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(54) **Title:** A PROCESS FOR THE PREPARATION OF NARATRIPTAN HYDROCHLORIDE

(57) **Abstract:** The present invention provides a process for the preparation of Naratriptan hydrochloride which comprises decarboxylation of 5-{2-[(methylamino) sulfonyl] ethyl}-1H-indole-2-carboxylic acid to get 2-(1H-indol-5-yl)-N-methylethanesulfonamide using sulfolane as a solvent, and further reacting 2-(1H-indol-5-yl)-N-methylethanesulfonamide to obtain Naratriptan hydrochloride.

WO 2009/016466 A2

A PROCESS FOR THE PREPARATION OF NARATRIPTAN HYDROCHLORIDE

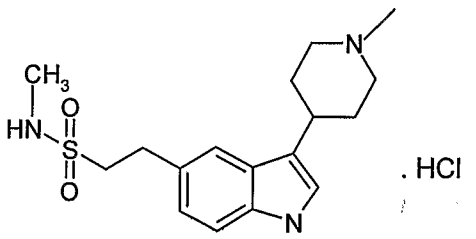
The following specification describes the nature of the invention and the manner in which it has to be performed.

Field of the invention

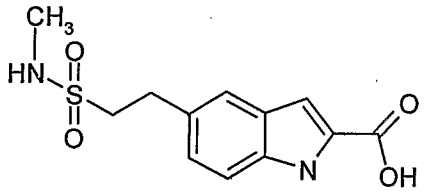
The present invention relates to an improved process for the preparation of Naratriptan and its pharmaceutically acceptable salt, an antimigraine drug.

Background of the invention

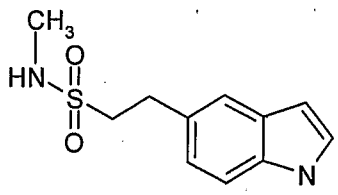
Naratriptan hydrochloride is a selective 5-hydroxytryptamine-1 receptor subtype agonist. It is chemically designated as N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulfonamide monohydrochloride and represented by the following formula I



I



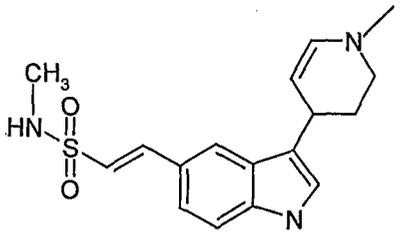
II



III

2-(1H-indol-5-yl)-N-methylethane sulfonamide of formula III is one of the key intermediates in the synthesis of Naratriptan hydrochloride, which is obtained by decarboxylation of 5-{2-[methylamino)sulfonyl]ethyl}-1H-indole-2-carboxylic acid of formula II.

N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulfonamide and its physiologically acceptable salts are reported in British patent GB2208646 for the treatment of human suffering from migraine, cluster headache and chronic paroxysmal hemicrania. This patent describes a process for the preparation of Naratriptan hydrochloride by reducing the N-methyl-2-[3-(1,2,3,6-tetrohydro-1-methyl-4-pyridinyl)-1H-indol-5-yl]-ethenesulphonamide of formula IV



IV

The Journal of Organic Chemistry 1957 (22), 85 describes that 7-nitroindole is obtained by decarboxylation of 7-nitroindole-2-carboxylicacid using quinoline and trace of copper chromate.

Another article Synthetic Communications 22(14), 2103-2109, (1992) describes the decarboxylation of 6-methoxyindole 2-carboxylicacid by using copper powder and quinoline solution to obtain 6-methoxyindole.

Most of the prior art processes used quinoline as a solvent for decarboxylation, which is sparingly soluble in water and hence needs high temperature to dissolve. The present inventors surprisingly found that the decarboxylation of indole carboxylic acid using copper or copper salts and sulfolane overcomes the drawbacks associated with the prior art processes.

