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(54) Title: PROCESS FOR THE PREPARATION OF FLUOXETINE

(57) Abstract

The invention relates to a process for the preparation of N-methyl-[3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl]-amine of the Formula (I) and pharmaceutically acceptable acid addition salts thereof by reaction of N,N-dimethyl-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine of the Formula (III) and ethyl chloro formate and hydrolysis and decarboxylation of the N-methyl-N-ethoxycarbonyl-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine of the Formula (II) and if desired salt formation which comprises carrying out the reaction of the compound of the Formula (III) and ethyl chloro formate in toluene or xylene or a mixture thereof at a temperature below 90 °C; removing the contaminations and by-products from the reaction mixture by treatment with a diluted acid; separating the organic phase which contains the urethane derivative of the Formula (II) and reacting said organic phase, without isolating the urethane derivative of the Formula (II), with an alkali hydroxide at the boiling point of the reaction mixture in the presence of water and optionally n-butanol; removing the inorganic compounds; and if desired converting the base of the Formula (I) thus obtained into a pharmaceutically acceptable acid addition salt thereof. The compounds of the Formula (I) are a known valuable antidepressant.

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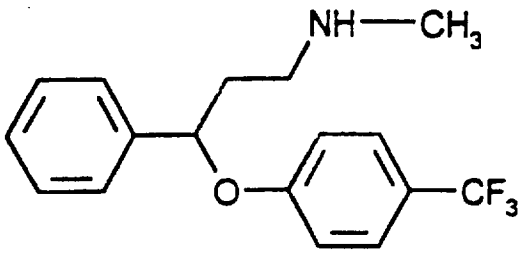
Process for the preparation of fluoxetine

Background of the invention

This invention relates to a new and improved process for the preparation of fluoxetine and pharmaceutically acceptable acid addition salts thereof.

State of the prior art

It is known that N-methyl-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine of the Formula I

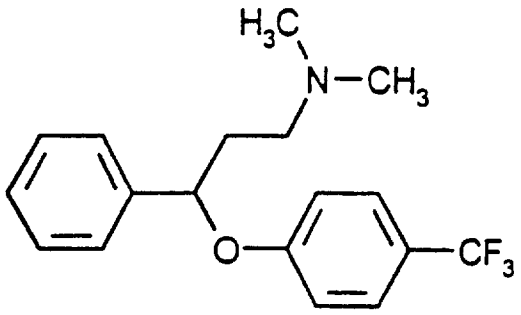


I.

(referred to furtheron as "fluoxetine") is a valuable antidepressant which exhibits its effect by a selective serotonine reuptake inhibiting activity (Hungarian patent № 172,723). In US patent № 4.018,895 the use of fluoxetine for the treatment of depression is described.

According to the Hungarian patent № 173,723 fluoxetine is prepared as follows. The compound 3-dimethylamino-propiophenone is reduced in tetrahydrofurane with diborane, the N,N-dimethyl-(3-hydroxy-3-phenyl-propyl)-amine thus obtained is treated with hydrochloric acid and

thionyl chloride. the N,N-dimethyl-(3-phenyl-3-chloro-propyl)-amine-hydrochloride is heated to boiling with 4-trifluoromethyl-phenol in alkaline medium for 5 days. The N,N-dimethyl-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine of the Formula III



III.

thus obtained is demethylated in two steps. In the first step the dimethylamino derivative of the Formula III is reacted with cyanogene bromide, whereupon the N-methyl-N-cyano-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine is heated to boiling with ethylene glycol in potassium hydroxide at 130°C for 2 hours. The fluoxetine base of the Formula I is purified via the oxalate salt and is finally converted into fluoxetine hydrochloride by reacting with gaseous hydrogen chloride in ether. This process is accompanied by several drawbacks. On the one hand poisonous materials detrimental to the environment (e.g. cyanogene bromide) are used, while on the other the synthesis comprises many steps with a long reaction time and this makes the overall process uneconomical. The total yield is below 20 %. A further disadvantage is that the 4-

trifluoromethyl-phenol is an expensive compound which is not readily available.

