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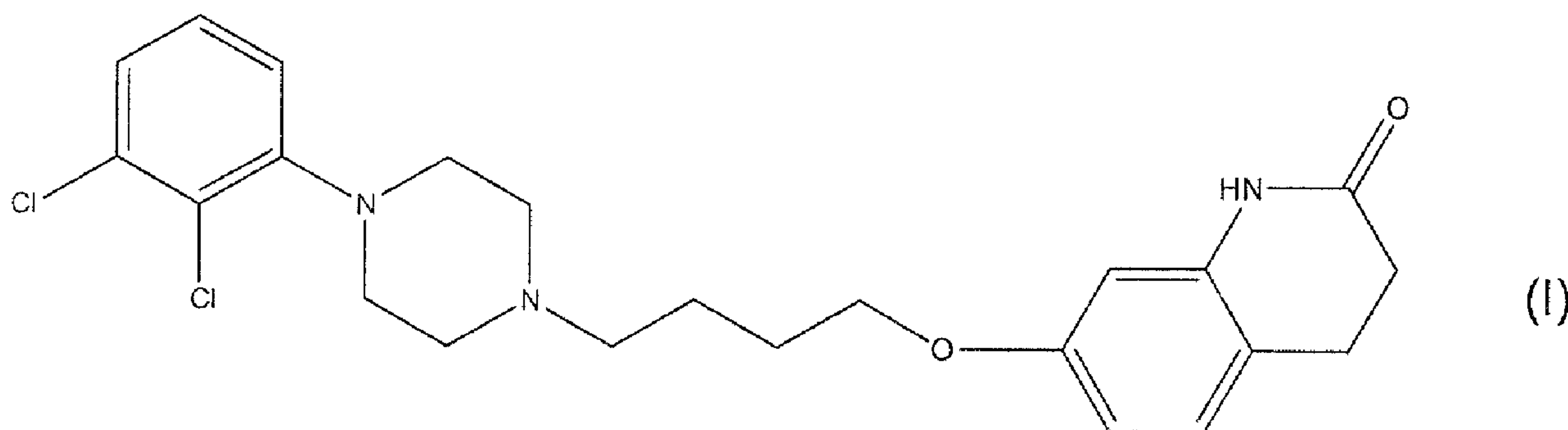
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(54) Titre : PROCEDE DE PREPARATION DE DERIVES DE CARBOSTYRIL

(54) Title: PROCESS FOR THE PREPARATION OF CARBOSTYRIL DERIVATIVES



(57) Abrégé/Abstract:

A process for preparing carbostyryl derivatives such as aripiprazole is described. Dichlorophenylpiperazine or an acid addition salt thereof is reacted with a compound of formula $X-C_4H_8-Y$ or $X-C_4H_6-Y$ to produce a novel quaternary spiro ammonium salt intermediate which is optionally isolated and purified. The quaternary spiro ammonium salt intermediate is reacted with 7-hydroxydihydrocarboxystyryl to produce the carbostyryl derivative.

ABSTRACT

A process for preparing carbostyryl derivatives such as aripiprazole is described. Dichlorophenylpiperazine or an acid addition salt thereof is reacted with a compound of formula $X-C_4H_8-Y$ or $X-C_4H_6-Y$ to produce a novel quaternary spiro ammonium salt intermediate which is optionally isolated and purified. The quaternary spiro ammonium salt intermediate is reacted with 7-hydroxydihydrocarboxystyryl to produce the carbostyryl derivative.

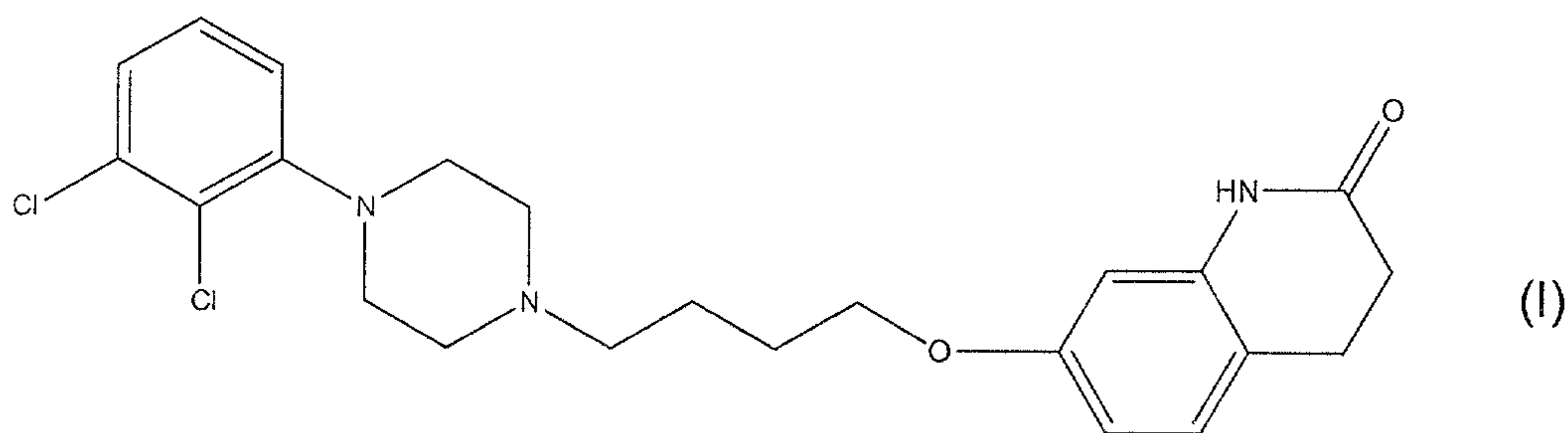
PROCESS FOR THE PREPARATION OF CARBOSTYRIL DERIVATIVES

FIELD OF THE INVENTION

The invention relates to novel processes and intermediates for preparing carbostyryl derivatives, and more particularly relates to processes and intermediates for preparing aripiprazole and derivatives thereof.