US patents 4,997,841 describes a process for preparation of N-methyl-3-(1-methyl-4-piperidinyl)-1H-indole-5-ethanesulfonamide which is obtained by condensation of 1-methylpiperidine-4-one with 2-(1H–indol-5yl)-N-methylethanesulfonamide in presence of methanol and followed by reduction. The obtained compound is purified by flash chromatography.

In most of the prior art process, where the condensation is carried out only in an alcohol, the duration of the reaction is longer. Further the purification of the reduced product i.e. Naratriptan base is carried out by flash chromatography which is not feasible at industrial scale.

The present inventors found that using water along with alcohol for the condensation of 1-methylpiperidine-4-one with 2-(1H–indol-5yl)-N-methylethanesulfonamide not only reduces the reaction time but it reduces the formation of impurity significantly. The inventors also surprisingly found that purification of the Naratriptan base by using an organic solvent or a mixture of it with water, gives a highly pure product.

The present invention has following advantages.

1. The process involves simple and cheap reagents like ethyl pyruvate, HBr in acetic acid, sulfolane etc.,
2. Decarboxylation of indole-2-carboxylic acid is carried out in sulfolane with Copper salts specially Copper oxide out at 185-200°C, which is highly soluble in water.
3. The workup after decarboxylation is simple as compared to the prior arts in which Quinoline with copper and its salt is used at temp. ranging from 200-240°C.
4. Hydrogenation of *N*-methyl-2-[3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indol-5-yl]ethane sulfonamide is carried out in a mixture of methanol 10 volume and 0.5 volume of acetic acid with 5% wet Pd/C at 60 psi. Whereas, the prior are process uses a mixture of methanol in dimethyl formamide in higher volumes.

Object of the invention

The main objective of the present invention is to provide a novel process for the preparation of Naratriptan Hydrochloride.

Another objective of the present invention is to provide a process which results in better yield and purity.

Yet another objective of the process is to provide a process, which is more economical and commercially viable in industrial scale.

Summary of the invention

The present invention provides a process for the preparation of Naratriptan and its pharmaceutical acceptable salts comprising the steps of:

a) condensation of 2-(4-hydrazinophenyl)-N-methylethanesulfonamide of Formula V with ethyl 2-oxopropanate of formula VI to get Ethyl (2Z)-2-[(4-{methylamino) sulfonyl]ethyl}phenyl) hydrazono] propanate of formula VII;

b) cyclisation of compound of formula VII to obtain ethyl 5-{2-[(methylamino) sulfonyl] ethyl}-1H-indole-2-carboxylate of formula VIII;

c) saponification of formula VIII to get 5-{2-[(methylamino) sulfonyl] ethyl}-1H-indole-2-carboxylic acid of formula II;

d) decarboxylation of formula II in presence of sulfolane and copper salts to get 2-(1H-indol-5-yl)-N-methylethanesulfonamide of formula III;

