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A CONCISE TWO-STEP METHOD FOR PREPARATION OF MEMANTINE HYDROCHLORIDE FROM 1, 3-DIMETHYLADAMANTANE

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Keywords:

1,3-Dimethyladamantane, 1-Acetamido-3,5-dimethyladamantane, Memantine hydrochloride, Receptor, Antagonist

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ABSTRACT: Memantine hydrochloride is a medicine used to medicate patients with moderately severe to severe Alzheimer's disease and other neurodegenerative disorders; because of mechanisms of neuroprotection, the efficiency of memantine have been delivered in preclinical and clinical experiments. Several approaches for preparing memantine hydrochloride have been announced. The process began with 1,3-dimethyladamantane or 1-bromo-3,5-dimethyladamantane using three or four reaction steps for the production of memantine hydrochloride, with overall yield fluctuating from 39% to 63%. In this article, a concise two-step for the synthesis of memantine hydrochloride from 1,3-dimethyladamantane *via* 1-acetamido-3,5-dimethyl-adamantane with an overall yield of 85% was developed. The parameters of the procedure were also optimized with a view to lessening the utilization of toxic solvents and reagents, making it more eco-friendly. And in particular, the condition reaction are specified in the preparation of 1-acetamido-3,5-dimethyladamantaneasreaction temperature = 70 ºC, time reaction =2.5 hrs, molar ratio of (acid nitric: acetonitril: 1,3-dimethyladamantane) = 7:10:1; in the synthesis of memantine hydrochloride as reaction temperature = 130 ºC, time reaction = 8 h, molar ratio of (NaOH: HCl:1-acetamido-3,5-dimethyl-adamantane) = 4:6:1; weight ratio of (PG: 1-acetamido-3,5-dimethyl-adamantane) = 2.5:1. The procedure can be regarded as being suitable for producing of Memantine hydrochloride on a large scale.

INTRODUCTION: Alzheimer's disease is an irreversible, progressive condition that step by step degrades a person's memory and thinking skills. That has been affecting more than 48 million people worldwide, and this number is predicted will rise to 130 million by 2050. Having 2 classes of medicine for Alzheimer's treatment is most used. One of them is drugs that stimulate acetylcholinesterase production for mild to moderate diseases such as galanthamine, donepezil, rivastigmine.

The other is memantine hydrochloride that is known as an active N-methyl D-aspartate (NMDA) receptor antagonist and it works by blocking the NMDA receptors in the brain. Thus, it can improve brain function in Alzheimer's disease and also blocks the glutamate activity that may further damage the brain cells. Memantine hydrochloride was first reported in 1968 by Jack Mills and Eriks Krumkalns [1]. Until now, many methods of synthesis have been announced from a myriad of

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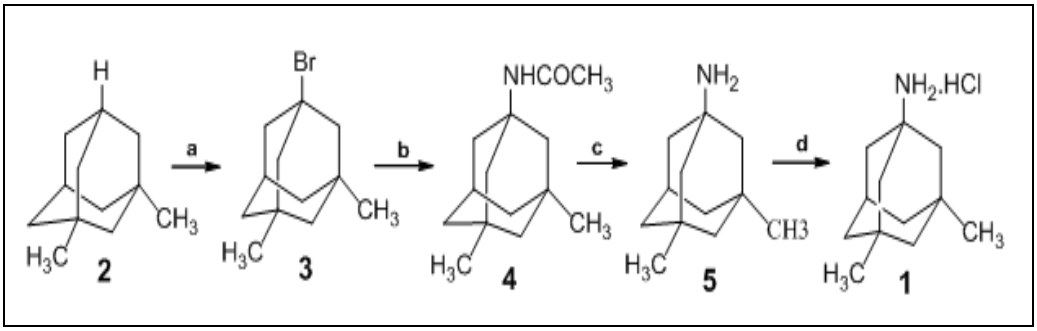
materials like 1, 3-dimethyladamantane [1-10], 1-halogeno-3, 5-dimethyladamantane [11-16], 1-hydroxy-3, 5-dimethyladamantane [17, 18]. However, it found that the overall yield of the methods would be altered even though the input materials were the same because of having differences in using of catalysts, reaction conditions, and the way of product refining. A number of groups of methods have disclosed [1, 3, 4, 6, 7] the preparation of memantine hydrochloride (1) with low efficiency (39%-63%), and complication by the utilizing liquid bromine to brominate 1,3-dimethyl-adamantane(2) to obtain 1-bromo-3,5-dimethyl-adamantane(3). The transformation of 3 to N-acetamido-3, 5-dimethyladamantane (4) *via* acetonitrile along with sulfuric acid (Ritter-type reaction) and then treatment of 4 with NaOH in the solvent as diethylene glycol (DEG) at reflux conditions (240-250 °C) in the wake of salt formation with anhydrous HCl in ethyl ether to generatememantine hydrochloride (1) (Scheme 1) [1, 7].



SCHEME 1: FOUR-STEP PROCESS FOR SYNTHESIS OF 1 FROM 1,3-DIMETHYLADAMANTANE (2) [1, 7]

Reagents, conditions and yields: (a) Br_2/reflux/6 h; 86% (b) i, CH_3CN/H_2SO_4, rt/overnight; ii, Benzene extraction; 90%. (c) i, NaOH/PEG/ref. 6 h; ii, Benzene extraction; 96%; (d) anhydrous HCl gas/ether/0-5 ºC; 66%. Overall yield of procedure: 49%

Overall, the weaknesses in this procedure have been considerable. Firstly, this process went through many steps that is the main reason to decrease the efficiency of the reaction. Secondly, bromination is carried with liquid bromine, which can have knock-on effects on the emergence of toxic bromine vapour. Thirdly, the molar ratio of compound 3: H_2SO_4: acetonitril was 1.0: 33.5: 17.4, which indicates that sulfuric acid and acetonitril were used lavishly. Fourthly, the using solvent for the extraction of 4 in this procedure was benzene that is known as a poison. Moreover, in the deacetylation of 4 into 5, diethylene glycol was utilized as a solvent, which would become a toxicant when heated to 245-250 °C with alkali base because it's decomposition will be exothermal and release explosive hydrogen gas, emits acid smoke, irritating fumes. Finally, using diethyl ether in the extraction of 5 and re-crystallization 1is a matter requiring attention by the risk of highly inflammable nature and tendency to become the peroxide form. In view of above factors, this process is really unsafe for enlarging, environmentally hazardous and along with lower performancing (49%). Other researches of 1 have been declared but that are either long time reaction or containing inappropriate stages, thus implementing them in industrial scale is impossible.

MATERIALS AND METHODS:

General Procedures: The solvent and reagents that are readily available in the market were utilized without further purification. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded in $CDCl_3$ on 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 spectro-photometer (USA). The mass spectra (70 eV) were recorded on AutoSpecPremier Spectrometer. The melting points were measured on the Stuart SMP-10 apparatus. Thin-layer chromatography (TLC) was implemented on Kieselgel 60F-254 plates.

Preparation of 1-acetamido-3,5-dimethyl-adamantane (4): Nitric acid (15 ml; 0.35 mol) at 25 ºC-30 ºC was slowly poured into 1,3-dimethyl-adamantane(2) (8.25 g; 0.05mol) with stirring within 15 min. This suspension mixture was maintained over 30 min, then acetonitrile (26 mL;

0.5 mol) was added with stirring at 25-30 ºC. We heated this reaction mixture to 70 ºC for 2.5 hours. After the reaction was finished off, the reaction mixture was put into ice-cold water (100 mL) and stirred at 5-10 ºC for 30 min and then extracted with dichloromethane (150 mL). The organic layer was cleaned with cold water 5-10 ºC and dried over anhydrous sodium sulfate.

The solvent vaporized under vacuum to obtain 1-acetamido-3.5-dimethyladamantane (4), which was crystallized with hexane to give a white yield 10.81 g (97.68%); mp: 111-113 ºC [5]; IR (cm^{-1}): 3294-3259 (N-H), 2945-2904 (C-H), 1651 (C=O). MS (m/e): 221.8 [M + 1]+, 179.9 [M-(CH_3CO)]+; 162.9 [M – (CH_3CONH)]+. ^{1}H NMR (500 MHz, $CDCl_3$), (δ): 0.84 (s. 6H), 1.11-1.19 (q. 2H), 1.27-1.29 (s, 2H), 1.36-1.39 (q, 2H), 1.60-1.67 (q. 4H), 1.83 (s, 2H), 1.90 (s, 3H), 2.13-2.14 (m, 1H), 5.28=5.30 (bs, 1H, NH).^{13}C-NMR (125 MHz, $CDCl_3$), δ (ppm): 169.42(C=O); 53.5 (C1) 50.6 (2C, C2 and C9); 47.6 (C4); 42.7(C10); 40.1 (C7); 32.4 (2C, C3 and C5); 30.1 (C8); 30.0(2C, C11 and C12); 24.6 (CH_3-CO) [11].