According to Hungarian patent № 204,769 fluoxetine of the Formula I is prepared starting from N-benzyl-N-methyl-(2-benzoyl-ethyl)-amine. The starting material is hydrogenated in the presence of a platin-palladium catalyst applied on a carbon support in ethyl acetate in an autoclave with hydrogen gas at 50°C at a pressure of 5.10^5 Pa. The N-methyl-(3-hydroxy-3-phenyl-propyl)-amine thus obtained selectively is O-arylated with 4-chloro-trifluoromethyl-benzene, in N-methyl-pyrrolidone, in the presence of potassium tertiary butylate and potassium iodide. Fluoxetine of the Formula I thus obtained is converted into the hydrochloride. The disadvantage of this process is that the N-methyl-benzyl-amine used as starting material is a difficultly available expensive substance. A further drawback resides in the fact that the process necessitates the use of a special catalyst and the purification of the product is complicated. In the cited patent the specification and availability of the catalyst is not disclosed.

According to Hungarian patent № 207,035 N-methyl-(3-hydroxy-3-phenyl-propyl)-amine is reacted in dimethyl sulfoxide with a small excess of sodium amide, whereupon to the homogeneous reaction mixture at 60-80°C a small excess of 4-chloro-trifluoromethyl-benzene or a solution thereof formed with dimethyl sulfoxide is added. The reaction having been completed the dimethylsulfoxide or a part of the solvent is distilled off in vacuo, the reaction mixture is poured into

water, the fluoxetine of the Formula I thus obtained is extracted, converted into hydrochloride and the salt is recrystallized.

This process has several drawbacks. The reaction must be carried out in anhydrous medium. Moreover on working up the reaction mixture the dimethyl sulfoxide, which is susceptible of thermal decomposition, is to be removed by distillation in vacuo and this step makes the working-up very difficult. An additional disadvantage is the insufficient purity of the product and for this reason recrystallization is to be performed.

The object of Hungarian laid-open patent application № P 92 02128 is to eliminate the above drawbacks. According to this laid-open patent application N-methyl-(3-hydroxy-3-phenyl-propyl)-amine is reacted with a 30 % excess of sodium hydroxide in dimethyl sulfoxide at 100°C for an hour, whereupon to the reaction mixture 4-chloro-trifluoromethyl-benzene is added dropwise and the reaction is made complete by heating at 100-120°C for 10-20 hours. The serious disadvantage of this process resides in the relatively long reaction time. An additional drawback is that dimethyl sulfoxide being strongly decomposable at a higher temperature is used and this renders the working-up of the reaction mixture difficult.

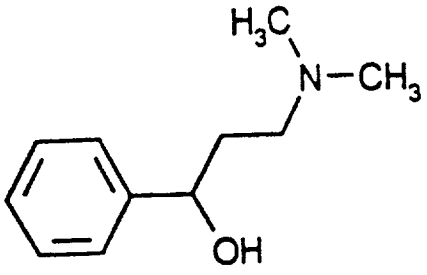
According to Spanish patent № 556,009 fluoxetine of the Formula I is prepared by reacting 4-trifluoromethyl-phenol with a molar equivalent amount of N-ethoxycarbonyl-N-methyl-

(3-phenyl-3-methanesulfonyloxy-propyl)-amine or N-acetyl-N-methyl-(3-phenyl-3-methanesulfonyloxy-propyl)-amine in the presence of alkali hydroxide in alcohol as medium at 60-100°C. The protective group is split off by treatment with 3-6 N mineral acid (e.g. hydrochloric acid, sulfuric acid, hydrogen bromide) in ethanol or aqueous medium or in aqueous ethanol. The reaction is carried out at the boiling point of the reaction mixture. The oily fluoxetine base of the Formula I thus obtained is purified on a silica column. This process is accompanied by several drawbacks. The 4-trifluoromethyl phenol used as starting material is a difficultly available, expensive substance detrimental to health. A further disadvantage resides in the fact that two protective groups are to be introduced onto the propyl amine derivative. The desired compound of the Formula I is formed as a contaminated oil which must be purified on a silica column. On reproducing the process according to Spanish patent № 556,009 it has been found that the hydrolysis of N-methyl-N-ethoxycarbonyl-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine with 4 N hydrochloric acid results a mixture of a small amount of strongly contaminated compound of the Formula I and unreacted starting material as major compound. This process is practically unsuitable for industrial scale production.

