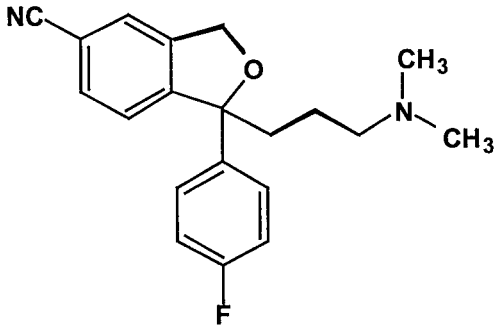
Method for the Preparation of Citalopram

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

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:



Formula **I**

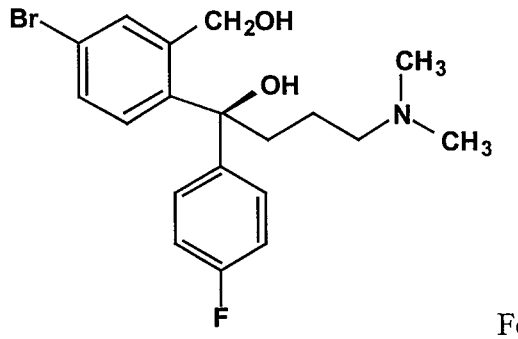
It is a selective, centrally acting serotonin (5-hydroxytryptamine; 5-HT) reuptake inhibitor, accordingly having antidepressant activities. The antidepressant activity of the compound has been reported in several publications, eg. J. Hyttel, *Prog. Neuro-Psychopharmacol. & Biol. Psychiat.*, **1982,** *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 2,657,271 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.

According to the method, which is only outlined in general terms, citalopram may be obtained by ring closure of the compound:

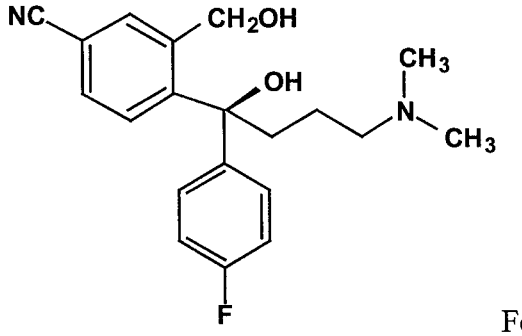
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Formula **II**

in the presence of a dehydrating agent and subsequent exchange of the 5-bromo group with cyano using cuprous cyanide. The starting material of Formula **II** is obtained from 5-bromophthalide by two successive Grignard reactions, i.e. with 4-fluorophenyl magnesium chloride and N,N-dimethylaminopropyl magnesium chloride, respectively.

A new and surprising method and an intermediate for the preparation of citalopram were described in US Patent No 4,650,884 according to which an intermediate of the formula



Formula **III**

is subjected to a ring closure reaction by dehydration with strong sulfuric acid in order to obtain citalopram. The intermediate of Formula **III** was prepared from 5-cyanophthalide by two successive Grignard reactions, *i.e.* with 4-fluorophenyl magnesium halogenide and N,N-dimethylaminopropyl magnesium halogenide, respectively.

Further processes are disclosed in International patent application Nos. WO 98019511, WO 98019512 and WO 98019513. WO 98019512 and WO 98019513 relate to methods wherein a 5-amino-, 5-carboxy- or 5-(sec. aminocarbonyl)phthalide is subjected to two successive Grignard reactions, ring closure and conversion of the resulting 1,3-dihydroisobenzofuran derivative to the corresponding 5-cyano compound, i.e. citalopram. International patent application No. WO 98019511 discloses a process for the manufacture of citalopram wherein a (4-substituted-2-hydroxymethylphenyl-(4-fluorphenyl)methanol compound is subjected to ring closure and the resulting 5-substituted 1-(4-fluorophenyl)-1,3-dihydroisobenzofuran converted to the corresponding 5-cyano derivative which is alkylated with a (3-dimethylamino)propylhalogenide in order to obtain citalopram.

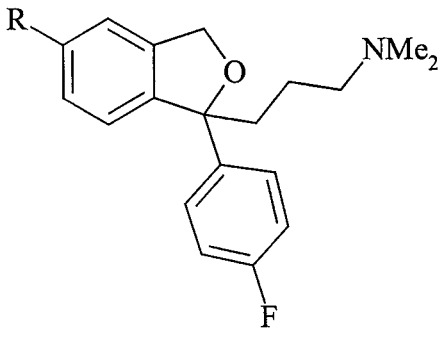
Finally, methods of preparing the individual enantiomers of citalopram are disclosed in US Patent No 4,943,590 from which it also appears that the ring closure of the intermediate of Formula **III** may be carried out via a labile ester with a base.

