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Synthesis and IR/MS Study of 3,5-Dimethyladamantanamine Hydrochloride Salt

HUIXUE REN[1,2,*], HANJIE YING[1], PINGKAI OUYANG[1], JIMAO LIN[3] and LIU JING[2]

[1]National Engineering Research Centre for Biotechnology and College of Life Science and Pharmaceutical Engineering, Nanjing University of Technology, Nanjing 210009, P.R. China
[2]School of Municipal and Environmental Engineering, Shandong Jianzhu University, Jinan 250101, P.R. China
[3]School of Chemistry and Chemical Engineering, Shandong University, Jinan 250010, P.R. China

*Corresponding author: Fax: +86 25 58133398; Tel: +86 25 86990001; E-mail: yinghanjie134@163.com

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This paper studied the synthesis of memantine hydrochloride characteristics by optimizing the synthetic route in the bromination of acid hydrolysis under the conditions of acetonitrile and the final salt formation reaction, so that memantine hydrochloride in an overall yield of the products from the 67.3 % reported in the literature increased to 81.5 %. Compared to 1,3-dimethyl adamantane and 3,5-dimethyl-adamantanamine, the infrared spectra showed the characteristic absorptions of 3,5-dimethyl-adamantanamine hydrochloride. Especially by the use of ESI method Spray ionization mass spectrometry analysis of fragments of memantine hydrochloride mass characteristics of ammonia compounds. By IR and MS studies to determine the spectrum of memantine hydrochloride microscopic molecular structure of ammonia.

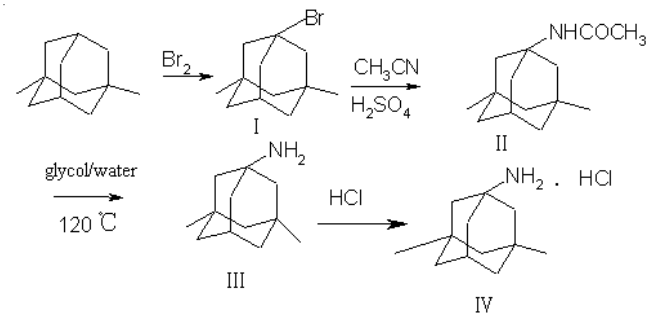
Key Words: 3,5-Dimethyladamantanamine hydrochloride, Synthesis, Infrared spectra, Electro-spray ionization mass spectrum.

INTRODUCTION

3,5-Dimethyl adamantanamine hydrochloride salt (namenda, menantine hydrochloride) is the first of a new class of medications for Alzheimer's disease with a mechanism of action distinct from currently available drugs[1-3]. 3,5-Dimethyl adamantanamine hydrochloride salt is a low to moderate affinity *N*-methyl-D-aspartate (NMDA) receptor antagonist. It is thought that over-excitation of *N*-methyl-D-aspartate receptors by neurotransmitter glutamate may play a role in Alzheimer's disease since glutamate plays an integral role in the neural pathways associated with learning and memory. The excitotoxicity produced by abnormal levels of glutamate is thought to be responsible for neuronal cell dysfunction and the eventual cell death observed in Alzheimer's disease. It is thought to selectively block the excitotoxic effects associated with abnormal transmission of glutamate, while allowing for the physiological transmission associated with normal cell functioning[4-6].

Compared to the old synthetic method[7-11], the present method described below (**Scheme-I**). 1,3-Dimethyl adamantane was brominated by bromine at 70-80 ºC, affording 1-bromo-3,5-dimethyl adamantane (I). Second, the obtained 1-bromo-3,5-dimethyl adamantane reacted with acetonitrile catalized by sulfuric acid at 0-5 ºC, affording 1-acetamido-3,5-dimethyl adamantane (II). Third, this intermediate(II) was hydrolyzed in alkaline solutions to prepare free base-3,5-dimethyl adamantanamine (III). The optimum molar ratio of glycol to water in hydrolysis was 10:1. Finally, the product of menantine hydrochloride (IV) was obtained by salting with HCl.

Compared with other methods, this synthetic method is carried out in a milder condition, with yields rising from 67.3 to 81.5 %.



