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(54) Title: PROCESS FOR PREPARING ITOPRIDE HYDROCHLORIDE

(57) Abstract: Process for preparing itopride hydrochloride comprising: a) Reacting 4-hydroxybenzaldehyde with 2-dimethylaminoethyl chloride in the 5 presence of a weak inorganic base to obtain 4-(2-dimethylaminoethoxy)- benzaldehyde, b) Reacting 4-(2-dimethylaminoethoxy)-benzaldehyde with hydroxylamine hydrochloride in an acid environment to obtain 4-(2-dimethylaminoethoxy)- benzaldoxime hydrochloride, 10 c) Reacting of 4-(2-dimethylaminoethoxy)-benzaldoxime hydrochloride in the presence a reducing agent to 4-(2-dimethylaminoethoxy)-benzylamine, d) Reacting 4-(2-dimethylaminoethoxy)-benzylamine with veratric acid chloride in the presence of a tertiary amine to obtain itopride, e) Salifying itopride with hydrochloric acid to obtain itopride hydrochloride, 15 characterized in that the reducing agent employed in step (c) is powdered zinc.

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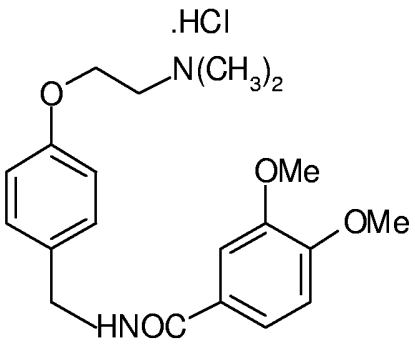
PROCESS FOR PREPARING ITOPRIDE HYDROCHLORIDE

Field of the invention

The present invention relates to a process for preparing itopride hydrochloride.

State of the art

Itopride hydrochloride, characterized by the following formula



is a drug capable of activating motor function.

In EP306827 the relative synthesis is described, involving the following steps: 4-hydroxybenzaldehyde is reacted with 2-dimethylaminoethyl chloride in the presence of a weak inorganic base to obtain 4-(2-dimethylaminoethoxy)-benzaldehyde, which is reacted with hydroxylamine hydrochloride to obtain 4-(2-dimethylaminoethoxy)-benzaldoxime, subsequently reduced by catalytic hydrogenation, in particular using Nickel Raney, to 4-(2-dimethylaminoethoxy)-benzylamine, which is subsequently reacted with veratric acid chloride in the presence of a tertiary amine to obtain itopride, which is then salified with an ethanol solution in which gaseous hydrochloric acid is dissolved.

This process has a drawback caused by the use, in the reducing step of the oxime to the corresponding amine, of hydrogen, in other words a highly explosive gas and moreover at high pressure (50 kg/cm ^{2}) for which expensive equipment (autoclaves and hydrogen lines) must be used.

Moreover it is necessary to use a costly and easily flammable catalyst like Nickel Raney, which moreover is highly polluting, and therefore its disposal requires costly and laborious processes for the treatment of waste water.

Summary of the invention

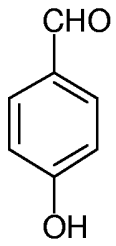
The Applicant has now found that with the process forming the object of the present invention the aforesaid drawbacks can be overcome.

In particular, the process of the present invention differs mainly for the use in reducing step of 4-(2-dimethylaminoethoxy)-benzaldoxime to 4-(2-dimethylaminoethoxy)-benzylamine of powdered Zinc as reducing agent.

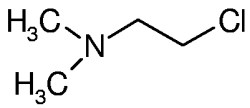
Detailed description of the invention

In particular, the process according to the present invention which comprises the following steps:

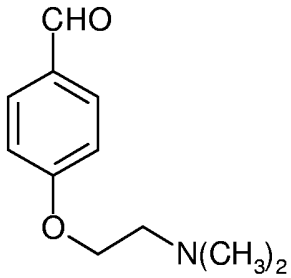
a) Reacting 4-hydroxy-benzaldehyde



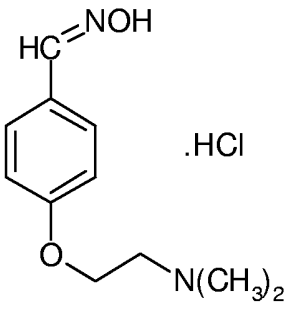
with 2-dimethylaminoethyl chloride



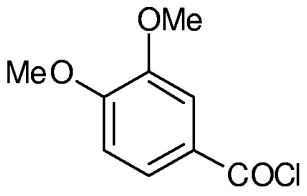
in the presence of a weak inorganic base to obtain 4-(2-dimethylaminoethoxy)-benzaldehyde



