SYNTHESIS OF MEMANTINE HYDROCHLORIDE BY DIRECT AMINOATION OF 1-BROMO-3,5-DIMETHYLADAMANTANE WITH UREA

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Summary

Objectives: To optimize the synthesis process of memantine hydrochloride by direct aminoation of 1-bromo-3,5-dimethyladamantane with urea. ***Materials and methods:*** Using the basic chemical reactions to optimize the reaction conditions. ***Results:*** The optimal conditions of the memantine hydrochloride synthesis process include: The reaction solution was diphenyl ether; the reaction temperature was 170^{o}C within 4 hours (in the first step) and 100^{o}C within 2 hours (in the second step); the molar ration of 1-bromo-3,5-dimethyladmantane: urea: diphenyl ether was 1:3:2.5; the duration of the reaction was 6 hours and the overall yields were 75.81%. ***Conclusion:*** The synthesis process of memantine hydrochloride by direct aminoation with urea was established. The finished products were determined by IR, MS, and NMR spectra and met the standards of USP 43.

** Keywords: Memantine hydrochloride; Urea; 1-bromo-3,5-dimethyladamantane; Synthesis; Amioation; Alzheimer's disease.*

INTRODUCTION

Dementia is a disease that damages the cognitive function of the human brain, especially in elderly people, in which the most common type is Alzheimer's. Researchers believe that the main reason for chronic neurodegeneration gradually is the persistent activation of the N-methyl-D-aspartate (NMDA) receptor. A lot of drugs are used for Alzheimer's treatment. Among them, memantine hydrochloride was able to block the NMDA receptor and excessive activity of glutamate.

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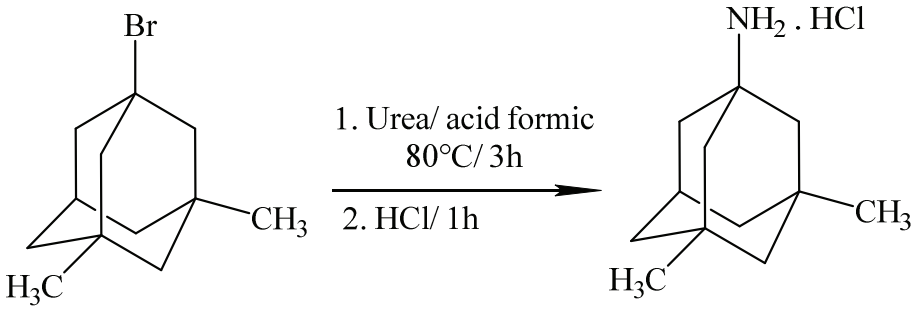
Thus, it can improve brain functions, i.e., thinking and learning [1]. Hence, the official approval of using memantine in the symptomatic treatment of this disease by the FDA in 2003 has led to high hopes for many patients.

Up to now, there have been a large number of researches regarding the synthesis of memantine hydrochloride [2 - 10], and Vietnamese scientists have also started to study this compound [3, 4, 10]. In the study by Fuli Zhang et al. (2008) [5], memantine hydrochloride was prepared by reaction with an aminating component, urea (*Scheme 1*).



Scheme 1: The process for preparing memantine hydrochloride from 1-bromo-3,5-dimethyladamantane and urea (Fuli Zhang, et al.)

At the start, 1-bromo-3,5-dimethyladamantane was added to formic acid and urea at 80^{o}C within 3 hours. After that, this mixture would be cooled to room temperature and hydrolyzed in HCl at 80^{o}C for 1 hour. To obtain memantine base, the reaction mixture was adjusted to pH 12 by adding sodium hydroxide 30%, extracted with toluene, and washed with water. This compound was converted to a salt formation of memantine by the HCl reaction.

Although having many advantages, such as the materials available and suitable reaction conditions for laboratories, the above procedure is essentially restricted, such as using formic acid as the reaction solvent and toluene as the extraction solvent; these are very toxic and have an unpleasant odor. Therefore, they are not safe to use. Moreover, the overall yield was only 68.8%, which is fairly low.

This study reports another reaction procedure in the synthesis of memantine hydrochloride with initiating material of 1-bromo-3,5-dimethyladamantane and urea agent, in which a more suitable reaction solvent was selected, the

reaction conditions were optimized to obtain a product with high yields while ensuring safety and economy.

MATERIALS AND METHODS

1. Materials and equipment

Memantine hydrochloride standard was obtained from Sigma-Aldrich USA. The adamantane standard was obtained from China.

