A PROCESS FOR PURIFICATION OF 7-(4-BROMOBOETOXY)-3,4-DIHYDROCARBOSTYRIL, AN INTERMEDIATE FOR MANUFACTURE OF ARIPIRAZOLE
FIELD OF THE INVENTION

The present invention is directed to a process for purification of 7-(4-bromobutoxy)-3,4-dihydrocarbostyril of formula (I),

\[
\text{(I)}
\]

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to make essentially free of impurities, predominantly the dimer impurity of formula (II)

\[
\text{(II)}
\]

15
The compound of formula I is an intermediate in the synthesis of aripiprazole of following formula:

\[
\text{(V)}
\]
BACKGROUND OF THE INVENTION

7-{4-[4-(2,3-dichlorophenyl)-1-piperazinyl] butoxy}-3,4-dihydro-2(1H)-quinolinone [CAS no 129722-12-9] of formula (V) generically called aripiprazole, is used for treating schizophrenia (EP 0 367 141) and is also used as an antipsychotic agent [J. Med. Chem., Vol. 41, 99 658-667 (1998)].

EP 0 367 141 discloses a process for preparing aripiprazole by reaction of carbostyril represented by the general formula (III)

![Formula III](image)

wherein \(X_i\) is a halogen atom or a group which can act as a substrate to carry out a nucleophilic substitution reaction, with the piperazine moiety represented by formula (IV)

![Formula IV](image)

The compound of formula III (wherein \(X_i\) is bromine) is chemically known as 7-(4-bromobutoxy)-3,4-dihydrocarbostyril, represented by formula (I).
Reference example 6 of EP '141 gives condition for synthesis of 7-(4-bromobutoxy)-3,4-dihydrocarbostyril, wherein the purification of the crude product is carried out by means of silica gel chromatography (eluent: dichloromethane) and recrystallised from n-hexane-ethanol. Impurity present in the crude are not identified or mentioned in the patent.

The present inventors reproduced the process of EP'141 and analyzed the product, and found that in spite of purification / recrystallisation, the product still contained the dimer impurity of formula II. Because of the low yield due to impurities and a tedious purification using column chromatography, the process described in the EP '141 is not economically viable for industrial application.

US 2006/0079689 A1 provides processes for synthesis of 7-(4-halobutoxy)-3,4-dihydro- (1H)-quinolinone, which is subsequently converted to aripiprazole. This application, for the first time discloses in detail the impurities associated with the crude 7-(4-halobutoxy)-3,4-dihydro- (1H)-quinolinone. The impurities identified in the application are:

a) 1,4-bis [3,4-dihydro-2 (1H)-quinolinone-7-oxy] butane of formula (II)
b) N-(4-bromobutyl)-7-hydroxy-3, 4-dihydro-2 (I H)-quinolinone

c) N-(4-bromobutyl)-7-(4-butoxy)-3,4-dihydro-2 (IH)-quinolinone.

The process described in US 2006/0079689 for preparation of the 7- (4-bromobutoxy)-3,4-dihydrocarbostyril comprises reaction of 7-hydroxy quinolinone with a 1,4-disubstituted butane, wherein the substitutions are from the group consisting of chlorine, bromine, iodine, and sulfonate; in a heterogeneous biphasic mixture containing water immiscible organic solvent, water soluble base with optional addition of water and a phase transfer catalyst.

This invention provides a process for purification of 7- (4-bromobutoxy)-3,4-dihydrocarbostyril by using various organic solvents like ethyl acetate, isopropyl acetate, toluene, xylene, chloroform, acetonitrile, acetone, methanol, isopropanol etc. The above method gives 7- (4-bromobutoxy)-3,4-dihydrocarbostyril containing dimer impurity of the range 1.5-6.1 % which is initially 4.5-15% in the reaction mixture.

Another method for synthesis of 7- (4-bromobutoxy)-3,4-dihydrocarbostyril is described in Journal of Medicinal Chemistry, 1998, Vol. 41, No. 5, 658-667. The crude product obtained herein is crystallized from ethanol. The inventors of the present invention, when repeated the same process observed that the reaction hardly proceeds even after 22 hours of the reaction 82% of the reactant was recovered.
Thus there is need for a process to produce pure 7-(4-bromobutoxy)-3,4-dihydrocarbostyril, which will consecutively lead to pure and economical synthesis of Aripiprazole.