BACKGROUND OF THE INVENTION

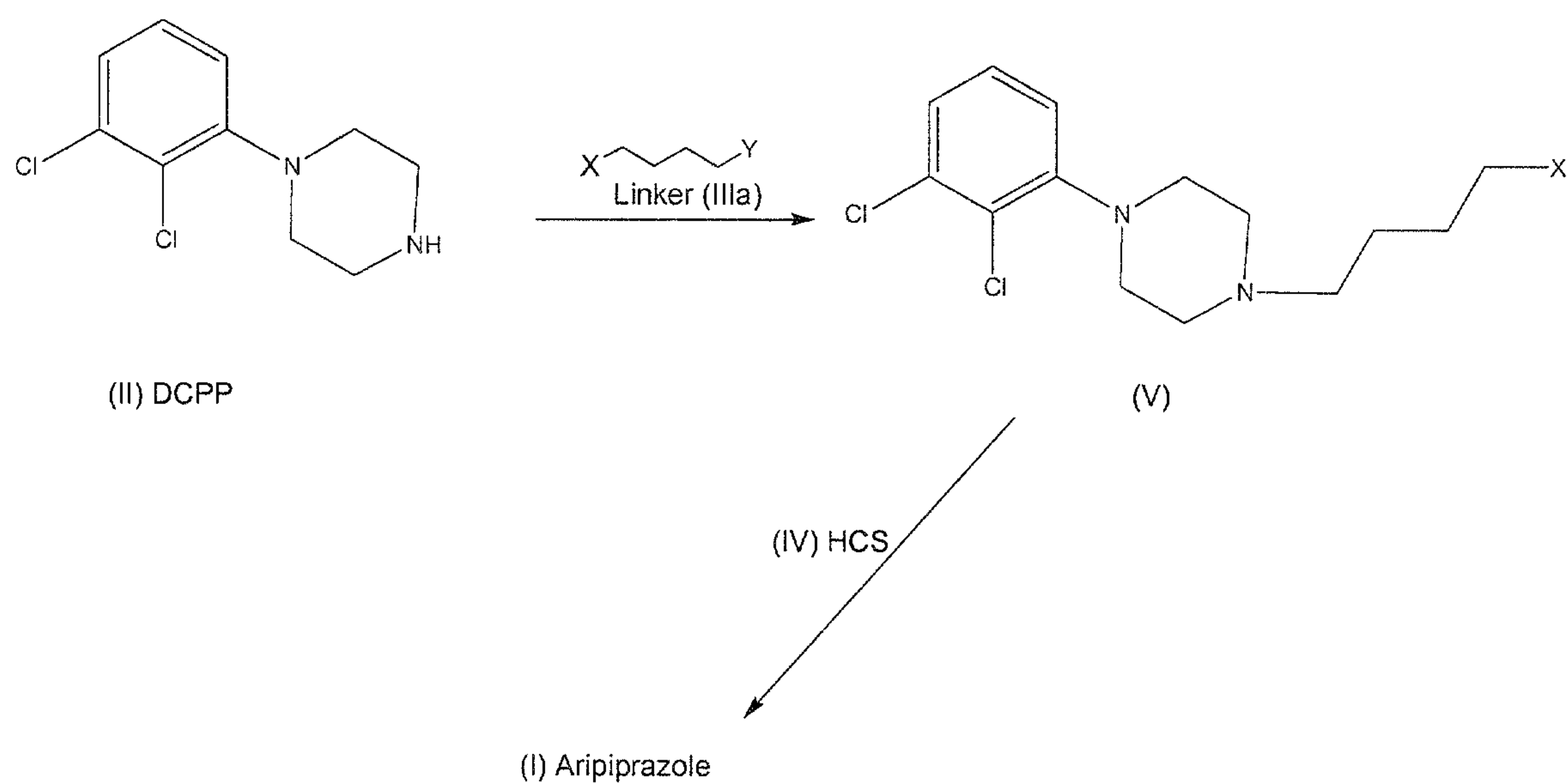
U.S. Patent No. 5,006,528 (Oshiro et al.) discloses a number of novel carbostyryl derivatives and methods for their preparation. One of the carbostyryl derivatives disclosed by Oshiro et al. is aripiprazole, also known as 2(1H)-Quinolinone, 7-[4-[4-(2,3-dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydro-(9Cl), or 7-[4-[4-(2,3-Dichlorophenyl)-1-piperazinyl]butoxy]-3,4-dihydrocarbostyryl. Aripiprazole is an atypical antipsychotic agent useful for the treatment of schizophrenia, and has the following structure:



As can be seen from its structure, aripiprazole is comprised of a dichlorophenylpiperazine (DCPP) moiety and a 7-hydroxydihydrocarboxystyryl (HCS) moiety connected by a linking group comprised of four methylene groups. The central location of the linker in the final product, combined with the functional handles on the DCPP (amine) and HCS (phenol) moieties, strongly suggest a stepwise double nucleophilic displacement at the ends of a linker bearing two

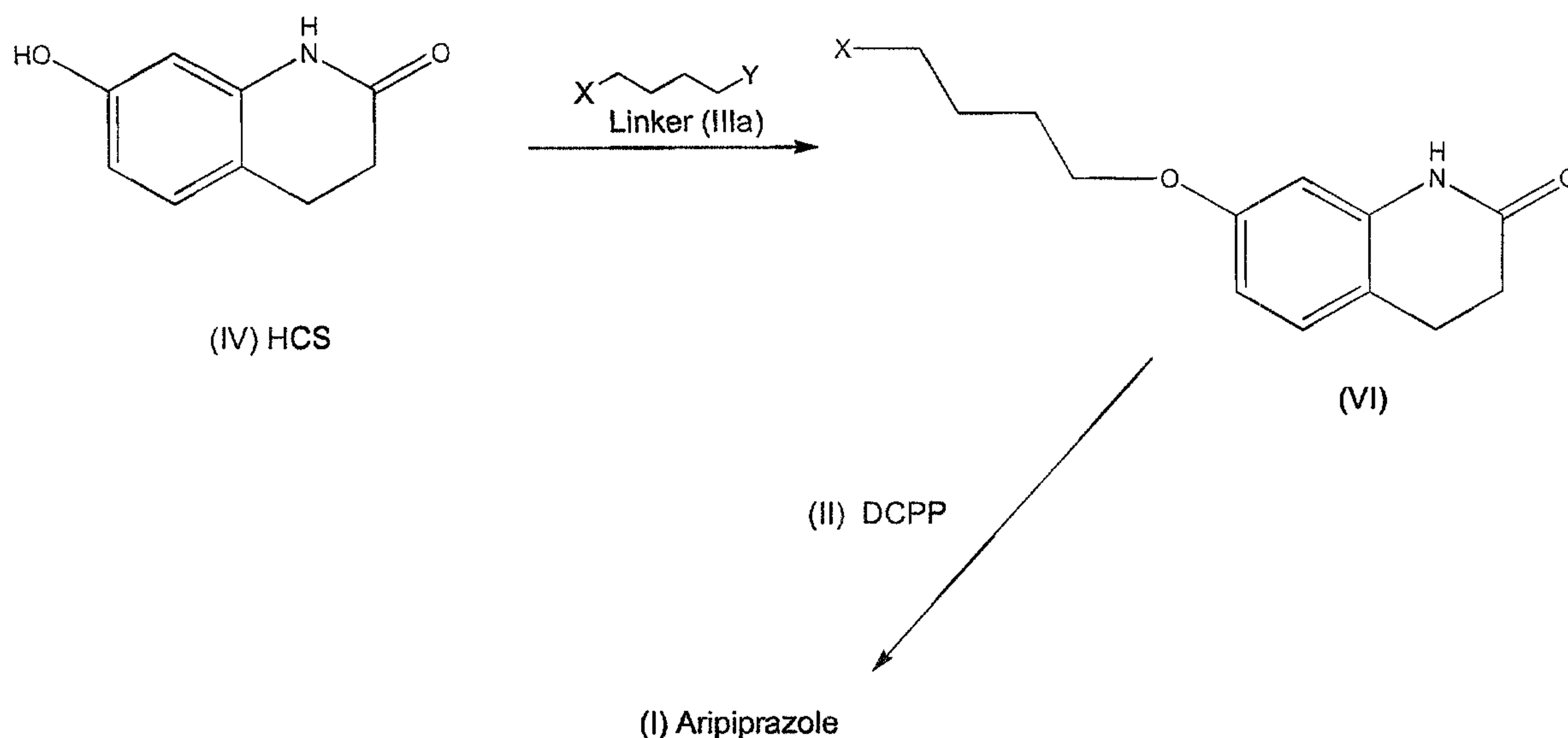
potential leaving groups. Scheme (I) shows one possible sequence for the double nucleophilic displacement reaction, in which DCPD (II) is first reacted with a linker (IIIa) to form intermediate (V), followed by reaction of intermediate (V) with HCS (IV) to form aripiprazole (I).

Scheme (I)



Scheme (II) illustrates another possible sequence for the double nucleophilic displacement reaction, in which the HCS (IV) is first reacted with the linker (IIIa) to form intermediate (VI), followed by reaction of intermediate (VI) with DCPD (II) to form aripiprazole (I).

Scheme (II)



Most of the synthetic routes to aripiprazole and related carbostyryl derivatives reported in the literature follow Scheme (II), in which intermediate (VI) is the key intermediate. Scheme (I) and intermediate (V), although mentioned in the Oshiro et al. patent and other publications, have attracted less interest.