According to EP-A 380,924 the compound of the Formula I is prepared by reducing ethyl benzoyl acetate in methanol as medium with sodium borohydride, reacting the ethyl-3-hydroxy-3-phenyl-propionate in alcoholic medium with

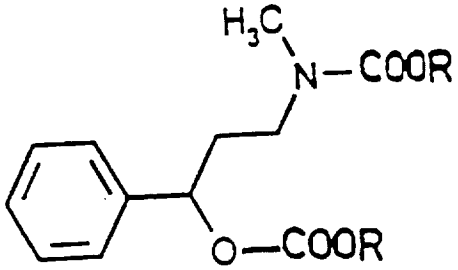
methyl amine and O-arylating the N-methyl-(3-hydroxy-3-phenyl-propionic)-amide in tetrahydrofurane, in the presence of triphenyl phosphine and azodicarboxylic acid, with 4-trifluoromethyl-chloro-benzene. The reaction mixture is worked up, reduced to fluoxetine base of the Formula I in tetrahydrofurane with lithium aluminium hydride, whereon salt formation is carried out in a manner known per se. The process necessitates the use of toxical combustible materials injurious to environment and for this reason the process is not suitable for industrial scale production. A further drawback is that the product obtained is of unsatisfactory purity and therefore complicated expensive purification is required which causes substantial losses.

According to Hungarian laid-open patent application № T/63144 fluoxetine of the Formula I and acid addition salts are prepared via new intermediates. According to this process N,N-dimethyl-(3-hydroxy-3-phenyl-propyl)-amine of the Formula IV



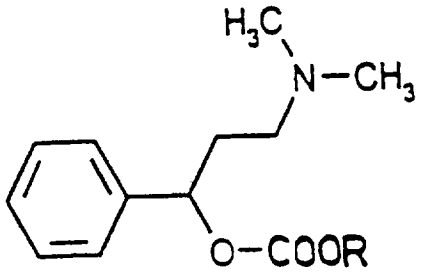
IV.

prepared in a known manner is reacted with ethyl chloro formate in an inert solvent (e.g. toluene) under reflux. As acid binding agent e.g. sodium carbonate, sodium hydrogen carbonate etc. is added. Thus the compound of the Formula VI



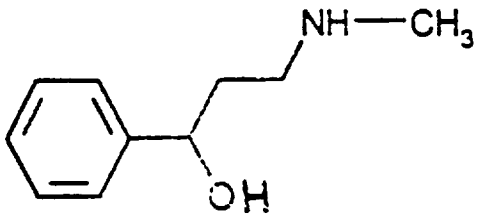
VI.

is obtained. If the reaction is performed in the absence of an acid binding agent, the desired carbamate derivative of the Formula VI is formed via the N,N-dimethyl-3-{phenyl-3-(ethoxycarbonyloxy)-propyl}-amine intermediate of the Formula VIII



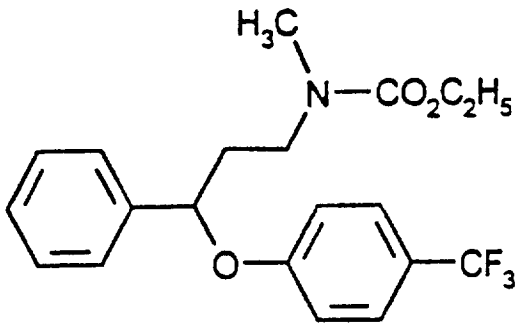
VIII.

in two steps. The carbamate derivative of the Formula VI is heated to boiling in aqueous alkaline ethanol to yield the N-methyl-(3-hydroxy-3-phenyl-propyl)-amine of the Formula VII.



