer is dissolved in water, whereupon acetone heated to a temperature of from 45°C to its boiling point is added and the monohydrate of (S)–(–)–1-propyl-2',6'-pipecoloxylidide hydrochloride is isolated.

2. A process according to claim 2 characterized in that the (S)–(–)–propyl-2',6'-pipecoloxylidide hydrochloride is dissolved in an amount of water which corresponds to 1–3 times of its weight, acetone of a volume 5–15 times of the water volume is added, whereupon the solution is filtered and the end product is isolated.

3. A process according to claim 2 characterized in that the weight of the water is equal to the weight of the (S)–(–)–1-propyl-2',6'-pipecoloxylidide hydrochloride and the volume of the acetone is 10 times of the volume of the added water.

4. A process according to claim 1 characterized in that the isolated compound is substantially optically pure.

5. A process according to claim 1 characterized in that the isolated compound contains less than 0.5% by weight of the corresponding (R)–(+)–enantiomer.

Example I illustrates a specially preferred way of carrying out the process according to the invention.

Example I

Preparation of the monohydrate of (S)-(-)-I-propyl-2',6'-pipecoloxylidide hydrochloride. 82 g of the hydrochloride of (S)-(-)-I-propyl-2',6'-pipecoloxylidide containing IO % of the (R)-(+)-enantiomer was dissolved in 85 ml of water, whereupon acetone heated to its boiling point was added to a final volume of 85O ml. The solution was filtered and left for crystallization. This first recrystallization yielded 7l,7 g. Another recrystallization was carried out by dissolving the obtained product in 72 ml of H_2O, whereupon boiling acetone to a final volume of 75O ml was added. The solution was filtered and left for crystallization. The final yield was 62.3 g (76 %) of an optically pure (≧ 99.5 %) product containing 5.4-5.6 % of water, being the monohydrate of (S)-(-)-I-propyl-2',6'-pipecoloxylidide hydrochloride, melting interval 266-267.5°C.

Example 2 (S)-(-)-I-propyl-2',6'-pipecoloxylidide hydrochloride monohydrate2.64 mg
Sodium chloride8.53 mg
Sodium hydroxide to pH5.5
Water for injection tol.O ml

2.64 mg of the monohydrate of S-(-)-I-propyl-2',6'-pipecoloxylidide hydrochloride was dissolved in I ml of sterile water. 8.53 mg of sodium chloride was added and the solution was adjusted to pH 5.5 with sodium hydroxide.

Example 3 (S)-(-)-I-propyl-2',6'-pipecoloxylidide hydrochloride monohydrate5.29 mg
Epinephrine hydrogentartratelO.O µg
Sodium chloride7.89 mg
Hydrochloric acid to pH3.6
Water for injection tol.O ml

The preparation was prepared as described in Example 2

Further attempts to purify the compound

In order to try to purify the product described in WO 85/OO599 further recrystallizations from 2-propanol, the solvent used according to that patent application, were performed. Although water was added it was not possible to obtain an optically more pure or, with respect to the water contents, more well defined product.

Other common solvents such as methanol and ethanol are not suitable because of the too high solubility of the hydrochloride of (S)-(-)-I-propyl-2',6'-pipecoloxylidide in methanol and ethanol. In solvents such as ethyl acetate and dioxan on the other hand the compound is almost insoluble.

Claims for the contracting states: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. (S)–(–)–1-propyl-2',6'-pipecoloxylidide hydrochloride characterized in that the compound is in the form of its monohydrate.

2. Compound according to claim 1 characterized in that it is substantially optically pure.

3. Compound according to claim 1 characterized in that it contains less than 0.5% by weight of the corresponding (R)–(+)–enantiomer.

4. A process for the preparation of substantially optically pure monohydrate of (S)–(–)–1-propyl-2',6'-pipecoloxylidide hydrochloride characterized in that (S)–(–)–1-propyl-2',6'-pipecoloxylidide hydrochloride containing the (R)–(+)–enantiomer is dissolved in water, whereupon acetone heated to a temperature of from 45°C to its boiling point is added and the monohydrate of (S)–(–)–1-propyl-2',6'-pipecoloxylidide hydrochloride is isolated.

5. A process according to claim 4 characterized in that the (S)–(–)–1-propyl-2',6'-pipecoloxylidide hydrochloride is dissolved in an amount of water which corresponds to 1–3 times of its weight, acetone of a volume 5–15 times of the water volume is added, whereupon the solution is filtered and the end product is isolated.

6. A process according to claim 5 characterized in that the weight of the water is equal to the weight of the (S)–(–)–1–propyl-2',6'-pipecoloxylidide hydrochloride and the volume of the acetone is 10 times of the volume of the added water.

7. Pharmaceutical preparation for local anesthesia characterized in that it contains the compound according to claim 1.

8. Compound according to claim 1 for use in inducing local anesthesia.

9. Use of the compound according to claim 1 in the manufacture of pharmaceutical preparations having local anesthetic effect.

