Abstract: 3,5-Dimethyladamantane is reacted with bromine to form 1-bromo-3,5-dimethyladamantane of formula (I), it is reacted with acetonitrile in the presence of acid to form 1-acetamido-3,5-dimethyladamantane of formula (II). Optionally formula (II) is treated with an organic acid to form the corresponding salt of formula (III), which is setting free of salt in the presence of base to get the pure formula (II). A formula (II) is subjected to hydrolysis followed by in-situ reaction with hydrochloric acid to form memantine hydrochloride. The memantine hydrochloride is treated with base to get the pure memantine base.
1. Title of the invention.

"A Process for the preparation of Memantine hydrochloride"
This application claims the benefit of Indian Provisional Application No.855/CHE/2006 filed on May 15, 2006 and Indian Provisional Application No.1942/CHE/2006 filed on October 23, 2006, both of which are hereby incorporated by reference.

Field of the Invention:

The present invention relates to a process for the preparation of Memantine optionally using acid addition salts of l-acetamido-3,5-dimethyladamantane and also relates to a process for the preparation of crystalline Memantine hydrochloride.

Background of the Invention:

Memantine hydrochloride, l-amino-3,5-dimethyladamantane hydrochloride has the formula as shown below

![Memantine hydrochloride structure](image)

Memantine hydrochloride is the first FDA approved member of a new class of Alzheimer drugs with a moderate affinity towards N-methyl-D-aspartate (NMDA)-receptor antagonist. It produces symptomatic improvements in learning under conditions of tonic NMDA receptor activation in Alzheimer's disease. In contrast to first generation therapies, Memantine hydrochloride is likely to show neuroprotective effect at a concentration used in the treatment of Alzheimer's disease and to slow down disease progression.

US 3,391,142 discloses a process for the preparation of Memantine hydrochloride by the following steps;
• treating l-bromo-3, 5-dimethyladamantane with a mixture of acetonitrile, and sulphuric acid at room temperature.
• pouring the above mass into crushed ice followed by extracting the product into benzene and isolating l-acetamido-3, 5-dimethyladamantane with melting point of about 97° C.
• treating l-acetamido-3, 5-dimethyladamantane with sodium hydroxide in diethylene glycol at reflux temperature for 6 hrs, quenching the reaction mass into crushed ice, extracting with benzene and concentrating the layer under vacuum affords the crude Memantine as an oil.
• converting crude Memantine to its hydrochloride salt in ether and recrystallization of the product from a mixture of alkanol and ether yields Memantine hydrochloride with melting point of 258° C.

US 4,122,193 discloses a method for preparation of Memantine hydrochloride by the following steps;
• heating 1-chloro-3, 5-dimethyladamantane and urea at 220° C in a closed vessel,
• cooling the reaction mass followed by pulverization and making it as paste with water,
• acidifying with hydrochloric acid and washing the mass with ether,
• basifying the aqueous layer with sodium hydroxide and extracting with ether,
• Combining the ether extractions, drying over potassium hydroxide and bubbling dry hydrogen chloride gas gives Memantine hydrochloride with melting point above 300° C.

CN 1400205 and CN 1335299 disclose a process for preparation of Memantine hydrochloride by the following steps;
• Reacting l-bromo-3, 5-dimethyladamantane with urea in a polyol solvent (such as ethylene glycol),
• Treating with sodium hydroxide followed by acidification with hydrochloric acid yields Memantine hydrochloride.
WO 2005/023753 discloses a process for the preparation of Memantine hydrochloride by reacting 1-bromo-3, 5-dimethyl adamantane with urea in formic acid followed by hydrolysis and converting into hydrochloride salt with melting point 332° C.

According to the prior art method, benzene used as a solvent for extraction in large quantities and continuous exposure to benzene vapors causes serious health effects, while low levels can cause drowsiness, dizziness, rapid heart rate, headaches, tremors, confusion, and unconsciousness. The major effect of benzene from chronic (long-term) exposure is to the blood. Benzene damages the bone marrow and can cause a decrease in red blood cells, leading to anemia. It can also cause excessive bleeding and depress the immune system, increasing the chance of infection.

As per the prior art, reaction is carried out at higher temperature at above 250° C, which leads to formation of impurities in the final product. The final product purification needs repeated crystallizations in different solvents to get the desired quality of the final product. The repeated crystallization leads the lower yield and it increases the cost of the final product.

