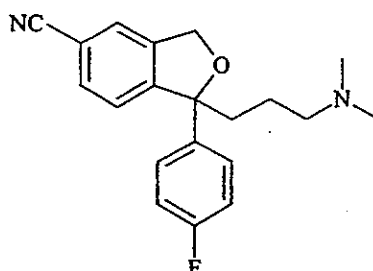


Method for the Preparation of Citalopram

The present invention relates to a method for the preparation of the well-known antidepressant drug citalopram, 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofuran-carbonitrile.

Background of the Invention

Citalopram is a well-known antidepressant drug that has now been on the market for some years and has the following structure:



It is a selective, centrally acting serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities. The antidepressant activity of the compound has been reported in several publications, eg. J. Hyttel *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.* 1982, 6, 277-295 and A. Gravem *Acta Psychiatr. Scand.* 1987, 75, 478-486. The compound has further been disclosed to show effects in the treatment of dementia and cerebrovascular disorders, EP-A-474580.

Citalopram was first disclosed in DE 2,657,013 corresponding to US 4,136,193. This patent publication describes the preparation of citalopram by one method and outlines a further method, which may be used for preparing citalopram.

According to the process described, the corresponding 1-(4-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile is reacted with 3-(N,N-dimethylamino)propyl-chloride in the presence of methylsulfinylmethide as condensing agent. The starting material was prepared from the corresponding 5-bromo derivative by reaction with cuprous cyanide.

International patent application No. WO 98/019511 discloses a process for the manufacture of citalopram wherein a (4-(cyano, alkyloxycarbonyl or alkylaminocarbonyl)-2-hydroxymethylphenyl-(4-fluorophenyl)methanol compound is subjected to ring closure. The resulting 5-(alkyloxycarbonyl or alkylaminocarbonyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran is converted to the correspond-

CONFIRMATION COPY

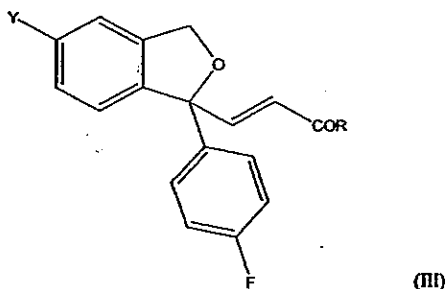
ing 5-cyano derivative and the 5-cyano derivative is then alkylated with a (3-dimethylamino)propylhalogenide in order to obtain citalopram.

It has now, surprisingly, been found that citalopram may be manufactured by a novel favourable process where a 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran is alkylated with a compound which may be converted to a dimethylaminopropyl group.

The alkylation process according to the invention is particularly advantageous because the formation of by-products by polymerisation of the alkylating agent is avoided whereby a reduction in the amount of alkylating reagent to be used is made possible. The process of the invention provides high yields.

Summary of the invention

In one aspect of the present invention, there is provided a method for the preparation of citalopram comprising subjecting, in either order, a compound of formula



wherein Y is a cyano group or a group which may be converted to a cyano group, R is hydrogen, -O-R¹, NH₂, NHCH₃ or -N(CH₃)₂ wherein R¹ is selected from hydrogen, alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl or aralkyl; to

- i) reduction of the double bond in the side chain of formula -CH=CH-COR; and
- ii) conversion of the group -COR or a reduced form thereof to a dimethylaminomethyl group; and
- iii) if Y is not cyano, conversion of the group Y to a cyano group;

followed by isolation of citalopram base or a pharmaceutically acceptable acid addition salt thereof.

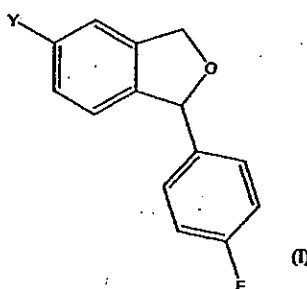
The conversions mentioned under i), ii) and iii) above may be carried out in any order.