VII.

from this compound sodium salt is formed in N,N-dimethyl acetamide with sodium hydride in a known manner, whereupon the sodium salt thus obtained is O-arylated with 4-chloro-trifluoromethyl-benzene. The hydrochloride is formed in toluene as medium with gaseous hydrogen chloride. The crude fluoxetine hydrochloride is purified by recrystallization from hot water and the hot aqueous solution is optionally treated with charcoal. It is noteworthy that it is specifically mentioned in the laid-open patent application that the N-methyl-N-ethoxycarbonyl-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine of the Formula II



II.

is stable up to 130°C under the alkaline hydrolysis reaction conditions used and the compound of the Formula II resists against alkaline treatment.

The above process has several drawbacks. An alkoxy-carbonyl group is to be introduced onto the hydroxy group and thereafter this group is to be removed. The process consists of many steps. The yields are poor. Moreover a contaminated product is obtained, which is to be purified.

It is noteworthy that - contrary to the compound of the Formula VI - the N-methyl-N-ethoxycarbonyl-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine of the Formula II resists to the reaction conditions of alkaline hydrolysis and is stable up to a temperature of 130°C.

According to EP-A 617,006 N-benzyl-N-methyl-(3-hydroxy-3-phenyl-propyl)-amine is reacted with 4-chloro-trifluoromethyl-benzene in dimethyl acetamide. The N-benzyl-N-methyl-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine obtained is reacted with methyl chloro formate, whereupon the N-methyl-N-methoxycarbonyl-{3-phenyl-3-[4-

(trifluoromethyl)-phenoxy]-propyl}-amine thus obtained is hydrolized into fluoxetine of the Formula I in methanol with sodium hydroxide. The fluoxetine base is converted into oxalate in a manner known per se. The drawback of the process is that two protective groups are to be used. The removal of the two protective groups and the hydrolysis carried out in alkaline-methanolic medium results in a strongly contaminated base of the Formula I, which is purified through the oxalate salt; the latter step is carried out by converting the oxalate salt into the base and forming hydrochloride from the free base.

According to the process disclosed by Robertson et al [J. Labelled Comp. Radiopharm. 24, 1937 (1987)] N,N-dimethyl-(3-hydroxy-3-phenyl-propyl)-amine is etherified with 4-chloro-trifluoromethyl-benzene, whereupon the dimethyl derivative thus obtained is demethylated with the less toxical phenyl-chloro formate in the place of the poisonous cyanogene bromide. However, in this process a strongly contaminated product is obtained which is to be purified by HPLC. The process is expensive and unsuitable for industrial scale production.

Summary of the invention

It is the object of the present invention to eliminate the drawbacks of the known procedures and to elaborate an industrially feasible process for the preparation of fluoxetine of the Formula I which is of high purity and meets the strict requirements of the Pharmacopoeia.

The above object is achieved by the process of the present invention.

According to the present invention there is provided a process for the preparation of N-methyl-[3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl]-amine of the Formula I and pharmaceutically acceptable acid addition salts thereof by reaction of N,N-dimethyl-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine of the Formula III and ethyl chloro formate and hydrolysis and decarboxylation of the N-methyl-N-ethoxycarbonyl-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine of the Formula II and if desired salt formation which comprises carrying out the reaction of the compound of the Formula III and ethyl chloro formate in toluene or xylene or a mixture thereof at a temperature below 90°C; removing the contaminations and by-products from the reaction mixture by treatment with a diluted acid; separating the organic phase which contains the urethane derivative of the Formula II and reacting said organic phase, without isolating the urethane derivative of the Formula II, with an alkali hydroxide at the boiling point of the reaction mixture in the presence of water and optionally n-butanol; removing the inorganic compounds; and if desired converting the base of the Formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof.

Detailed description of the invention

The present invention is based on the recognition that in the course of the preparation of the compound of the Formula I the majority of the contaminations is formed during the demethylation of the compound of the Formula III on the one hand and during the alkaline hydrolysis and decarboxylation of the compound of the Formula II on the other.