WO 2005/069742 discloses crystalline form II of Memantine hydrochloride with characteristic XRD, DSC. This patent further discloses that the product obtained by the prior art process (US 3,391,142) is crystalline form I.

US 2005/0222271 discloses the amorphous form of Memantine hydrochloride and a process for its preparation.
Summary of the invention:

The main objective of the present invention is to provide a process for the preparation of Memantine hydrochloride through optionally preparing acid addition salts of 1-acetamido-3,5-dimethyl adamantane.

An objective of the invention is to provide a process for preparation of memantine hydrochloride which is Form I.

Another objective of the invention is to provide a process for the preparation of memantine base from memantine salt and optionally converting into pharmaceutically acceptable salt.

Detailed description of the invention:

Thus in accordance with the present invention preparation of Memantine hydrochloride comprises the following steps:

a) reacting 1,3-dimethyladamantane with bromine to form 1-bromo-3,5-dimethyladamantane of formula-I,

b) reacting formula-I with acetonitrile in the presence of acid to form formula-II,

c) optionally reacting formula-II with an organic acids in a solvent medium to form a salt of formula-II,

d) setting salt free of formula-III in the presence of base to form pure formula-II,

e) hydrolyzing formula-II and converting in-situ to hydrochloride salts by dissolving base in a first solvent then adding the second solvent in the presence of hydrochloride to form memantine hydrochloride and

f) treating memantine hydrochloride with base to form pure memantine base.

In one embodiment, the present invention provides a process for the preparation of memantine hydrochloride, which involves reacting 1-bromo-3,5-dimethyl adamantane of formula-I in acetonitrile with sulphuric acid at about 15 to 30°C under nitrogen purging, for about 10-18 hrs, which is continued for further 2-6 hrs at the same temperature to form 1-acetamido-3,5-dimethyl adamantane of formula -II. The 1-acetamido-3,5-dimethyl adamantane is quenched into DM water below 15°C and extracted with chlorinated hydrocarbon such as
dichloromethane, dichloroethane, chloroform preferably dichloromethane followed by distillation of organic solvent and further purification with hydrocarbon solvents like hexane, heptane, toluene.

In one aspect of the invention memantine hydrochloride is also prepared by the purification of intermediate 1-acetamido-3,5-dimethyl adamantane by converting into its acid addition salt to get rid of isomeric impurities. The reaction mass obtained after reacting 1-bromo-3,5-dimethyl adamantane in acetonitrile with sulphuric acid is transferred to a mixture of water, aromatic hydrocarbon solvent, such as toluene, xylene at a temperature below 20°C, preferably below 10°C. Reaction mass temperature is slowly raised to about 20 to 35°C, mixed for 10 to 30 min, and separated the layers. Aqueous layer is extracted with the same aromatic hydrocarbon solvent. Combined the organic layers, dried over sodium sulphate and
optionally treated with activated carbon. The filtrate is concentrated under vacuum at a temperature below 50°C to get residue.

The above obtained residue is dissolved in lower alkanols such as methanol, ethanol, propanol, butanol preferably ethanol followed by the addition of organic acid either as such or in the form of solution in a suitable solvent in lots or by slow addition over a period of 10 min to 120 min, at temperature of 10 to 45°C preferably at 20 to 35°C and maintained for about 30 min to 6 hrs. Organic acids are selected from oxalic acid, tartaric acid, mallic acid, benzene sulfonic acid, p-toluene sulfonic acid preferably benzene sulfonic acid and p-toluene sulfonic acid.

The above resulting solution is diluted with an anti solvent such as hydrocarbons and ethers. Hydrocarbons are selected from hexane, heptane, toluene and ethers are selected from diethyl ether, diisopropyl ether, methyl tert butyl ether. The preferred antisolvent is diisopropyl ether. The temperature was maintained for about 30 min to 120 min. The reaction mass is cooled to a temperature of about -5 to 20°C preferably to a temperature of 0-10°C and maintained till the crystallization is completed. Crystallized product is isolated, washed with the same anti solvent and dried at 35 to 65°C to obtain the organic acid addition salt of l-acetamido-3, 5-dimethyl adamantane of formula (III).