With respect to the above methods for the preparation of citalopram the proces comprising exchange of the 5-bromo group with cyano proved not to be very convenient in commercial scale, since it was the yield was rather low, the product was impure and in particular that it was difficult to separate the resulting citalopram from the corresponding 5-bromo compound.

It has now been found that citalopram may be obtained in a high yield as a very pure product by a new catalytic process in which 5-cyano is exchanged for 5-bromo or 5-chloro group in 1-[3-(dimethylamino)propyl]-1-(4-fluorophenyl)-1,3-dihydro-isobenzofuran thus avoiding the extensive work up of the old cyanide exchange process.

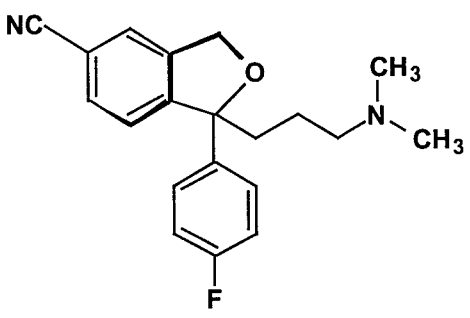
Summary of the invention

Accordingly, the present invention relates to a novel method for the preparation of citalopram comprising reaction of a compound of Formula **IV**



Formula **IV**

wherein R is Cl or Br with a with a cyanide source, for example KCN, NaCN or $(R'_4N)CN$ where R'_4 indicates four groups which may be the same of different and are selected from hydrogen and straight chain or branched C_{1-6} alkyl, in the presence of a nickel catalyst and isolation of the corresponding 5-cyano compound, i.e. citalopram



Formula **I**

as the base or a pharmaceutically acceptable salt thereof.

In a further aspect the invention relates to the above process in which the compound of Formula **IV** is the S-enatiomer.

In yet another aspect, the present invention relates to an antidepressant pharmaceutical composition comprising citalopram manufactured by the process of the invention.

By the process of the invention citalopram is obtained as a pure product in high yield thus reducing costly purification processes. Furthermore, the reaction may be carried out in more convenient solvents, at a low temperature and at a low excess of CN^- compared to the known cyano exchange process. The process has environmental advantages in that it only uses small amounts of heavy. Finally, this process gives an improved crystalline product enabling easy conversion to desired salts.

The cyanide source used may be any useful source. Preferred sources are KCN, NaCN or $(R'_4N)CN$ where R'_4 is as defined above. The cyanide source is used in a stoichiometric amount or in excess, preferably 1-2 equivalents are used pr. equivalent starting material of Formula IV. R'_4N^+ may conveniently be $(Bu)_4N^+$. The cyanide compound is preferably NaCN or KCN or $Zn(CN)_2$.

The nickel catalyst may be any suitable Ni(0) or Ni(II) containing complex which acts as a catalyst, such as $Ni(PPh_3)_3$, (σ-aryl)-$Ni(PPh_3)_2Cl$, etc. The nikkel catalysts and their preparation is described in WO 96/11906, EP-A-613720 or EP-A-384392.

In one embodiment of the invention the reaction is carried out in the presence of a catalytic amount of Cu^+ or Zn^{2+} .

In a particularly preferred embodiment a Nickel(0) complex is prepared *in situ* before the cyanation reaction by reduction of a Nickel(II) precursor such as $NiCl_2$ or $NiBr_2$ by a metal, such as zinc, magnesium or mangan in the presence of excess of complex ligands, preferably triphenylphosphin.

The Ni-catalyst is conveniently used in an amount of 0.5-10, preferably 2-6, most preferably about 4-5 mol%.

Catalytic amounts of Cu^+ and Zn^{2+} , respectively, means substoichiometric amounts such as 0.1 - 5, preferably 1 - 3 eq. %.. Any convenient source of Cu^+ and Zn^{2+} may be used. Cu^+ is

preferably used in the form of CuI and Zn^{2+} is conveniently used as the $Zn(CN)_2$ salt or formed in situ by reduction of a Nikkel (II) compounds using zinc.

In a preferred embodiment of the invention, R chloro.

In a particularly preferred embodiment of the invention a compound of Formula IV wherein R is Cl is reacted with NaCN or KCN in the presence of a $Ni(PPh_3)_3$ which is preferably prepared in situ as described above

The intermediate of Formula **IV** wherein R is bromo or chloro may be prepared from bromo- and chlorophthalide, respectively, as described in DE 2,657,271 and the corresponding US 4,136,193.

The reaction may be performed in any convenient solvent, preferably acetonitril, propionitrile, THF and ethylacetate.