Synthesis of Memantine Hydrochloride (1) from 1-Acetamido-3,5-dimethyladamantane (4): To a mixture of sodium hydroxide (8 g, 0.2mol), water (5 mL), and propylene glycol (26 mL), which was stirred at room temperature for 0.5 h, then 1-acetamido-3,5-dimethyladamantane(4) (11.15 g; 0.05 mol) was added. We increased the reaction temperature to 130 ºC and sustained it for 8.0 h. The whole reaction was monitored by TCL (solvent system: chloroform/ methanol = 9/1, v/v; visualization: Dragendorff reagent). The total duration is calculated from the time that material compound 4was put into it completely disappeared.

After it finished, the reaction mixture was cooled to room temperature and then put into ice-cold water (100 mL). We continued to use dichloromethane (200 mL) to extract for 3 times. The separated organic layer was concentrated (to 1/3 volume) and then to which 5N HCl (60 mL) was added. After heating the reaction mixture to 55-60 ºC for 1 h, it was evaporated under vacuum to get white solid, then washed by ethyl acetate (10 mL). Finally, this compound was re-crystallized in mixture of ethanol - ethyl acetate 5: 4 (v/v) give 9.36 g (86.79%) 1-amino-3,5-dimethyladamantane hydrochloride (1); mp 290-295 ºC [9, 10, 12]. IR (KBr), (cm^{-1}): 3503-3209 (N-H); 3010-2901 (C-H); 1358 (C-N); MS, m/z: 179.9[M- (HCl)]+ ; 162.9 [M-(NH_2.HCl)]+; 1H-NMR (500 MHz, $CDCl_3$), δ (ppm) 8.29 (s, 3H); 2.20-2.21 (m, 1H); 1.89 (s, 2H); 1.74-1.72 (d, J=11.5, 2H); 1.68-1.66 (d, J=11.5, 2H); 1.41-1.39 (d, J=12.5, 2H); 1.32-1.29 (d, J=12.5 2H); 1.22-1.20 (d, J=12.5Hz, 1H); 1.16-1.14 (d, J=12.5Hz, 1H); 0.86 (s, 6H) ; ^{13}C-NMR (125 MHz, $CDCl_3$), δ (ppm): 54.4 (C1); 49.8 (2C, C2 and C9); 46.4 (C4); 41.8 (2C, C6 and C10); 39.2 (C7); 32.6 (C3 and C5); 29.8 (C8); 29.6 (2C, C11 and C12) [9, 10].

Synthesis of Memantine Hydrochloride (1) from 1,3-Dimethyladamantane (2) in one-pot procedure: Nitric acid (450 ml; 10.5 mol) at 25 ºC-30 ºC was poured slowly into 1,3-dimethyl-adamantane (247.5 g; 1.5 mol) with stirring within 30 min. This suspension mixture was maintained for 1 h, then acetonitrile (787.5 mL; 15mol) was added with stirring at 25-30 ºC. This reaction mass was heated to 70 ºC for 2.5 h. After reaction was finished off, the reaction mixture was put into ice-cold water (3000 mL) and stirred at 5-10 ºC for 30 min and then extracted with dichloromethane (3500 mL). The organic layer was rinsed with cold water 5-10 ºC and dried over anhydrous sodium sulfate.

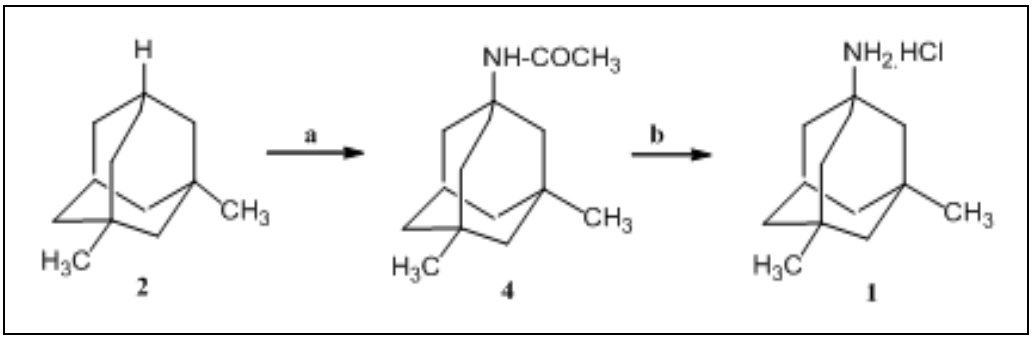
The solvent was vaporized under vacuum to obtain 1-acetamido-3,5-dimethyladamantane (4) as a white solid. This compound was added to a mixture of sodium hydroxide (240 g, 6.0mol), water (30 mL), propylene glycol (787.5 mL), and stirred at room temperature for 0.5h. We increased the reaction temperature to 130 ºC and maintained for 8.0 hours. The whole reaction was monitored by TCL (solvent system: chloroform/ methanol = 9/1, v/v; visualization: Dragendorff reagent).

The total duration is calculated from the time that material compound 4 was put into it completely disappeared. After it finished, the reaction mixture was cooled to room temperature and then put into ice-cold water (2.0 L). We continued to use dichloromethane (3000 mL) to extract 3 times. The separated organic layer was concentrated (to 1/3 volume) and then to which 5N HCl (1440 mL) was added. The reaction mixture was heated to 55-60 ºC for 1 h and evaporated under vacuum to give a white solid, then washed by ethyl acetate (250 mL). Finally, this compound was re-crystallized in

mixture of ethanol - ethyl acetate 5: 4 (v/v) give 278.2 g (86.3%) 1-amino-3,5-dimetyl-adamantane hydrochloride (1);mp 290-295 ºC [9, 10, 12]. Purity (GC) = 99.86%.

RESULTS AND DISCUSSION: In this article, 4 was prepared in one step directly from 1,3-dimethyladamantane (2) and acetonitrile, along with nitric acid. The reaction was implemented at 70 °C for 2.5 h and then quenched with water and extracted by dichloromethane. The organic phase is rinsed with water and vaporized under vacuum to attain 4 yield 98%.

Compound 4 was hydrolyzed via using NaOH in a mixture of water and propylene glycol (PG)to give 5, which was transformed into its hydrochloride salt 1 using 5N aq. HCl. Transformation of 2 directly into 4 is a main step in the synthesis of 1 (Scheme 2).



SCHEME 2:TWO-STEP PROCESS FOR SYNTHESIS OF 1 FROM 1,3-DIMETHYLADAMANTANE (2) PRESENT WORK

*Reagents, conditions and yields:(a) HNO_3, CH_3CN/70ºC/2.5h; 98%; (b)i, NaOH, water, PG, 130ºC/ 8 h; ii, 5N HCl; 87%. The overall yield of procedure: 85%

Preparation of 1-Acetamido-3,5-dimethyl-adamantane (4): Compound 4 was generated from 2 and acetonitrile along with nitric acid via one single step. The nature of this reaction is the amidation of the tertiary C-H link in compound 2 by a Ritter-type reaction. In this reaction, nitric acid induced the addition of a nitrile group (−C≡N) to one the carbenium ion of 2, which on treatment with water produces [4]. The bromination of 2was skipped in this method (Scheme 1, step a); thus liquid bromine is not required. We evaluated the impact of reaction temperature ranging from 40 ºC to 80 ºC to define the reaction time respectively. As a result, we found that the optimal reaction temperature is 70 ºC and the time reaction is 2.5h (Scheme 2, step a) (see Table S1-2). After optimizing the molar ratio of reagents, it dawned on us that the molar ratio of (nitric acid: acetonitril: 2) was 7: 10: 1(see Table S3-4) instead of (nitric acid : acetonitril: 2) was33.5 : 17.4: 1, which was a substantial decrease in the amount of mixture (2,sulfuric acid and acetonitril) over the previous report [1, 4, 7]. In addition, in order to extract 4 from reaction mixture by using dichloromethan instead of benzene. Hence, it reduced the toxicity level of the described procedure. The yield of 4 was high (98% compared to an overall yield of ranging 47-60% in previous work [1, 4, 7]).

Synthesis of Memantine Hydrochloride (1): This reaction's nature is deacetylation of 4 into memantine and formation of memantine hydro-chloride (1). The deacetylation of 4 into memantine can be executed under base or acid catalysis conditions. It was shown in our experiments that using but alkali hydroxide is more convenient and gives a memantine base with a higher yield. In the hydrolysis stage, we optimized parameters of reaction, including the type of hydroxide, selection of solvent, reaction temperature and time, the molar ratio between (hydroxide and compound 4) and (HCl and compound 4). The results indicated that optimal condition to have memantine base was with NaOH in mixture of water - propylene glycol (PG) on 130 ºC for 8 h and weight ratio between (NaOH : PG : 4) = 0.72: 2.3 : 1 (molar ratio = 4: 6.8 : 1 relatively), (see Table S5-8) instead of sodium hydroxide in diethylene glycol (DEG) in weight ratio (NaOH : DEG : 4) = 150: 1200 :100 (molar ratio = 8.3 : 27.3 : 1 relatively) on 240-250 ºC for 6 - 8 h [1, 8]. The conversion of memantine base to 1is carried out by 5N aq. HCl in place of anhydrous HCl in ether solution, which will help reduce the risk of explosion from ether. The overall yield of 1 from 2 is 85% (compared to the prior

yield of 49%) [1]. In summary, the process described in Scheme 2 is a safe and economically competitive synthesis because it does not use toxic solvents like bromine. Hence, it is clear that the procedure can be easily scaled up. Additionally, this process with only two steps will increase the overall yield of 85% (compared to previous studies with four steps getting the overall yields of 36-63%).