**OBJECT OF THE INVENTION**

Thus the object of the present invention is to provide a process for purification of 7-(4-bromobutoxy)-3,4-dihydrocarbostyril, an intermediate for synthesis of aripiprazole.

**SUMMARY OF THE INVENTION**

Accordingly, there is provided a process for the purification of 7-(4-bromobutoxy)-3,4-dihydrocarbostyril, substantially free of dimer impurity, said process comprising the steps:

1. Providing a solution of crude 7-(4-bromobutoxy)-3,4-dihydrocarbostyril containing the dimer impurity in an organic solvent selected from halogenated hydrocarbon solvent, aromatic hydrocarbon, alcohols, alkyl esters of C1-C4 alkanoic acids, ethers, diethyl ester and ketones.
2. Converting to a salt by the addition of an inorganic acid,
3. Separation of 1,4-bis [3,4-dihydro-2 (1H)-quinolinone-7-oxy] butane salt (dimer impurity salt) from the mixture, based on the difference in at least one physical property of 7-(4-bromobutoxy)-3,4-dihydrocarbostyril salt and the salt of dimer impurity,
4. Liberating the 7-(4-bromobutoxy)-3,4-dihydrocarbostyril salt by treating with an inorganic base,
5. Precipitating 7-(4-bromobutoxy)-3,4-dihydrocarbostyril by adding an anti-solvent.
DETAILED DESCRIPTION OF THE INVENTION
The present invention provides a process for purification of 7-(4-bromobutoxy)-3,4-dihydrocarbostyril, which is an intermediate for synthesis of aripiprazole. The crude 7-(4-bromobutoxy)-3,4-dihydrocarbostyril was obtained as per an example of US 2006/0079689. The impurity characterized in the crude was the dimer 1,4-bis [3,4-dihydro-2 (1H)-quinolinone-7-oxy] butane of formula (II). The intermediate if not purified would lead to aripiprazole with higher impurity levels, which would require number of purification, resulting in the yield loss of the final product.

The formation of the dimer impurity is explained in the following reaction sequence:

The 7-hydroxy 3,4-dihydrocarbostyril (VI) when reacts with 1,4-dibromo butane (VII) gives the 7-(4-bromobutoxy)-3,4-dihydrocarbostyril (I), its bromo group further reacts with hydroxy group of another molecule of 7-hydroxy 3,4-dihydrocarbostyril to give 1,4-bis [3,4-dihydro-2(1 H)-quinolinone-7-oxy] butane, i.e. the dimer impurity of formula (II).

As the formation of product increases in the reaction, the rate of formation of the dimer impurity also increases, it was difficult to control the formation of the impurity
in the reaction, so a method for purification of the intermediate 7- (4-bromobutoxy)-3,4-dihydrocarbostyril (I), had to be developed.

The purification of intermediate 7- (4-bromobutoxy)-3,4-dihydrocarbostyril (I) was done taking advantage of difference in physical properties of corresponding salts of 7- (4-bromobutoxy)-3,4-dihydrocarbostyril (I) and the dimer impurity (II).

The inventors found that when the reaction mixture containing 7- (4-bromobutoxy)-3,4-dihydrocarbostyril (I) and the dimer impurity was treated with an inorganic acid in an organic solvent, corresponding salt of 7- (4-bromobutoxy)-3,4-dihydrocarbostyril (I) remained in the solution whereas corresponding salt of the dimer impurity was insoluble in the said solvent and was precipitated. The salt of impurity was separated.

Organic solvent suitable for the purpose of the invention was selected from group of halogenated hydrocarbon solvent, aromatic hydrocarbon like toluene, alcohols like methanol, ethanol, alkyl esters of C₁-C₄ alkanoic acids, ethers such as diisopropyl ether, diethyl ester and ketones such as acetone.

The inorganic acid suitable for the purpose of the invention was selected from the group of hydrochloric acid, sulphuric acid and the like.