Scheme-I: Synthetic method of menantine hydrochloride

However, the structure has not been previously proved by spectrum. As is known, infrared spectroscopy can give direct evidence of functional groups and has been used for identification of organic compounds containing drugs[12,13]. The

mass spectrometric method has commonly been used for organic compounds analysis[14,15]. It would be of interest to analyze these spectra to obtain more information regarding their structure. The present paper is devoted to the vibrational spectra and the mass spectra of this compound. By comparing 3,5-dimethyl adamantanamine and 1,3-dimethyl adamantane, assignments of the vibrational spectrum of 3,5-dimethyl adamantanamine hydrochloride salt is made.

EXPERIMENTAL

Samples of 3,5-dimethyl adamantanamine and its hydrochloride salt were synthesized from 1,3-dimethyl adamantane by following the established procedures. All reagents are analytical without purification and they were purchased from Jinan Zhizun Chemicals Reagent. Co. Ltd.

Preparation of 1-bromo-3,5-dimethyl adamantane (I): In a typical experiment, 32.8 g (0.2 mol) of 1,3-dimethyl adamantane was put into a 250 cm^{-3} three-necked round-bottomed flask. Then, bromine (48.0 g, 0.3 mol) was added from a dropping funnel at a speed of 15-20 drops/min. The mixture was refluxed with stirring for 12 h. At the same time, the released hydrobromide gas was extracted by an alkaline solution. When stirring finished, the extra bromine was distilled off and reclaimed and the residue of bromine was dissolved by $NaHSO_3$. The remainder was extracted with three 50 mL portions of chloroform. The chloroform extract was dried by sodium sulfate and chloroform was distilled off at static pressure, which afforded the crude product of compound **I**, which was distilled immediately at reduced pressure collecting a distillate at 99-101 ºC/13.3 Pa, yielding colourless liquids 44.47 g, 91.5 %, n_d^{25} = 1.5147, lit[11] = 1.5182-1.5199.

Preparation of 1-acetamido-3,5-dimethyl adamantane (II) : (36.5 g, 0.15 mol)1 and acetonitrile (105.75 g, 2.58 mol) were combined in a 500 mL three-necked round-bottomed flask. While the temperature was maintained at 5-10 ºC, concentrated sulfuric acid (280 mL) was added drop-wise with a static-pressure dropping funnel. During the addition, the reaction mixture released red smoke and became sticky and the mixture changed from pale red to colourless. Subsequently, the reaction mixture was stirred at room temperature for 12 h, to produce a pale yellow sticky liquid. Then the yellow liquid was poured into fragmented ice and mixed with stirring to become well-distributed. A white precipitate was obtained after the solution was allowed to stand for 10 h. The resulting white solid, which was the crude of 2(32.49 g), was filtered, washed by two 50-mL portions of water and dried. The crude of compound **II** was re-crystallized with chloroform, yielding a purity product of 31.78 g, 96 %, m.p. 98-100 ºC which was the same as in the literature[11].

Preparation of 1-amine-3,5-dimethyl adamantane (3) and memantine hydrochloride (IV): A mixture of (**II**) (22.1 g, 0.1 mol), glycol (20.1 g, 0.3 mol), sodium hydroxide (20 g) and water (5.5 cm^{-3}) was stirred at 150 ºC for 12 h. After stirring, the mixture was cooled to room temperature and poured into fragmented ice to produce with stirring, well-distributed oil. After standing for 1 h, the oil was separated out, by extracting with three 50-mL portions of petroleum ether. The petroleum ether extracts were dried by sodium sulfate and then petroleum ether was distilled off, which produced a thin yellow liquid of compound **3**, n_d^{25} = 1.4957, lit[11] = 1.4941. Dry hydrochloride gas was put into compound **3** and then a white solid was separated out at pH = 6. The white solid was filtered and washed by two 50 mL portions of water, to give 19.93 g of crude menantine hydrochloride after drying. Finally repeated recrystallization from chloroform yielded a purity of 18.8 g, 88 %, m.p. 290-295 ºC, which was the same as in the literature[6]. Its NMR and elemental analysis data as follows:

^{1}H NMR (400 MHz, $CDCl_3$), δ:8.34 (s, 3H, NH_3), 2.20 (S, 1H, CH), 1.89 (S, 2H, CH_2), 1.73 (d, 2H, CH_2) 1.40 (d, 2H, CH_2), 1.30 (d, 2H, CH_2), 1.21 (d, 1H, CH_2), 1.15 (d, 1H, CH_2), 0.99 (S, 3H, CH_3), 0.85 (S, 3H, CH_3). ^{13}C NMR (100 MHz, $CDCl_3$) δ: 53.96, 49.27, 45.86, 41.30, 38.55, 32.07, 32.03, 29.26, 29.08. Calcd. for $C_{12}H_{21}N.HCl$ (215.5): C, 66.82; H, 10.21; N, 6.49 %. Found: C, 66.97; H, 10.09; N, 6.78 %.

Detection method: IR spectra were recorded on a Bruker VECTOR22 spectrometer. The electro-spray ionization (ESI) mass spectrum was obtained on an ABI-API400 LC-MS spectrometer. The NMR spectra were recorded on 400 MHz Brucker spectrometers in $CDCl_3$ solvent. TMS was used as the internal standard. Elemental analysis was carried out on a CEST 1106 instrument. Melting points were determined using a calibrated thermometer by Remi digital. Diopter was carried out on a WAY-2S instrument.

RESULTS AND DISCUSSION

Influence of reactants of molar ratio to bromination: In the first step of bromination, owing that 1,3-dimethyladamantane has two position, which can be attacked by bromine, the more polybrominated products were produced if more bromine was added, whereas the bromination reaction would not react completely with deficient bromine. So the other reaction condition was used (refluxed time for 12 h) to select the most adaptive reactants molar ratio. The specific data is given in Table-1.

TABLE-1
INFLUENCE OF MOLAR RATIO OF 1,3-DIMETHYL ADMANTANE TO BROMINE ON THE YIELD AND PURITY OF COMPOUND **1**

Mole ratio of 1,3-dimethyl admantane to bromine	Per cent ratio of monobrominated to polybrominated compounds	Yield of product (%)
1:1	91:9	64:3
1:1.2	94:6	69:2
1:1.5	98:2	91:5
1:2	87:13	61:7
1:2.5	71:29	53:4

As can be seen from the Table-1, if the molar ratio of 1,3-dimethyladmantane to bromine is lower than 1:1.5, the product yields decreased, while when the molar ratio exceeded 1:1.5, the purity of products was worse and the yield was lower as well. The above phenomena resulted from bromine, which was so volatilizable that if the molar ratio was low, the reaction would be incomplete, but when the molar ratio was high, the polybromination byproducts were high and influenced the purity of the products.

Influence of reactionary time on the yield and purity of compound I: The reactants molar ratio of 1,3-dimethyl

admantane to bromine was kept at 1:1.5 and reacted under refluxing, then compared to the influence of different reaction times on the bromination. The specific data is in Table-2.

TABLE-2
INFLUENCE OF REACTIONARY TIME ON THE YIELD AND PURITY OF COMPOUND **I**

Reactionary time (h)	Percent ratio of monobrominated to polybrominated compounds	Yield of product (%)
6	99:1	69.3
8	98:2	78.5
10	97:3	83.6
12	97:3	91.2
14	93:7	85.4

According to Table-2, if the reaction time was shorter than 12 h, although the purity of product compound **I** was high, the yield of compound **I** was low. However the longer reaction time would result in more polybrominated byproducts and poor purity of compound **I**, so the optimum reaction time was 12 h.

Influence of different reaction conditions on hydrolysis: The influence of different reaction conditions on hydrolysis was presented in a previous work[16]. According to this work, the optimum reaction condition of hydrolysis was carried out with a molar ratio of glycol to water of 10:1 as solvent at 150 ºC for 12 h, the molar ratio of 1-acetimdolyl-3,5-dimethyl admantane to sodium hydroxide was 1:5. Through optimization of the hydrolysis reaction condition, the overall yield of the reaction can be increased from 67.3 to 81.5 %[11].