Raw materials and reagents utilized in our procedure are inexpensive and commercially available. Each reaction step was optimized to decrease or abolish the usage of toxic reagents and solvents. Total preparation time was considerably shortened compared to those methods described previously formerly [1, 4, 6, 7]. Our results suggest that this method is economically advantageous over the earlier reported approaches owing to its high yields and the utilization of less expensive raw materials

General procedure the Synthesis of Memantine hydrochloride:

Effect of reaction parameters on the yield of 1-acetamido-3,5-dimethyladamantane (4):

TABLE 1: EFFECT OF REACTION TEMPERATURE ON THE YIELD OF 1-ACETAMIDO-3,5-DIMETHYL-ADAMANTANE (4)

S. no.	Reaction temperature (^{0}C)	Compound 4 (M-NHCOCH$_3$)		
		Weight (g)	Yield (%)	Mp (^{0}C)
1	40	0.92	42.08	110-112
2	50	1.30	58.82	111-113
3	60	1.68	76.01	110-112
4	70	1.97	89.14	112-113
5	80	1.91	86.43	110-112

Other Reaction Parameters: Reaction time = 3.5 hrs; Molar ratio of (nitric acid: acetonitril-compound2) = (20: 20: 1)

TABLE 2: EFFECT OF REACTION TIME ON THE YIELD OF 1-ACETAMIDO-3, 5-DIMETHYL-ADAMANTANE

S. no.	Reaction time (h)	Compound 4 (M-NHCOCH$_3$)		
		Weight (g)	Yield (%)	Mp (^{0}C)
1	2.0	1.81	81.90	111-112
2	2.5	2.03	91.86	111-113
3	3.0	1.95	88.26	111-112
4	3.5	1.84	83.25	112-113
5	5.0	1.82	82.35	110-112

Other Reaction Parameters: Temperature: 70 ºC; Molar ratio of (nitric acid: acetonitril: compound 2) = (20: 20:1)

TABLE 3: EFFECT OF MOLAR RATIO BETWEEN NITRIC ACID AND COMPOUND 2 ON THE YIELD OF 1-ACETAMIDO-3,5-DIMETHYLADAMANTANE

S. no.	Molar ratio of HNO$_3$: 2	Compound 4(M-NHCOCH$_3$)		
		Weight (g)	Yield (%)	Mp (^{0}C)
1	15:1	2.08	94.11	111-112
2	10:1	2.09	94.57	111-113
3	7:1	2.10	95.02	110-112
4	6:1	2.07	93.66	112-113
5	5:1	1.77	80.09	111-112

Other Reaction Parameters: Temperature = 70 ºC; Reaction time = 2.5 h; Molar ratio of (acetonitril: compound 2) = (20: 1)

TABLE 4: EFFECT OF MOLAR RATIO BETWEEN ACETONITRIL AND COMPOUND 2 ON THE YIELD OF 1-ACETAMIDO-3,5-DIMETHYLADAMANTANE

S. no.	Molar ratio of acetonitril: 2	Compound 4(M-NHCOCH$_3$)		
		Weight (g)	Mp (^{0}C)	Yield (%)
1	15:1	2.11	95.47	110-112
2	10:1	2.13	96.38	111-113
3	9:1	2.05	92.76	110-112
4	7:1	1.98	89.59	112-113
5	5:1	1.83	82.84	110-112

Reaction Parameters: Temperature = 70 ºC; Reaction time = 2.5 h; Molar ratio of (nitric acid: compound 2) = 7: 1

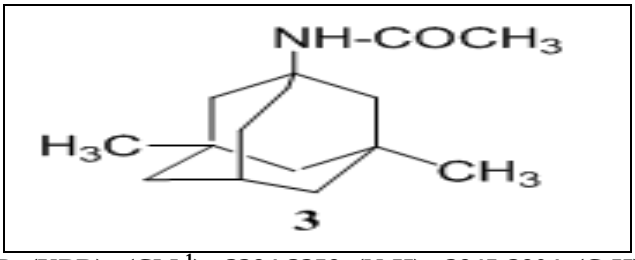
Results: The combination of reaction parameters found that the highest yield of 1-acetamido-3,5-dimethyladamantane (4): Temperature = 70 ºC; Reaction time = 2.5 hrs; Molar ratio of (nitric acid: acetonitril: 1,3-dimethyladamantane) = (7: 10: 1)

Experimental Section:

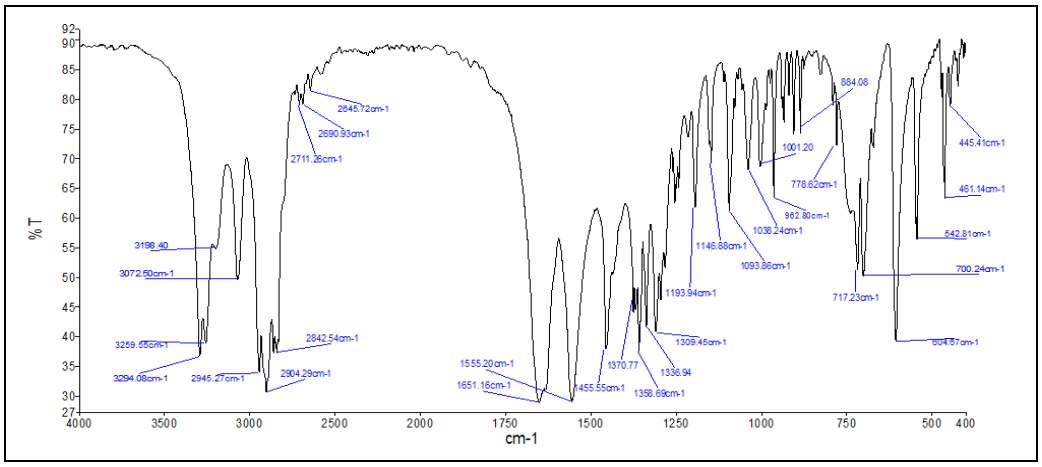
1-acetamido-3,5-Dimethyladamantane(4): Nitric acid (30 ml; 0.7 mol) at 25 ºC-30 ºC was slowly poured into 1,3-dimethyladamantane(2) (16.5 g; 0.1 mol) with stirring within 15 min. This suspension mixture was maintained over 30 min, then acetonitrile (52 mL; 1 mol) was added with stirring at 25-30 ºC. We heated this reaction mixture to 70 ºC for 2.5 hours. After reaction was finished off, the reaction mixture was put into ice-cold water (150 mL) and stirred at 5-10 ºC for 30 min and then extracted with dichloro-methane (200 mL). The organic layer was cleaned with cold water 5-10 ºC and dried over anhydrous sodium sulfate. The solvent vaporized under vacuum to obtain 1-acetamido-3.5-dimethyladamantane (4), which was crystallized with hexane to give a white yield 21.7

g (98.2%);mp: 111-113 ºC;IR (cm^{-1}): 3294-3259 (N-H), 2945-2904 (C-H), 1651 (C=O). MS (m/e): 221.8 [M + 1]+, 179.9 [M-(CH_3CO)]+; 162.9 [M – (CH_3CONH)]+. 1H NMR (500 MHz, $CDCl_3$), (δ): 0.84 (s. 6H), 1.11-1.19 (q. 2H), 1.27-1.29 (s, 2H), 1.36-1.39 (q, 2H), 1.60-1.67 (q. 4H), 1.83 (s, 2H), 1.90 (s, 3H), 2.13-2.14 (m, 1H), 5.28=5.30 (bs, 1H, NH).^{13}C-NMR (125 MHz, CDCl3), δ (ppm): 169.42(C=O); 53.5 (C1) 50.6 (2C, C2 and C9); 47.6 (C4); 42.7(C10); 40.1 (C7); 32.4 (2C, C3 and C5); 30.1 (C8); 30.0(2C, C11 and C12); 24.6 (CH_3-CO.).