The essential elements of the present invention can be summarized as follows:

- acylation is carried out in toluene or xylene as medium;
- the intermediate of the Formula II is not isolated;
- from the reaction mixture the great majority of the contaminations and by-products is substantially removed by extraction with a diluted acid;
- hydrolysis of the urethane derivative of the Formula II is carried out in the presence of water and optionally n-butanol, in the same reaction mixture, at the boiling point of the reaction mixture.

According to the process of the present invention the side-reactions leading to the formation of contaminations are suppressed.

It has been found that when carrying out the reaction of the compound of the Formula III and ethyl chloro formate in place of the hitherto used benzene in toluene or xylene, at a temperature below 90°C and treating the reaction mixture after

the termination of the reaction with a diluted acid, the contaminations are transferred into the aqueous-acidic phase and as organic phase a contamination-free solution of the compound of the Formula II is obtained. The compound of the Formula II is not isolated but directly hydrolized in the toluene or xylene solution.

The reaction of the compound of the Formula III and ethyl chloro formate is carried out in toluene or xylene at 80-90°C. One may work preferably by 80-85°C. As reaction medium industrial xylene consisting of a mixture of o-, m- and p-xylene may also be used. The xylene isomers do not influence the reaction and for this reason pure xylene isomers may be successfully replaced by the industrial xylene consisting of an isomer mixture. The reaction is continued until the evolution of methyl chloride gas stops.

The reaction having been completed the reaction mixture is extracted with an aqueous acid. For this purpose preferably diluted hydrochloric acid may be used. It is preferred to use 0.75-0.85 moles - particularly 0.8 mole - of a diluted mineral acid, particularly diluted hydrochloric acid, related to 1 mole of the starting material of the Formula III. The contaminations are present in the aqueous acidic phase which can be simply separated from the upper organic layer. The organic layer is a clear contamination-free solution of the compound of the Formula II and can be directly used for the alkaline hydrolysis without isolating the compound of the Formula II.

The present invention is based on the further recognition that the compound of the Formula II can be hydrolized with an alkali hydroxide in toluene or xylene as medium in the presence of a small amount of water within a very short reaction time to yield the compound of the Formula I. The recognition is so much the more surprising as it is known from prior art that the trifluoromethyl group is hydrolyzed in alkaline medium to a carboxy group. This according to J. Org. Chem. 26, 2707 (1961) on heating 2-trifluoromethyl-4-nitro-chloro-benzene with potassium hydroxide 5-nitro-salicylic acid is formed as single reaction product. It is disclosed furtheron in J. Am. Chem. Soc. 79, 1745 (1957) that on heating 6-trifluoromethyl-2-indole-carboxylic acid or the methyl ester thereof with a sodium hydroxide solution 2,6-indole-dicarboxylic acid is formed. On treating the corresponding 4-trifluoromethyl isomer with sodium hydroxide 2,4-indole-dicarboxylic acid is obtained in a similar way. According to J. Am. Chem. Soc. 69, 2346 (1947) the reaction of p-trifluoromethyl-phenol and sodium hydroxide yields p-hydroxy-benzoic acid. In the summary of this article the authors state that o- and p-trifluoromethyl-phenols readily decompose under the effect of an aqueous alkali hydroxide solution. In the knowledge of the above teaching of the prior art it could not be aforeseen that when treating the compound of the Formula II in toluene or xylene with an alkali hydroxide the trifluoromethyl group would not enter into reaction but a

contamination-free highly pure compound of the Formula I would be obtained.

The hydrolysis of the compound of the Formula II in methanol or ethanol as medium is very time-consuming and requires about 30 hours. The reaction time may be shortened to about 12-15 hours by carrying out the reaction in ethylene glycol but in this case the quality of the product does not meet the strict requirements of Pharmacopoeia even after repeated purification. The long reaction time and the severe reaction conditions cause the formation of secondary and tertiary decomposition products having very similar chemical-physical properties to the desired compound of the Formula I and for this reason such contaminations can be removed only very difficultly.