Infrared spectra: The infrared spectra of 1,3-dimethyl adamantane, 3,5-dimethyl adamantanamine and its hydrochloride salt are presented in Table-3. Assignments of the spectrum of 3,5-dimethyl adamantanamine hydrochloride salt is made by comparison with 3,5-dimethyl adamantanamine (free base) and 1,3-dimethyl adamantane spectra.

The region 3500-2600 cm^{-1}, which is due to the N-H asymmetric and symmetric stretching vibrations of salt, are observed at 3430 cm^{-1} in a broad band with medium intensity, whereas in free base two lower-frequency bands with weak intensity occur at 3335 and 3268 cm^{-1}. The weak band 3189 cm^{-1} in the salt and 3174 cm^{-1} in the free base are attributed to Fermi resonance of ν(N-H) with 2δ(N-H). The 3171 cm^{-1} and 2993 cm^{-1}, appearing as strong bands in the salt but not observed in the free base are characteristic absorptions of salt, being due to overtones of NH_3^+ deformation vibrations. The C-H stretching vibrations of methyl, methylene and methylidyne groups of salt in region 3100-2800 cm^{-1} do not show an obvious difference to the free base and this observation is indicative of being unconcerned with hydrochloric acid bonding between protons and nitrogen. The bands 2692 cm^{-1} in salt, 2644 cm^{-1} in free base and 2665 cm^{-1} in 1,3-dimethyl adamantane are believed to be the interactions between the fundamental vibrations of the methyl group and the overtones of their deformation vibrations[12-14].

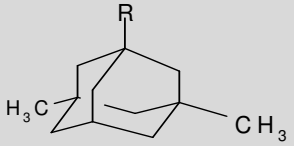
The visible differences between salt and free base fall in this region 2600-2000 cm^{-1}. New bands are distinctly observed in the salt spectrum. The salt appears in five bands at 2598, 2552, 2529, 2505 and 2009 cm^{-1} with weak intensity but is absent in the free base, being due to overtones involving NH_3^+ deformation vibration[15].

The 2000-1000 cm^{-1} region comprise deformation vibrations of NH_3^+, CH_3, CH_2 and CH and stretching motion of C-N. The highest frequencies 1596 and 1503 cm^{-1} with a

TABLE-3
VIBRATIONAL FREQUENCIES AND ASSIGNMENTS

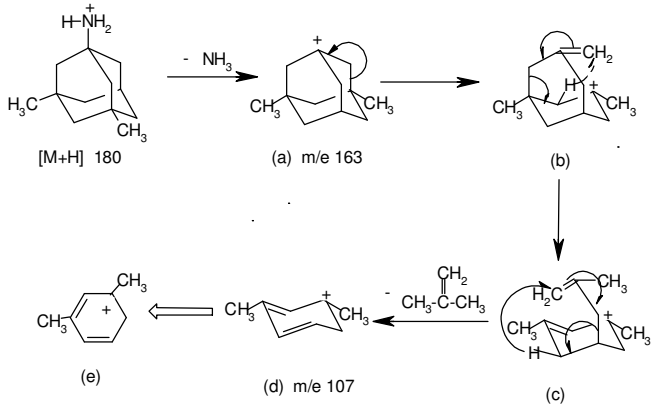
R=H frequency (cm^{-1})		R=NH_2 frequency (cm^{-1})		R=NH_3Cl frequency (cm^{-1})	
		3335 (w)	$\nu_{as}(NH_2)$	3430 (m)	$\nu_{as}(NH_3)$, $\nu_s(NH_3)$
		3268 (w)	$\nu_s(NH_2)$		
		3174 (w)	NH_2 Fermi	3189 (w)	NH_3 Fermi
				3071	$\delta_{as}(NH_3$ overtone)
				2993 (s)	$\delta_s(NH_3$ overtone)
		2943 (s)	$\nu_{as}(CH_2, CH_3)$	2946 (s)	$\nu_{as}(CH_2, CH_3)$
2900	$\nu_{as}(CH_2,CH_3)$, ν(CH)	2899 (s)	ν(CH)	2909 (s)	ν(CH)
		2864 (s)	$\delta_s(CH_3)$	2864 (s)	$\delta_s(CH_3)$
2845	$\nu_s(CH_2,CH_3)$	2839 (s)	$\delta_s(CH_2)$	2848 (s)	$\delta_s(CH_2)$
2665 (w)	$\delta(CH_3$ overtone)	2644 (w)	$\delta(CH_3$ overtone)	2692 (w)	$\delta(CH_3$ overtone)
				2600-2000 (w)	Overtone
		1587 (m)	$\delta(NH_2)$	1596 (m)	$\delta_{as}(NH_3^+)$
				1503 (m)	$\delta_s(NH_3^+)$
1451	$\delta_{as}(CH_3)$, $\delta(CH_2)$	1463 (m)	$\delta_{as}(CH_3)$, $\delta(CH_2)$	1456 (m)	$\delta_{as}(CH_3)$, $\delta(CH_2)$
1359	$\delta_s(CH_3$, δ(CH)	1373 (m)	$\delta_s(CH_3)$	1362 (m)	$\delta_s(CH_3)$
		1339 (w)	δ(CH)		
		1321 (w)	γ(C-N)	1311 (m)	γ(C-N)
		1191 (w)	ν(C-N)	1192 (w)	ν(C-N)
1171, 1113	ν(C-C)				