An embodiment may relate to the reduction of the double bond mentioned under i) above may be carried out before the group -COR or a reduced form thereof may be converted to a dimethylaminomethyl group as under ii) above.

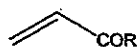
5

Conversion of the group Y to a cyano group may be carried out at any suitable point during the reaction. In a particular embodiment, the compound of formula (III) used is a compound wherein Y is cyano.

- 10 Another preferred embodiment, may be the compound of formula (III) may be prepared by reaction of a compound of formula



wherein Y is a cyano group or a group which may be converted to a cyano group, with a compound having the formula

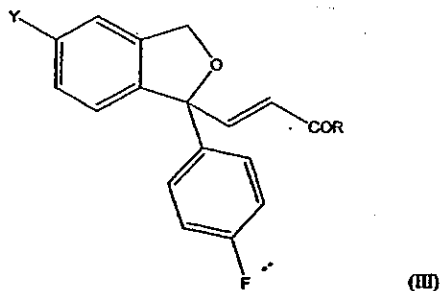


(II)

15

wherein R is hydrogen, -O-R¹, -NH₂, -NHCH₃, -N(CH₃)₂ wherein R¹ is selected from hydrogen, alkyl, alkenyl, alkynyl, and optionally alkyl substituted aryl or aralkyl; to form a compound of formula (III).

In another aspect, the present invention there is provided a compound having the formula



wherein Y is a cyano group or a group which can be converted to a cyano group, R is hydrogen, -O-
5 R¹, NH₂, NHCH₃ or -N(CH₃)₂ wherein R¹ is selected from hydrogen, alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl or aralkyl, or an acid addition salt thereof.

Yet another embodiment may relate to an antidepressant pharmaceutical composition comprising citalopram manufactured by the process of the invention.

The group Y which may be converted to a cyano group may be selected from halogen,

5 wherein U is O or S;

The alkylation step where the compound of formula (I) is reacted with a compound of formula (II) is suitably carried out by treatment of the compound of formula (I) with a base such as for example LDA (lithiumdiisopropylamine), LiHMDS (hexamethyldisilazan lithium), NaH, NaHMDS (hexamethyldisilazan sodium) or metalalkoxides such as NaOMe, KOMe, LiOMe, NaO*tert*Bu, KO*tert*Bu or LiO*tert*Bu in an aprotic organic solvent such as THF (tetrahydrofuran), DMF (dimethylformamide), NMP (N-methylpyrrolidon), ethers such as diethylether or dioxalane, toluene, benzene, or alkanes and mixtures thereof. The anion formed is then reacted with a compound of formula (II) whereby a group of formula

Compounds wherein the group -COR is -CON(CH₃)₂ may be converted to the corresponding compound wherein this group is a dimethylaminomethyl group by reduction, suitably in toluene using Red-Al as a reducing agent

When -COR is -CONHCH₃ or -CONH₂, conversion to the dimethylaminomethyl group may be carried out by, in either order, reduction to form an amine and methylation or reductive amination form a dimethylaminomethyl group.

30 The reduction of the amide may be carried out in toluene using Red-Al as a reducing agent.

The methylation of the amine may be carried out with methylating agents such as MeI or Me₂SO₄, wherein Me is methyl. The methylation is carried out using conventional procedures for carrying out such reactions.

- 5 Alternatively, methylation to form a dimethylaminomethyl group may be carried out by reductive amination. According to this procedure, the compound carrying a -NH₂ or a -NHCH₃ group is reacted with compounds such as formaldehyde, paraformaldehyde or trioxane in presence of a reducing agent such as NaBH₄ or NaBH₃CN. The reductive amination is carried out using conventional procedures for carrying out such reactions.

10

When R is -CHO, conversion to the dimethylaminomethyl group may be carried out by reductive amination with dimethylamine or a salt thereof. Suitably by reaction with dimethylamine in the presence of a reducing agent such as NaBH₄ or NaBH₃CN. Dimethylamine may be added to the reaction in the form of the dimethylammonium chloride salt or as a metal salt of dimethylamine.