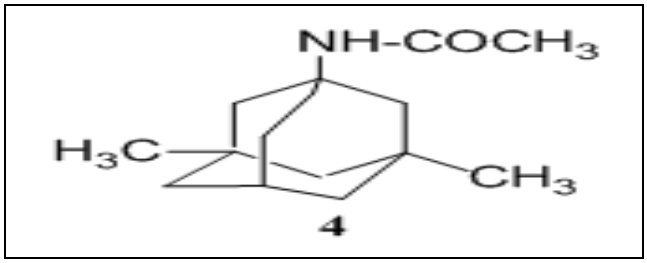
IR spectrum of 1-acetamido-3,5-dimethyl-adamantane (4):



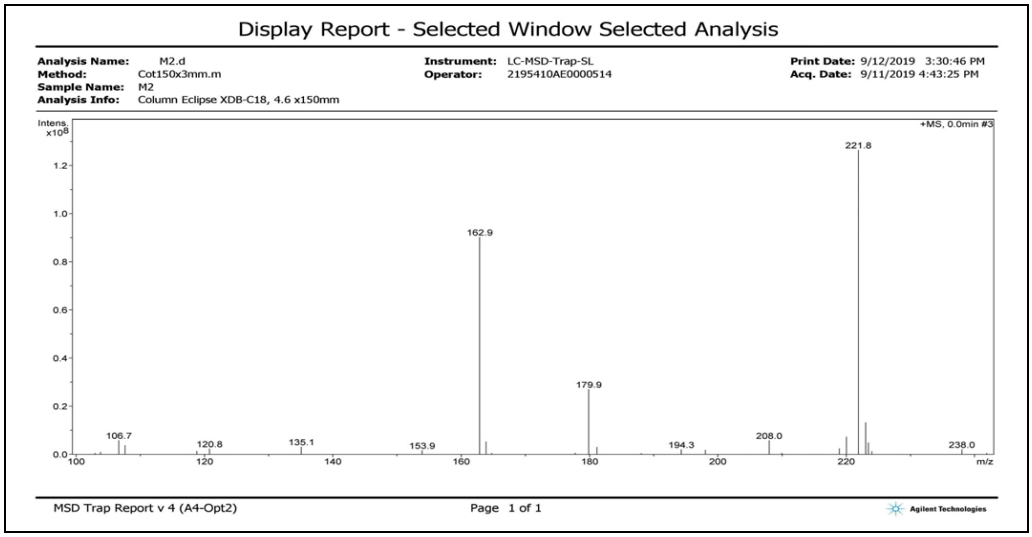
IR (KBR), (CM^{-1}): 3294-3259 (N-H); 2945-2904 (C-H); 1651 (C=O).



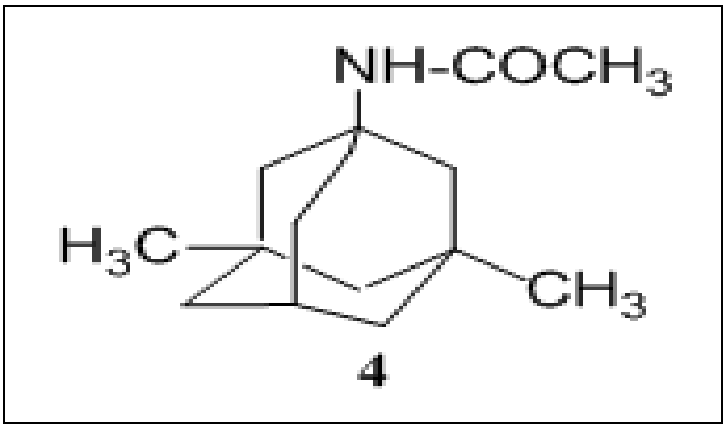
MS Spectrum of 1-Acetamido-3,5-Dimethyladamantane (4):



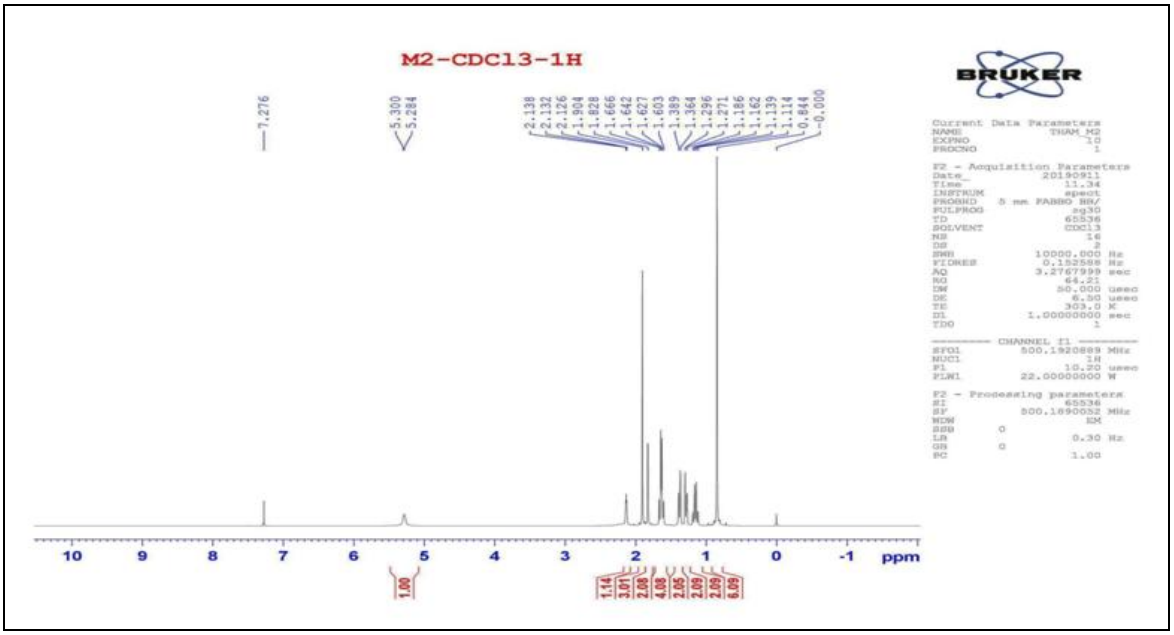
MS (M/Z): 221.8 [M+1]+, 179.9 [M-(CH3CO)]+, 162.9 [M-(CH3CONH)]+

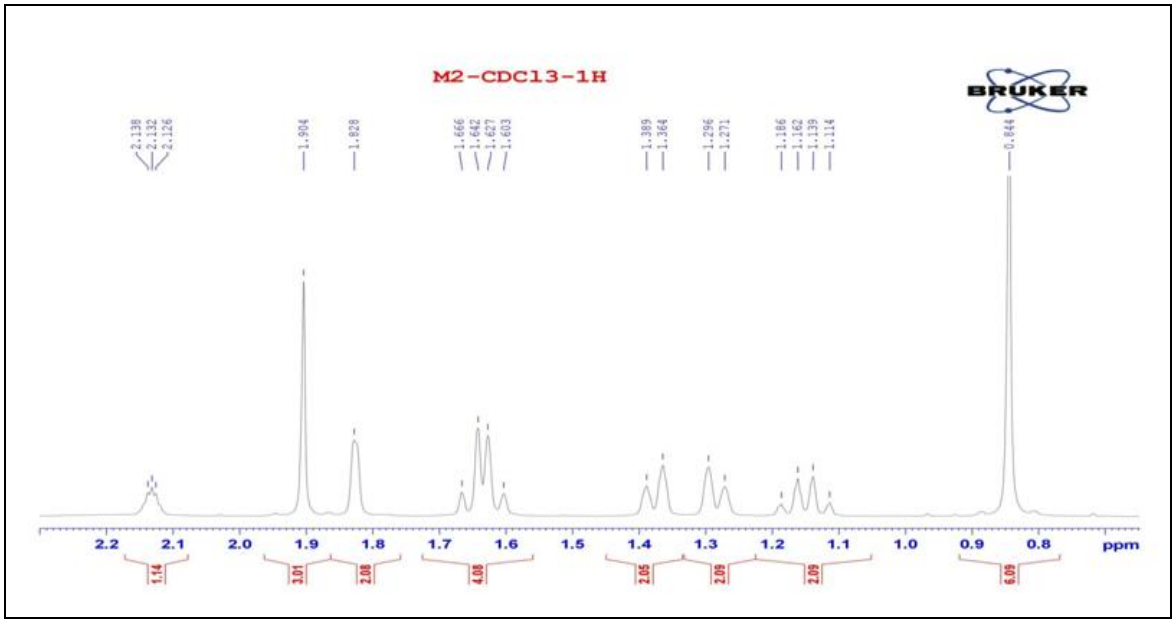


^{1}H-NMR Spectrum of 1-Acetamido-3,5-Dimethyladamantane (4):

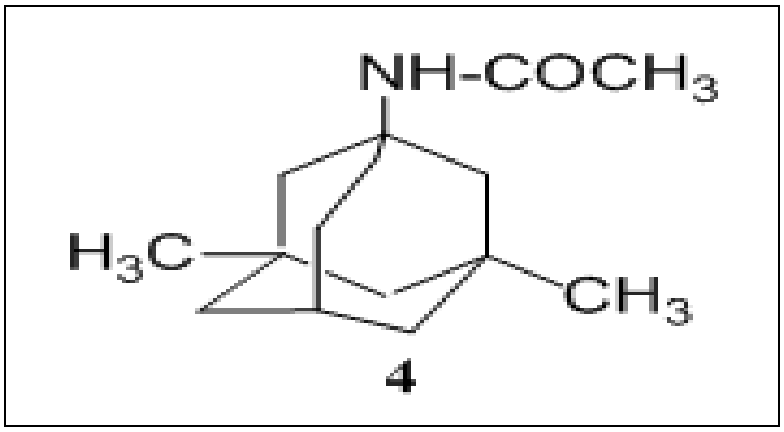


^{1}H NMR (500 MHz, $CDCl_3$), (δ): 0.84 (s. 6H), 1.11-1.19 (q. 2H), 1.27-1.29 (s, 2H), 1.36-1.39 (q, 2H), 1.60-1.67 (q. 4H), 1.83 (s, 2H), 1.90 (s, 3H), 2.13-2.14 (m, 1H), 5.28-5.30 (bs, 1H, NH).