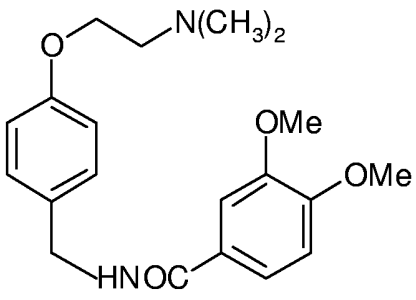
b) reacting 4-(2-dimethylaminoethoxy)-benzaldehyde with hydroxylamine hydrochloride in an acid environment to obtain 4-(2-dimethylaminoethoxy)-benzaldoxime hydrochloride



c) reducing 4-(2-dimethylaminoethoxy)-benzaldoxime hydrochloride in the presence of a reducing agent to 4-(2-dimethylaminoethoxy)-benzylamine



d) reacting 4-(2-dimethylaminoethoxy)-benzylamine with veratric acid chloride to obtain itopride



e) salifying itopride with hydrochloric acid to obtain itopride hydrochloride, is characterized in that in the reducing step (c) of 4-(2-dimethylaminoethoxy)-benzaldoxime hydrochloride to 4-(2-dimethylaminoethoxy)-benzylamine powdered Zinc is used as reducing agent.

The reducing reaction is preferably carried out in an acidic aqueous solution of an organic acid, preferably concentrated acetic acid, more preferably 80% in weight.

According to a particularly preferred solution, the reducing reaction (c) is carried out directly on the reaction mixture obtained from step (b) and not on the previously isolated benzaldoxime.

This represents a further advantage compared to the process described in EP306827 where the reducing reaction is carried out on the previously isolated benzaldoxime.

Preferably, 4-(2-dimethylaminoethoxy)-benzylamine obtained from reducing reaction (c) is salified with hydrochloric acid to obtain the corresponding dihydrochloride salt. In this way the benzylamine is isolated from the impurities and by-products obtained in the reducing reaction, to obtain an HPLC purity higher than 98%.

In this way and unlike the case of the process described in EP306827, the itopride in step (d) is obtained with high purity; therefore, not only is it no longer necessary to purify it through crystallization prior to salification, but wet itopride separated by means of simple centrifugation of the reaction mixture obtained from step (d) of the process of the invention, is actually used as starting reactant during salification step (c).

Another preferred embodiment of the process forming the subject of the present invention is based on the fact that in the salification reaction of itopride, to obtain the corresponding itopride hydrochloride, concentrated aqueous hydrochloric acid (37%) in an alcohol solvent, preferably sec-butanol, is used instead of gaseous hydrochloric acid dissolved in an alcohol solvent.

In fact, with this type of salification, a product is obtained with a purity higher than 99.8% and which therefore does not require further purification by means of crystallization which cause inevitable decreases of the reaction yield.

Therefore, a further subject of the present invention is a salification process of itopride with hydrochloric acid characterized in that concentrated aqueous hydrochloric acid is used in an alcohol solution, in which the alcohol is preferably sec-butanol.

Step (a) is preferably carried out in phase transfer in the presence of a catalyst consisting of a quaternary ammonium salt.

Even more preferably, in step (a) a mixture of ethyl acetate, toluene and water is used as the solvent and the quaternary ammonium salt is tetrabutylammonium bromide.

The following examples of the process to prepare itopride hydrochloride and the relative intermediates according to the present invention are indicated for illustrative and non-limiting purposes.

EXAMPLE 1 - Preparation of 4-(2-dimethylaminoethoxy)benzaldehyde

17.5 kg of 2-dimethylaminoethylchloride hydrochloride, 75 kg of deionized water and 2.50 kg of toluene are charged into a batch, 17.5 kg of 30% sodium hydroxide are then dropped into. The mixture obtained is kept under stirring until complete solution of the solid. The aqueous phase is removed while the organic phase is used for the following preparation.

10 kg of 4-hydroxy-benzaldehyde, 12.5 kg of potassium carbonate, 0.27 kg of tetrabutylammonium bromide and 70 kg of ethyl acetate are charged into a reactor. The mixture obtained is heated under reflux and then the aforesaid toluene solution is added dropwise.

The mixture is kept under stirring and reflux for at least 5 hours.

50 kg of deionized water are then added, the mixture obtained is stirred for at least 5 minutes, the aqueous phase is removed and the organic phase is distilled, to obtain an oily residue. The residue is cooled to 20-30°C and 35 kg of 80% acetic acid are added dropwise.

The reaction mixture is then stirred for 5 minutes until complete solution.

