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(54) Titre : METHODE AMELIOREE POUR LA PREPARATION D'OPIPRAMOL
(54) Title: IMPROVED METHOD FOR PREPARING OPIPRAMOL

(57) Abrégé/Abstract:
An improved method for preparing opipramol is disclosed, wherein iminostilbene is reacted with 1-bromo-3-chloropropane in the presence of a weak base selected from a hydrogen phosphate salt and an acetate salt and in the presence of a phase transfer agent to produce N-(3-halopropyl)iminostilbene, which is mixture of N-(3-chloropropyl)iminostilbene and N-(3-bromopropyl)iminostilbene, and then N-(3-halopropyl)iminostilbene is reacted with N-(2-hydroxyethyl)piperazine to form opipramol.

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(54) Title: PREPARATION OF N-(3-HALOPROPYL)IMINOSTILBENE AND ITS CONVERSION TO OPIPRAMOL

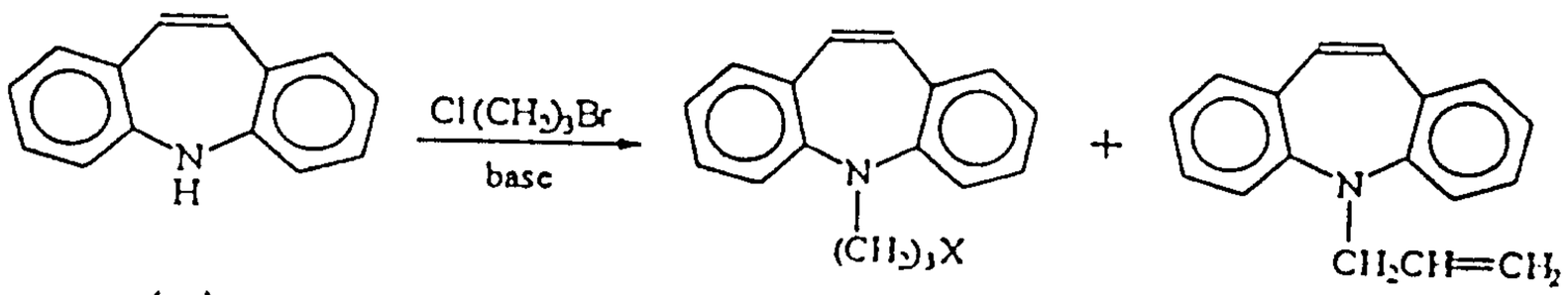
(57) Abstract

An improved method for preparing opipramol is disclosed, wherein iminostilbene is reacted with 1-bromo-3-chloropropane in the presence of a weak base selected from a hydrogen phosphate salt and an acetate salt and in the presence of a phase transfer agent to produce N-(3-halopropyl)iminostilbene, which is mixture of N-(3-chloropropyl)iminostilbene and N-(3-bromopropyl)iminostilbene, and then N-(3-halopropyl)iminostilbene is reacted with N-(2-hydroxyethyl)piperazine to form opipramol.

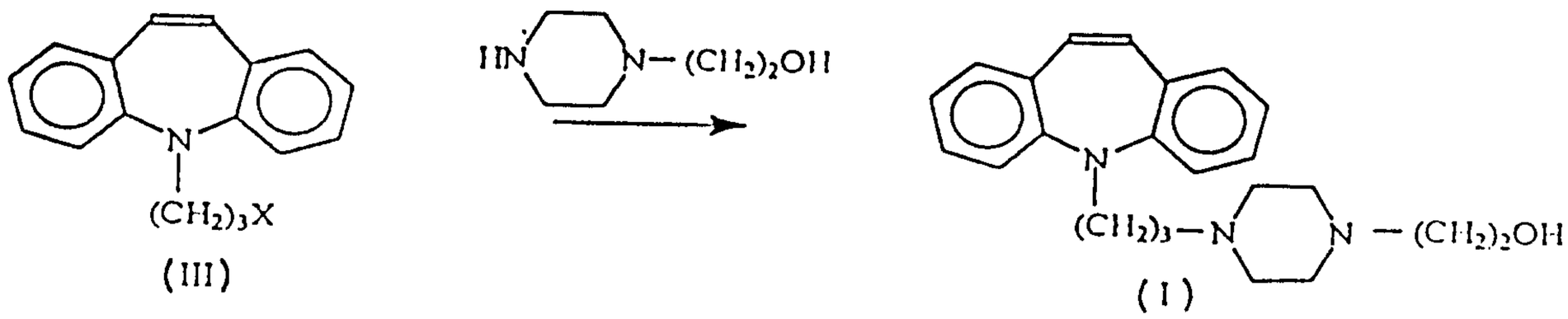
PREPARATION OF N-(3-HALOPROPYL)IMINOSTILBENE AND ITS CONVERSION TO OPIPRAMOL

This invention relates to an improved method of preparing opipramol which is an antipsychotic and antidepressant drug. More particularly, the invention is concerned with a method of converting iminostilbene also known as dibenzo[b,f]azepine into N-(3-halopropyl)-iminostilbene, a mixture of 3-chloro-and 3-bromopropyl derivatives, which is a precursor one step removed from opipramol.