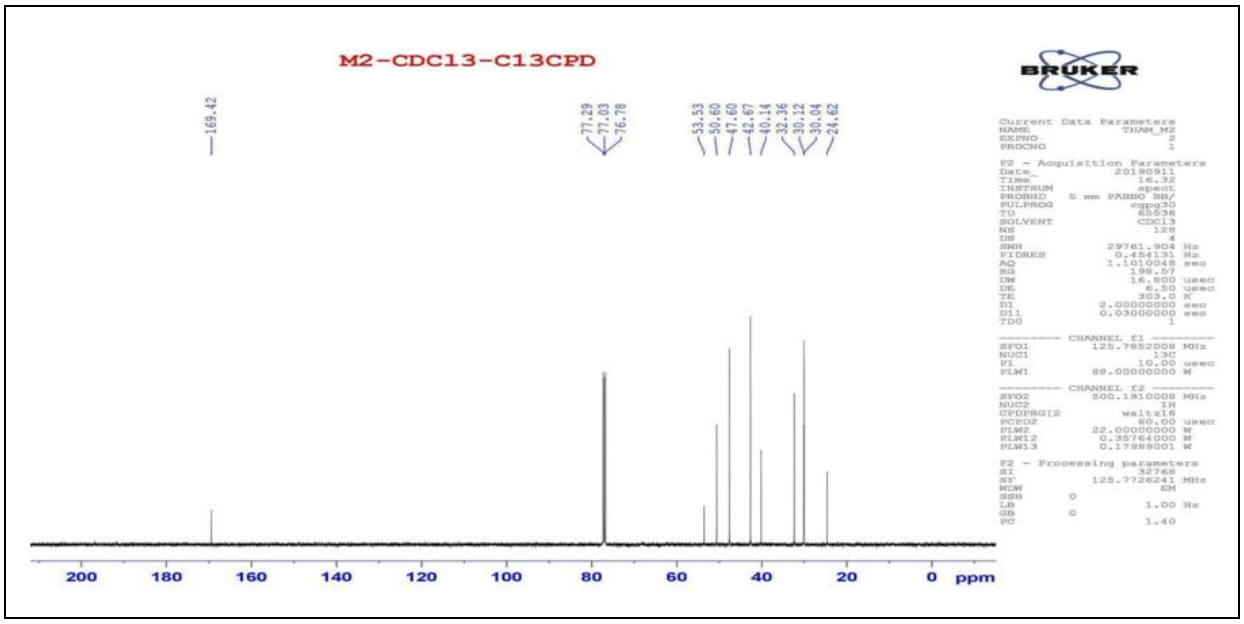


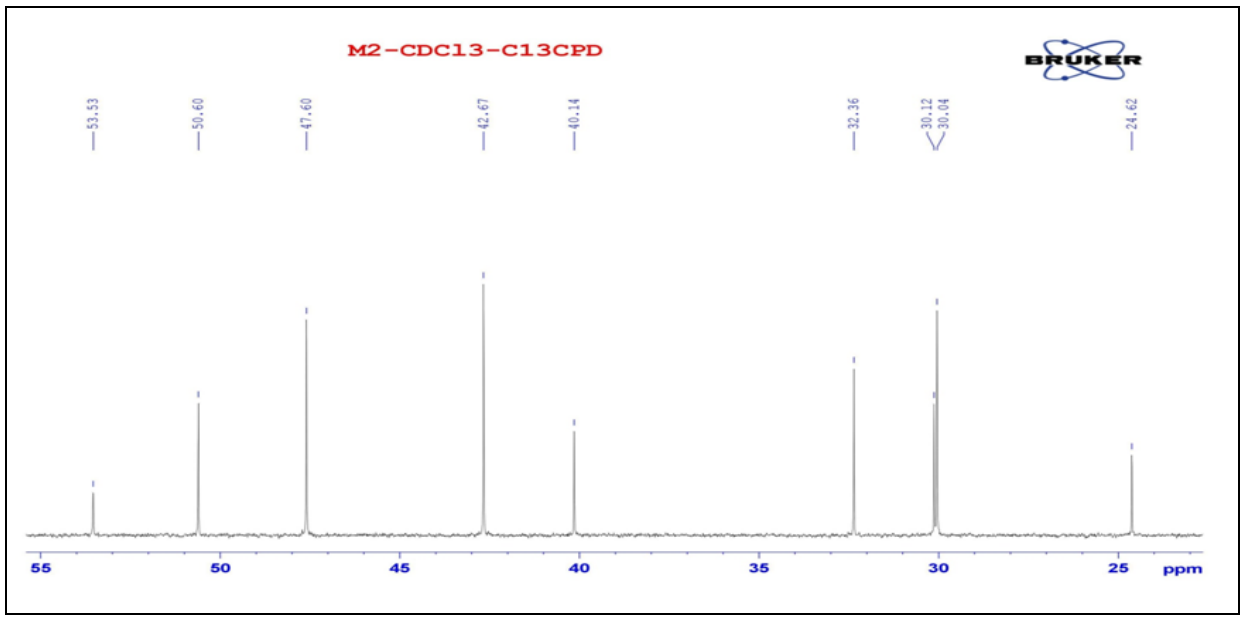


^{13}C-NMR Spectrum of 1-Acetamido-3,5-Dimethyladamantane (4):



^{13}C-NMR (125 MHZ, CDCL3), Δ (PPM): 169.42(C=O); 53.5 (C1) 50.6 (2C, C2 AND C9); 47.6 (C4); 42.7(C10); 40.1 (C7); 32.4 (2C, C3 AND C5); 30.1 (C8); 30.0(2C, C11 AND C12); 24.6 (CH3-CO.).





Effect of Reaction Parameters on the Yield of Memantine Hydrochloride:

TABLE 5: EFFECT OF TEMPERATURE AND REACTION TIME ON THE YIELD OF MEMANTINE HYDROCHLORIDE (1)

S. no.	Reaction Temperature (^{0}C)	Reaction Time* (h)	Compound 1 (M-NH_2.HCl)		
			Weight (g)	Yield (%)	Mp(^{0}C)
1	150	4.5	1.20	55.64	>290
2	140	5.5	1.43	66.23	>290
3	135	7.5	1.67	77.24	>290
4	130	8.0	1.72	79.76	>290
5	125	8.5	1.71	79.15	>290
6	120	10.0	1.65	76.49	>290
7	110	17.0	1.47	68.20	>290

Other Reaction Parameters: Molar ratio of (NaOH: HCl: Compound 4) = 7: 8:1, weight ratio of (PG: compound 4) = 5:1

TABLE 6: EFFECT OF MOLAR RATIO OF NAOH AND 1-ACETAMIDO-3,5-DIMETHYLADAMANTANE ON THE YIELD OF MEMANTINE HYDROCHLORIDE (1)

S. no.	Molar ratio of NaOH: Compound 4	Compound 1 (M-NH_2.HCl)		
		Weight (g)	Yield (%)	Mp (^{0}C)
1	3.0: 1	1.72	79.53	>290
2	3.5: 1	1.79	83.28	>290
3	4.0: 1	1.83	84.75	>290
4	5.0: 1	1.83	84.78	>290
5	6.0: 1	1.80	83.45	>290
6	7.0: 1	1.78	82.54	>290

Other Reaction Parameters: Temperature: 130 ºC; Reaction time: 8 hrs; Molar ratio of (HCl: Compound 4) = 8: 1; Weight ratio of (PG: compound 4) = 5: 1

TABLE 7: EFFECT OF WEIGHT RATIO OF PG AND 1-ACETAMIDO-3,5-DIMETHYLADAMANTANE ON THE YIELD OF MEMANTINE HYDROCHLORIDE

S. no.	Weight ratio of PG: Compound 4	Compound 1 (M-NH_2.HCl)		
		Weight (g)	Yield (%)	Mp (^{0}C)
1	2.0: 1	1.80	83.45	>290
2	**2.5: 1**	**1.84**	**85.10**	**>290**
3	3.0: 1	1.83	84.96	>290
4	3.5: 1	1.82	84.59	>290
5	4.0: 1	1.83	84.67	>290
6	5.0: 1	1.81	83.87	>290

Other Reaction Parameters: Temperature: 130 ºC; Reaction time: 8hrs; Molar ratio of (NaOH: HCl: Compound 4) = 4: 8: 1.