If required organic acid addition salt of l-acetamido-3, 5-dimethyladamantane can be purified by dissolving the salt in chlorinated hydrocarbon such as dichloromethane, dichloroethane, chloroform and isolating the pure product by the addition of anti-solvent selected from acetone, methyl ethyl ketone. Thus prepared l-acetamido-3, 5-dimethyl adamantane organic acid addition salts are novel, identified and characterized.

l-Acetamido-3,5-dimethyladamantane organic acid addition salt is neutralized with base such as alkali hydroxide, alkali carbonates, ammonia solution or organic amine bases, preferably ammonia, in presence of mixture of water and chlorinated hydrocarbon such as dichloromethane, dichloroethane, chloroform, preferably dichloromethane. Organic layer is separated and the aqueous layer is extracted with chlorinated hydrocarbon as described.
above. The organic layer was washed with water, dried over dehydrating agents like sodium sulphate or magnesium sulphate. Dried organic layer is concentrated to get residue. To the obtained residue hydrocarbons such as hexane, heptane, toluene, xylene or ethers such as diethyl ether, diisopropyl ether, methyl tert butyl ether is added and isolated the pure 1-acetamido-3,5-dimethyl adamantane.

In one embodiment of the present invention memantine salt is prepared, wherein 1-acetamido-3,5-dimethyl adamantane is suspended in diethylene glycol and sodium hydroxide is added. Temperature of the reaction mass is raised and maintained at 155-160° C for about 8 to 12 hrs. The reaction mass is quenched into a mixture of ice, water and hydrocarbon such as heptane, hexane, toluene, xylene, preferably toluene at temperature of 0 to 20° C, preferably below 10° C. Optionally the temperature is raised to 20-35° C and maintained for about 10 to 30 min, allowed to settle and separated the layers. Aqueous layer is extracted with the hydrocarbon. The organic layer is treated with activated carbon (if necessary). The filtrate is concentrated below 50° C to get residue. The obtained residue is dissolved in ethanol and a second solvent such as diethyl ether, isopropyl ether, methyl tert butyl ether or acetone is added. The solution is cooled to about 0 to 15° C followed by the slow addition of mineral acid, preferably as alkanolic solution such as in methanol, ethanol, isopropanol, preferably as solution in isopropanol over a period of 30 to 120 min at temperature of about 0 to 25° C preferably at about 10 to 15°C. The reaction mass is maintained for about 30 min to about 4 hrs. Product is isolated as a wet cake and is washed with the corresponding ether solvent and dried at a temperature of about 40 to 65° C under vacuum to afford the crystalline Memantine salt.

Memantine inorganic salt is purified by dissolving the salt is C₁-C₄ alkanols completely. The alkanolic solution is given activated carbon treatment with usual workup like stirring with activated carbon and filtering it to get clear solution. To the filtrate ether solvents are added at about 40-50°C and cooled to room temperature and maintained for one hour. Pure and crystalline memantine hydrochloride thus obtained is filtered. C₁-C₄ alkanols are selected from methanol, ethanol, isopropanol, butanol and ethers are selected from diethyl ether, diisopropyl ether, methyl tertiary butyl ether or mixtures thereof.
In one aspect of the present invention memantine base is prepared from memantine salt wherein the inorganic acid addition salt is dissolved in chlorinated solvents selected from dichloromethane, dichloroethane, chloroform and like and the reaction mass pH is adjusted with a base. Base is selected from alkali, alkaline earth metal hydroxides, carbonates or bicarbonates or ammonia. Alkali and alkaline earth metal hydroxides, carbonates or bicarbonates are those conventionally used for pH adjustment like sodium carbonate, magnesium carbonate, sodium bicarbonate, sodium hydroxide, potassium hydroxide calcium hydroxide and like. After neutralization the organic and aqueous layers are separated and the organic solvent is distilled off to get memantine base which can optionally be converted to memantine inorganic acid addition salt as described above.

Mineral acids used for the preparation of memantine salt are hydrochloric acid, sulphuric acid, phosphoric acid, boric acid and like. If hydrochloric acid is used the obtained Memantine hydrochloride has the XRD as shown in Fig 1 with particle size distribution of about 75% particles which are more than 25 microns. The DSC has the endotherm at about 325 - 335°C. This crystalline Memantine hydrochloride which is Form I on grinding, results the X-ray diffraction pattern changes, to X-ray diffraction pattern of form-II.

1-Bromo-3,5-dimethyl adamantane used as starting material can be prepared by the prior art processes.

The major advantages according to the present invention are

a) Hazards solvents like benzene is not used for extractions as well as reactions,
b) The higher temperature reactions are avoided,
c) Intermediate is purified by making the simple addition salts to improve the intermediate purity.
d) The repeated crystallizations are avoided.