In a known method of synthesizing opipramol of formula (I) hereinbelow, iminostilbene of formula (II) is used as starting material and is first alkylated with 1-bromo-3-chloropropane to yield N-(3-halopropyl)iminostilbene of formula (III), which is used in turn to alkylate N-(2-hydroxyethyl)piperazine at the secondary amine site to yield opipramol, as shown by the following equations:



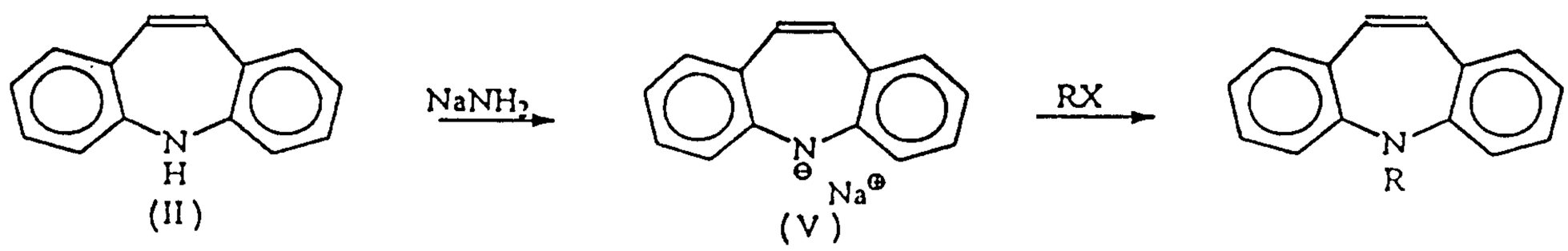
(II) (III) (IIIa)



(III) (I)

where X is chlorine or bromine.

According to German Patent No. 1133729, alkylation of iminostilbene of formula (II) requires the use of a strong base catalyst such as sodamide. Sodamide has been employed in non-aqueous media to convert iminostilbene of formula (II) into its anion of formula (V), which may then be alkylated, as shown by the following equations:



(II) (V)

where R is lower alkyl and X is halogen, preferably Br.

When R is free of base-sensitive groups, such a procedure is effective and efficient. However, when 1-bromo-3-chloropropane is the alkylating reagent, the desired product, N-(3-halopropyl)iminostilbene of formula (III) is converted by the strongly basic medium at least in part to the illustrated dehydrohalogenated by-product, N-allyl-iminostilbene of formula (IIIa), which is unsuitable for direct conversion to opipramol of formula (I).

It is therefore an object of the present invention to provide an improved method of preparing opipramol.

It is another object of the present invention to provide an improved method of preparing the immediate precursor, N-(3-halopropyl)iminostilbene, for use in the preparation of opipramol.

Surprisingly, it has been discovered that alkylation of iminostilbene of formula (II) can be carried out with

excellent results using a weak base selected from the group consisting of hydrogen phosphate salts of formula M_xHPO_4 and acetate salts of formula CH_3COOM, wherein M is an alkali metal, alkaline earth metal or ammonium and x is 1 or 2. Desirably, the alkylation is also carried out in the presence of a phase transfer agent.

According to the present invention, there is thus provided a method of preparing opipramol of formula (I), which comprises reacting iminostilbene of formula (II) with 1-bromo-3-chloropropane in the presence of a weak base of formula M_xHPO_4 or CH_3COOM, where M and x are as defined above, and a phase transfer agent to obtain N-(3-halopropyl)iminostilbene of formula (III) which is thereafter reacted with N-(2-hydroxyethyl)piperazine to yield opipramol of formula (I).

A particularly preferred method of preparing opipramol comprises the steps of:

a) reacting iminostilbene with 1-bromo-3-chloropropane in the presence of a weak base selected from the group consisting of hydrogen phosphate salts of formula M_xHPO_4 and acetate salts of formula CH_3COOM, wherein M and x are as defined above, in the presence of a phase transfer agent and in a substantially inert solvent, to form an N-(3-halopropyl)iminostilbene, which is a mixture of N-(3-bromopropyl)iminostilbene and N-(3-chloropropyl)iminostilbene;

b) separating any unreacted 1-bromo-3-chloropropane and any salt present from the reaction mixture;

c) reacting the thus formed N-(3-halopropyl)iminostilbene *in situ*, without isolation from the reaction mixture, with N-(2-hydroxyethyl)piperazine in the presence of a base to form opipramol; and

d) separating opipramol from the reaction mixture.