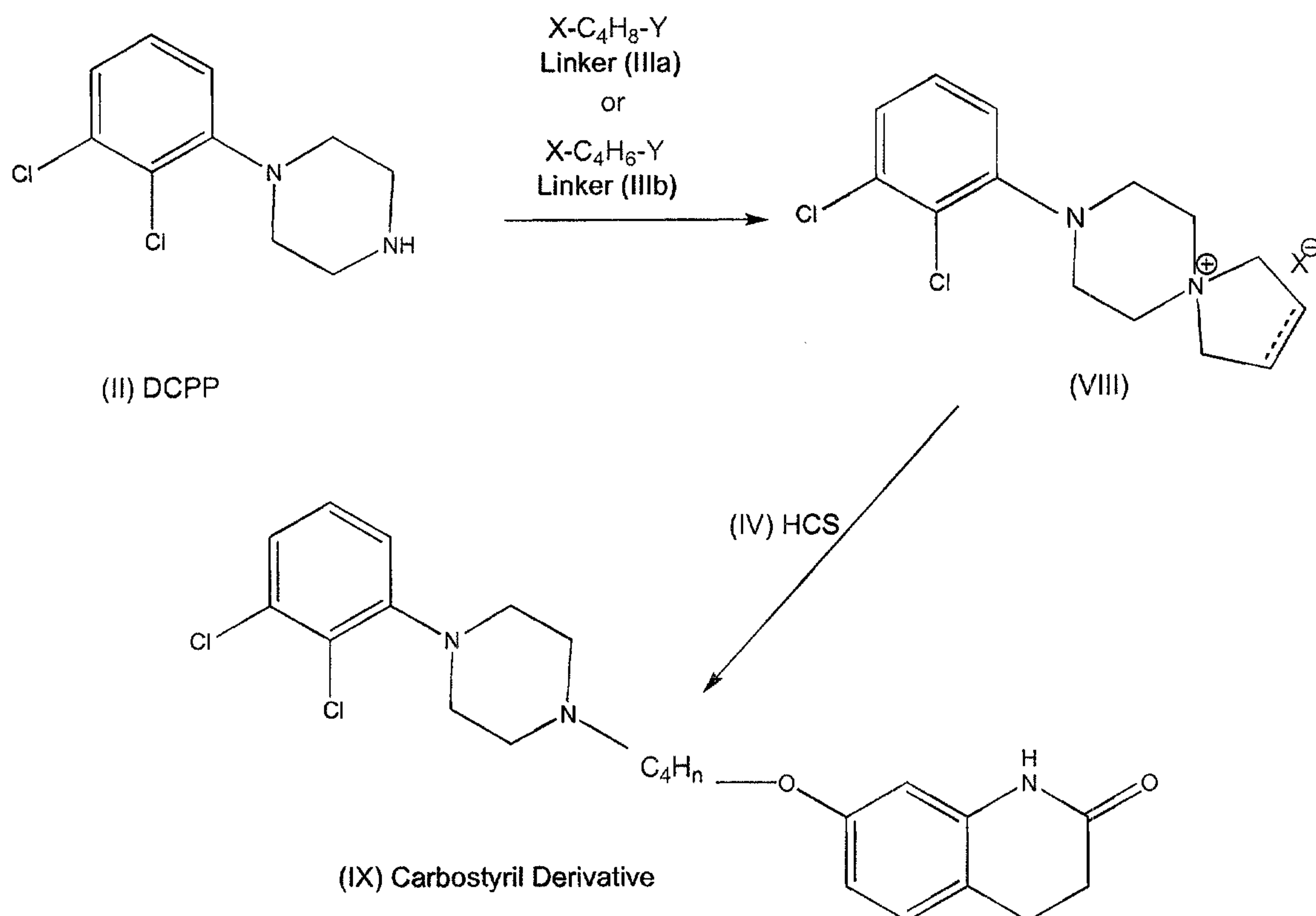
The alkylated intermediates (V) and (VI) both have a leaving group X for further substitution, and may lack sufficient stability for easy isolation and purification prior to the final step of the synthesis. Therefore, the need exists for an improved process for preparing aripiprazole and other carbostyryl derivatives.

SUMMARY OF THE INVENTION

The inventors have developed an improved process for producing aripiprazole and other carbostyryl derivatives, in which alkylated intermediates (V) and (VI) are avoided. In the process of the invention, shown in Scheme (III) below, DCPD (II) or a salt thereof is reacted with a linker (III) so as to produce a novel quaternary spiro ammonium salt intermediate (VIII), which is an easily isolable and purifiable solid. Intermediate (VIII) is then reacted with HCS (IV) to produce a carbostyryl derivative (IX), in which n is either 6 or 8, depending on whether saturated linker

(IIIa) or unsaturated linker (IIIb) is used.

Scheme (III)



The unsaturated linker (IIIb) results in the formation of an unsaturated 3-pyrrolinyl moiety in the quaternary spiro ammonium salt (VIII), which forms a carbostyryl derivative (IX) in which n is 6. On the other hand, the use of the saturated linker (IIIa) results in the formation of a saturated pyrrolidinyl moiety in salt (VIII), which forms a carbostyryl derivative (IX) in which n is 8, i.e. aripiprazole (I).

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The following are detailed descriptions of preferred processes according to the invention for preparing carbostyryl derivatives (IX).

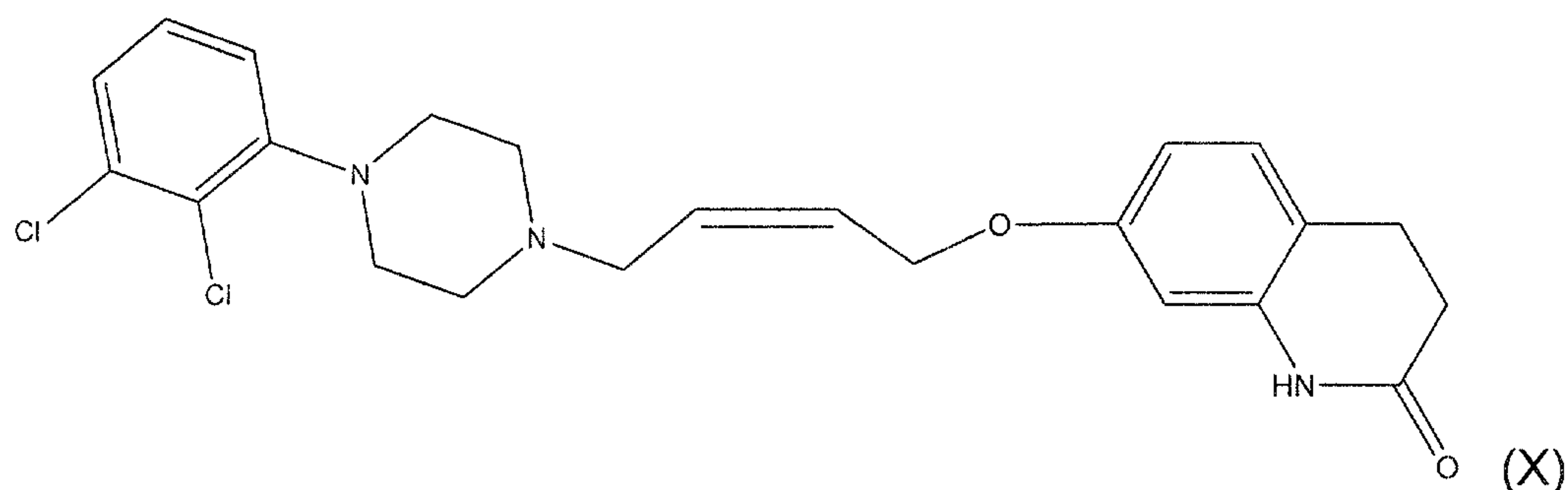
As mentioned above, the starting material in the process of the present invention

is dichlorophenylpiperazine (DCPP), having formula (II) shown above. DCPP can either be obtained commercially or can be prepared from commercially available reagents. One method for preparing piperazine derivatives such as DCPP is described in Reference Example 1 of the Oshiro et al. patent, and involves the reaction of a substituted aniline with di(2-bromoethyl)amine hydrobromide.

The first step in the process according to the invention comprises reaction of DCPP with linker (III) as described above with reference to Scheme III according to the invention. The leaving groups X and Y of linker (III) may either be the same or different and are preferably selected from the group comprising halogens and sulfonates. Preferred examples of halogens include chlorine, bromine and iodine. Preferred examples of sulfonates include mesylate and tosylate.

In some preferred embodiments, the linker (III) comprises the saturated linker (IIIa), which results in the production of aripiprazole (I). A particularly preferred linker (IIIa) of this type is 1,4-dibromobutane.