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

The compound of general Formula **I** may be used as the free base 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 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.

The acid addition salts of the compounds 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.

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 tabletting maschine. 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.

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

Examples

The invention is further illustrated by the following examples.

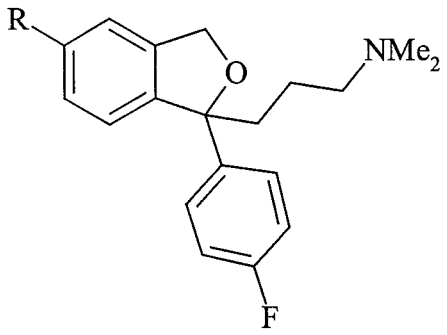
Example 1

Citalopram, Oxalate

Under a nitrogen atmosphere a mixture of $NiCl_2$ (0.077g, 0.006mol) and triphenylphosphine (0.63g, 0.0024 mol) in acetonitrile (50 ml)was heated at reflux for 45 minutes. After cooling to room temperature zinc powder was added (0.39 g, 0.006 mol) at stirred for 15 minutes before a solution of 1-(4´-fluorophenyl)-1-(3-dimethylaminopropyl)-5-chlorophtalane (5.0g, 0.015 mol) in acetonitrile (25 mL) was added. After stirring for a further 10 minutes NaCN (0.32 g, 0.0065 mol) was added and the reaction heated at reflux overnight, cooled , diluted with diethyl ether, and then filtered through celite. The filtrate was washed with brine, dried ($MgSO_4$) and concentrated under reduced pressure. The residue was dissolved in acetone (50mL) and a solution of oxalic acid (1.35g, 0.015mol) in acetone 10mL) was added with stirring. The Citalopram oxalate was isolated by filtration, then recrystalized from ethanol and dried in vacco to pure citalopram, oxalate (3.4g, 55%).

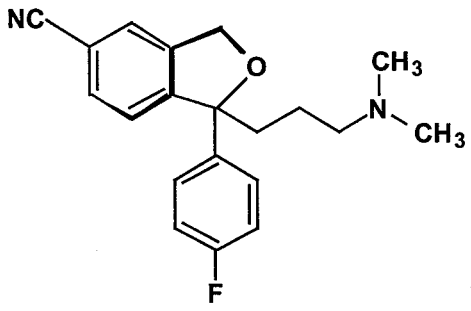
CLAIMS

1. A method for the preparation of citalopram comprising reaction of a compound of Formula **IV**



Formula **IV**

wherein R is Cl or Br with a cyanide source in the presence of a nickel catalyst and isolation of the corresponding 5-cyano compound, i.e. citalopram



Formula **I**

as the base or a pharmaceutically acceptable salt thereof.

2. The method of Claim **1**, wherein R is chloro.

3. The method of Claim **1** or **2** wherein the cyanide source is KCN, NaCN, $Zn(CN)_2$ or $(R'_4N)CN$ where R'_4 indicates four groups which may be the same of different and are selected from hydrogen and straight chain or branched C_{1-6} alkyl,.

4. The method of any of Claims **1 - 3** wherein the cyanide source is NaCN or KCN.

5. The method of any of Claims **1 - 4** wherein the Nickel catalyst is $Ni(PPh_3)_3$ or (σ-aryl)-$Ni(PPh)_2Cl$.

6. The method of any of Claims **1 - 5** wherein the Nickel catalyst is a Nickel(0) complex prepared *in situ* before the cyanation reaction by reduction of a Nickel(II) precursor such as

$NiCl_2$ by a metal, such as zinc, magnesium or mangan in the presence of excess of complex ligands.

7. The method of Claims **6** wherein the Nickel(II) precursor is $NiCl_2$, the metal is zinc, and the complex ligands are triphenylphosphins.

8. The method of Claim **1** wherein a compound of Formula IV wherein R is Cl is reacted with NaCN or KCN in the presence of a $Ni(PPh_3)_3$ catalyst.

9. The method of Claims **10** wherein the $Ni(PPh_3)_3$ is prepared in situ before the cyanation reaction by reduction of $NiCl_2$ by zinc, in the presence of excess of complex triphenylphosphine ligands.

10. The method of any of Claims **1 - 9** wherein the reaction is carried out in the presence of a catalytic amount of Cu^+ , preferably in the form of CuI.

11. The method of any of Claims **1 - 9** wherein the reaction is carried out in the presence of a catalytic amount of Zn^{2+}.

12. The method of any of Claims **1 - 11** wherein compound of Formula **IV** is the S-enatiomer.

13. An antidepressant pharmaceutical composition comprising citalopram manufactured by the process of any of Claims **1 - 12**.