Claims for the contracting states: AT, ES, GR

1. A process for the preparation of substantially optically pure monohydrate of (S)–(–)–1-propyl-2',6'-pipecoloxylidide hydrochloride characterized in that (S)–(–)–1-propyl-2',6'-pipecoloxylidide hydrochloride containing the (R)–(+)–enantiomer is dissolved in water, whereupon acetone heated to a temperature of from 45°C to its boiling point is added and the monohydrate of (S)–(–)–1-propyl-2',6'-pipecoloxylidide hydrochloride is isolated.

2. A process according to claim 2 characterized in that the (S)–(–)–propyl-2',6'-pipecoloxylidide hydrochloride is dissolved in an amount of water which corresponds to 1–3 times of its weight, acetone of a volume 5–15 times of the water volume is added, whereupon the solution is filtered and the end product is isolated.

3. A process according to claim 2 characterized in that the weight of the water is equal to the weight of the (S)–(–)–1-propyl-2',6'-pipecoloxylidide hydrochloride and the volume of the acetone is 10 times of the volume of the added water.

4. A process according to claim 1 characterized in that the isolated compound is substantially optically pure.

5. A process according to claim 1 characterized in that the isolated compound contains less than 0.5% by weight of the corresponding (R)–(+)–enantiomer.

* C L M S *

6. A process for the preparation of a pharmaceutical preparation for local anesthesia characterized in that it contains the compound isolated according to claim 1.

7. Use of the compound isolated according to claim 1 in the manufacture of pharmaceutical preparations having local anesthetic effect.

Patentansprüche für die Vertragsstaaten: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. (S)-(-)-1-Propyl-2',6'-pipecoloxylidid-hydrochlorid, dadurch gekennzeichnet, daß die Verbindung in Form des Monohydrats vorliegt.

2. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß sie im wesentlichen optisch rein ist.

3. Verbindung nach Anspruch 1, dadurch gekennzeichnet, daß sie weniger als 0,5 Gew.-% des entsprechenden (R)-(+)-Enantiomeren enthält.

4. Verfahren zur Herstellung von im wesentlichen optisch reinem Monohydrat von (S)-(-)-1-Propyl-2',6'-pipecoloxylidid-hydrochlorid, dadurch gekennzeichnet, daß das (R)-(+)-Enantiomeres enthaltende (S)-(-)-1-Propyl-2',6'-pipecoloxylidid-hydrochlorid in Wasser gelöst wird, worauf auf eine Temperatur von 45°C bis zum Kochpunkt erhitztes Aceton zugegeben wird und das Monohydrat von (S)-(-)-1-Propyl-2',6'-pipecoloxylidid-hydrochlorid isoliert wird.

5. Verfahren nach Anspruch 4, dadurch gekennzeichnet, daß das (S)-(-)-1-Propyl-2',6'-pipecoloxylidid-hydrochlorid in einer Wassermenge, die dem 1–3fachen seines Gewichtes entspricht, gelöst wird, Aceton in einem Volumen, das dem 5–15fachen des Wasservolumens entspricht, zugegeben wird, worauf die Lösung filtriert und das Endprodukt wird.

6. Verfahren nach Anspruch 5, dadurch gekennzeichnet, daß das Gewicht des Wassers gleich dem Gewicht des (S)-(-)-1-propyl-2',6'-pipecoloxylidid-hydrochlorids ist und das Volumen des Acetons das Zehnfache des Volumens des zugegebenen Wassers ist.

7. Pharmazeutische Präparation zur Lokalanästhesie, dadurch gekennzeichnet, daß sie die Verbindung nach Anspruch 1 enthält.

8. Verbindung nach Anspruch 1 zur Verwendung zur Bewirkung einer Lokalanästhesie.

9. Verwendung einer Verbindung nach Anspruch 1 zur Herstellung pharmazeutischer Präparationen mit lokalanästhetischer Wirkung.

Patentansprüche für die Vertragsstaaten: AT, ES, GR

1. Verfahren zur Herstellung eines im wesentlichen optisch reinen Monohydrats von (S)-(-)-1-Propyl-2',6'-pipecoloxylidid-hydrochlorid, dadurch gekennzeichnet, daß das (R)-(+)-Enantiomeres enthaltende (S)-(-)-1-Propyl-2',6'-pipecoloxylidid-hydrochlorid in Wasser gelöst wird, worauf auf eine Temperatur von 45°C bis zum Kochpunkt erhitztes Aceton zugegen wird und das Monohydrat von (S)-(-)-1-Propyl-2',6'-pipecoloxylidid-hydrochlorid isoliert wird.

2. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß das (S)-(-)-1-Propyl-2',6'-pipecoloxylidid-hydrochlorid in einer Wassermenge, die dem 1–3fachen seines Gewichtes entspricht, gelöst wird, Aceton in einem Volumen, das dem 5–15fachen des Wasservolumens entspricht, zugegeben wird, worauf die Lösung filtriert und das Endprodukt isoliert wird.