15

When R is -COOR¹, the conversion to the dimethylaminomethyl group may be carried out by conversion to the corresponding amide followed by reduction, and optionally methylation or reductive amination to form a dimethylaminomethyl group.

- 20 The amide may be prepared by reaction of the ester with an amine, preferably NH(Me)₂ or a salt thereof

When R is -COOR¹, the conversion of this group to the dimethylaminomethyl group may also be carried out by reduction to the corresponding alcohol followed by conversion of the alcohol group to a feasible leaving group and consecutively reaction

- 25 a) with dimethylamine or a salt thereof,
b) with methylamine followed by methylation or reductive amination to form a dimethylamino group, or
c) with an azide followed by reduction to form the corresponding amino compound and thereafter methylation or reductive amination to form a dimethylamino group.

30

In still another aspect of the present invention, there is provided a citalopram prepared as defined in the above aspects and embodiments.

The alcohol may be formed from a compound wherein -COR is -COOR¹ by reduction of the ester using Red-A1 as a reducing agent.

The alcohol group may be converted to a feasible leaving group such as halogen, or a sulphonate of formula $-O-SO_2-R^0$ wherein R^0 is alkyl, alkenyl, alkynyl or optionally alkyl substituted aryl or aralkyl, by reaction with reagents such as thionylchloride, mesylchloride, tosylchloride, etc.

- 5 The resulting compound carrying a suitable leaving group is then reacted with dimethylamine or a salt thereof, e.g. M^+ , $N(CH_3)_2$ wherein M^+ is Li^+ or Na^+ . The reaction is suitably carried out in an aprotic organic solvent such as THF (tetrahydrofuran), DMF (dimethylformamide), NMP (N-methyl pyrrolidon), ethers such as diethylether, or dioxalane, toluene, benzene or alkanes and mixtures thereof. The leaving group may also be replaced by dimethylamino by reaction with
- 10 dimethylammonium chloride in presence of a base. Alternatively, the compound carrying a suitable leaving group, such as a sulphonate of formula $-O-SO_2-R^0$ wherein R^0 is as defined above, may be reacted with an azide, such as sodium azide, followed by reduction using Pd/C as a catalyst to form the free amino group and thereafter methylation or reductive amination to form a dimethylamino group.

15

The leaving group, may also be replaced by dimethylamino by reaction with methylamine followed by methylation or reductive amination to form a dimethylamine.

- 20 Methylation may be carried out with methylating agents such as MeI and Me_2SO_4 , wherein Me is methyl. The methylation is carried out using conventional procedures for carrying out such reactions.

Alternatively, methylation is carried out by reductive amination as described above.

- 25 When Y is halogen or $CF_3-(CF_2)_n-SO_2-O-$ wherein n is 0-8, the conversion to a cyano group may be carried out by reaction with a cyanide source, for example KCN, NaCN, CuCN, $Zn(CN)_2$ or $(R^{15})_4NCN$ where $(R^{15})_4$ indicates four groups which may be the same or different and are selected from hydrogen and straight chain or branched alkyl, in the presence of a palladium catalyst and a catalytic amount of Cu^+ or Zn^{2+} , or with $Zn(CN)_2$ in the presence a palladium catalyst. The
- 30 conversion of a compound wherein Y is halogen, or $CF_3-(CF_2)_n-SO_2-O-$ wherein n is 0-8, by reaction with a cyanide source in presence of a palladium catalyst, may be carried out as described in WO 0013648.

- 35 When Y is Cl or Br the conversion to a cyano group may also be carried out by reaction with a cyanide source, for example KCN, NaCN, CuCN, $Zn(CN)_2$ or $(R^{15})_4NCN$ where $(R^{15})_4$ indicates four groups which may be the same or different and are selected from hydrogen and straight chain or branched alkyl, in the presence of a nickel catalyst. The conversion of a compound wherein Y is

halogen or $\text{CF}_3-(\text{CF}_2)_n-\text{SO}_2-\text{O}-$ wherein n is 0-8, by reaction with a cyanide source in presence of a nickel catalyst may be carried out as described in WO 0011926.