The invention is further illustrated with a few non-limiting examples
Example-1: Preparation of l-Bromo-3,5-dimethyl adamantane

100 gm of 1,3-Dimethyl adamantane was taken into a 500 ml 4-necked RBF at room temperature (25-35°C). 403 gm of bromine was added at 25-35°C over 30-120 minutes and stirred for 10-20 minutes at room temperature. The temperature was raised to reflux (Temp: 60-66°C.) and maintained at reflux for about 6 hrs. The reaction was monitored for completion. The reaction mass was cooled and excess bromine was distilled off completely under vacuum to get residue. The residue was cooled to room temperature (25-35°C). Dichloromethane (400 ml) was added and stirred for 5-15 minutes to make clear solution. 10% Sodium metabisulphite solution (500ml) was added at RT over 15-60 min. Stirred for 30 minutes and separated the layers. With usual workup organic layer was separated. The organic layer was dried over anhydrous sodium sulphate, filtered and washed the bed with dichloromethane (50ml). Carbon treatment was given with usual workup and dichloromethane was distilled off completely to get 1-Bromo-3,5-dimethyl adamantane weight: 135 grams Purity by GC: 99.1%

Example-2A: Preparation of Memantine hydrochloride

Step I: Preparation of l-Acetamido-3,5-dimethyl adamantane

736 gm of Sulphuric acid was taken into a one litre 4-necked round bottom flask at room temperature (25-35°C). Nitrogen purging was applied and cooled to 10-15°C. 100ml of acetonitrile was added over 30-60 minutes followed by 100gms of l-Bromo-3,5-dimethyl adamantane and 100ml of acetonitrile. Slowly the temperature was raised to 20-25°C. The reaction was maintained at 20-25°C for 15 hrs and monitored for completion. The reaction mass was quenched into 2500ml of DM water at a temperature below 10°C. 750ml of dichloromethane was added at below 10°C and stirred for 30 minutes. The organic and aqueous layers were separated at 5-10°C and the aqueous layer was extracted with 750ml of dichloromethane. The organic layer was washed with 500ml of 10% NaHCO₃ at below 20°C followed by 500ml of D M Water. Carbon treatment was given with usual workup and dichloromethane was distilled off completely. 80ml of Cyclohexane was added to the semi-solid mass and distilled of cyclohexane completely under vacuum to get semi-solid.
(Weight: 70-80gms). Cyclohexane (80ml) was added to the semi-solid and stirred for 15min. at RT. The reaction mass was filtered and washed with cyclohexane (20ml). The compound 1-Acetamido-3, 5-dimethyl adamantane obtained was dried at 45-50°C for 4-8 hrs till LOD is not more than 3.0%. Yield 81gms Purity by GC: 99.8%

Step II: Preparation of Memantine hydrochloride

To 1200ml of diethyleneglycol added 100 gms of 1-Acetamido-3,5-dimethyl adamantane under nitrogen. 150gms of Sodium hydroxide flakes were added and the temperature was raised to reflux. The reaction was maintained at reflux for 10 hrs. The reaction mass was cooled to room temperature, quenched into a mixture of 1000ml of toluene and 3.0 Kgs of Ice below 10°C. The reaction mass was stirred for 15-30 minutes. Reaction temperature was raised to 25-30°C and maintained for 30 minutes. Toluene layer was separated and the aqueous layer was extracted with 1800ml of toluene. The toluene layer was given carbon treatment with usual workup and toluene was distilled off completely under high vacuum to get residue. The residue was dissolved in 160ml of ethanol at 25-35°C. 320ml of acetone was added and cooled the mixture to 10-15°C. 160ml of 20% IPA.HCl was added at 10-15°C over 60 minutes and Stirred for 30-60 minutes. The reaction mass was filtered and washed the cake with 40ml of chilled IPE (5°C). The compound memantine hydrochloride obtained was dried at 45-55°C for 4-8 hrs under vacuum till LOD reached less than 1.0%. Yield 72gm