It has been found that when carrying out the alkaline hydrolysis of the compound of the Formula II in toluene or xylene as medium in the presence of a small amount of water, the reaction becomes complete within 2-10 hours and at the same time by-products and decomposition products are formed either not at all or only in a minimal amount. The reaction is carried out in the presence of 20-40 ml - preferably 30 ml - of water, related to 1 mole of the urethane derivative of the Formula II. The working-up of the reaction mixture can be facilitated by carrying out hydrolysis in the presence of n-butanol added in the same amount as water. In this case the reaction mixture is more easy to be filtered and during

extraction with water no difficultly decomposable emulsion is formed.

One may proceed preferably by treating the organic phase - obtained on the reaction of the compound of the Formula III with ethyl chloro formate in toluene or xylene as medium, extraction of the reaction mixture with a diluted aqueous acid and separation of the aqueous acidic phase - with alkali hydroxide in the presence of water and n-butanol. As alkali hydroxide sodium hydroxide, potassium hydroxide or a mixture thereof may be used. The reaction is carried out at the boiling point of the reaction mixture. The reaction time is 2-4 hours.

The inorganic compounds (the mixture of the alkali hydroxide used and the salts) may be easily removed from the reaction mixture by filtration or centrifuging. The organic phase containing the compound of the Formula I is washed with water, dried and the base of the Formula I is isolated by evaporating the solution. One may also proceed by directly precipitating a pharmaceutically acceptable acid addition salt from the toluene or xylene solution by adding a solution of the desired mineral acid formed with an organic solvent. According to a particularly preferred embodiment of the process the hydrochloride of the compound of the Formula I is directly precipitated from the toluene or xylene solution with ethyl acetate containing hydrochloric acid. This method provides directly, without a further purification, Pharmacopoeia-grade compound of the Formula I.

The pharmaceutically acceptable acid addition of the compounds of the Formula I may be formed with inorganic or organic acids (e.g. hydrogen halides, carbonate, hydrogen carbonate, sulfate, acetate, fumerate, maleate, citrate, ascorbinate etc.). For pharmaceutical purposes the hydrochloride of the compound of the Formula I is particularly advantageous.

The advantages of the process of the present invention can be summarized as follows:

- the process is carried out without isolating the urethane of the Formula II ("one-pot-process");
- during demethylation of the compound of the Formula III only a minimal amount of by-products is formed;
- the by-products formed in small amount in the course of the reaction can be simply removed;
- under the reaction conditions used hydrolysis and decarbolyation take place very quickly - i.e. by one order of magnitude more rapidly -, consequently the reaction time is much shorter and the side-reactions are suppressed;
- the inorganic salts formed during the reaction can be simply removed from the reaction mixture by filtration or centrifuging;
- the desired compound of the Formula I precipitates from the water non-miscible organic solvents as the

preferred hydrochloride in a pure form which can be readily filtered even on industrial scale production;

- the use of starting materials detrimental to health and environment is eliminated;
- a high quality product meeting the requirements of Pharmacopoeia is obtained with good yields.

Further details of the present invention are to be found in the following Examples without limiting the scope of protection to said Examples.

Example 1

N-methyl-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine

22.1 g (0.0683 mole) of N,N-dimethyl-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine are dissolved in 75 ml of xylene. For this purpose a commercially available mixture of o-, m- and p-xylene is used which contains about 20 % by weight of o-xylene, about 60 % by weight of m-xylene and about 20 % by weight of p-xylene. To this solution at 80-85°C under stirring a solution of 22.4 g (0.203 mole) of ethyl chloro formate and 20 ml of xylene is added dropwise. The reaction mixture is stirred at this temperature until the evolution of gaseous methyl chloride stops.

The reaction mixture is diluted with 25 ml of xylene, whereupon it is extracted with a mixture of 5 ml of concentrated hydrochlorid acid and 20 ml of water. The lower acidic-aqueous phase is separated, the organic layer is washed with 10 ml of an N sodium hydroxide solution. The xylene phase is separated and diluted with fresh xylene to 140 ml. According to gas chromatography the solution contains 22.4 g of N-methyl-N-ethoxycarbonyl-{3-phenyl-3-[4-(trifluoro methyl)-phenoxy]-propyl}-amine (urethane).