A solution containing 13.5 kg of 4-(2-dimethylaminoethoxy)-benzaldehyde is obtained. Reaction yield referred to 4-hydroxybenzaldehyde: 85.33%

EXAMPLE 2 - Preparation of 4-(2-dimethylaminoethoxy)-benzylamine

27 kg of 80% acetic acid are charged into a reactor, 5.3 kg of hydroxylamine hydrochloride are added, the mixture is cooled to 0-5°C and the solution prepared in the previous step containing 13.5 kg of 100% 4-(2-dimethylaminoethoxy)-benzaldehyde in acetic solution is added. The reaction mixture is kept at 0-5°C for at least 2 hours.

When the reaction is complete, 10.8 kg of powdered zinc are added in portions, allowing the temperature to rise up to a maximum of 50°C.

This mixture is kept under stirring at 45-50°C for at least 5 hours, and then heated to 65-70°C for at least 2 hours. Upon completion of the reaction, the reaction mixture is distilled to obtain a dense but stirrable residue.

20.3 kg of deionized water are then added to the residue thus treated, the mixture thus obtained is cooled to 20-30°C and 54 kg of 30% ammonia are added dropwise. The reaction mixture is then stirred at 20-30°C for at least 10 minutes, the pH is checked to ensure it is above 9.5. The reaction mixture is then extracted at 20-25°C with 40.5 kg of methylene chloride. The organic phase is separated while the aqueous phase is reextracted with 27 kg of methylene chloride and the mixture is stirred for at least 5 minutes; the organic phase is added to the previous organic phase. Then the solvent is removed until an oily residue is obtained.

54 kg of sec-butanol and 20.3 kg of N,N – dimethylformamide are added. The solution thus obtained contains 11.5 kg of 4-(2-dimethylaminoethoxy)-benzylamine Yield: 84.7%.

EXAMPLE 3 - Preparation of 4-(2-dimethylaminoethoxy)benzylamine dihydrochloride

11.5 kg of 4-(2-dimethylaminoethoxy)-benzylamine dissolved in sec-butanol and DMF obtained as described in the previous example are charged into a reactor and 12.7 kg of 37% hydrochloric acid are added dropwise. The pH is checked to ensure it is <1.0 and the precipitated mixture is stirred at 45-50°C for at least 30 minutes.

The mixture is cooled to 0-5°C, centrifuged and the precipitate washed with 11.5 kg of sec-butanol. It is dried under vacuum at 70-80°C. 13.5 kg of 4-(2-dimethylaminoethoxy)benzylamine dihydrochloride are obtained with HPLC purity higher than 98%. Reaction yield calculated on the 4-(2-dimethylaminoethoxy)-benzylamine 85.8%.

EXAMPLE 4 - Preparation of itopride

10.1 kg of veratric acid and 27.0 kg of toluene are charged into a reactor, the mixture is heated under reflux (105-115°C) and 7.4 kg of thionyl chloride are added dropwise. The mixture is kept under reflux for at least 2 hours, and is

distilled under vacuum, to obtain an oily residue which 10.1 kg of toluene are added to. The solution is then brought to 20-50°C, and the aforesaid reaction mixture is added dropwise to a stainless steel reactor, which 13.5 kg of 4-(2-dimethylaminoethoxy)-benzylamine dihydrochloride, 81 kg of toluene, 11.5 kg of triethylamine, were previously charged into, at a temperature ranging from 75 to 80°C.

After adding the reaction mixture dropwise, the reaction mixture thus obtained is stirred at 75-80°C for at least two hours. Upon completion of the reaction, 40.5 kg of deionized water are added, 11.5 kg of 30% ammonia are added dropwise and the reaction mixture is taken to 55-60°C until complete solution. The aqueous phase is separated and removed. 27.0 kg of deionized water are added and the mixture is cooled to 40-45°C until obtaining a good degree of precipitation.

The mixture is then centrifuged, the precipitate is washed with 10.1 kg of deionized water and the same quantity of toluene.

A sample of product is taken and the loss of weight determined; this analysis shows that the wet product contains 16 kg of dry itopride.

Reaction yield compared to 4-(2-dimethylaminoethoxy) benzylamine dihydrochloride: 88.3%.

EXAMPLE 5 - Preparation of itopride hydrochloride

The equivalent wet product corresponding to 16 kg of dry itopride coming from Example 4 and 56 kg of sec-butanol are charged into a reactor and heated to 50-55°C until solution. 4.8 kg of 37% hydrochloric acid are added dropwise, the pH is checked to ensure it is <2.0, and the mixture is stirred at 50-55°C for at least 30 minutes; it is cooled to 15-25°C and it is then centrifuged, the precipitate is washed with 16.0 kg of sec-butanol. The product is then dried at 70-80°C. 16.5 kg of itopride hydrochloride with HPLC purity higher than 99.8% are obtained. Reaction yield compared to itopride: 93.7%.