- 5 When Y is an oxazoline or a thiazoline of the formula (IV) the conversion to a cyano may be carried out as described in WO 0023431.

When Y is CHO, the conversion to a cyano group may be carried out by conversion of the formyl group to an oxime or similar group by reaction with a reagent of formula $\text{R}^{16}-\text{V}-\text{NH}_2$ wherein R^{16} is
10 hydrogen, alkyl, aryl or heteroaryl and V is O, N or S, followed by dehydration with a common dehydrating agent, for example thionylchloride, acetic anhydride/pyridine, pyridine/HCl or phosphor pentachloride. Preferred reagents $\text{R}^{16}-\text{V}-\text{NH}_2$ are hydroxylamin and compounds wherein R^{16} is alkyl or aryl and V is N or O.

- 15 When Y is $-\text{COOH}$, the conversion to a cyano group may be carried out via the corresponding acid chloride, ester or amide.

The acid chloride is conveniently obtained by treatment of the acid with POCl_3 , PCl_5 or SOCl_2 neat or in a suitable solvent, such as toluene or toluene comprising a catalytic amount of N,N-dimethylformamide. The ester is obtained by treatment of the acid with an alcohol, in the presence
20 of an acid, preferably a mineral acid or a Lewis acid, such as HCl, H_2SO_4 , POCl_3 , PCl_5 or SOCl_2 . Alternatively, the ester may be obtained from the acid chloride by reaction with an alcohol. The ester or the acid chloride may then converted to an amide of by amidation with ammonia or an alkylamine, preferably t-butyl amine.

25 The conversion to amide may also be obtained by reaction of the ester with ammonia or an alkylamine under pressure and heating.

The amide group is then converted to a cyano group by dehydration. The dehydrating agent may be
30 any suitable dehydrating agent, and the optimal agent may easily be determined by a person skilled in the art. Examples of suitable dehydrating agents are SOCl_2 , POCl_3 and PCl_5 , preferably SOCl_2 .

In a particularly preferred embodiment, the carboxylic acid is reacted with an alcohol, preferably ethanol, in the presence of POCl_3 , in order to obtain the corresponding ester, which is
35 then reacted with ammonia thereby giving the corresponding amide, which in turn is reacted with SOCl_2 in toluene comprising a catalytic amount of N,N-dimethylformamide.

Alternatively, a compound where Y is -COOH may be reacted with chlorosulfonyl isocyanate in order to form the nitrile, or treated with a dehydrating agent and a sulfonamide as described in WO 0044738.

5 When Y is -NHR^m, where R^m is hydrogen, the conversion into cyano is preferably performed by diazotation and followed by reaction with CN⁻. Most preferably, NaNO₂ and CuCN and/or NaCN is used. When R^m is alkylcarbonyl, the compound is initially subjected to hydrolysis thereby obtaining the corresponding compound wherein R^m is H which is then converted as described above. The
10 hydrolysis may be performed either in acidic or basic environment.

Starting materials of formula (I) wherein Y is halogen may be prepared as described in GB 1526331, compounds of formula (I) wherein Y is -O-SO₂-(CF₂)_n-CF₃ may be prepared analogously to the compounds described in WO 99/00640, compounds of formula (I) wherein Y is an oxazoline or a
15 thiazoline group may be prepared analogous to the compounds described in WO 00/23431, compounds wherein Y is formaldehyde may be prepared analogously to the compounds described in as WO 99/30548, compounds wherein Y is
-COOH, and esters and amides thereof may be prepared analogously to the compounds described in WO 98/19511 and compounds of formula I wherein is -NHR^m may be prepared analogously to the
20 compounds described in WO 98/19512.

The reaction conditions, solvents, etc. used for the reactions described above are conventional conditions for such reactions and may easily be determined by a person skilled in the art.

25 The starting material, of formula (I) wherein Y is a cyano group may be prepared as described in US patent No. 4,136,193 or as described in WO 98/19511.