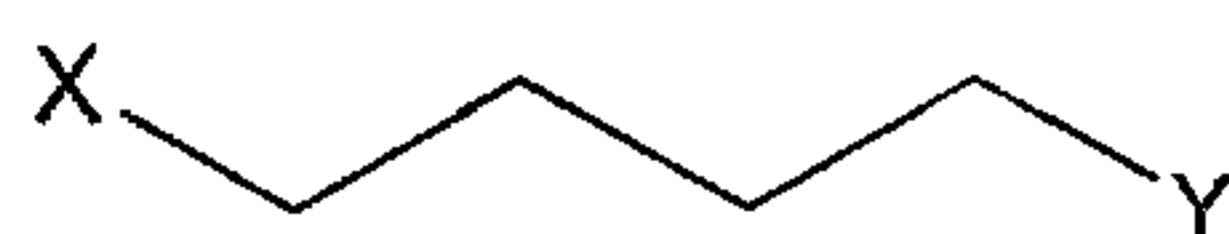
In other preferred embodiments, the linker (III) comprises the unsaturated linker (IIIb), and most preferably comprises $X-CH_2-CH=CH-CH_2-Y$. The use of linker (IIIb) will result in the production of the compound shown below having formula (X), referred to herein as "dehydroaripiprazole", in which the double bond in the linker moiety is preferably cis. A particularly preferred unsaturated linker (IIIb) is 1,4-dichloro-cis-2-butene.



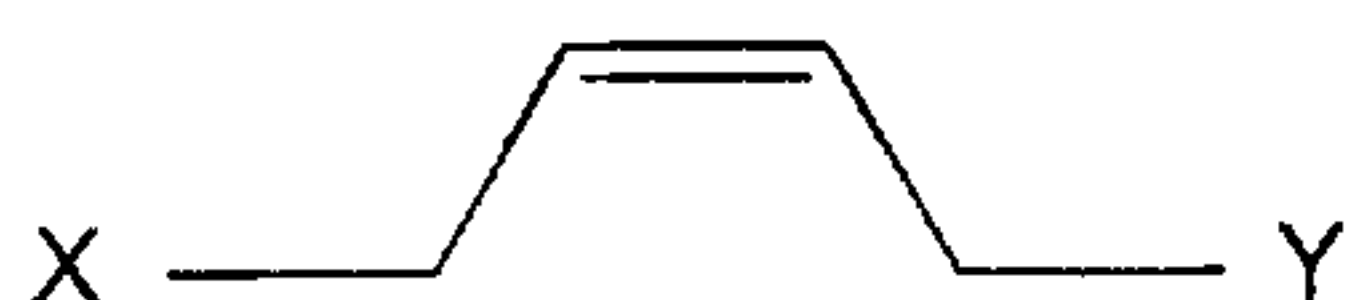
The DCPD (II), in the form of a free base or a hydrochloride, is reacted with linker (III) as shown above in Scheme (III). The reaction is conducted in an organic solvent, in the presence of a base, and is optionally catalyzed by a metal halide. The solvent preferably comprises one or more ketones, with acetone and methyl ethyl ketone (MEK) being particularly preferred. The base can be either organic or inorganic, with metal carbonates or bicarbonates being preferred examples of inorganic bases, and alkali metal carbonates or bicarbonates being particularly preferred. The metal halide catalyst may preferably comprise an alkali metal halide, with alkali metal bromides or iodides being particularly preferred. The reaction is conducted at a temperature of from about 50°C to about 120°C for a period of about 8 to 24 hours, typically 15 hours, depending on the nature of the leaving groups X and Y.

The following are the structures of particularly preferred quaternary spiro ammonium salts (VIII) which can be prepared according to the process of the invention, shown alongside the linkers (III) used in their preparation.

Linker (III)

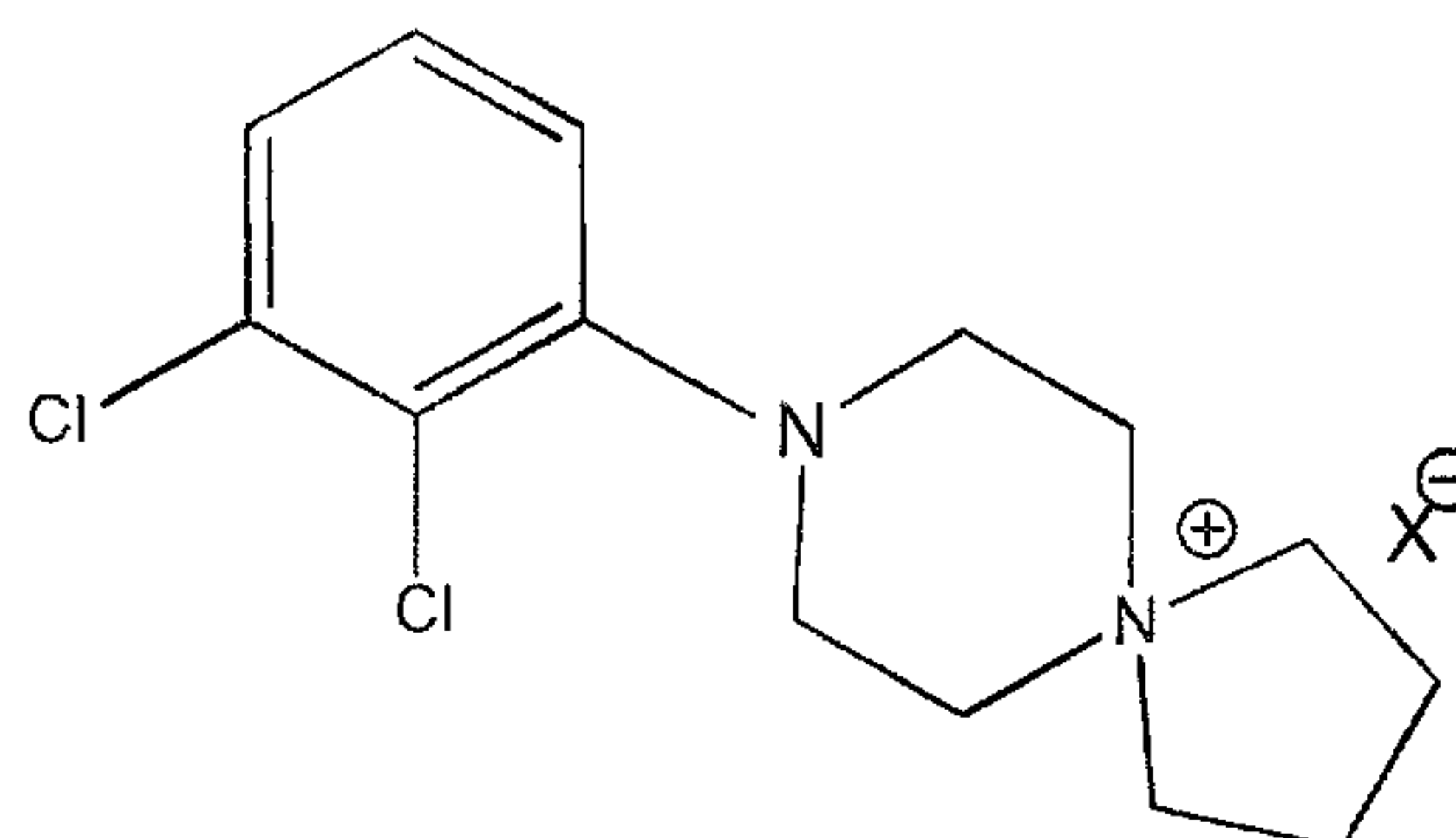


(IIIa)