The reagents and solvents were made in China and used without further purification, including 1-bromo-3,5-dimethyladamantane; toluene; diphenyl ether; glycerol, propylene glycol; ethylene glycol; dichloromethane; ethanol; ethyl acetate…

The ^{1}H-NMR and ^{13}C-NMR spectra were recorded in standard substance on a Bruker-AV500 spectrometer; the chemical shifts are reported in δ (ppm) relative to TMS.

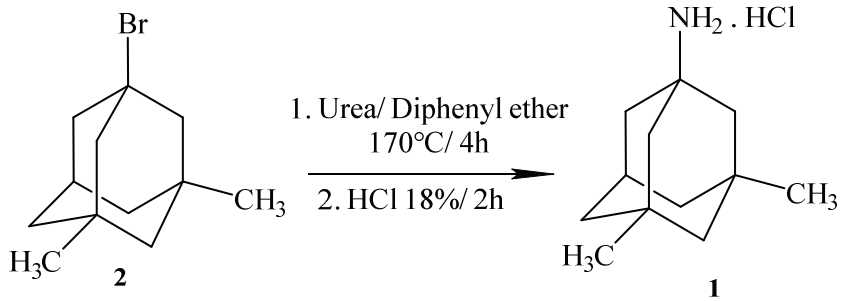
The IR spectra were recorded in the solid state as KBr dispersion using a GX-Perkin Elmer spectrophotometer (USA).

The mass spectra (70 *eV*) were recorded on the Auto Spec Premier Spectrometer. The melting points were measured on the Stuart SMP-10 apparatus. Thin-layer chromatography (TLC) was implemented on Kieselgel 60F-254 plates.

2. Methods

** Synthesis of memantine hydrochloride:*

In our current study, memantine hydrochloride (**1**) was prepared from 1-bromo-3,5-dimethyladamantane (**2**) by using the direct aminoation method. In this condition, urea was dissolved into ammonium, which was directly reacted upon by compound (**2**) to give a memantine base, which was treated with a solution of aq. HCl (18%) to obtain memantine hydrochloride (**1**) (*Scheme 2*).



Scheme 2: The process for the preparation of memantine hydrochloride (1) from 1-bromo-3,5-dimethyladamantane (2) and urea.

Experiment: Preparation of memantine hydrochloride from 1-bromo-3,5-dimethyladamantane and urea.

In a round-bottom flask, at 25^{o}C, 1-bromo-3,5-dimethyladamantane 10 mL (12.15 g; 0.05 mol) was added to urea 9g (0.15 mol), diphenyl ether 20 mL (21.25g; 0.125 mol). This mixture was heated to 170^{o}C and kept at that temperature for 4 hours (as indicated by TLC until the original material 1-bromo-3,5-dimethyladamantane completely disappeared; a solvent mixture of acetone:n-hexane = 2:4, visualization: Dragendorff reagent. After the reaction ended, the mixture reaction was cooled to 80^{o}C, then HCl 18% (20 mL; 0.1 mol) was added gradually and sustained at 100^{o}C for 2 hours. Cool the reaction mixture to room temperature and adjust the pH to 10 - 12 with NaOH 10% (60 mL; 0.15 mol). This mixture was extracted with dichloromethane three times (100 mL). The separated organic layer was washed with water three times, dried over Na_2SO_4 and evaporated in a vacuum until the remaining 1/3 volume of mixture, then added HCl 18% (50 mL; 0.25 mol), stirring at 60^{o}C for 10 minutes and cooling by ice-water within 30 minutes. The white solid part was filtered and washed with dichloromethane (3 × 5 mL), then dried in a vacuum to give raw memantine hydrochloride. Finally, this compound was re-crystallized in a mixture of ethanol and ethyl acetate (5:4, (v/v)) to obtain 1-amino-3,5-dimethyladmantane hydrochloride.

The final product obtained was determined by IR, MS, and NMR spectrum.

* *Determination of the quality standards of memantine hydrochloride:*

Determination of the quality standards of memantine hydrochloride according to the monographs of the USP 43 [11]:

- Identification: IR spectrum and comparison of the retention time of the major peak of the sample solution and standard solution (GC).
- Residue on ignition:
- Organic impurities: GC.
- Water determination: Method I.
- Definition: GC.