The compounds of formula (II) are commercially available or may be prepared from commercially available starting materials using conventional techniques.

30 Citalopram is on the market as an antidepressant drug in the form of the racemate. However, in the near future, the active S-enantiomer of citalopram is also going to be introduced to the market.

S-citalopram may be prepared by separation of the optically active isomers by chromatography.

35

Throughout the specification and claims, the term alkyl refers to a branched or unbranched alkyl group having from one to six carbon atoms inclusive, such as methyl, ethyl, 1-propyl, 2-propyl, 1-butyl, 2-butyl, 2-methyl-2-propyl, 2,2-dimethyl-1-ethyl and 2-methyl-1-propyl.

- 5 Similarly, alkenyl and alkynyl, respectively, designate such groups having from two to six carbon atoms, including one double bond and triple bond respectively, such as ethenyl, propenyl, butenyl, ethynyl, propynyl, and butynyl.

- 10 The term aryl refers to a mono- or bicyclic carbocyclic aromatic group, such as phenyl and naphthyl, in particular phenyl.

The term aralkyl refers to aryl-alkyl, wherein aryl and alkyl is as defined above.

- 15 Optionally alkyl substituted aryl and aralkyl refers to aryl and aralkyl groups, which may optionally be substituted with one or more alkyl groups.

Halogen means chloro, bromo or iodo.

- 20 Citalopram may be used as the free base, in particular in crystalline form, or as a pharmaceutically acceptable acid addition salt thereof. As acid addition salts, such salts formed with organic or inorganic acids may be used. Exemplary of such organic salts are those with maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bismethylenesalicylic, methanesulfonic, ethanedisulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene sulfonic and theophylline
25 acetic acids, as well as the 8-halotheophyllines, for example 8-bromotheophylline. Exemplary of such inorganic salts are those with hydrochloric, hydrobromic, sulfuric, sulfamic, phosphoric and nitric acids.

- 30 The acid addition salts of citalopram may be prepared by methods known in the art. The base is reacted with either the calculated amount of acid in a water miscible solvent, such as acetone or ethanol, with subsequent isolation of the salt by concentration and cooling, or with an excess of the acid in a water immiscible solvent, such as ethylether, ethylacetate or dichloromethane, with the salt separating spontaneously.

- 35 The pharmaceutical compositions of the invention may be administered in any suitable way and in any suitable form, for example orally in the form of tablets, capsules, powders or syrups, or parenterally in the form of usual, sterile solutions for injection.

The pharmaceutical formulations of the invention may be prepared by conventional methods in the art. For example, tablets may be prepared by mixing the active ingredient with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a conventional tableting machine.

- 5 Examples of adjuvants or diluents comprise: Corn starch, potato starch, talcum, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive, colourings, aroma, preservatives etc. may be used provided that they are compatible with the active ingredients.

- 10 Solutions for injections may be prepared by dissolving the active ingredient and possible additives in a part of the solvent for injection, preferably sterile water, adjusting the solution to the desired volume, sterilising the solution and filling it in suitable ampoules or vials. Any suitable additive conventionally used in the art may be added, such as tonicity agents, preservatives, antioxidants, etc.

The invention is further illustrated by the following examples.

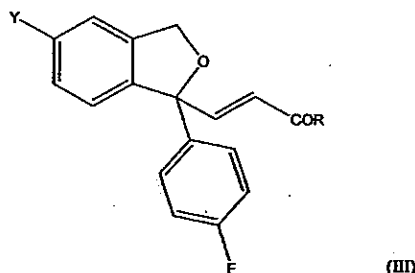
15

Example 1

- A solution of 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile (4.8 g, 0.02 mol) in THF (50 mL) was added dropwise to a solution of LDA (Butyl lithium 1.6 M (15 mL) , diisopropylamine (2.6 g) at -30 °C under an atmosphere of nitrogen. After stirring at - 30 °C for 10 minutes a solution of a compound of formula (II) (0.02 mol) in THF (25 mL) was added dropwise and allowed to warm to room temperature and stirred for a further 60 minutes. The reaction was then quenched with ice, extracted with toluene (3 x 50 mL), washed with water (50 mL) and concentrated under reduced pressure. The residue was purified by chromatography on silica gel using mixtures of n-heptane/EtOAc as the eluent.
- 20
- 25