To the xylene solution 27.32 g (0.683 mole) of sodium hydroxide, 1.85 ml of water and 1.85 ml of n-butanol are added. The reaction mixture is heated to boiling under strong stirring. The reaction time is 3.5 hours. The end-point of the reaction is detected by thin layer chromatography (TLC).

(Eluent: a 9:1:1 mixture of methanol, dichloromethane and ammonium hydroxide; sorbent:silicagel; development: UV light; iodine, Dragendorff-reagent.)

The reaction having been completed the reaction mixture is cooled to 25°C, filtered in vacuo through a sintered glass filter and the precipitated product is washed with xylene. The organic phase is washed three times with 40 ml of water each to pH 4 and dried over anhydrous magnesium sulfate. The xylene solution is acidified with a calculated amount of hydrogen chloride in ethyl acetate (hydrogen chloride content about 10-20 %), the precipitated crystals are filtered and dried to constant weight. Thus 17.06 g of N-methyl-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine hydrochloride are obtained in the form of white crystals.

Yield: 83.95 %.

Purity (TLC): maximum 1 strange spot (maximum 1 % impurity).

Mp.: 155-158°C.

Content (based on the base): 98.5-101.5 %

HPLC content: 98.5-101.5 %

HPLC impurities:

- total max. 1.5 %;
- impurities of unknown origin, each max. 0.1 %;
- impurities of known origin (intermediates, products of decomposition), each max. 0.3 %.

The product complies with the requirements of BP and USP.

Example 2

N-methyl-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine

87.4 g (0.27 mole) of N,N-dimethyl-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine and 300 ml of toluene are introduced into an apparatus equipped with a stirrer. To the solution under heating and stirring at 80°C a solution of 89.7 g (0.81 mole) of ethyl chloro formate and 68 ml of toluene is added dropwise. The temperature of the reaction mixture amounts to 80-82°C. Heating and stirring is continued until the evolution of methyl chloride stops. The reaction mixture is diluted with 100 ml of toluene whereupon a mixture of 20.6 ml of concentrated hydrochloric acid and 80 ml of water is added dropwise under stirring within 5 minutes. The layers are separated. The organic phase contains 92.7 g (90 %) of N-methyl-N-ethoxycarbonyl-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine.

The compound obtained according to the previous paragraph is hydrolized with a mixture of 45 g of potassium hydroxide and 65.2 g of sodium hydroxide while 7.66 ml of water and 7.66 ml of n-butanol are added. The reaction mixture is heated to boiling under stirring for 8 hours, whereby the boiling point decreases from 110°C to 106°C (external temperature 134-136°C). The reaction mixture is worked up as described in Example 1. Thus 65.6 g of the desired compound are obtained in the form of the hydrochloride, yield 78 %. The

purity of the product is identical with that of the product obtained according to Example 1.

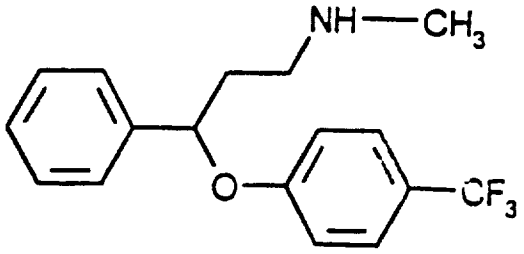
Example 3

One proceeds as described in Example 2 except that hydrolysis of N-methyl-N-ethoxycarbonyl-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine is carried out with 97.2 g of sodium hydroxide, under adding 7.66 ml of water and 7.66 ml of n-butanol. Reaction time 8 hours.

Thus 74 g of N-methyl-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine-hydrochloride are obtained, yield 88 %. The purity of the product is identical with that prepared according to Example 2.