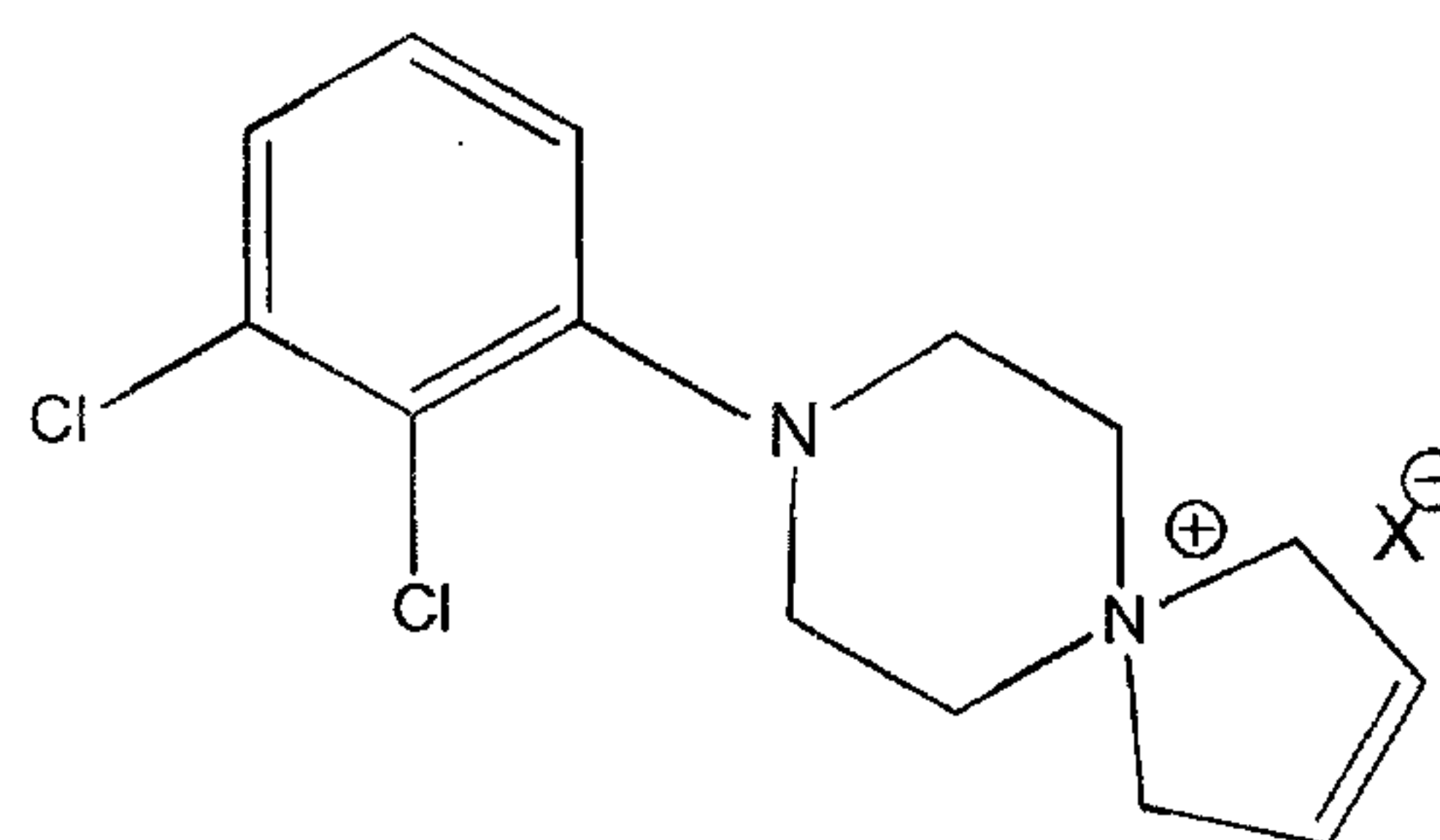


(IIIb)

Quaternary Spiro Ammonium Salt (VIII)



(VIIIa)



(VIIIb)

The anion of the quaternary spiro ammonium salt is shown herein as X^- , an anion having a net charge of -1 which originates from one of the leaving groups of the linker (III). It will be appreciated that the anion of the quaternary spiro ammonium salt (VIII) is not restricted to X^- and may be selected from a large group anions having a net charge of -1 or greater.

The quaternary spiro ammonium salts of general formula (VIII) can be isolated by direct filtration, rinsing and drying, and may comprise a mixture of organic and inorganic salts. This mixture can be further purified or can be used directly in the second step of the process.

The second step of the process comprises reaction of the quaternary spiro ammonium salt (VIII) with HCS (IV), thereby producing a carbostyryl derivative of formula (IX) as shown in Scheme (III). The HCS is deprotonated by a base, which may be carried over from the first step of the process or which may be added during the second step. Preferably, the base is a carbonate or

bicarbonate as in the first step of the process. The HCS is preferably present in the reaction mixture in a stoichiometric or sub-stoichiometric amount relative to the quaternary spiro ammonium salt (VIII), and is typically present in an amount of about 0.95 molar equivalents.

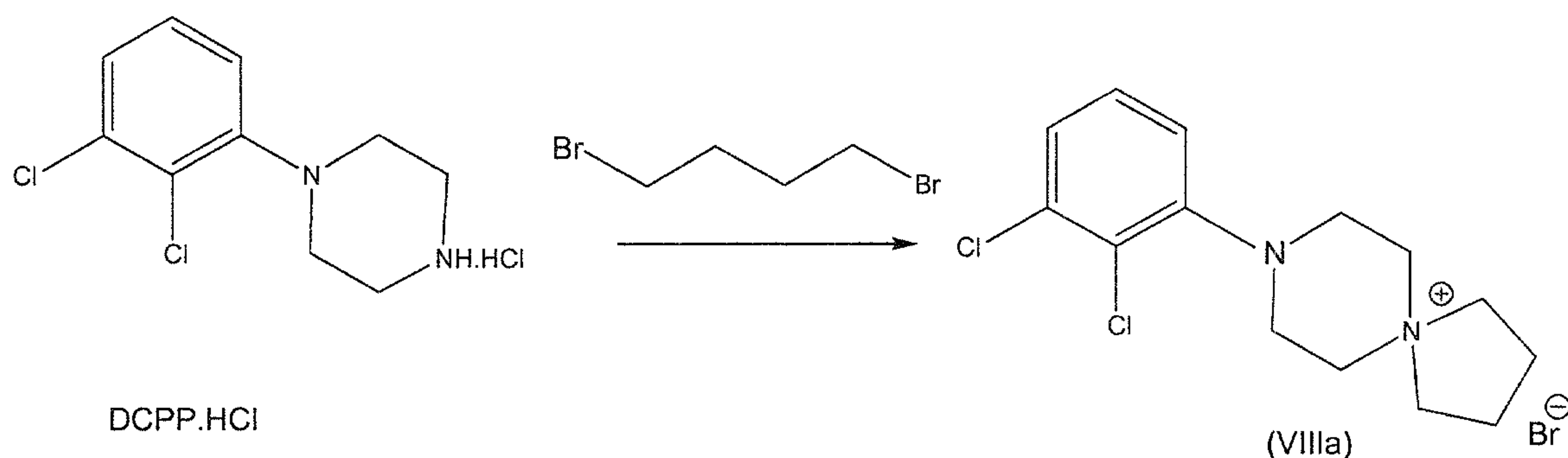
Although many solvents may be suitable for use in the second step of the process, the solvent is preferably selected from one or more members of the group of polar aprotic solvents and ketones. Preferred examples of polar aprotic solvents include dimethyl sulfoxide (DMSO), dimethyl formamide (DMF), 1-methyl-2-pyrrolidinone (NMP), hexamethylphosphoramide (HMPA), and hexamethylphosphorous triamide (HMPT). Preferred ketones include MEK and methyl isobutyl ketone (MIBK). A particularly preferred solvent system comprises a mixture of an aprotic solvent with a ketone, with a mixture of DMF-MIBK being particularly preferred.

Depending at least partly on the solvent system chosen, the reaction temperature of the second step ranges from about 80°C to about 140°C, and is preferably about 120°C. The time of reaction ranges from about 15 to 48 hours, typically about 18 hours.

The carbostyryl derivative resulting from the second step can be worked up and purified by known methods, which are further described in the following examples. Cis-dehydroaripiprazole (X) may be converted to aripiprazole (I) by reduction of the double bond in the linker moiety. The double bond may be reduced by a standard catalytic hydrogenation with palladium on charcoal (50 psi, 20°C, 3h, methanol).

The invention is further illustrated by the following non-limiting examples.