Calculate the percentage of memantine hydrochloride in the portion of memantine hydrochloride taken:

$$X\ (\%) = \frac{F_t \times m_c \times 100\% \times 10}{F_c \times m_t \times 10} \times 100$$

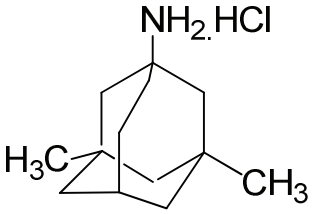
F_t, F_c: Peak response ratio of the sample solution, standard solution, and internal standard;

m_c, m_t: Standard compound and sample mass (mg);

RESULTS

The experiment was carried out as described above. The researchers obtained 1.63 g of memantine hydrochloride (75.81%); mp: 293- 295^{o}C [9, 10].

IR spectrum of memantine hydrochloride:



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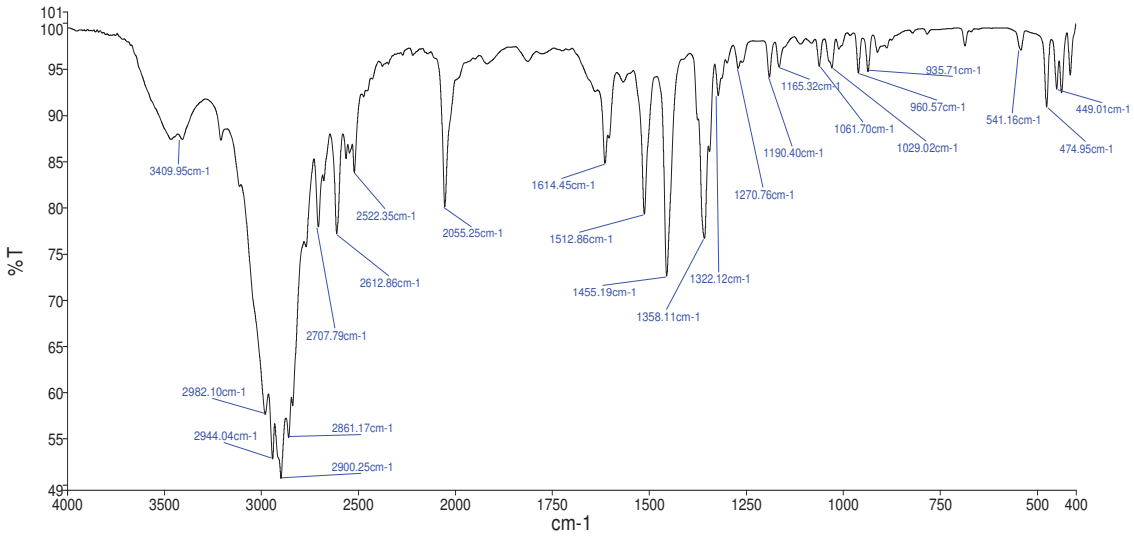
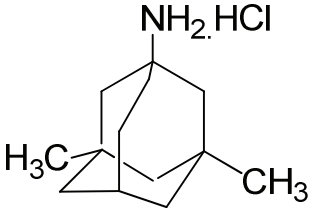
IR (KBr), (cm^{-1}): 3409 (N-H), 2982-2707 (C-H), 1358 (C-N).



Scheme 3: IR spectrum of memantine hydrochloride.

MS spectrum of memantine hydrochloride:



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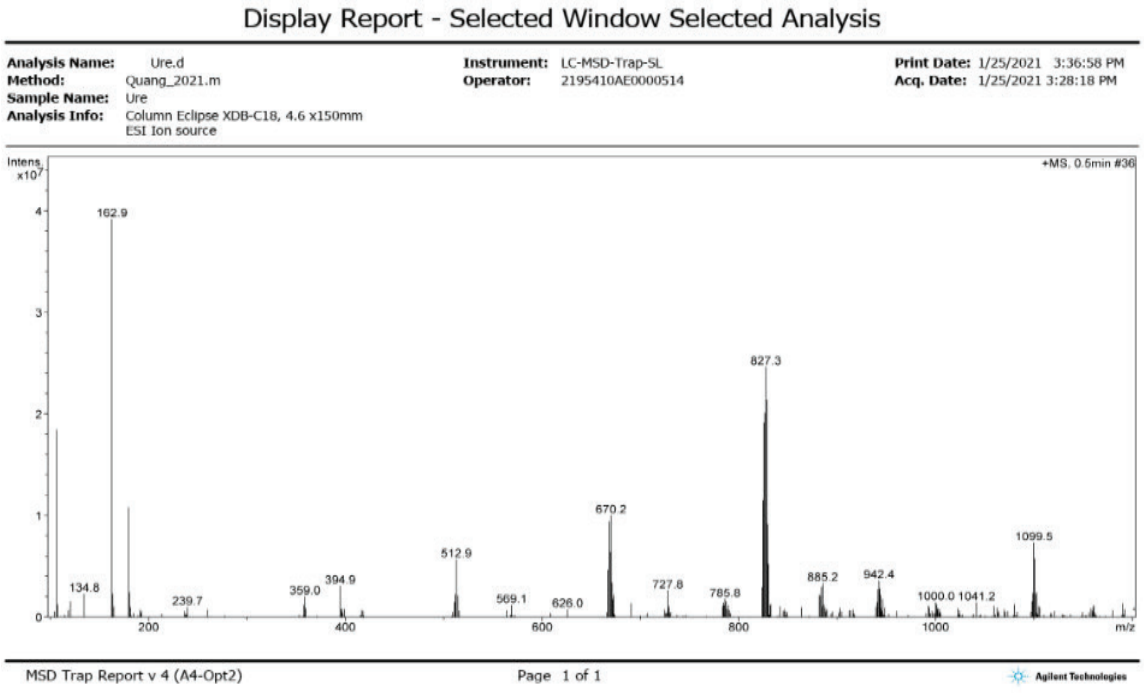
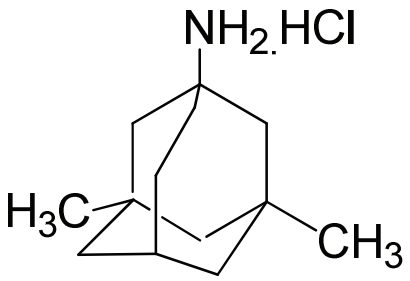
MS, m/z: 162.9 [M-(NH_2. HCl)]$^+$;



Scheme 4: MS spectrum of memantine hydrochloride.

^{1}H-NMR spectrum of memantine hydrochloride:



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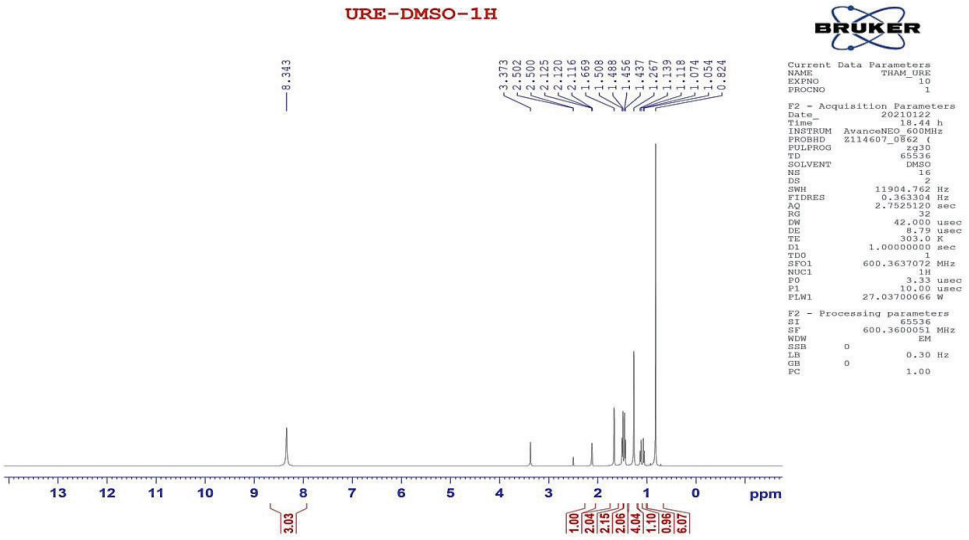
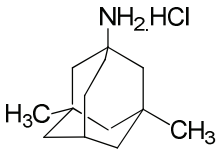
^{1}H-NMR (600MHz. DMSO-d6), δ (ppm): 8.34 (s. 3H. NH_2. HCl); 2.50-2.12 (m. 1H); 1.67 (d. J = 11.5 Hz. 2H); 1.51-1.44 (d. J = 12.5Hz. 4H); 1.27 (d. J = 11.5. 2H); 1.14 -1.12 (d. J = 12.5 Hz. 1H); 1.08-1.05 (d. J = 12.5 Hz; 1H); 0.82 (s. 6H).