TABLE 8: EFFECT OF MOLAR RATIO OF HCl AND 1-ACETAMIDO-3,5-DIMETHYLADAMANTANE ON THE YIELD OF MEMANTINE HYDROCHLORIDE

S. no.	Molar ratio of HCl: Compound 4	Compound 1 (M-NH_2.HCl)		
		Weight (g)	Yield (%)	Mp (^{0}C)
1	3: 1	1.82	84.36	>290
2	4: 1	1.84	85.47	>290
3	5: 1	1.85	85.94	>290
4	6: 1	1.87	86.47	>290
5	7: 1	1.85	85.79	>290
6	8: 1	1.84	85.24	>290

Other Reaction Parameters: Temperature: 130 ºC; Reaction time: 8hrs; Molar ratio of (NaOH: Compound 4) = 4: 2.5: 1; Weight ratio of (PG: compound 4) = 2.5:1

Results: The combination of reaction parameters that gives the highest yield of memantine. HCl: Temperature = 130 °C; Time = 8.0 h; Molar ratio of (NaOH: HCl: 4) = (4: 6: 1); Weight ratio of (PG: compound 4) = 2.5:1.

Experimental Section:

Memantine Hydrochloride(1): To a mixture of sodium hydroxide (16 g, 0.4 mol), water (10 mL) and propylene glycol (52 mL), which was stirred at room temperature for 0,5 h, then 1-acetamido-3,5-dimethyladamantane(4) (22.3 g; 0.1 mol) was added. We increased the reaction temperature to 130 ºC and sustained it for 8.0 h. The whole reaction was monitored by TCL (solvent system: chloroform/ methanol = 9/1, v/v; visualization: Dragendorff reagent). The total duration is calculated from the time that material compound 4 was put into it completely disappeared. After it finished, the reaction mixture was cooled to room temperature and then put into ice-cold water (150 mL). We continued to use dichloromethane (250 mL) to extract 3 times. The separated organic layer was concentrated (to 1/3 volume) and then to which 5N HCl (60 mL) was added. After heating the reaction mixture to 55-60 ºC for 1 h, it was evaporated under vacuum to get a white solid, then washed by ethyl acetate (20 mL). Finally, this compound was re-crystallized in mixture of ethanol - ethyl acetate 5: 4 (v/v) give 18.8 g (87.4%) 1-amino-3,5-dimethyladamantane hydrochloride (1); mp 290-295 ºC.IR (KBr), (cm-1): 3503-3209 (N-H); 3010-2901 (C-H); 1358 (C-N);MS, m/z: 179.9[M- (HCl)]+ ; 162.9 [M-(NH_2.HCl)]+; ^{1}H-NMR (500 MHz, CDCl3), δ (ppm) 8.29 (s, 3H);

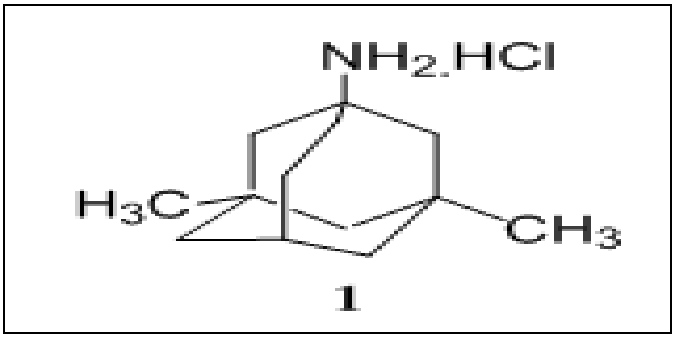
2.20-2.21 (m, 1H); 1.89 (s, 2H); 1.74-1.72 (d, J=11.5, 2H); 1.68-1.66 (d, J=11.5, 2H); 1.41-1.39 (d, J=12.5, 2H); 1.32-1.29 (d, J=12.5 2H); 1.22-1.20 (d, J=12.5Hz, 1H); 1.16-1.14 (d, J=12.5Hz, 1H); 0.86 (s, 6H); ^{13}C-NMR (125 MHz, $CDCl_3$), δ (ppm): 54.4 (C1); 49.8 (2C, C2 and C9); 46.4 (C4); 41.8 (2C, C6 and C10); 39.2 (C7); 32.6 (C3 and C5); 29.8 (C8); 29.6 (2C, C11 and C12);.

Synthesis of Memantine Hydrochloride (1) from 1,3-Dimethyladamantane (2) in one-pot procedure: Nitric acid (450 ml; 10.5 mol) at 25ºC-30 ºC was poured slowly into 1,3-dimethyl-adamantane (247.5 g; 1.5 mol) with stirring within 30 min. This suspension mixture was maintained for 1 h, then acetonitrile (787.5 mL; 15 mol) was added with stirring at 25-30 ºC. This reaction mass was heated to 70 ºC for 2.5 hours. After the reaction was finished off, the reaction mixture was put into ice-cold water (3000 mL) and stirred at 5-10 ºC for 30 min and then extracted with dichloromethane (3500 mL).

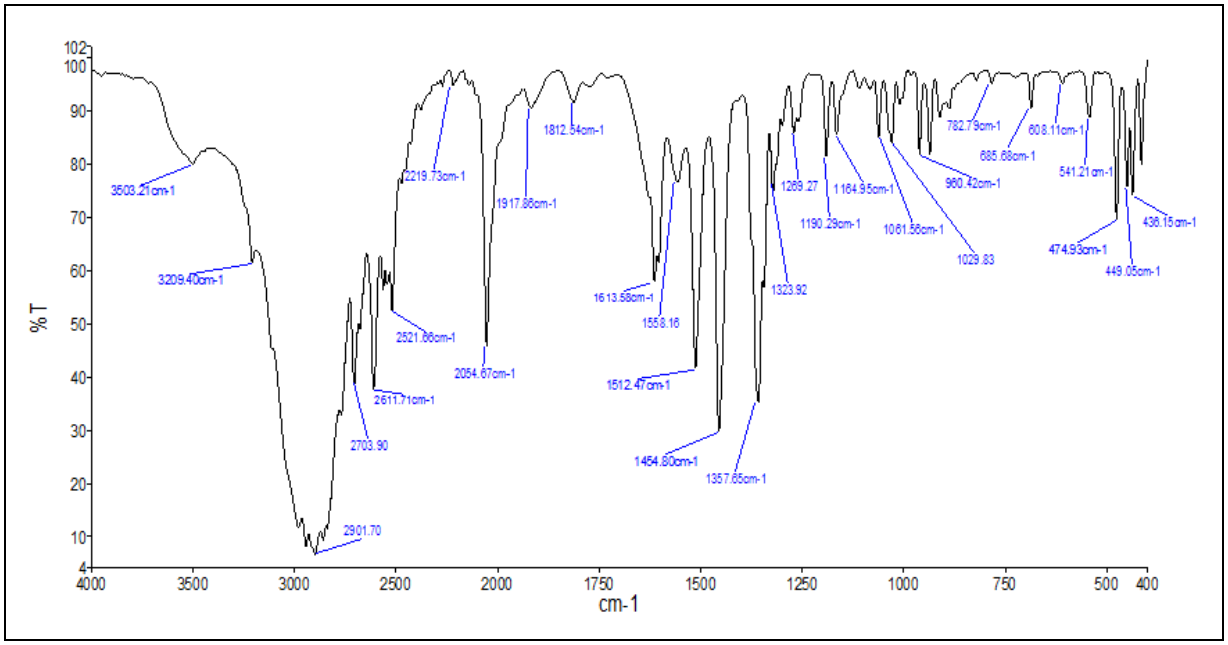
The organic layer was rinsed with cold water 5-10 ºC and dried over anhydrous sodium sulfate. The solvent was vaporized under vacuum to obtain 1-acetamido-3,5-dimethyladamantane (4) as a white solid. This compound was added to a mixture of sodium hydroxide (240 g, 6.0 mol), water (30 mL), propylene glycol (787.5 mL), and stirred at room temperature for 0,5h. We increased the reaction temperature to 130 ºC and maintained it for 8.0 hours. The whole reaction was monitored by TCL (solvent system: chloroform/ methanol = 9/1, v/v; visualization: Dragendorff reagent).