EXAMPLE 1 - Preparation of 8-(2,3-Dichlorophenyl)-8-aza-5-azoniaspiro[4,5]decane Bromide (VIIIa)



To a suspension of DCPH-HCl (100g) and potassium carbonate (124g) in acetone (700 mL) was added 1,4-dibromobutane (55.8 mL). The resulting mixture was refluxed with vigorous stirring for 15h. After cooling to room temperature, the suspension was filtered. The filter cake was rinsed twice with 100 mL of acetone, and dried under vacuum (35°C, 1 torr) for one hour. The crude quaternary spiro ammonium salt (VIIIa) was obtained as a mixture with inorganic salts (potassium carbonate, bicarbonate, chloride and bromide) in the form of a white powder: 288g. The ratio of organic/inorganic salts was 40/60 (w/w), and therefore the yield was 85%. HPLC at 254 nm (Waters XTerra RP18, 3.5 μ M, 3x150 mm, acetonitrile/water (0.1% TFA) - 28/72 (v/v), 0.5 mL/min., retention time: 4.27 min.) detected the quaternary spiro ammonium salt as the sole organic compound.

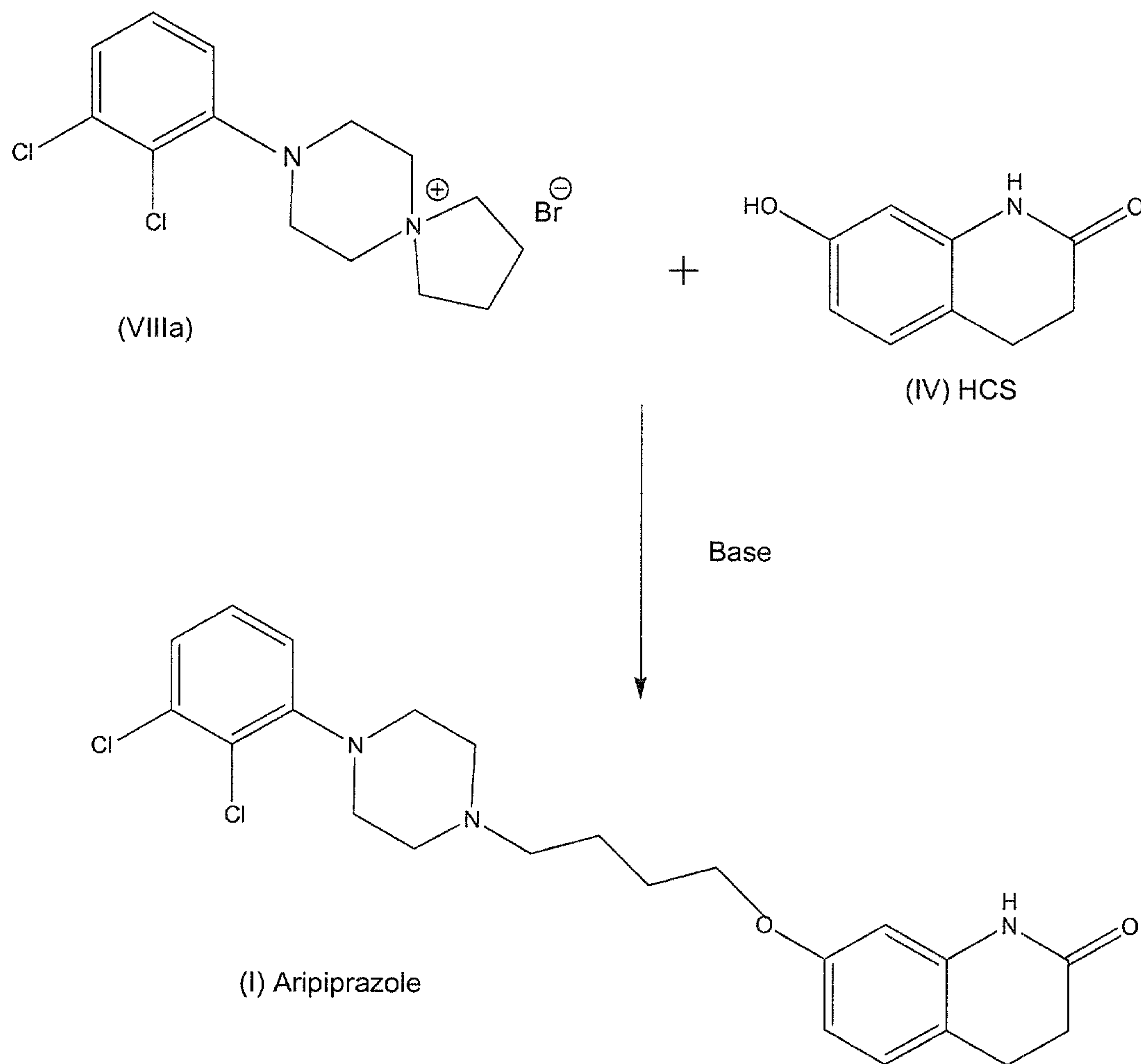
¹H NMR 300 MHz (D₂O, δ ppm): 6.95 (m, 3H); 3.42 (s, 4H); 3.39 (s, 4H); 3.02 (s, 4H); 2.02 (s, 4H); ¹³C NMR: 148.76; 133.44; 128.61; 126.89; 126.04; 119.96; 63.33; 60.00; 46.67; 21.54.

EXAMPLE 2 - Purification of 8-(2,3-Dichloro-phenyl)-8-aza-5-azoniaspiro[4,5]decane Bromide (VIIIa)

The crude quaternary spiro ammonium salt (1g) prepared in Example 1 was suspended in isopropyl alcohol (20 mL) and stirred at room temperature for 1 hour. The suspension was filtered and the filtrate was concentrated to a volume of 7 mL. To this solution was added 7 mL of hexanes, and gentle stirring allowed crystallisation of pure quaternary spiro ammonium salt. The salt was filtered and

rinsed with a 1/1 mixture of isopropyl alcohol/ hexanes and dried under vacuum, to yield 400 mg of white crystals.

Example 3 - Preparation of Aripiprazole



To a suspension of the crude quaternary spiro ammonium salt (VIIIa) of Example 1 (288g) in MIBK (1440 mL) and DMF (215 mL), was added the 7-hydroxy-4,5-dihydrocarbostyryl (HCS) (48.8g). The resulting mixture was refluxed under vigorous stirring for 18h. The reaction temperature was then adjusted in a manner to distil under a water pump vacuum 1150 mL of MIBK, with a column-head temperature ranging from 60 to 70°C. After cooling to room temperature, water (1440 mL) and hexanes (1440 mL) were added, and the suspension stirred

