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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification [6] : **C07D 223/22, 223/26**	**A1**	**(11) International Publication Number:** **WO 96/15113** **(43) International Publication Date:** 23 May 1996 (23.05.96)

(21) International Application Number: PCT/US95/14320

(22) International Filing Date: 9 November 1995 (09.11.95)

(30) Priority Data:
08/336,837 9 November 1994 (09.11.94) US

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(81) Designated States: AL, AM, AU, BB, BG, BR, BY, CA, CH, CN, CZ, EE, FI, GE, HU, IS, JP, KG, KP, KR, KZ, LK, LR, LT, LV, MD, MG, MK, MN, MX, NO, NZ, PL, RO, RU, SG, SI, SK, TJ, TM, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, LS, MW, SD, SZ, UG).

Published
With international search report.

(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.

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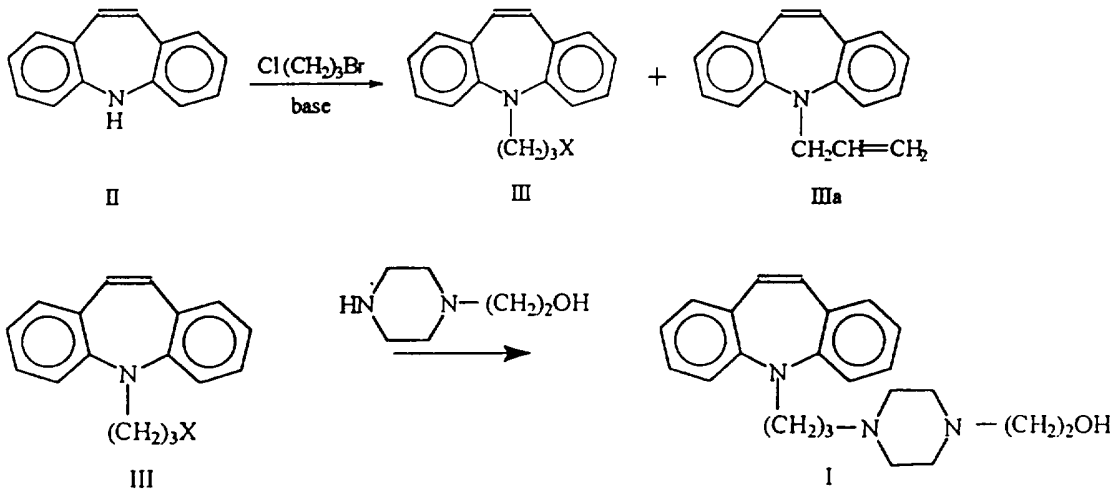
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PREPARATION OF N-(3-HALOPROPYL)IMINOSTILBENE AND ITS CONVERSION TO OPIPRAMOL

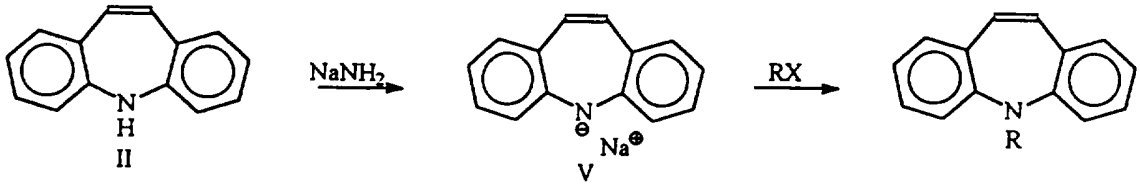
Background of Invention

This invention is concerned with a novel and improved method for preparing the antipsychotic and antidepressant drug, opipramol (I). More particularly, this invention is concerned with a novel method for converting iminostilbene (II), 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(I).

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



According to German Patent 1133729, alkylation of iminostilbene (II) requires the use of a strong base catalyst, such as sodamide. Sodamide has been employed in non-aqueous media, to convert iminostilbene (II) into its anion (V), which may then be alkylated, a shown by the equations below.



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 (III) is converted by the strongly basic medium, at least in part, to the illustrated dehydrohalogenated by-product, N-allyl-iminostilbene (IIIa), which is unsuitable for direct conversion to opipramol (I).

Summary of the Invention

The object of this invention is a new and improved method for the preparation of opipramol.

Another object of the invention is a new and improved method for the preparation of the immediate precursor, N-(3-halopropyl)-iminostilbene, in the preparation of opipramol.

These and other objects are achieved by the invention described below.

Surprisingly, it has been discovered that alkylation of iminostilbene (II) can be carried out with excellent results using a weak base, selected from a phosphate of the formula, M_xHPO_4 (IV), or an acetate of the formula, CH_3COOM (IVa), wherein M is an alkali metal, alkaline earth metal or ammonium and x is 1 or 2, determined by the valence of M. Desirably, the alkylation is also carried out in the presence of a phase transfer agent.

According to the invention, iminostilbene (II) is alkylated with 1-bromo-3-chloropropane in the presence of a weak base of the formula M_xHPO_4 (IV) or CH_3COOM (IVa), where M and x are as defined above, and a phase transfer agent, and the resultant N-(3-halopropyl)iminostilbene (III) is reacted with N-(2-hydroxyethyl)-piperazine to yield opipramol (I).