7- (4-bromobutoxy)-3,4-dihydrocarbostyril (I) was liberated from its salt by treating with an inorganic base selected from potassium carbonate / bicarbonate or its equivalent.

7- (4-bromobutoxy)-3,4-dihydrocarbostyril (I) was isolated using antisolvent like hexane or cyclohexane.
(4-bromobutoxy)-3,4-dihydrocarbostyril (I) obtained has HPLC purity of at least 97% and contains not more than 0.5% of 1,4-bis [3,4-dihydro 2 (1H)-quinolinone-7-oxy] butane of formula (II).

The HPLC parameters were as follows:
Column: Agilent Zorbax XDB C-18 (4.6 X 150 mm), 5 µm
Flow rate: 1.5 mL/minute.
Detector: UV at 220 nm.

Buffer preparation:
A homogenous mixture of 0.2% (v/v) triethylamine in HPLC grade water is prepared.

Mobile phase-A:
A homogenous mixture buffer and acetonitrile (95:5) is prepared. pH of the solution is adjusted to 4.0 with phosphoric acid. Filtered and degased.

Mobile phase-B:
A homogenous mixture buffer and acetonitrile (25:75) is prepared. pH of the solution is adjusted to 4.0 with phosphoric acid. Filtered and degased.

The invention is illustrated by the following non limiting examples:

Example 1
A mixture of 7-hydroxy 3,4-dihydrocarbostyril (50g, 0.306 mole, 1 eq.), anhydrous potassium carbonate (50.7 g, 0.367 mole, 1.2 eq.) in acetonitrile (750 ml) was heated under reflux for 2 hours, the hot reaction mixture cooled to 25-30°C A mixture of dibromo butane (200g, 0.926 mole, 3.02 eq.), tetrabutylammonium iodide (2.2g, 0.006 mole, 0.02 eq.) in acetonitrile (250 ml) was heated under reflux for 15 min, the
above potassium salt of 7-hydroxy 3,4-dihydrocarbostyril added to it. The resultant mixture was heated under reflux for 2-4 hrs, monitored by HPLC till 7-hydroxy 3,4-dihydrocarbostyril is present less than 1.0%, (the reaction mixture contained 14-15 % of the dimer impurity), mixture was cooled to 25-30°C, filtered, residue washed with acetonitrile (250 ml), the filtrate was concentrated, dichloromethane (750 ml) was added to it, Hydrogen chloride gas was purged into it, the filtrate was monitored by HPLC for dimer content to be less than 0.5 %, carbon (5g) was added to the solution, filtered through celite bed. water (250 ml) was added to the filtrate, pH of the solution was adjusted to 6.8-7.5 using 20% potassium carbonate solution, the organic layer separated, washed with water (250 ml), washed with 20% brine solution (250 ml). The organic layer further concentrated, cyclohexane (500 ml) was added to it, stirred for 15 minutes, then cooled to 5-10°C, the solid was filtered, washed with cyclohexane (100 ml), dried under vacuum at 40-45°C, for 5-6 hours, to give 7-(4- Bromo butoxy)-3,4-dihydro carbostyril (62 g, yield 66%, purity by HPLC 97.4 %, dimer impurity 0.28%).

Example 2
A mixture of 7-hydroxy 3,4-dihydrocarbostyril (50g, 0.306 mole, 1 eq.), anhydrous potassium carbonate (50.7 g, 0.367 mole, 1.2 eq.) in acetonitrile (750 ml) was heated under reflux for 2 hours, the hot reaction mixture cooled to 25-30°C A mixture of dibromo butane (200g, 0.926 mole, 3.02 eq.), tetrabutylammonium iodide (2.2g, 0.006 mole, 0.02eq.) in acetonitrile (250 ml) was heated under reflux for 15 min, the above potassium salt of 7-hydroxy 3,4-dihydrocarbostyril added to it. The resultant mixture heated under reflux for 2-4 hrs, monitored by HPLC till 7-hydroxy 3,4-dihydrocarbostyril is present less than 1.0%, (the reaction mixture contained 14-15 % of the dimer impurity), mixture was cooled to 25-30°C, filtered, residue washed with acetonitrile (250 ml), the filtrate was concentrated, dichloromethane (750 ml) was added to it, sulphuric acid (55g) was added to it, the filtrate was monitored by HPLC for dimer content to be less than 0.5 %, carbon (5g) was added to the
solution, filtered through celite bed. Water (250 ml) was added to the filtrate, pH of the solution was adjusted to 6.8-7.5 using 20% potassium carbonate solution, the organic layer separated, washed with water (250 ml), washed with 20% brine solution (250 ml). The organic layer further concentrated, cyclohexane (500 ml) was added to it, stirred for 15 minutes, then cooled to 5-10°C, the solid was filtered, washed with cyclohexane (100 ml), dried under vacuum at 40-45°C, for 5-6 hours, to give 7-(4- Bromo butoxy)-3,4-dihydro carbostyril (52 g, yield 55%, purity by HPLC 98.05 %, dimer impurity 0.08%).
CLAiMS