Note: The structure of assignment is as follows



medium intensity in the salt spectrum are attributed to NH_3^+ asymmetry and symmetry deformation vibration. Corresponding to NH_2 deformation vibration of the free base was found at 1587 cm^{-1} and is absent in the spectrum of 1,3-dimethyl adamantane. The CH_3 asymmetry deformation vibration is overlaped by the CH_2 deformation vibration in the 1470-1450 cm^{-1} region in the three spectra. The CH_3 symmetry deformation vibration is overlapped by the CH deformation vibration in both the salt spectrum and in the 1,3-dimethyl adamantane spectrum, but split into two bands at 1373 cm^{-1} and 1339 cm^{-1} in the free base. The 1311 cm^{-1} and 1192 cm^{-1} are attributed to rocking vibration and C-N bond stretching vibration, respectively.

Mass spectrum: Electrospray ionization (ESI) mass spectrometry is a soft modern ionization method, whose advantage is minimum energy excess. ESI mass spectrometry permits a reduction of fragmentation and gives a simple spectrum. Thus, the ESI spectrum of 3,5-dimethyl adamantanamine hydrochloride salt only gives three peaks but shows essential information of molecular structure. The basic peak is protonated free base [M+H] *m/e* 180. The [M+H] ion undergoes C-N bond cleavages with elimination of NH_3, forming *m/e* 163 (b). The m/e 107 (d) is formed first by charge-induced carbon-carbon cleavage of CH_3-CH_2 with charge migration, forming intermediate (c), then by two-step six-numbered MacLafferty rearrangements/fragmentation pathways, accompanying lose of isobutene[15] (**Scheme-II**).



Scheme-II: Fragmentation of 3,5-dimethyladamantanamine hydrochloride salt by ESI

Conclusion

Through optimization, the most adaptive reaction condition of bromination and hydrolysis was selected and this improved the overall yield of the reaction which rose from 67.3 to 81.5 %.

The Infrared spectrum shows that the characteristic absorptions of 3,5-dimethyl adamantnaamine hydrochloride are at the frequencies of 3171 cm^{-1} and 2993 cm^{-1}, appearing as strong bands in the salt but not observed in the free base due to overtones of NH_3^+ deformation vibrations and the frequencies in 2600-2000 cm^{-1} region which are overtones involving NH_3^+ deformation vibration. The NH_3^+ asymmetry and symmetry deformation vibrations were found at 1596 and 1503 cm^{-1} with a medium intensity. The 1311 cm^{-1} and 1192 cm^{-1} are attributed to rocking vibration and C-N bond stretching vibration, respectively. The absorption at 2950-2850 cm^{-1} indicates the presence of CH_3, CH_2 and CH groups. The ESI mass spectrum of salt only shows three peaks but shows essential information of molecular structure. The [M+H] ion undergoes elimination of NH_3, forming *m/e* 163. The *m/e* 107 peak is produced by simple carbon-carbon fission of CH_3-CH_2 and then by two times six-numbered MaLafferty rearrangements with elimination of isobutene.

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