Example 2B: Preparation of Memantine hydrochloride

Step-I: Preparation of 1-acetamido-3,5-dimethyl adamantane p-toluene sulfonate

To a solution of 1-Bromo-3,5-dimethyl adamantane (100 gm) in acetonitrile (370 ml), sulphuric acid (760 ml) was added slowly at a temperature of 10-15°C over 4hrs under nitrogen atmosphere. Temperature of the reaction mass was slowly raised over 2 hrs and maintained at 20-25°C for 12 hrs under nitrogen purging. Nitrogen purging was continued for further 4 hrs. Reaction mass was transferred into a mixture of toluene (1000 ml) and ice (3.0 Kg) at temperature below 10°C. Temperature of reaction mass was raised, maintained for 30 min at 25 -30°C and allowed to settle for 15 min. Layers were separated and the
aqueous layer was extracted with toluene (1800 ml), dried over sodium sulfate, treated with activated carbon (5 gm) and filtered. Clear filtrate was collected and toluene was distilled off under vacuum below 50°C. The obtained residue was dissolved in ethanol (80 ml) and p-toluene sulfonic acid (90.8 gm) was added in 4 lots at temperature of 25-35°C over 30 min. Reaction mass was maintained for 60 min and diisopropyl ether (240 ml) was added over 30 min. Reaction mixture was maintained at 25-35°C for 30 min, cooled and maintained at 0-5°C for 1 hr. Product was filtered, wet cake was washed with chilled diisopropyl ether (50 ml) and dried at a temperature of 45-50°C for 4 hrs. The dried product (100 gm) was dissolved in methylene chloride (150 ml) and acetone (300 ml) was added slowly over 30 min. Reaction mixture was maintained at 25 - 30°C for 30 min. Cooled the mass to 10-15°C and maintained for 60 min. The precipitated product was filtered, wet cake was washed with chilled acetone (50 ml) and dried at 45-50°C. Yield: 51.2%.

**Step-2: Preparation of l-acetamido-3,5-dimethyl adamantane (pure)**

1-Acetamido-3, 5-dimethyl adamantane p-toluene sulfonate (80 gm) was dissolved in methylene chloride (240 ml). To the solution water (160 ml) was added and pH of the mass was adjusted to 9.5 to 10.0 with ammonia solution and maintained at 25-30°C for 30 min. The reaction mixture was allowed to settle and layers were separated. The aqueous layer was extracted with methylene chloride (160 ml). Combined organic layer was washed with water (160 ml) and dried over anhydrous sodium sulphate. Methylene chloride was completely distilled off under vacuum to get residue. To the obtained residue cyclohexane (80 ml) was added and maintained for 15 min to precipitate the product. Product was filtered and dried at 45 -50°C till constant weight. Yield : 40 gm

**Step-3: Preparation of crystalline Memantine hydrochloride**

1-Acetamido-3, 5-dimethyl adamantane (100 gm) was suspended in diethylene glycol (1200 ml), under nitrogen atmosphere and sodium hydroxide (150 gm) was added. Temperature of reaction mass was raised and maintained at reflux for 10 hrs, cooled the mass to room temperature and quenched into a mixture of ice (3.0 Kg) and toluene (1000 ml) below 10°C. Temperature of the mass was raised and maintained for 30 min at 25 -30°C. Allowed the reaction mass to settle for 15 min and layers were separated. Aqueous layer was extracted
with toluene (1800 ml), and the toluene layer was treated with activated carbon (5 gm). The
reaction mass was filtered and toluene was distilled off under vacuum below 50°C to get
residue. The obtained residue was dissolved in ethanol (80 ml) and diisopropyl ether (240
ml) was added and maintained at 25-35°C for 30 min. Reaction mass was cooled to 10°C
and IPA.HCl (18%, 160 ml) was slowly added at a temperature of 10-15°C over 60 min.
The reaction mass was maintained at a temperature of 10-15°C for 1 hr and filtered the
product. Wet cake was washed with chilled diisopropyl ether (40 ml) and dried at 45-55°C
till constant weight.

Dry weight of Memantine hydrochloride is 75 gm (Yield: 72.1 %)

Example 3: Preparation of crystalline memantine hydrochloride  (By recrystallization)

Memantine hydrochloride (100 gm) was dissolved in ethanol (600 ml) and maintained at
55-60°C for 15 min. The solution was treated with activated carbon. Reaction mass was
filtered and to the clear filtrate diisopropyl ether (1200 ml) was added slowly at 45-50°C
over 60 min. Reaction mass was cooled and maintained at 25-30°C for 60 min. Product was
filtered, wet cake was washed with diisopropyl ether (50 ml) and dried at 45-55°C till
constant weight.