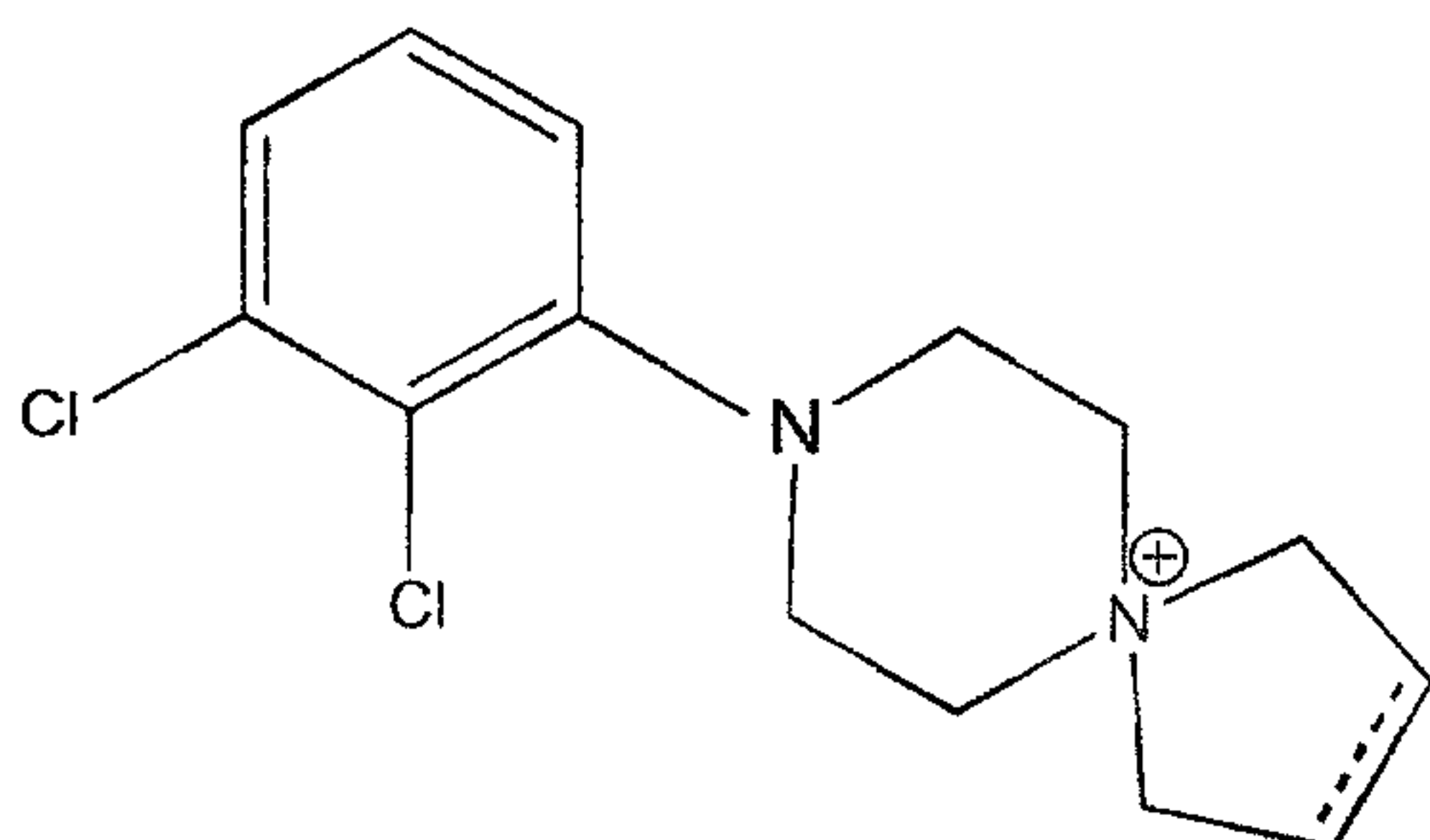
for 30 min. The medium was filtered, and the filter cake washed 4 times with 290 mL water and suctioned. The wet filter cake was then recrystallized in ethanol (900 mL), to yield Aripiprazole as a white powder (107.65g). HPLC at 254 nm (Waters XTerra RP18, 3.5 μ M, 3x150 mm, acetonitrile/water (0.1% TFA) - 28/72 (v/v), 0.5 mL/min., retention time: 10.55 min.; 99.75%).

Although the invention has been described in connection with certain preferred embodiments, it is not limited thereto. Rather, the invention includes all embodiments which fall within the following claims.

What is claimed is:

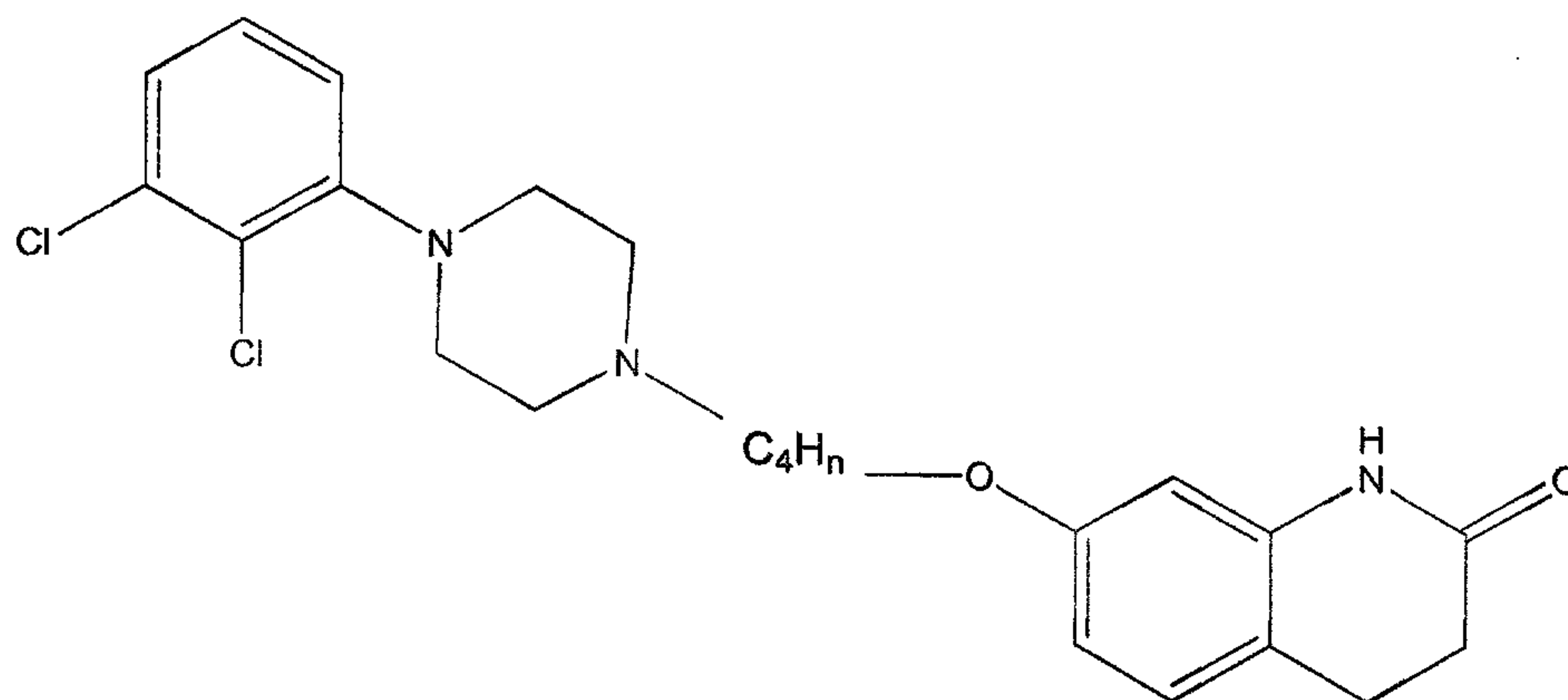
1. A process for preparing carbostyryl derivatives, comprising:

(a) reacting dichlorophenylpiperazine (DCPP) or an acid addition salt thereof with a compound of formula $X-C_4H_8-Y$ or $X-C_4H_6-Y$ to produce a quaternary spiro ammonium salt having a cation of the general formula



wherein X and Y are leaving groups; and

(b) reacting the quaternary spiro ammonium salt with 7-hydroxydihydrocarboxystyryl (HCS) to produce said carbostyryl derivative having the general formula