The total duration is calculated from the time that material compound 4 was put into it completely disappeared. After it finished, the reaction mixture was cooled to room temperature and then put into ice-cold water (2.0 L). We continued to use dichloromethane (3000 mL) to extract for three times. The separated organic layer was concentrated (to 1/3 volume) and then to which 5N HCl (1440 mL) was added. The reaction mixture was heated to 55-60 ºC for 1 h and evaporated under vacuum to give a white solid, then washed with ethyl acetate (250 mL). Finally, this compound was re-crystallized in mixture of ethanol - ethyl acetate 5: 4 (v/v) give 278.2 g (86.3%) 1-amino-3,5-dimetyl-adamantane hydrochloride (1); mp 290-295 ºC. Purity (GC) = 99.86%.

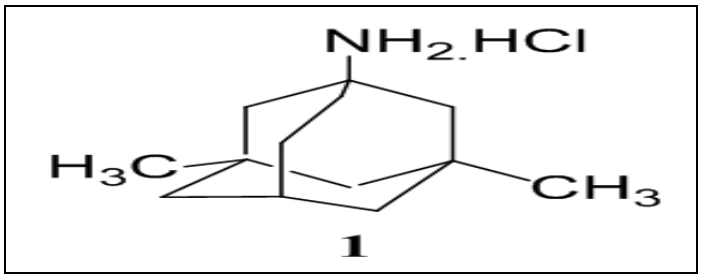
IR spectrum of Memamtine Hydrochloride:



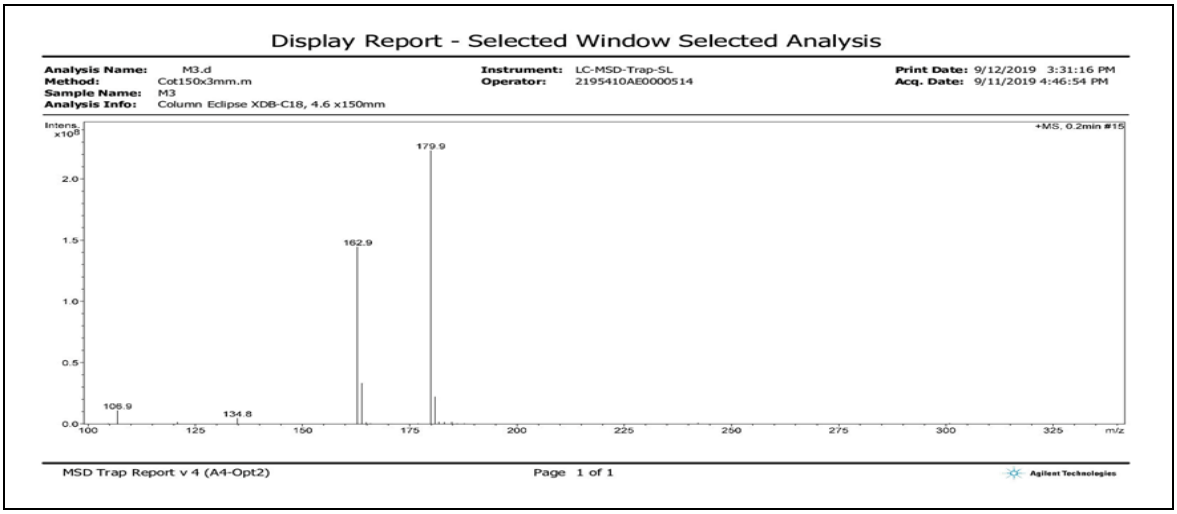
IR (KBR), (CM-1): 3503-3209 (N-H); 3010-2901 (C-H); 1358 (C-N);



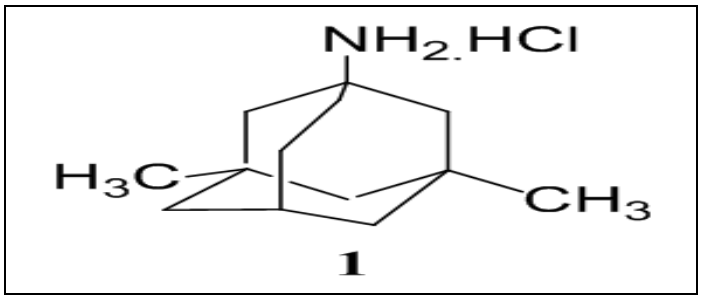
MS spectrum of Memantine Hydrochloride:



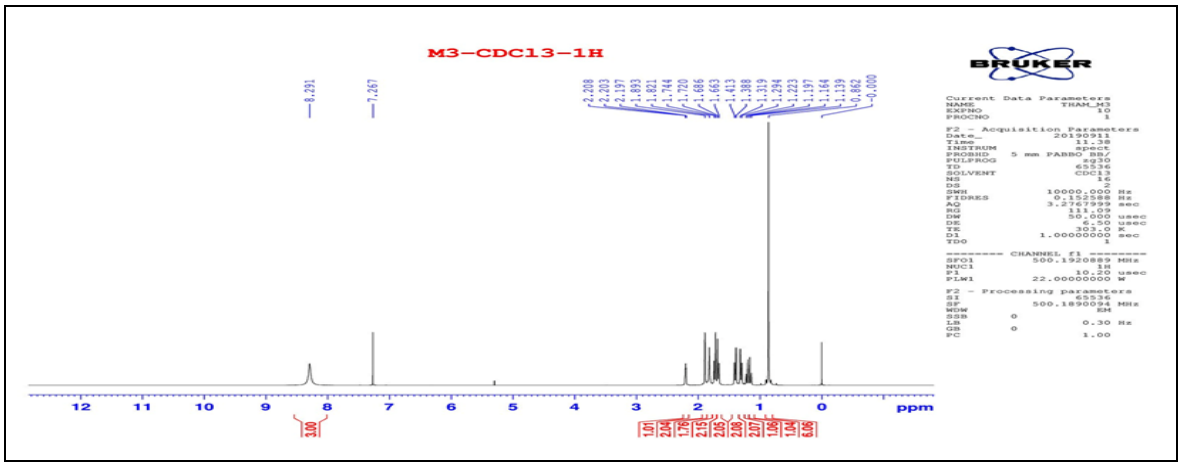
MS, M/Z: 179.9[M-(HCL)]+ ; 162.9 [M-(NH2.HCL)]+;

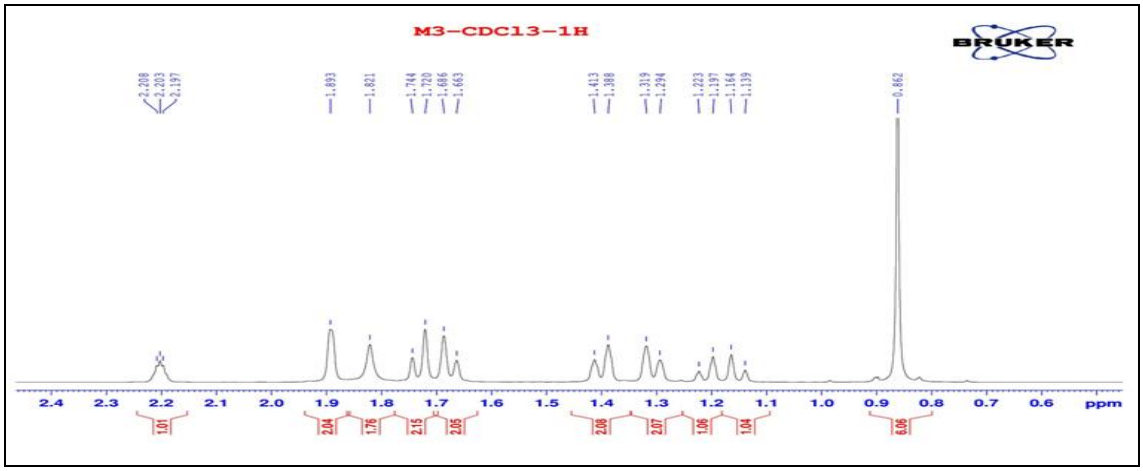


^{1}H-NMR spectrum of Memantine Hydrochloride:

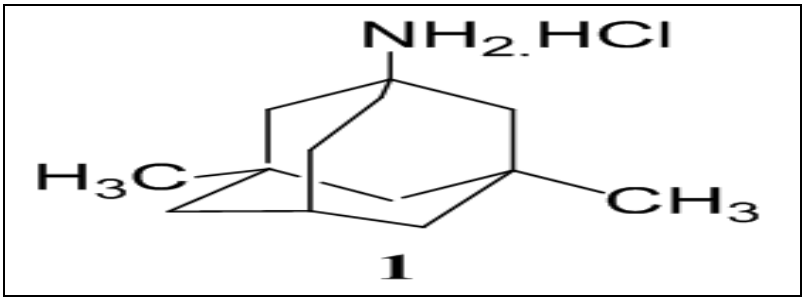


^{1}H-NMR (500 MHZ, CDCL3), Δ (PPM) 8.29 (S, 3H); 2.20-2.21 (M, 1H); 1.89 (S, 2H); 1.74-1.72 (D, J=11.5, 2H); 1.68-1.66 (D, J=11.5, 2H); 1.41-1.39 (D, J=12.5, 2H); 1.32-1.29 (D, J=12.5 2H); 1.22-1.20 (D, J=12.5HZ, 1H); 1.16-1.14 (D, J=12.5HZ, 1H); 0.86 (S, 6H) ;