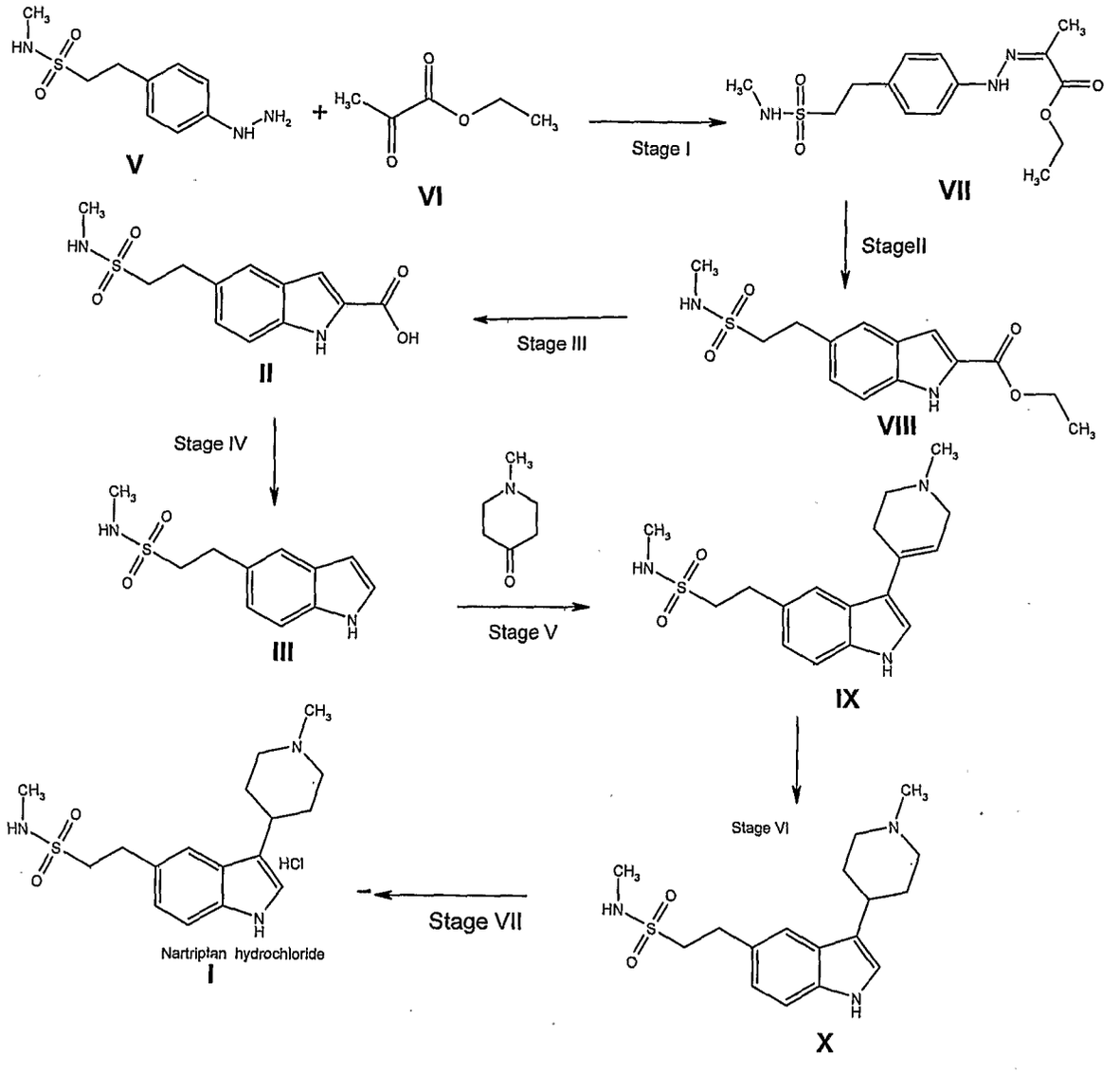
e) condensation of formula III with 1-methylpiperidin-4-one using an organic solvent or its mixture with water to get N-methyl-2-[3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-5-yl]ethanesulfonamide of formula IX;

f) hydrogenation of Formula IX to get Naratriptan free base of formula X;

g) optionally purifying Naratriptan free base of formula X in aqueous organic solvent; and

h) conversion of Naratriptan free base of formula X to its pharmaceutically acceptable salts.

The above process may be represented by the following reaction scheme:



Detailed description of the invention

In an embodiment of the present invention the condensation of 2-(4-hydrazinophenyl)-N-methylethanesulfonamide of Formula V with ethyl 2-oxopropanate of formula VI to get Ethyl (2Z)-2-[(4-{methylamino) sulfonyl]ethyl}phenyl) hydrazono] propanate of formula VII is carried out in an alcohol selected from the group consisting of methanol, ethanol, propanol and isopropanol, preferably methanol.

In another embodiment of the present invention the cyclisation is carried out using HBr in acetic acid.

In another embodiment of the present invention saponification is carried out in aqueous alkali solution, where alkali solution is selected from NaOH, KOH and the like,

In another embodiment of present invention, the decarboxylation of 5-{2-[(methylamino) sulfonyl] ethyl}-1H-indole-2-carboxylic acid is carried out using catalytic amount of copper or copper salts and sulfolane as a solvent.

