The present invention relates to a process for preparing \(1-[3-(4-	ext{chlorophenyl})propoxy]propyl\)-piperidine (I) by reaction of 3-piperidinopropanol (II) with sodium hydride in an aprotic polar solvent and further reaction with 3-(4-chlorophenyl)propyl mesylate (III).
Process for preparing 1-[3-[3-(4-chlorophenyl)propoxy]propyl]-piperidine

Field of the invention

The present invention relates to a process for preparing 1-[3-[3-(4-chlorophenyl)propoxy]propyl]-piperidine.

Background of the invention

1-[3-[3-(4-chlorophenyl)propoxy]propyl]-piperidine belongs to the pharmacological class of ligands of histamine H3 receptors and has the structural formula:

\[
\text{Cl} \quad \text{O} \quad \text{N}
\]

The specification EP 982300 discloses the preparation of said compound in a heterogeneous phase, which comprises the use of crown ether phase transfer catalysts, resulting in an inappropriate industrial process because of its high cost and toxicity.

Moreover, compound (I) obtained according to the prior art method yields an improper purity profile to be used directly in the preparation of pharmaceutically acceptable salts thereof.

The purification of compound (I) obtained according to the prior art process would require an additional column chromatography and/or a molecular distillation process. Column chromatography techniques are not widely used in manufacturing processes, partly because of the large
quantities of solvents needed, which may result in environmental problems. On the other hand, fractioned distillation of compound (I) is not convenient because of its high boiling point (180°C / 0.01 mmHg). This fact forces to use a molecular distillation equipment, which limits its industrial feasibility.

**Description of the invention**

The present invention discloses a process for preparing 1-[[3-[3-(4-chlorophenyl)propoxy]propyl]-piperidine (I) which is more efficient than the process reported in the prior art. Thus, by using reaction conditions in a homogeneous phase, a sufficiently pure free base compound is obtained, which can then be used directly in the manufacturing of pharmacologically acceptable salts thereof, without any isolation or subsequent purification steps.

The present invention also circumvents phase transfer catalysts thus providing a more convenient industrial process. Also, operating temperatures in the process of the present invention are lower than in the heterogeneous phase reaction disclosed in the prior art. In fact, in the present invention, reaction occurs at room temperature, i.e. 20-25°C, in contrast to 80-110°C needed in the prior art process. Such new smoother reaction conditions generate less impurities than those appearing in processes already described.

The present invention comprises a process for the manufacture of 1-[[3-[3-(4-chlorophenyl)propoxy]propyl]-piperidine (I), which involves the formation of 3-piperidinopropanol (II) sodium salt in an aprotic polar solvent and subsequent reaction with 3-(4-
chlorophenyl) propyl mesylate (III), according to Scheme 1.

\[
\begin{align*}
\text{Cl} & \quad \text{I} \\
\text{O} & \quad \text{N} \\
\text{S} & \quad \text{O} \\
\text{O} & \quad \text{Cl}
\end{align*}
\]

Scheme 1

In another embodiment, the aprotic polar solvent is selected from N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, 1-methyl-2-piperidone, 1,3-dimethyl-2-imidazolidinone, and the like, and mixtures thereof.

In another embodiment of the present invention process, molecular equivalents of both sodium hydride and 3-(4-chlorophenyl) propyl mesylate (III) are used in excess to the molecular equivalents of 3-piperidinopropanol (II). Thus, the quantity of sodium hydride is from about 1.1 to about 2.0 molecular equivalents, more preferably from about 1.4 to about 1.7. Regarding 3-(4-chlorophenyl) propyl mesylate (III), the quantity thereof is from about 1.1 to about 2.0 molecular equivalents, preferably from about 1.2 to about 1.5. Accordingly, the excess of sodium hydride assures that 3-piperidinopropanol (II) remains as its reactive sodium salt specie. Likewise, 3-(4-chlorophenyl) propyl mesylate (III) should be in excess because of its chemical lability.

In another embodiment, the reaction of the sodium salt of compound (II) with compound (III) is performed at room temperature (i.e. 20-25°C).
In the process of the present invention, the limiting reactant 3-piperidinopropanol (II) is fully converted, thus providing 1-[3-[3-(4-chlorophenyl) propoxy] propyl]-piperidine (I) as the unique nitrogen-bearing compound obtained.