1. A process for the purification of 7-(4-bromobutoxy)-3,4-dihydrocarbostyril, substantially free of dimer impurity, said process comprising the steps:
   i) providing a solution of crude 7-(4-bromobutoxy)-3,4-dihydrocarbostyril containing the dimer impurity in an organic solvent selected from the group of halogenated hydrocarbon solvent, aromatic hydrocarbon, alcohols, alkyl esters of CrC₄ alkanoic acids, ethers, diethyl ester and ketones
   ii) converting to a salt by the addition of an inorganic acid,
   iii) separation of 1,4-bis [3,4-dihydro-2 (1H)-quinolinone-7-oxy] butane salt (dimer impurity salt) from the mixture, based on the difference in at least one physical property of 7-(4-bromobutoxy)-3,4-dihydrocarbostyril salt and the salt of dimer impurity,
   iv) liberating the 7-(4-bromobutoxy)-3,4-dihydrocarbostyril salt by treating with an inorganic base,
   v) precipitating 7-(4-bromobutoxy)-3,4-dihydrocarbostyril by adding an anti-solvent.

2. A process according to claim 1, wherein the separation of the salts is based on the difference in solubility.

3. A process according to claim 1, wherein organic solvent used for providing the solution of crude 7-(4-bromobutoxy)-3,4-dihydrocarbostyril is selected from dichloromethane, toluene, methanol, ethanol, diisopropyl ether, acetone.

4. A process according to claim 3 wherein the organic solvent used for providing the solution of crude 7-(4-bromobutoxy)-3,4-dihydrocarbostyril is dichloromethane.

5. A process according to claim 1, wherein inorganic acid is hydrochloric acid.
6. A process according to claim 1, wherein inorganic acid is sulphuric acid.

7. A process according to claim 1, wherein inorganic base used is potassium carbonate.

8. A process according to claim 1, wherein anti-solvent is cyclohexane or hexane.

9. A process according to claim 1 wherein 7-(4-bromobutoxy)-3,4-dihydrocarbostyril (I) has purity of at least 97% and contains not more than 0.5% of dimer impurity 1,4-bis [3,4-dihydro 2 (1H)-quinolinone-7-oxy] butane of formula (II).
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D401/12 A61K31/496

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

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)
EPO-Internal , CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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<td>WO 2006/079549 A (SANDOZ AG [CH]); LUDESTCHER JOHANNES [AT]; STURM HUBERT [AT]) 3 August 2006 (2006-08-03) page 8, paragraph 3</td>
<td>1-9</td>
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<tr>
<td>A</td>
<td>WO 2006/038220 A (SUVEN LIFESCIENCES LTD IN); CHINNAPILLAI RAJENDIRAN RAJEND [IN]; ARAV 13 April 2006 (2006-04-13) the whole document</td>
<td>1-9</td>
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<td>A</td>
<td>WO 2004/099152 A (DELMAR CHEMICALS INC CA); SALAMA PAUL [CA]; MEUNIER JEAN-FRANCOIS [CA] 18 November 2004 (2004-11-18) the whole document</td>
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X Further documents are listed in the continuation of Box C

A1 document defining the general state of the art which is not considered to be of particular relevance
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Date of the actual completion of the international search
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