In another embodiment of present invention, the condensation of 2-(1H-indol-5-yl)-N-methylethanesulfonamide with 1-methylpiperidin-4-one is carried out in presence of alkali using Organic or aqueous organic solution, wherein, organic solvent is selected from methanol, ethanol, n-propanol, isopropanol and the like, preferably methanol.

In yet another embodiment of present invention, the hydrogenation of N-methyl-2-[3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-5-yl]ethane sulfonamide is carried out in presence of Pd/C using organic solvent with acetic acid to get Naratriptan free base. Preferably the organic solvent is methanol.

In another embodiment of present invention, the conversion of Naratriptan free base to hydrochloride salt is carried out by dissolving Naratriptan free base in an organic solvent and converting to hydrochloride using alcoholic HCl. The organic solvent is selected from methanol, ethanol, n-propanol, isopropanol, esters such as ethyl acetate and the like and alcoholic HCl is MeOH/HCl, EtOH/HCl or IPA/HCl.

In yet another embodiment of the present invention wherein the reaction is performed at a temperature in the range of –10 ^{0}C to reflux temperature preferably 20 to 200 ^{0}C.

The invention is further illustrated by the following examples, which should not be construed to limit the scope of the invention in anyway.

Example 1

Ethyl (2Z)-2-[(4-{2-[(methylamino) sulfonyl] ethyl} phenyl) hydrazono] propanoate

2-(4-hydrazinophenyl)-N-methylethanesulfonamide (1 mole) and ethyl 2-oxopropanoate (1.1Mole) was taken in methanol at room temperature and stirred for 2 hours. The reaction mass was cooled to 10-15°C filtered and washed with methanol to get solid.

Yield 60-80%

Example 2

Ethyl 5-{2-[(methylamino) sulfonyl] ethyl}-1H-indole-2-carboxylate

Ethyl (2Z)-2-[(4-{2-[(methylamino) sulfonyl] ethyl} phenyl) hydrazono] propanoate was taken in glacial aceticacid. 33% HBr in acetic acid was added drop wise at 20-30°C and stirred for 2 hours then cooled. Water was added drop wise to separate the solid, filtered and washed with water.

Example 3

5-{2-[(methylamino) sulfonyl] ethyl}-1H-indole-2-carboxylic acid

Ethyl 5-{2-[(methylamino) sulfonyl] ethyl}-1H-indole-2-carboxylate was taken in sodium hydroxide in water. The reaction mass was heated for 1 hours at 50-60°C, stirred and cooled. The pH was adjusted to ~ 2-3 by using 1:1 hydrochloric acid. The solid was separated out, filtered and washed with water. The solid was dried at 60-70°C

Yield -80%.

Example 4

2-(1H-indol-5-yl)-N-methylethanesulfonamide

5-{2-[(methylamino) sulfonyl] ethyl}-1H-indole-2-carboxylic acid and copper oxide (0.1%w/W/W) was taken in sulfolane. The reaction mass was heated to 185-200°C for 2-3 hours. The reaction mass was cooled to room temperature and filtered. The filtrate

was added to water and stirred for 30 minutes and filtered. The solid was washed with water and purified with ethyl acetate and hexane.

Yield 60-80% M.P 115°C

Example 5

N-methyl-2-[3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-5-yl]ethane sulfonamide

2-(1H–indol-5yl)-N-methylethanesulfonamide and 1-methylpiperidine-4-one was added to a mixture of (1:1) methanol and water and potassium hydroxide solution. The reaction mass was heated upto reflux temperature. After completion of the reaction, the reaction mass was cooled, stirred and filtered. The solid obtained was washed with water and dried.

Example 6

Preparation of N-methyl-2-[3-(1-methyl-1,2,3,6 tetrahydopyridin-4-yl)-1H-indol-5yl]-ethanesulfonamide

2-(1H–indol-5yl)-methylethanesulfonamide and 1-methylpiperidine-4-one was added to a solution of methanol and potassium hydroxide. The reaction mass was heated upto reflux temperature. After completion of the reaction, the reaction mass was cooled and of isopropanol was added to the reaction mass. The reaction mass was cooled and stirred for 30 minutes and then filtered. The solid obtained was washed with chilled isopropanol and dried.