Further washes of the aqueous phase containing the formed salt of 1-[3-[3-(4-chlorophenyl) propoxy] propyl]-piperidine (I) with an organic solvent removes all non-nitrogen by-products, yielding a product (I) with a quality good enough to be used in subsequent process steps without any kind of purification.

Example 1: 1-[3-[3-(4-chlorophenyl) propoxy] propyl]-piperidine (I)

3-piperidinopropanol (1 Kg, 6.98 mol) was dissolved in anhydrous N,N-dimethylacetamide (8.8 L) under a nitrogen atmosphere. Then sodium hydride 60% (0.449 Kg, 11.23 mol) was slowly added. The mixture was heated at 50°C for 1 hour with stirring. Then the mixture was cooled at 25°C and a solution of 3-(4-chlorophenyl) propyl mesylate (2.08 Kg, 8.36 mol) in anhydrous N,N-dimethylacetamide (3.5 L) was added for 2 hours. The mixture was stirred for 7 hours at 22°C. Then the mixture was cooled at 10°C and a solution of sodium chloride (1.1 Kg) in water (13.3 L) was slowly added. After extraction of the aqueous phase several times with toluene, the organic extracts were combined and extracted with HCl (7 L, 2N). The aqueous phase was then washed with toluene (1.75 L). The aqueous phase was treated with sodium hydroxide (6N, 2.5 L) and taken to pH 12, and then extracted twice with 7 L of toluene. The toluene extracts were washed thrice with 7 L of water. Toluene was distilled at reduced pressure to
yield 1.99 Kg of 1-[[3-[3-(4-chlorophenyl)propoxy]propyl]-piperidine (I) as an oil. Yield 99.3%. Purity (GC) 99.2%.
CLAIMS

1. A process for the preparation of 1-[3-[3-(4-chlorophenyl) propoxy] propyl]-piperidine (I):

\[
\text{Cl} \quad \begin{array}{c}
\text{O} \\
\text{N}
\end{array} \\
\text{I}
\]

which comprises reaction of 3-piperidinopropanol (II):

\[
\text{HO} \quad \begin{array}{c}
\text{N}
\end{array} \\
\text{II}
\]

with sodium hydride to form the sodium salt of (II) wherein the quantity of sodium hydride is from about 1.1 to about 2.0 molecular equivalents, in an aprotic polar solvent and subsequent reaction with 3-(4-chlorophenyl) propyl mesylate (III):

\[
\text{Cl} \quad \begin{array}{c}
\text{O} \\
\text{SO} \\
\text{CH}_3
\end{array} \\
\text{III}
\]

wherein the quantity of (III) is from about 1.1 to about 2.0 molecular equivalents.

2. A process according to claim 1 wherein the quantity of sodium hydride is from about 1.4 to about 1.7 molecular equivalents.
3. A process according to claim 1 wherein the quantity of compound (III) is from about 1.2 to about 1.5 molecular equivalents.

4. A process according to claim 1 wherein the aprotic polar solvent is selected from N,N-dimethylformamide, N,N-dimethylacetamide, 1-methyl-2-pyrrolidone, 1-methyl-2-piperidone, 1,3-dimethyl-2-imidazolidinone and mixtures thereof.

5. A process according to claim 4 wherein the aprotic polar solvent is N,N-dimethylacetamide.

6. A process according to claim 1 wherein the reaction of the sodium salt of (II) with (III) is performed at room temperature.
INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/063927

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D295/088

According to International Patent Classification (IPC) or 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 database consulted during the international search (name of database and, where practical, search terms used)

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>MEIER GALINA ET AL: &quot;Influence of imidazole replacement in different structural classes of histamine H3-receptor antagonists&quot; EUROPEAN JOURNAL OF PHARMACEUTICAL SCIENCES, ELSEVIER, AMSTERDAM, NL, vol. 13, no. 3, June 2001 (2001-06), pages 249-259, XP002269929 ISSN: 0928-0987 compound 6; synthesis 2.1.2.6 on p. 252</td>
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D Further documents are listed in the continuation of Box C

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"Y" 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

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Date of the actual completion of the international search

26 September 2006

Date of mailing of the international search report

06/10/2006

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