

A NOVEL PHOSPHATE SALT OF ISOPROPYL-METHYL-[2-(3-n-PROPOXYPHENOXY)ETHYL]AMINE*Field of the invention*

5 The present invention relates to a novel phosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine. Additionally, the present invention also relates to a process for the preparation of a phosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine as well as a pharmaceutical formulation containing it and its use in medicine.

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Background of the invention and prior art

Isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine is a compound with anaesthetic properties. It is therefore useful as an anaesthetic compound for the treatment of pain,
15 including localised pain.

WO 9715548 discloses isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine as well as a process for its preparation. Said process comprises a couple of reaction steps starting with reacting 3-n-propoxyphenol with 1,2-dibromoethane resulting in 1-(2-bromoethoxy)-3-n-propoxybenzene. Further, 1-(2-bromoethoxy)-3-n-propoxybenzene is reacted with N-methylisopropylamine in an autoclave. The product, isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine, was thereafter further purified by distillation *in vacuo*.

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Summary of the Invention

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The object of the present invention is to provide a monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine.

According to the invention there is also provided a process for the preparation of the monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine which comprises treating isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine with phosphoric acid in a solvent system.

The monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine is a crystalline and stable salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine and therefore has advantageous properties.

10 Additionally, the crystalline monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine can be used to introduce a crystalline intermediate in the process for the preparation of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine. This introduces a simple and convenient purification step in a reaction sequence where all other intermediates are syrups. Thereby, the time and energy consuming distillation used in
15 processes according to prior art is avoided. The crystallization of the monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine results in an intermediate of a high purity that can be further converted to the corresponding isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine by a simple alkalization step.

20 *Preparation*

In the preparation of the monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine the content of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine in ethyl acetate is first assayed and adjusted to 6-10 ml ethyl acetate per gram of isopropyl-
25 methyl-[2-(3-n-propoxyphenoxy)ethyl]amine. The content of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine in ethyl acetate is preferably 7-9 ml ethyl acetate per gram of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine. To the assayed solution of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine in ethyl acetate, methanol and a solution of phosphoric acid in methanol are added. The amount of phosphoric acid should

be around 0.9 to 1.0 molar equivalents, preferably 0.95 equivalents. The total amount of methanol added to the assayed solution should be adjusted to the amount of phosphoric acid used. The concentration of phosphoric acid in the resulting solution of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine in metanol/ ethyl acetate should be around 5-15%, by volume, preferably 9-11%, by volume. The precipitated salt is collected, for example by filtration or centrifugation, and thereafter washed with ethyl acetate.

The monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine can thereafter be further processed by processes known in the art, e.g. converted back to its basic form, *i.e.* isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine, by treatment of aqueous base.

Medical and pharmaceutical use

The monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine is useful because it possesses pharmacological activity and especially for the use as an anaesthetic compound. It is therefore indicated as a pharmaceutical, especially in the treatment of pain, including localised pain.

According to a further aspect of the invention there is thus provided the monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine for use as a pharmaceutical, especially in the treatment of pain.

Pharmaceutical Formulations

The monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine will normally be administered parenterally, especially injected in the form of pharmaceutical formulations comprising the active ingredient in a pharmaceutically acceptable dosage form. Compositions comprising the monophosphate salt of isopropyl-methyl-[2-(3-n-

propoxyphenoxy)ethyl]amine for parenteral administration may include other ingredients commonly used in the parenteral administration of pharmaceutically-active compounds.

According to a further aspect of the invention there is thus provided a pharmaceutical
5 formulation containing the monophosphate salt of isopropyl-methyl-[2-(3-n-propoxy-
phenoxy)ethyl]amine in admixture with a pharmaceutically acceptable adjuvant, diluent or
carrier. Formulations including the monophosphate salt of isopropyl-methyl-[2-(3-n-
propoxyphenoxy)ethyl]amine may be prepared by techniques which are known per se.
Usually the active substance will constitute between 0.5 and 10% by weight of the
10 preparation, more specifically between 1 and 5% by weight.

According to a further aspect of the present invention, there is provided a method for
treatment of a pain which method comprises administration of a therapeutically effective
amount of the monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)-
15 ethyl]amine to a person suffering from, or susceptible to pain.

The present invention is described in more detail in the following non-limiting examples

Examples

20 **Example 1. Preparation of the monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine**

To an assayed solution of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine (19.0 kg,
75.7 mol) in ethyl acetate (8 ml EtOAc/g isopropyl-methyl-[2-(3-n-propoxyphenoxy)-
ethyl]amine) is added MeOH (9.6 L) followed by H₃PO₄ (4.85 L, 72.5 mol) dissolved in
25 MeOH (19.2 L) over 3 hours at ambient temperature. The resulting slurry of the title
compound is then isolated by filtration and the solid material is washed with EtOAc. Yield
89% (41.8 kg wet compound, corresponds to 67.6 mol dry compound); Mp: 131-134°C.



Claims

1. A phosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine.
2. A monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine.
3. A process for the preparation of the monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine comprising the following steps:
 - i) adding phosphoric acid to a solution of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine in an organic solvent system;
 - ii) allowing the solution to crystallize;
 - iii) isolating the monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine thus obtained.
4. A process according to claim 3, characterized in that the organic solvent system used in step i) is ethyl acetate.
5. A process according to claim 3, characterized in that the phosphoric acid added in step i) is added as an alcoholic solution of phosphoric acid.
6. A process according to claim 5, characterized in that the alcoholic solution is a methanolic solution.
7. A process according to claim 3, characterized in that 0.9-1.0 equivalents of phosphoric acid is used in step i)
8. A process according to claim 3, characterized in that 0.95 equivalents of phosphoric acid is used in step i)



9. A process according to claim 3, characterized in that the concentration of phosphoric acid in the resultant solution after complete addition is between 5-15%, by weight.
10. A process according to claim 3, characterized in that the concentration of phosphoric acid in the resultant solution after addition should be between 9-11%, by weight.
11. A pharmaceutical formulation comprising the monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine and a pharmaceutically acceptable carrier or diluent.
12. Use of the monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)-ethyl]amine in therapy.
13. Use of the monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)-ethyl]amine in the manufacture of a medicament for treatment of pain.
14. The phosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine prepared by a process according to any of claims 3-10.
15. A method of treatment of pain which comprises administration of a therapeutically effective amount of the monophosphate salt of isopropyl-methyl-[2-(3-n-propoxyphenoxy)ethyl]amine to a patient suffering from pain.