Example 7

Preparation of Naratriptan base

N-methyl-2-[3-(1-methyl-1,2,3,6 tetrahydopyridin-4-yl)-1H-indol-5yl]-ethane sulfonamide (5 g) was dissolved in methanol and acetic acid in 1 lit autoclave. To this solution, 5% wet Pd/C was added. Hydrogen was flushed to the reaction mass at room temperature. The pressure was maintained at 10 kg. After completion of the reaction,

the reaction mass was filtered through Hyflow and concentrated. A solution of sodium carbonate and ethyl acetate was added to the reaction mass and stirred. The aqueous layer was extracted with ethylacetate and combined organic layer was charcolised with 10% carbon. The filtrate was distilled up and cooled to room temperature and stirred for another 30 minutes. The reaction mass was filtered and washed with ethylacetate. The solid obtained was dried to obtain 3.5gm of the title product.

Example 8

Purification of Naratriptan base using acetonitrile: water

The Naratriptan base was dissolved in acetonitrile and it was heated to get clear solution. Water was added slowly to the reaction mass. The reaction mass was stirred and cooled. The separated solid was washed with water and then dried.

Example 9

Purification of Naratriptan base using methanol: water

The Naratriptan base was dissolved in methanol and it was heated to get a clear solution. Water was added slowly to the reaction mass. The reaction mass was stirred and cooled. The separated solid was washed with water and then dried.

Example 10

N-methyl-2-[3-(1-methyl-4-piperidyl)-1H-indol-5-yl]-ethane sulfonamide. Hydrochloride (Naratriptan hydrochloride)

N-methyl-2-[3-(1-methyl-4-piperidyl)-1H-indol-5-yl]-ethane sulfonamide is dissolved in ethyl acetate and heated to get a clear solution. The solution was filtered through hyflow and the filterate was cooled to 25-30°C. Methanolic /HCl was added drop wise and the reaction mass was stirred for 2Hours. The solid was separated out and washed with ethyl acetate. The solid was dried at 80-85°C to get N-methyl-2-[3-(1-methyl-4-piperidyl)-1H-indol-5-yl]-ethane sulfonamide. Hydrochloride

M.p 237-240°C.

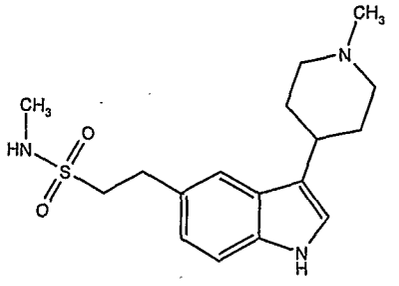
Example 11

Preparation of Naratriptan Hydrochloride

The Naratriptan base (10 g) was dissolved in methanol and heated to get clear solution. The reaction mass was cooled to room temperature and treated with carbon. The reaction mass was stirred and filtered through Hyflow. IPA/HCl was added to the filtrate at room temperature and stirred. The separated solid was filtered, washed with methanol and dried to obtain 7g title product.

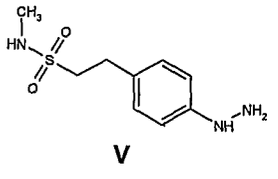
We claim:

1. A process for the preparation of Naratriptan of formula X and its pharmaceutical acceptable salts comprising the steps of:

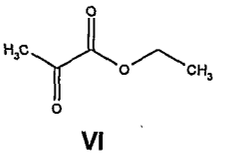


X

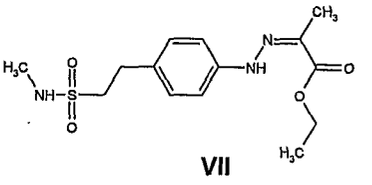
a) condensation of 2-(4-hydrazinophenyl)-N-methylethanesulfonamide of Formula V with ethyl 2-oxopropanate of formula VI to get Ethyl (2Z)-2-[(4-{methylamino) sulfonyl]ethyl}phenyl) hydrazono] propanate of formula VII;