The present invention also provides, in another aspect thereof, a method of preparing N-(3-halopropyl)-iminostilbene, which comprises reacting iminostilbene with 1-bromo-3-chloropropane in the presence of a weak base selected from the group consisting of hydrogen phosphate salts of formula M_xHPO_4 and acetate salts of formula CH_3COOM, wherein M and x are as defined above, in the presence of a phase transfer agent and in a substantially inert solvent to obtain N-(3-halopropyl)iminostilbene.

With the use of a weak base of formula M_xHPO_4 or CH_3COOM and a phase transfer agent, the undesirable elimination of HX from N-(3-halopropyl)iminostilbene of formula (III) does not occur, thereby increasing the net yield of N-(3-halopropyl)iminostilbene, improving the efficiency of the process and avoiding the necessity of removing unwanted by-products.

As a weak base, phosphate salts are preferred and M is preferably sodium, potassium or ammonium.

According to the invention, the action of M_xHPO_4 and CH_3COOM is best achieved by heating the reactants in a solvent in the presence of the phase transfer agent. Useful phase transfer agents include quaternary ammonium salts; aryltrialkylammonium salts, such as benzyltriethylammonium chloride, are preferred. The phase transfer agent is used in a catalytically effective amount, preferably 3-10% by weight, based on the weight of iminostilbene.

Suitable solvents include those which are substantially inert to the reagents of the reaction, including alkylbenzenes such as toluene and also dimethylformamide, dimethylacetamide, isopropanol, butanol, and diethylene glycol; alkylbenzenes and particularly

toluene are preferred. The alkylation is preferably carried out at a temperature of 80-140°C, most preferably at 110°C.

1-Bromo-3-chloropropane and the weak base are each used in approximately stoichiometric equivalents or in excess of the amount required to alkylate iminostilbene of formula (II). The product of this alkylation, N-(3-halopropyl)iminostilbene of formula (III), is a mixture of N-(3-bromopropyl)iminostilbene and N-(3-chloropropyl)iminostilbene. The particular proportion of 3-chloro- and 3-bromopropyl derivatives is of no importance, since both compounds are readily converted to opipramol of formula (I) by reaction with N-[2-hydroxyethyl]piperazine.

In a preferred embodiment of the invention, the first step is carried out by heating a solution of iminostilbene of formula (II) containing 1-bromo-3-chloropropane and disodium hydrogen phosphate in the presence of a catalytic amount of benzyltriethylammonium chloride. After removal of salts by washing and any excess unreacted 1-bromo-3-chloropropane by co-distillation with a higher boiling solvent, N-(3-halopropyl)iminostilbene of formula (III) in the resultant solution is converted without further isolation into opipramol of formula (I) by reaction *in situ* with N-[2-hydroxyethyl]piperazine.

The reaction of N-(3-halopropyl)iminostilbene of formula (III) with N-[2-hydroxyethyl]piperazine is preferably carried out with an excess of N-[2-hydroxyethyl]piperazine at a temperature of about 50° to 150°C, most preferably at about 110°C, in the presence of a base until the alkylation is substantially complete. The mole ratio of N-(3-halopropyl)iminostilbene of formula (III) to N-[2-hydroxyethyl]piperazine is preferably about 1:1 to 1:3, and most preferably about 1:2. A weak base, such as

sodium carbonate or potassium carbonate is preferred and is used in amounts effective to achieve reaction between iminostilbene of formula (III) and N-[2-hydroxy-ethyl]piperazine.

The following non-limiting examples illustrate the invention.

EXAMPLE 1

Preparation of N-(3-Halopropyl)iminostilbene

To a stirred solution of 360 g (2.185 moles) of 1-bromo-3-chloropropane in 750 ml of toluene, 150 g (0.777 moles) of iminostilbene, 270 g (1.9 moles) of disodium hydrogen phosphate and 7.5 g of benzyltriethylammonium chloride are added. The resulting mixture is heated to reflux until the reaction is substantially complete, which requires about 18 hours, as shown by tlc (petroleum ether : ether, 96:4); about 95% of iminostilbene is consumed.