CLAIMS

1. Process for preparing itopride hydrochloride comprising:

a) Reacting 4-hydroxybenzaldehyde with 2-dimethylaminoethyl chloride in the presence of a weak inorganic base to obtain 4-(2-dimethylaminoethoxy)-benzaldehyde,

b) Reacting 4-(2-dimethylaminoethoxy)-benzaldehyde with hydroxylamine hydrochloride in an acid environment to obtain 4-(2-dimethylaminoethoxy)-benzaldoxime hydrochloride,

c) Reducing 4-(2-dimethylaminoethoxy)-benzaldoxime hydrochloride in the presence of a reducing agent to 4-(2-dimethylaminoethoxy)-benzylamine,

d) Reacting 4-(2-dimethylaminoethoxy)-benzylamine with veratric acid chloride in the presence of a tertiary amine to obtain itopride,

e) Salifying itopride with hydrochloric acid to obtain itopride hydrochloride,

characterized in that the reducing agent employed in step (c) is powdered zinc.

2. Process as claimed in claim 1, characterized in that the reducing reaction of step (c) is carried out in an acidic aqueous solution of an organic acid.

3. Process as claimed in claim 2, characterized in that said organic acid is concentrated acetic acid.

4. Process as claimed in claim 3, characterized in that said concentrated 80% acetic acid by weight.

5. Process as claimed in claim 1-4, characterized in that the reducing reaction of step (c) is carried out directly on the reaction mixture obtained from step (b).

6. Process as claimed in any one of claims 1-5, characterized in that 4-(2-dimethylaminoethoxy)-benzylamine obtained from the reducing reaction of step (c) is salified with hydrochloric acid to obtain the corresponding dihydrochloride salt.

7. Process as claimed in any one of claims 1-6, characterized in that concentrated aqueous hydrochloric acid in an alcohol solvent is used in the salification reaction of the itopride of step (e).

8. Process for salifying itopride to the corresponding itopride hydrochloride with a purity higher than 99.8% consisting in treating said itopride with concentrated aqueous hydrochloric acid (37%) in an alcohol solvent.

9. Process as claimed in claim 7 or 8, characterized in that said alcohol is sec-butanol.

10. Process as claimed in any one of claims 1-7, 9 characterized in that step (a) is carried out in phase transfer catalysis in the presence of a catalyst consisting of a quaternary ammonium salt.

11. Process as claimed in claim 10, characterized in that in step (a) a mixture of ethyl acetate, toluene and water is used as the solvent and the quaternary ammonium salt is tetrabutylammonium bromide.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/055839

A. CLASSIFICATION OF SUBJECT MATTER
C07C231/10 C07C235/48 C07C235/60

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)
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)
EPO-Internal, CHEM ABS Data, BEILSTEIN Data, WPI Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	EP 0 306 827 A (HOKURIKU PHARMACEUTICAL CO.,LTD) 15 March 1989 (1989-03-15) cited in the application page 3, line 1 - page 6, line 17; claims 1-11 ; Reference 7	1-11
Y	EP 0 388 188 A (SUNTORY LIMITED) 19 September 1990 (1990-09-19) Reference example 4; page 3, line 39 - page 4, line 15	1-11

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
27 February 2006	06/03/2006

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Butkowskyj-Walkiw, T

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/055839

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JUN SAKAGUCHI ET AL: "Synthesis, Gastrointestinal Prokinetic Activity and Structure-Activity Relationships of Novel N-''2-(Dialkylamino)ethoxy!benzyl!-benzamide Derivatives" CHEMICAL AND PHARMACEUTICAL BULLETIN, PHARMACEUTICAL SOCIETY OF JAPAN, TOKYO, JP, vol. 40, no. 1, 1992, pages 202-211, XP002152593 ISSN: 0009-2363 page 1; table I; compounds II-41	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2005/055839

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0306827 A	15-03-1989	AU 606988 B2	21-02-1991
		AU 2186288 A	09-03-1989
		BG 48932 A3	14-06-1991
		CA 1335101 C	04-04-1995
		DE 3864636 D1	10-10-1991
		DK 492288 A	06-03-1989
		ES 2037779 T3	01-07-1993
		FI 884077 A	06-03-1989
		HU 47531 A2	28-03-1989
		KR 9400058 B1	05-01-1994
		SU 1627082 A3	07-02-1991
		US 4983633 A	08-01-1991
		YU 160088 A1	30-06-1990
EP 0388188 A	19-09-1990	DE 69005861 D1	24-02-1994
		DE 69005861 T2	28-04-1994
		DK 388188 T3	14-02-1994
		ES 2062336 T3	16-12-1994
		JP 2243687 A	27-09-1990
		JP 2851054 B2	27-01-1999
		US 5041444 A	20-08-1991