Scheme 5: ^{1}H-NMR spectrum of memantine hydrochloride.

^{13}C-NMR spectrum of memantine hydrochloride:



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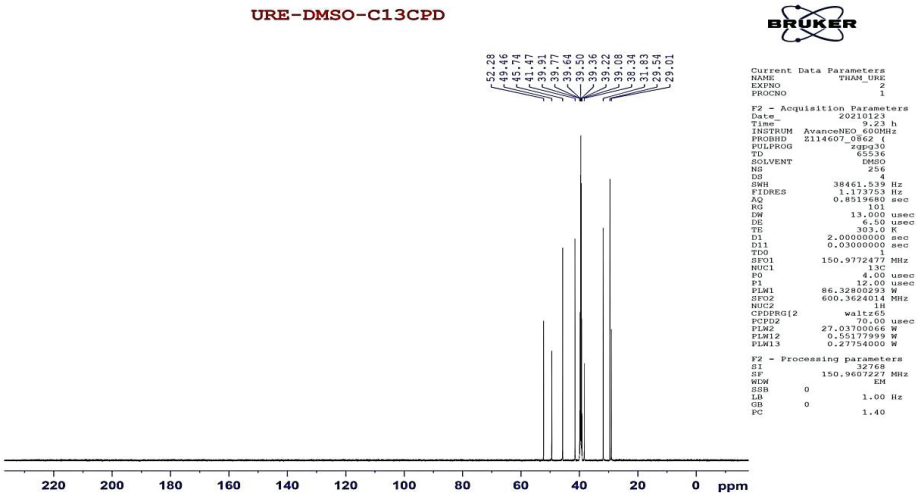
^{13}C-NMR (600MHz. DMSO-d6), δ (ppm): 52.3 (C_1). 49.5 (2C. C_2 và C_9); 45.7 (C_4); 41.5 (2C. C_6 và C_{10}; 39.9 (C_7); 31.8 (C_3 và C_5); 29.5 (C_8); 29.01 (2C. C_{11} và C_{12}). [9, 10].



Scheme 6: ^{13}C-NMR spectrum of memantine hydrochloride.

Memantine hydrochloride met the standards of USP 43 [11], including:

Identification: The IR spectrum and retention time of the major peak of the *sample solution* corresponds to that of the *standard solution.*

- Residue on ignition: 0.1% (≤ 0.1%).

- Water determination (method I): 0.4% (< 1.0%)

- Organic impurities:

Memantine related compound B: 0.14 (≤ 0.15);

Memantine related compound D: 0.06 (≤ 0.15);

Any individual unspecified impurity: 0.03 (≤ 0.1);

Total impurities: 0.23 (≤ 0.5).

- Definition: 99.6% (98.0 - 102.0%).

In summary, the process described in scheme 2 is a safe and economically competitive synthesis, in which memantine hydrochloride may be obtained from 1-bromo-3,5-dimethyladamantane in two steps. The major advantages of the process are as follows:

Firstly, instead of using formic acid as a solvent reaction and toluene as an extraction solvent in study by Fuli Zhang, et al., we used diphenyl ether and dichloromethane to reduce the toxicity and unpleasant smell during the reaction. Furthermore, the reaction mixture did not contain residual acid, so it was easy to handle to ensure environmental safety.

Secondly, we decreased the number of chemical materials used for reactions. In our study, the molar ratio of 1-bromo-3,5-dimethyladamantane:urea: diphenyl ether was 1:3:2.5 (the molar ration of 1-bromo-3,5-dimethyladamantane:urea:formic acid in Fuli Zhang's report was 1:3.5:4). As a result, the obtained yield of this process is 75.81% (higher than that of Fuli Zhang's 68.8%).

CONCLUSION

The process for synthesizing memantine hydrochloride from 1-bromo-3,5-dimethyladamantane and urea has been established, which is simpler, safer, and more economical. The reaction parameters were optimized, including the reaction temperature was 170^{o}C within 4 hours in the first step and 100^{o}C within 2 hours in the second step; the total time reaction was 6 hours; the molar ratio of 1-bromo-3,5-dimethyladamantane:urea:diphenyl ether was 1:3:2.5; and the overall yield was 75.81%. The obtained product has been determined by IR, MS, and H-NMR spectra and meets the standards of USP 43.

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