Claims

1. A method for the preparation of citalopram comprising subjecting, in either order, a compound of formula



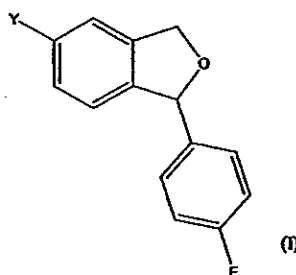
5

wherein Y is a cyano group or a group which may be converted to a cyano group, R is hydrogen, -O-R¹, NH₂, NHCH₃ or -N(CH₃)₂ wherein R¹ is selected from hydrogen, alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl or aralkyl; to

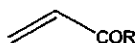
- 10 i) reduction of the double bond in the side chain of formula -CH=CH-COR:
- ii) conversion of the group -COR or a reduced form thereof to a dimethylaminomethyl group; and
- 15 iii) if Y is not cyano, conversion of the group Y to a cyano group;

followed by isolation of citalopram base or a pharmaceutically acceptable acid addition salt thereof.

2. The method according to claim 1 wherein the compound of formula (III) is prepared by
- 20 reaction of a compound of formula



wherein Y is a cyano group or a group which may be converted to a cyano group, with a compound having the formula



(II)

wherein R is hydrogen, -O-R¹, -NH₂, -NHCH₃ or -N(CH₃)₂ wherein R¹ is selected from hydrogen, alkyl, alkenyl, alkynyl, and optionally alkyl substituted aryl or aralkyl;

5 to form a compound of formula (III).

3. The method according to claim 1, wherein -COR is -CON(CH₃)₃ and the conversion of this group to the dimethylaminomethyl group is carried out by reduction.

10 4. The method according to claim 1, wherein -COR is -CONHCH₃ or -CONH₂ and the conversion of these groups is carried out by, in either order, reduction and methylation or reductive amination to form a dimethylaminomethyl group.

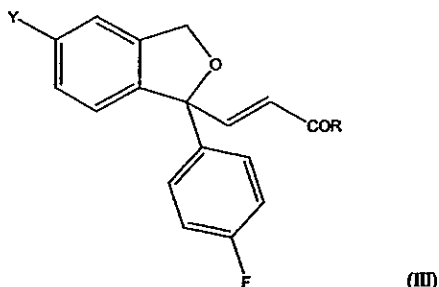
5. The method of claim 1 wherein R is -CHO and the conversion to the
15 dimethylaminomethyl group is carried out by reductive amination with dimethylamine or a salt thereof.

6. The method of claim 1 wherein R is -COOR¹ and the conversion to the
dimethylaminomethyl group is carried out by conversion to the corresponding amide followed by
20 reduction and optionally methylation or reductive amination to form a dimethylaminomethyl group.

7. The method of claim 1 wherein R is -COOR¹ and the conversion of this group to the dimethylaminomethyl group is carried out by reduction to the corresponding alcohol, followed by conversion of the alcohol group to a feasible leaving group and consecutively reaction

- a) with dimethylamine or a salt thereof,
- 25 b) with methylamine followed by methylation or reductive amination to form a dimethylamino group, or
- c) with an azide followed by reduction to form the corresponding amino compound and thereafter methylation or reductive amination to form a dimethylamino group.

8. A compound having the formula



- 5 wherein Y is a cyano group or a group which can be converted to a cyano group, R is hydrogen, -O-R¹, NH₂, NHCH₃ or -N(CH₃)₂ wherein R¹ is selected from hydrogen, alkyl, alkenyl, alkynyl and optionally alkyl substituted aryl or aralkyl, or an acid addition salt thereof.

9. Citalopram prepared according to the method of claims 1-7.