3. Verfahren nach Anspruch 2, dadurch gekennzeichnet, daß das Gewicht des Wassers gleich dem Gewicht des (S)-(-)-1-Propyl-2',6'-pipecoloxylidid-hydrochlorids ist und das Volumen des Acetons das Zehnfache des Volumens des zugegebenen Wassers ist.

4. Verfahren nach Anspruch 1, dadurch gekennzeichnet, das die isolierte Verbindung im wesentlichen optisch rein ist.

5. Verfahren nach Anspruch 1, dadurch gekennzeichnet, daß die isolierte Verbindung weniger als 0,5 Gew.-% des entsprechenden (R)-(+)-Enantiomeren enthält.

6. Verfahren zur Herstellung einer pharmazeutischen Präparation zur Lokalanästhesie, dadurch gekennzeichnet, daß sie die nach Anspruch 1 isolierte Verbindung enthält.

7. Verwendung der nach Anspruch 1 isolierten Verbindung zur Herstellung pharmazeutischer Präparationen mit lokalanästhetischer Wirkung.

Revendications pour les Etats Contractants: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Chlorhydrate de (S)–(–)–1-propyl-2',6'-pipécoloxylidide, caractérisé en ce que le composé est sous la forme de son monohydrate.

2. Composé selon la revendication 1, caractérisé en ce qu'il est pratiquement pur optiquement.

3. Composé selon la revendication 1, caractérisé en ce qu'il contient moins de 0,5% en poids de l'énantiomère (R)–(+) correspondant.

4. Procédé pour la préparation du monohydrate du chlorhydrate de (S)–(–)–1-propyl-2',6'-pipécoloxylidide pratiquement pur optiquement, caractérisé en ce que l'on dissout dans de l'eau du chlorhydrate de (S)–(–)–1-propyl-2'-6'-pipécoloxylidide contenant l'énantiomère (R)–(+), puis on ajoute de l'acétone chauffée à une température dans la plage de 45°C à son point d'ébullition, et on isole le monohydrate du chlorhydrate de (S)–(–)–1-propyl-2',6'-pipécoloxylidide.

5. Procédé selon la revendication 4, caractérisé en ce que l'on dissout le chlorhydrate du (S)–(–)–1-propyl-2',6'-pipécoloxylidide dans une quantité d'eau qui correspond à 1–3 fois sont poids, on ajoute de l'acétone en un volume égal à 5–15 fois le volume d'eau, à la suite de quoi on filtre la solution et on isole le produit final.

6. Procédé selon la revendication 5, caractérisé en ce que le poids de l'eau est égal au poids du chlorhydrate du (S)–(–)–1-propyl-2',6'-pipécoloxylidide et le volume de l'acétone est égal à 10 fois le volume de l'eau ajoutée.

7. Composition pharmaceutique pour anesthésie locale, caractérisée en ce qu'elle contient le composé selon la revendication 1.

8. Composition selon la revendication 1, pour utilisation dans l'induction d'anesthésie locale.

9. Utilisation du composé selon la revendication 1 dans la fabrication de compositions pharmaceutiques ayant un effet anesthésique local.

Revendications pour les Etats Contractants: AT, ES, GR

1. Procédé pour la préparation du monohydrate du chlorhydrate de (S)–(–)–1-propyl-2′,6′-pipécoloxylidide pratiquement pur optiquement, caractérisé en ce que l'on dissout dans de l'eau le chlorhydrate du (S)–(–)–1-propyl-2′,6′-pipécoloxylidide contenant l'énantiomère (S)–(+), puis on ajoute de l'acétone chauffée à une température dans la plage de 45°C à son point d'ébullition, et on isole le monohydrate du chlorhydrate de (S)–(–)–1-propyl-2′,6′-pipécoloxylidide.

2. Procédé selon la revendication 1, caractérisé en ce que l'on dissout le chlorhydrate de (S)–(–)–1-propyl-2′,6′-pipécoloxylidide dans une quantité d'eau qui correspond à 1–3 fois sont poids, on ajoute de l'acétone en un volume égal à 5–15 fois le volume d'eau, à la suite de quoi on filtre la solution et on isole le produit final.

3. Procédé selon la revendication 2, caractérisé en ce que le poids de l'eau est égal au poids du chlorhydrate de (S)–(–)–1-propyl-2′,6′-pipécoloxylidide et le volume de l'acétone est égal à 10 fois le volume de l'eau ajoutée.

4. Procédé selon la revendication 1, caractérisé en ce que le composé isolé est pratiquement pur optiquement.

5. Procédé selon la revendication 1, caractérisé en ce que le composé isolé contient moins de 0,5% en poids de l'énantiomère (R)–(+) correspondant.

6. Procédé pour la préparation d'une composition pharmaceutique pour anesthésie locale, caractérisée en ce qu'elle contient le composé isolé selon la revendication 1.

7. Utilisation du composé isolé selon la revendication 1, dans la fabrication de compositions pharmaceutiques ayant un effet anesthésique local.

* C L M S *