V

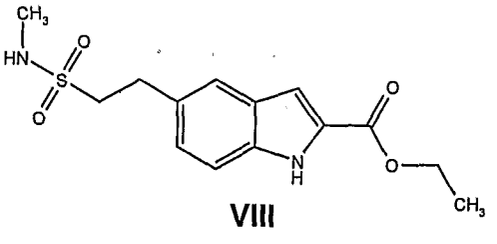


VI



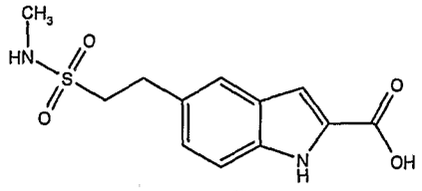
VII

b) cyclisation of compound of formula VII to obtain ethyl 5-{2-[(methylamino) sulfonyl] ethyl}-1H-indole-2-carboxylate of formula VIII;



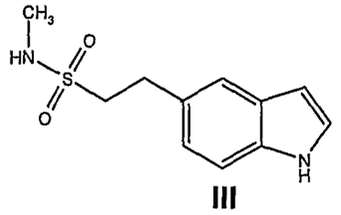
VIII

c) saponification of formula VIII to get 5-{2-[(methylamino) sulfonyl] ethyl}-1H-indole-2-carboxylic acid of formula II;



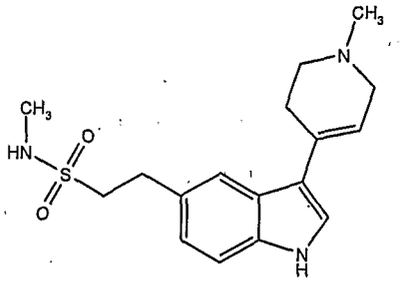
II

d) decarboxylation of formula II in presence of sulfolane and copper salts to get 2-(1H-indol-5-yl)-N-methylethanesulfonamide of formula III;



III

e) condensation of formula III with 1-methylpiperidin-4-one using an organic solvent or its mixture with water to get N-methyl-2-[3-(1-methyl-1,2,3,6-tetrahydropyridin-4-yl)-1H-indol-5-yl]ethanesulfonamide of formula IX;



IX

f) hydrogenation of Formula IX to get Naratriptan free base of formula X;

g) optionally purifying Naratriptan free base of formula X in aqueous organic solvent; and

h) conversion of Naratriptan free base of formula X to its pharmaceutically acceptable salts.

2. The process according to claim 1, wherein condensation of step (a) is carried out in an alcoholic solvent, preferably methanol.

3. The process according to claim 1, wherein cyclisation of step (b) is carried out in HBr and acetic acid.
4. The process according to claim 1, wherein saponification of step (c) is carried out in an aqueous alkali solution, preferably aqueous sodium hydroxide.
5. The process according to claim 1, wherein the organic solvent of step (e) is alcoholic solvent, preferably methanol.
6. A process for the purification of Naratriptan free base which comprises
   i. dissolving naratriptan in a first solvent;
   ii. adding second solvent to the reaction mass; and
   iii. isolating pure Naratriptan
7. The process according to claim 6, wherein the first solvent is selected from acetonitrile, methanol, ethanol, isopropanol and the second solvent is water.
8. A process according to claim 1, wherein Naratriptan free base is converted to its pharmaceutically acceptable salts by dissolving Naratriptan free bas in a lower aliphatic alcohol, ethyl acetate followed by treating with alcoholic solution of hydrogen chloride.
9. The process according to claim 8, wherein the lower aliphatic alcohol is selected from methanol, ethanol, isopropanol and butanol.
10. The process according to claim 8, wherein alcoholic solution of hydrogen chloride is IPA/HCl, ethanol/HCl or methanol/HCl.