After the reaction mixture is cooled to room temperature, solids are removed from the reaction mixture by filtration and washed with toluene. The toluene and excess 1-bromo-3-chloropropane are removed by distillation under vacuum to a temperature of about 100°C; 150 ml of Isopar G, a high boiling hydrocarbon, are added to the residue and distillation under vacuum is continued to about 100°C. The residue is cooled and 450 ml of toluene are added to provide a crude solution of N-(3-halopropyl)iminostilbene.

EXAMPLE 2

Preparation of Opipramol

N-(3-halopropyl)iminostilbene in a toluene solution, as prepared in Example 1, in an amount of 600 ml is mixed with

150 g of N-(2-hydroxyethyl)piperazine and 50 g of sodium carbonate and then heated slowly to 110°C, while CO_2 evolves. The reaction mixture is heated to reflux for another 16 hours, after which the mixture is cooled to 80°C; 400 ml water are added, mixed and then separated from the toluene layer. The toluene layer is cooled to 30-40°C and 500 ml of a 1.5 N aqueous solution of HCl or H_2SO_4 is mixed with the toluene layer; the aqueous layer is separated; the extraction is repeated with an additional 100 ml of the acidic solution and the aqueous extracts are combined. Toluene in an amount of 600 ml is added to the combined aqueous extracts; the mixture is heated to 50°C and ammonium or sodium hydroxide is added until a pH≥9. The mixture is agitated for 1/2 hour at 60-70°C, after which the toluene layer is separated and washed with 100 ml of water and then dried by azeotropic distillation. The toluene layer is then cooled to 0-10°C and centrifuged to obtain the solid product, opipramol. Additional product is obtained by concentrating the toluene residue to about 1/4 of its initial volume and cooling to 0-10°C. The total amount of product obtained is 215 g, having a m.p. of 96°C.

Opipramol can be further purified by dissolving 200 g of the opipramol thus obtained in 600 ml of acetone, mixing 7 g of active carbon and 5 g of CELITE* into the solution, filtering and then cooling the solution to 0-10°C and finally collecting the purified product on a centrifuge. The m.p. of the purified product is 101°C.

* Trade-mark

THE EMBODIMENTS OF THE INVENTION IN WHICH AN EXCLUSIVE PROPERTY OR PRIVILEGE IS CLAIMED ARE DEFINED AS FOLLOWS:

1. A process for the preparation of opipramol comprising

a) reacting iminostilbene with 1-bromo-3-chloropropane in the presence of a weak base selected from a hydrogen phosphate salt of the formula M_xHPO_4, wherein M is an alkali metal, alkaline earth metal or ammonium and x is 1 or 2 depending on the valence of M, and an acetate salt of the formula CH_3COOY, wherein Y is an alkali metal or ammonium, in the presence of a catalytically effective amount of a compatible phase transfer agent and in a solvent inert to the reagents in the reaction, to form a N-(3-halopropyl)iminostilbene, which is a mixture of N-(3-bromopropyl)iminostilbene and N-(3-chloropropyl) iminostilbene;

b) separating any unreacted 1-bromo-3-chloropropane and any salt present from the reaction mixture;

c) reacting the thus formed N-(3-halopropyl)iminostilbene *in situ*, without isolation from the reaction mixture, with N-(2-hydroxyethyl)piperazine in the presence of a base to form opipramol; and

d) separating opipramol from the reaction mixture.

2. The process according to claim 1 wherein the weak base is a hydrogen phosphate salt of the formula Na_2HPO_4 or K_2HPO_4.

3. The process according to claim 1 in which the phase transfer agent is a quaternary ammonium chloride.

4. The process according to claim 1 in which the phase transfer agent is benzyltriethylammonium chloride.

5. The process according to claim 1 in which the reaction of iminostilbene with 1-bromo-3-chloropropane is carried out at a temperature of about 80°-140°C.

6. The process according to claim 1 in which said 1-bromo-3-chloropropane and said weak base are each present in an amount equal to or greater than their stoichiometric equivalents based on the amount of iminostilbene in the reaction.

7. The process according to claim 1 in which the reaction of iminostilbene with 1-bromo-3-chloropropane is carried out at a temperature of about 80°-140°C, the hydrogen phosphate salt is Na_2HPO_4 or K_2HPO_4, the phase transfer agent is benzyltriethylammonium chloride and the solvent is toluene.

8. The process according to claim 1 in which the reaction of N-(3-halopropyl)-iminostilbene with N-(2-hydroxyethyl)-piperazine is carried out with an excess of N-(2-hydroxyethyl)-piperazine at a temperature of about 50° to 150°C in the presence of a weak base.

9. The process according to claim 1 in which the phase transfer agent is a quaternary ammonium salt.

10. The process according to claim 1 in which the mixture of N-(3-halopropyl) iminostilbene formed by the first reaction step is essentially free of N-allyl-iminostilbene.