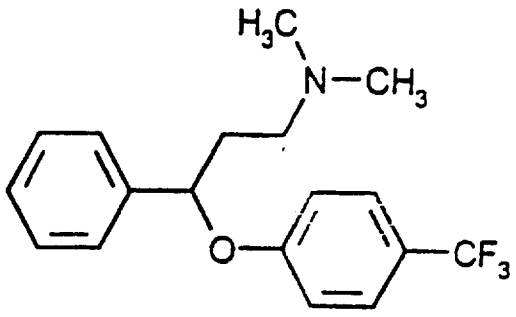
What we claim is,

1. Process for the preparation of N-methyl-[3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl]-amine of the Formula I



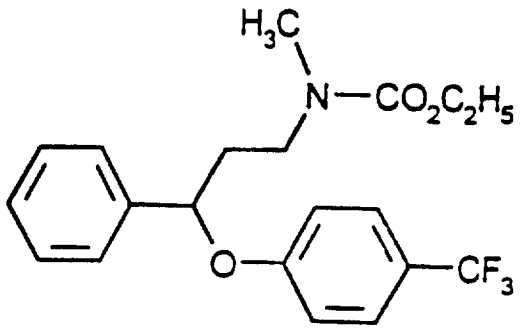
I.

and pharmaceutically acceptable acid addition salts thereof by reaction of N,N-dimethyl-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine of the Formula III



III.

and ethyl chloro formate and hydrolysis and decarboxylation of the N-methyl-N-ethoxycarbonyl-{3-phenyl-3-[4-(trifluoromethyl)-phenoxy]-propyl}-amine of the Formula II



II.

and if desired salt formation which comprises carrying out the reaction of the compound of the Formula III and ethyl chloro formate in toluene or xylene or a mixture thereof at a temperature below 90°C; removing the contaminations and by-products from the reaction mixture by treatment with a diluted acid; separating the organic phase which contains the urethane derivative of the Formula II and reacting said organic phase, without isolating the urethane derivative of the Formula II, with an alkali hydroxide at the boiling point of the reaction mixture in the presence of water and optionally n-butanol; removing the inorganic compounds; and if desired converting the base of the Formula I thus obtained into a pharmaceutically acceptable acid addition salt thereof.

2. Process according to Claim 1 which comprises carrying out the reaction of the compound of the Formula III and ethyl chloro formate at 80-90°C, preferably at a temperature between 80°C and 85°C.

3. Process according to Claim 1 or 2 which comprises adding to the reaction mixture which contains the urethane derivative of the Formula II a mineral acid in an amount of 0.75-0.85 mole, related to 1 mole of the starting material of the Formula III.

4. Process according to Claim 3 which comprises using 0.8 mole of diluted hydrochlorid acid, related to 1 mole of the compound of the Formula III.

5. Process according to any of Claims 1-4 which comprises adding to the organic phase which contains the urethane derivative of the Formula II sodium hydroxide and/or potassium hydroxide.

6. Process according to Claim 5 which comprises using a 1:99-99.1 mixture of potassium hydroxide and sodium hydroxide.

7. Process according to any of Claims 1-6 which comprises carrying out hydrolysis of the compound of the Formula II in the presence of 20-40 ml of water, related to 1 mole of the compound of the Formula II.

8. Process according to any of Claims 1-7 which comprises carrying out hydrolysis of the compound of the Formula II in the presence of 20-40 ml of n-butanol, related to 1 mole of the compound of the Formula II.

INTERNATIONAL SEARCH REPORT

Intern al Application No
PCT/HU 97/00050

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07C213/08 C07C217/48

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 C07C

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	US 4 018 895 A (BRYAN B. MOLLOY ET AL.) 19 April 1977 cited in the application see example 1	1-8
A	EP 0 617 006 A (PLIVA D.D. ZAGREB) 28 September 1994 cited in the application see claims; examples 7,8	1-8
A	EP 0 529 842 A (TEVA PHARMACEUTICAL INDUSTRIES) 3 March 1993 cited in the application see page 6, column 21 - column 50; claims	1-8

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 January 1998	20/01/1998

Name and mailing address of the ISA	Authorized officer
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