Description of the Invention

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

As the weak base, phosphate salts (IV) are preferred and M is preferably sodium, potassium or ammonium in formulas (IV) and (IVa).

According to the invention, the action of M_xHPO_4 (IV) and CH_3COOM (IVa) is best achieved by heating the reactants in a solvent in the presence of a phase transfer agent. Useful phase transfer agents include quaternary ammonium salts; aryltrialkyl-ammonium 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.

Solvents suitable for the first step of the process include those substantially inert to the reagents of the reaction, which include alkylbenzenes, such as toluene, and also dimethyl-formamide, 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 (IV) or (IVa) are each used in approximately stoichiometric equivalents or in excess of the amount required to alkylate iminostilbene (II). The product of this alkylation, N-(3-halopropyl)iminostilbene (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 (I) by reaction with N-[2-hydroxyethyl]-piperazine.

In a preferred embodiment of the invention, the first step of the process is carried out by heating a solution of iminostilbene (II) containing 1-bromo-3-chloropropane and disodium hydrogen phosphate in the presence of a catalytic amount of benzyltriethyl-ammonium 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 (III) in the resultant solution is converted without further isolation into opipramol (I) by reaction *in situ* with N-[2-hydroxyethyl]-piperazine.

The reaction of N-(3-halopropyl)iminostilbene (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 (III) to N-[2-hydroxy-ethyl]-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 amount effective to achieve reaction between iminostilbene (III) and N-[2-hydroxyethyl]-piperazine.

The following examples further illustrate the best mode currently contemplated for carrying out the invention, but the illustrative examples must not be construed as limiting the invention in any manner.

EXAMPLE 1

Preparation of N-(3-Halopropyl)iminostilbene (III)

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 (I), 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 (I) 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 (III).

EXAMPLE 2

Preparation of Opipramol (I)

N-(3-halopropyl)iminostilbene (III) 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 (I). 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 (I) can be further purified by dissolving 200 g of the above-obtained opipramol (I) 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.

What we desire to claim and protect by Letters Patent is:

1. A method for the preparation of N-(3-halopropyl)-iminostilbene, which is mixture of N-(3-chloropropyl)-iminostilbene and N-(3-bromopropyl)iminostilbene, comprising 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 and an acetate salt of the formula CH_3COOM, wherein M is an alkali metal, alkaline earth metal or ammonium and x is 1 or 2, depending on the valence of M, in the presence of a phase transfer agent and in a solvent substantially inert to the reaction reagents and removing solvent, any excess 1-bromo-3-chloropropane and solids present in the reaction mixture to obtain N-(3-halopropyl)iminostilbene.

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 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 is carried out at a temperature of about 80-140°C, the weak base is Na_2HPO_4 or K_2HPO_4, the phase transfer agent is benzyltriethyl-ammonium chloride and the solvent is toluene.

8. A process for the preparation of opipramol comprising

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 and an acetate salt of the formula CH_3COOM, wherein M is an alkali metal, alkaline earth metal or ammonium and x is 1 or 2 depending on the valence of M, in the presence of a phase transfer agent and in a solvent inert to the reagents in the reaction, to form a N-(3-halopropyl)iminostilbene, which is a a mixture of N-(3-bromopropyl)iminostilbene and N-(3-chloropropyl)iminostilbene;

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

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

separating opipramol from the reaction mixture.

9. The process according to claim 8 wherein the weak base is a hydrogen phosphate salt of the formula Na_2HPO_4 or K_2HPO_4.

10. The process according to claim 8 in which the phase transfer agent is a quaternary ammonium chloride.

11. The process according to claim 8 in which the phase transfer agent is benzyltriethylammonium chloride.

12. The process according to claim 8 in which the reaction of iminostilbene with 1-bromo-3-chloropropane is carried out at a temperature of about 80-140°C.

13. The process according to claim 8 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.

14. The process according to claim 8 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 benzyltriethy-ammonium chloride and the solvent is toluene.

15. The process according to claim 8 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.

INTERNATIONAL SEARCH REPORT

Inter nal Application No
PCT/US 95/14320

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D223/22 C07D223/26

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	DE,B,11 33 729 (J.R. GEIGY A.-G.) 26 July 1962 cited in the application see the whole document ---	1-15
A	JOURNAL OF HETEROCYCLIC CHEMISTRY, vol. 19, 1982 PROVO, US, pages 1569-71, I. GOZLAN ET AL. 'Phase transfer catalysis in N-alkylation of the pharmaceutical intermediates 5H-Diben[b,f]azepine and 5H-10,11-dihydrodibenz[b,f]azepine' see the whole document --- -/--	1-15

[X] Further documents are listed in the continuation of box C.

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Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SYNTHESIS, no. 1, January 1984 STUTTGART, DE, pages 29-31, S.J. SCHMOLKA ET AL. 'N-dimethylaminopropylation in a solid-liquid two phase system: synthesis of chlorpromazine, its analogs, and related compounds' see the whole document	1-15

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INTERNATIONAL SEARCH REPORT

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
DE-B-1133729		CH-A- 359143 CH-A- 360061 CH-A- 364263	