Dry weight of crystalline Memantine hydrochloride was 80 gm (Yield: 80.0 %)

Example 4: Preparation of memantine base:

Charged 800ml of methylene dichloride into a 2.0 Lt RB Flask at RT (25-35°C) and added
100 gms of memantine HCl ,stirred at RT (25-35°C) for 5 min.Charged 400 ml of DM
Water at RT (25-35°C).Cooled the reaction mass to 15°C.Adjusted the pH of reaction mass
to 9.3 pH with Aq. Ammonia (Qty: 64 ml) over 20-30 min. at 15-20°C. Slowly raised the
temperature to 25°C,Stirred for 30 min. at 25-30°C. Separated the layers and extracted the
aqueous layer with 400 ml of methylene dichloride. Combined the methylene chloride
layers and washed 2 x 400 ml of DM Water .Dried the MDC layer over 30 gms of sodium
sulphate and filtered and washed with 50 ml of methylene dichloride.Distilled off methylene
dichloride initially in normal distillation and finally applied high vacuum and distilled off
methylene dichloride completely below 40°C to get memantine. Yield 80gm.
We claim:

1. A process for the preparation of Memantine hydrochloride comprising the steps of:

   a) reacting 1,3-dimethyladamantane with bromine to form 1-bromo-3,5-dimethyladamantane of formula-I

   b) reacting formula-I with acetonitrile in the presence of acid to form formula-II

   c) optionally reacting formula-II with an organic acid in a solvent medium to form a salt of formula-III
d) setting salt free of formula-III in the presence of base to form pure formula-II

e) hydrolyzing formula-II and converting in-situ to hydrochloride salts by dissolving base in a first solvent then adding the second solvent in the presence of hydrochloride to form memantine hydrochloride

2. A process according to claim 1c, wherein the organic solvent is selected from oxalic acid, tartaric acid, maleic acid, benzene sulphonic acid, methane sulphonic acid and p-toluene sulphonic acid.

3. A process according to the claim 2, wherein preferred organic acid is p-toluene sulphonic acid.

4. A process according to claim 1c, wherein solvent is selected from group comprising alcohol such as methanol, ethanol, isopropyl alcohol and butanol.

5. A process according to claim 1d, wherein the base is selected from the group comprising of alkali, alkaline earth metal hydroxides, carbonates, bicarbonates, organic amines or ammonia.

6. A process according to claim 5, wherein the preferred base is ammonia.

7. A process according to claim 1e, wherein the first solvent is selected from the group comprising alcohol such as methanol, ethanol, propanol, or isopropanol.

8. A process according to claim 7, wherein the preferred solvent is methanol and ethanol.

9. A process according to claim 1e, wherein the second solvent is selected from diethyl ether, isopropyl ether, methyl tert butyl ether or acetone.

10. A process according to claim 9, wherein the preferred solvent is acetone.
11. A process for the preparation of Memantine hydrochloride comprising the steps of:

a) reacting 1,3-dimethyladamantane with bromine to form 1-bromo-3,5-dimethyladamantane of formula-I

\[ \text{1,3-Dimethyl adamantane} \xrightarrow{\text{Bromine}} \text{Br} \]

\[ H_C \quad CH_3 \quad H_C \quad CH_3 \]

\[ \text{Formula-I} \]

b) reacting formula-J with acetonitrile in the presence of acid to form formula-II

\[ \text{Br} \quad \xrightarrow{\text{Acetonitrile Acid}} \quad H_N \quad CH_3 \]

\[ H_C \quad CH_3 \quad H_C \quad CH_3 \]

\[ \text{Formula-I} \quad \text{Formula-II} \]

c) hydrolyzing formula-II and converting \textit{in-situ} to hydrochloride salts by dissolving base in a first solvent then adding the second solvent in the presence of hydrochloride to form memantine hydrochloride

\[ H_N \quad CH_3 \quad \xrightarrow{\text{Base}} \quad NH_2 \cdot HCl \]

\[ H_C \quad CH_3 \quad \text{Memantine Hydrochloride} \]

12. A process according to claim 11c, wherein the first solvent is selected from the group comprising alcohol such as methanol, ethanol, propanol, or isopropanol.

13. A process according to claim 12, wherein the preferred solvent is methanol and ethanol.
14. A process according to claim 13, wherein the second solvent is selected from diethyl ether, isopropyl ether, methyl tert butyl ether or acetone.

15. A process according to claim 14, wherein the preferred solvent is acetone.

16. Process for the preparation of memantine base which comprises treating memantine hydrochloride with base to form pure memantine base.

![Chemical structure of Memantine Hydrochloride and Memantine Base]

17. A process according to claim 16, wherein the base is selected from the group comprising of alkali, alkaline earth metal hydroxides, carbonates, bicarbonates, organic amines or ammonia.

18. A process according to claim 17, wherein the preferred base is ammonia.