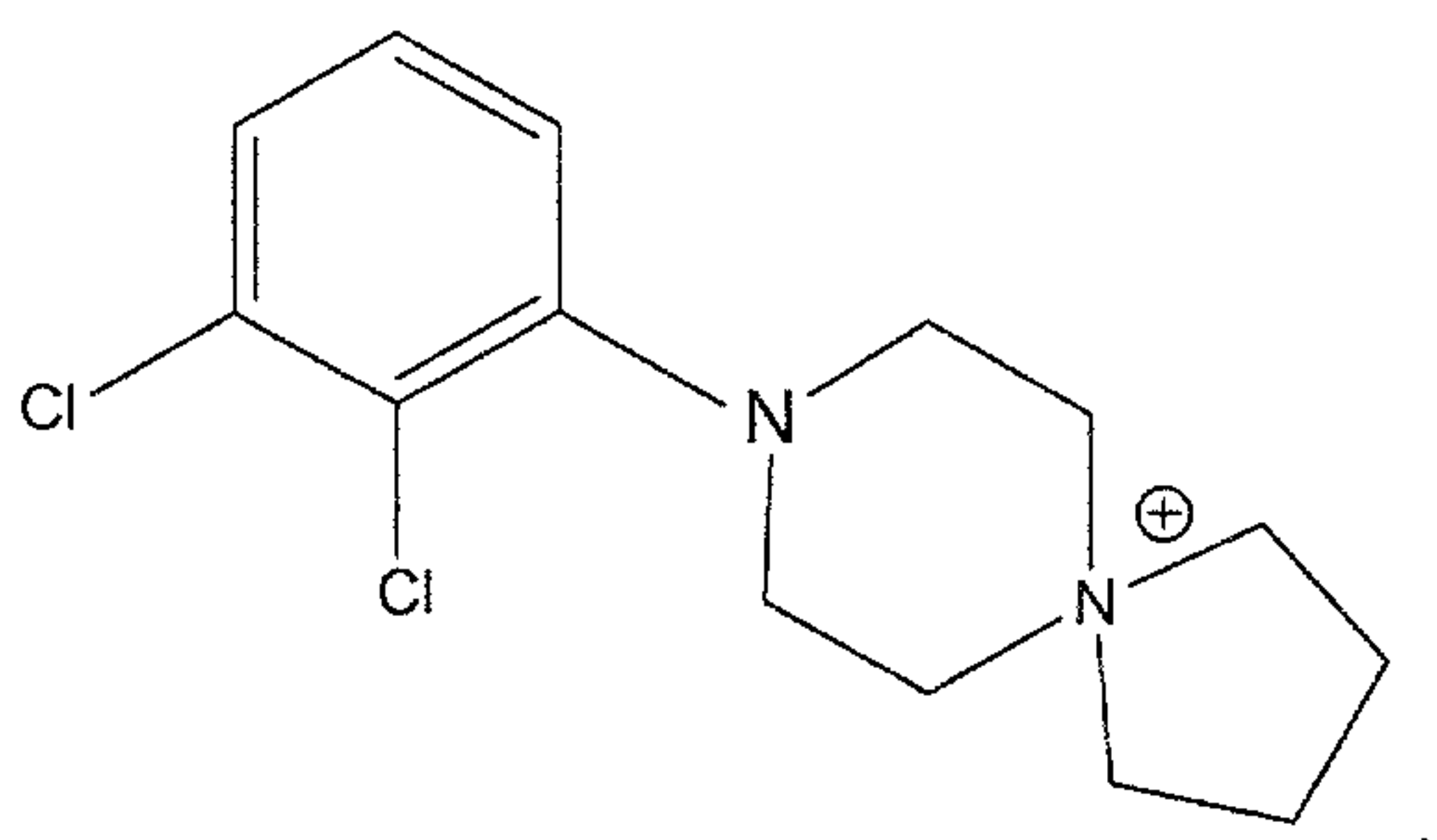
wherein n is 6 or 8.

2. The process according to claim 1, wherein DCPP or an acid addition salt thereof is reacted with a compound of formula $X-C_4H_8-Y$ and wherein n is 8.

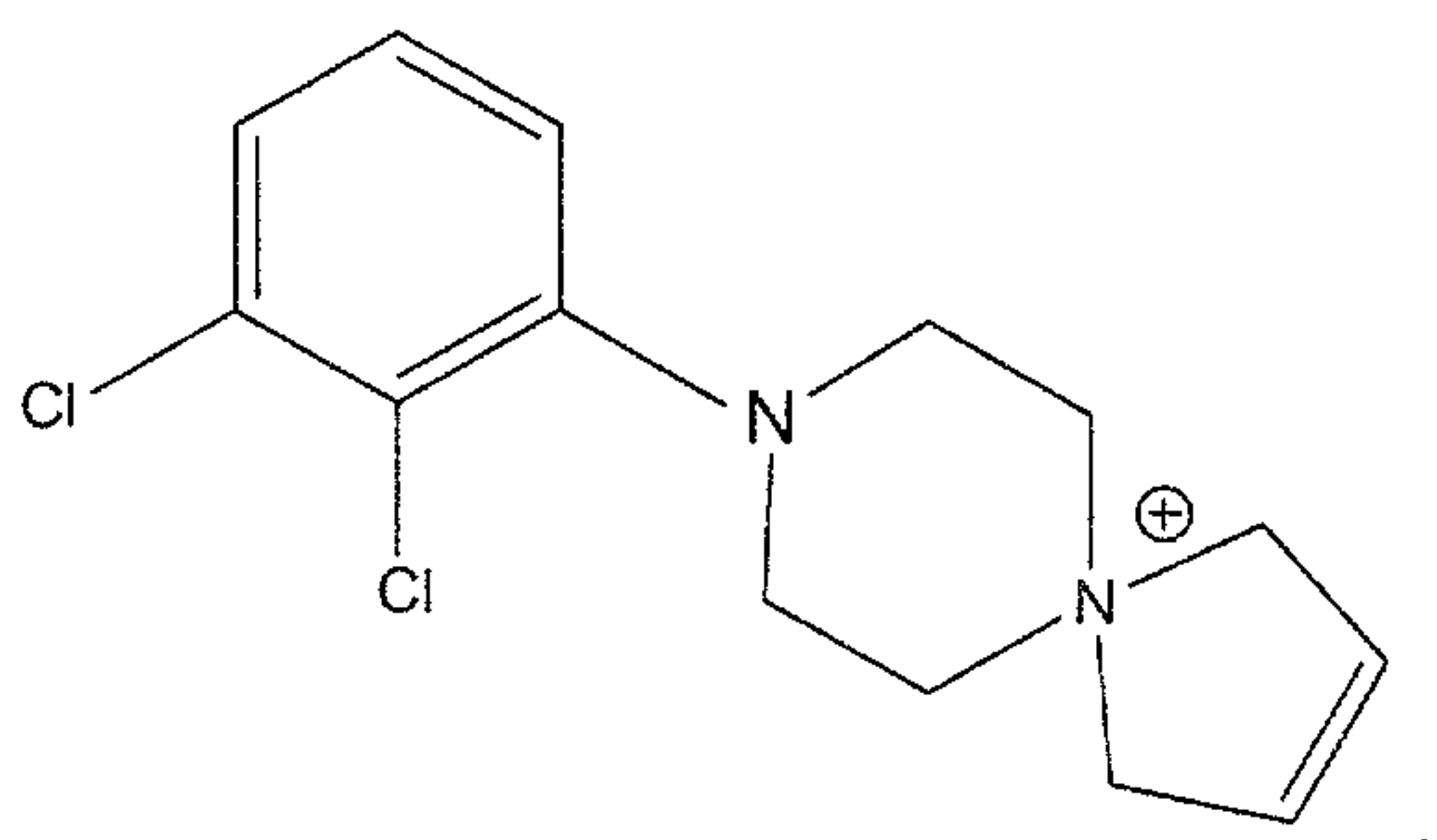
3. The process according to claim 1, wherein the carbostyryl derivative is aripiprazole.

4. The process according to claim 1, wherein DCPD or an acid addition salt thereof is reacted with a compound of formula $X-C_4H_6-Y$ and wherein n is 6.
5. The process according to claim 1, wherein DCPD or an acid addition salt thereof is reacted with a compound of formula $X-CH_2-CH=CH-CH_2-Y$.
6. The process according to claim 1, wherein the carbostyryl derivative is dehydroaripiprazole.
7. The process according to claim 6, wherein the carbostyryl derivative is cis-dehydroaripiprazole.
8. The process according to claim 1, wherein X and Y are each independently selected from the group comprising halogens and sulfonates.
9. The process according to claim 8, wherein the halogens are selected from the group comprising chlorine, bromine and iodine.
10. The process according to claim 8, wherein the sulfonates are selected from the group comprising mesylate and tosylate.
11. The process according to claim 1, wherein the compound reacted with DCPD in step (a) comprises 1,4-dibromobutane.
12. The process according to claim 1, wherein the compound reacted with DCPD in step (a) comprises 1,4-dichloro-cis-2-butene.
13. The process according to claim 1, wherein the DCPD is reacted in step (a) as its hydrochloride acid addition salt.

14. A quaternary spiro ammonium salt having a cation comprising



15. A quaternary spiro ammonium salt having a cation comprising



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