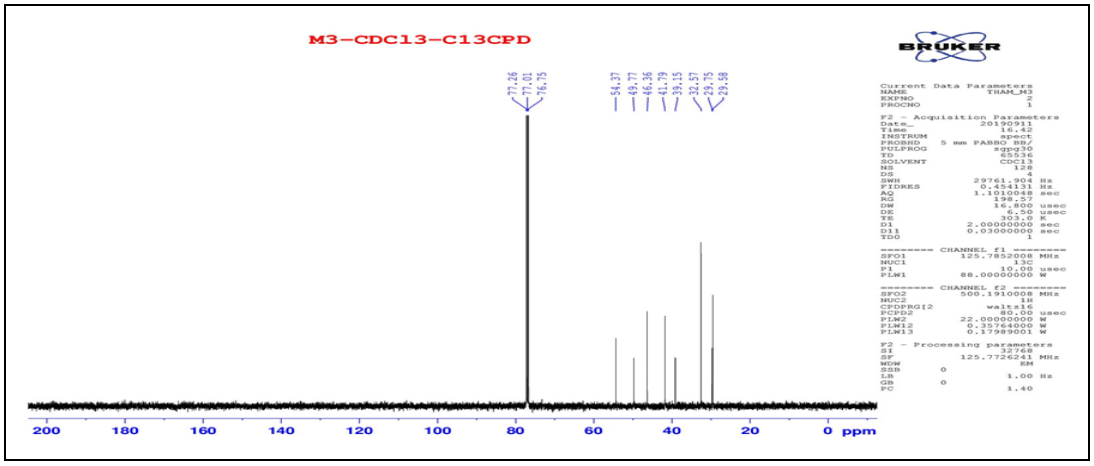


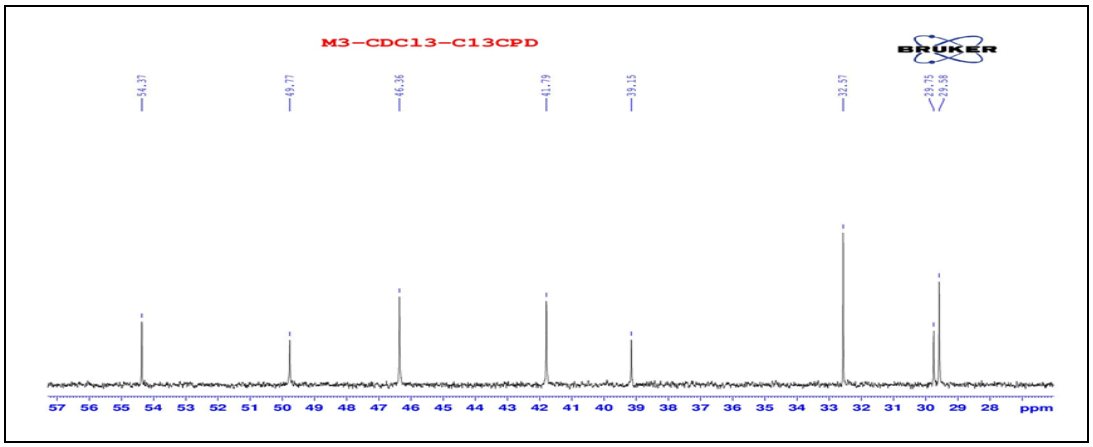


^{13}C-NMR spectrum of Memantine Hydrochloride:

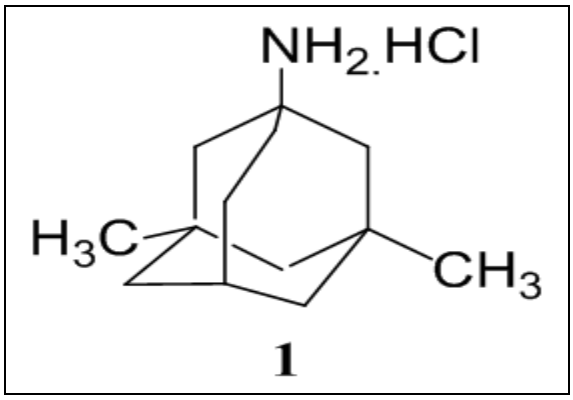


^{13}C-NMR (125 MHZ, CDCL3), Δ (PPM): 54.4 (C1); 49.8 (2C, C2 AND C9); 46.4 (C4); 41.8 (2C, C6 AND C10); 39.2 (C7); 32.6 (C3 AND C5); 29.8 (C8); 29.6 (2C, C11 AND C12).





GC Data of the Synthesised Amantadine Hydrochloride (1):



1

Gas Chromatoghraphy Condition:

Detector: Flame ionization; 300 °C;

Column: HP5 (5% Phenyl-95% methyl-polysiloxane; length of 30 m; diameter of 0,32 µm; film layer of 0,25 µm)

Oven temperature:

Temperature Ramp (°C/min)	Temperature (°C)	Hold (min)	Runtime (min)
	50	0	0
5	145	0	19
10	250	5	34,5

Carrier Gas: nitrogen.

Flow Rate: 2.0 mL/min.

Injection Volume: 1 µL.

Inlet: 220 °C; Split ratio: (1:50).

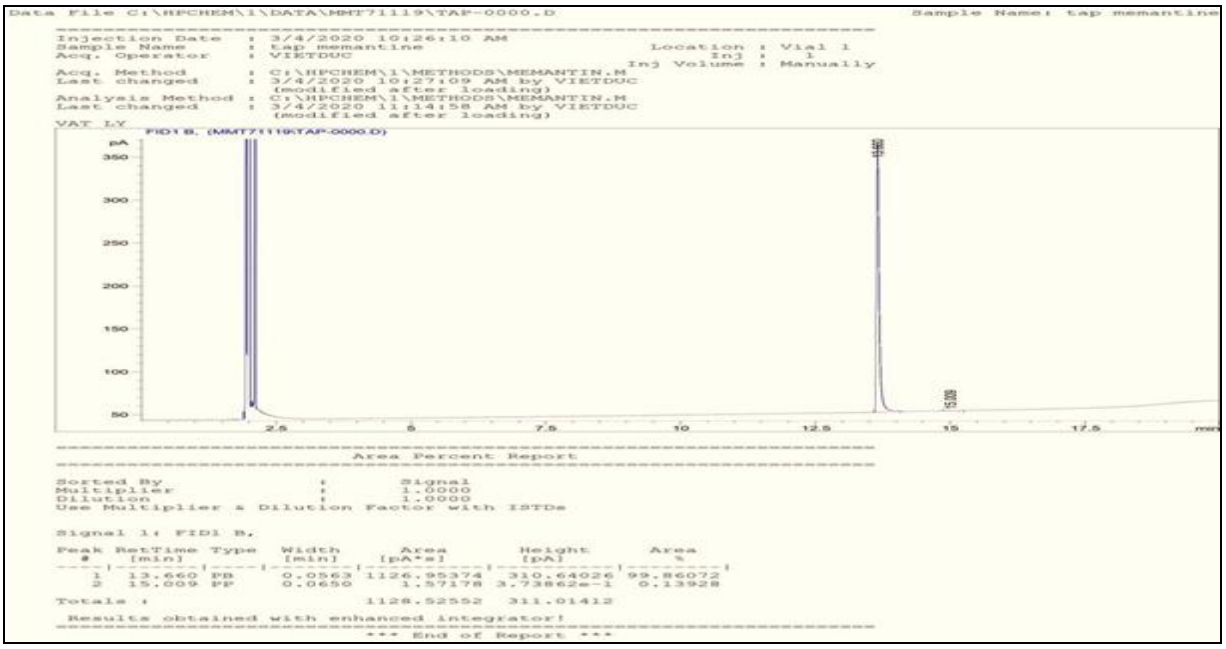


FIG. S1: GC CHROMATOGRRAPHY OF THE SYNTHESISEDMEMANTADINE HYDROCHLORIDE (1)

CONCLUSION: A concise two-step procedure for preparation of Memantine Hydrochloride (1) from 1,3-dimethyladamantane (2) has been provided. It produces a combined yield of 85%witha purity (GC) of 99.86% in two steps.

The one-pot synthesis of 4 from 2 was successfully accomplished via a Ritter-type reaction with acetonitrile and nitric acid.

This method does not utilize liquid bromine as reactants. The subsequent transformation of 4 to 1 was implemented under milder reaction conditions with NaOH in a mixture of water and propylene glycol at 130 ºC, without the utilization of dangerous solvents. These merits enable us to generatememantine hydrochloride in an effective, economical and industrially convenient method.

ACKNOWLEDGMENT: This research was financially supported by Drug R&D Center, VMMU, Vietnam.

CONFLICTS OF INTEREST: Nil

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