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A SIMPLE METHOD FOR SYNTHESIS OF AMANTADINE HYDROCHLORIDE

Binh Duong Vu [1], Thi Phuong Dung Phan [* 2], Thi Van Tran [3], Anh Tuan Dang [4], Phuong Linh Nguyen [5] and Dinh Chau Phan [* 3]

Vietnam Military Medical University [1], No.160, Phung Hung str, Phuc La ward, Ha Dong district, Ha Noi, Viet Nam.
Hanoi University of Pharmacy [* 2], No.15, Le Thanh Tong str, HoanKiem district, Ha Noi, Viet Nam.
School of Chemical Engineering [3], Hanoi University of Science and Technology, No.1, Dai Co Viet str, Bach Khoa ward, Hai Ba Trung district, Hanoi, Vietnam.
National Institute of Medicinal Materials [4], No.3B Quang Trung, Hoan Kiem District, Ha Noi, Viet Nam.
School of Pharmacy [5], University of Birmingham, Edgbaston, Birmingham, United Kingdom, B29 6AG.

Keywords:

Amantadine hydrochloride, adamantane, N-(1-adamantyl) acetamide, antiviral, anti-dyskinetic, Parkinson's disease, one-pot

Correspondence to Author:
Anh Tuan Dang

National Institute of Medicinal Materials, No. 3B Quang Trung, Hoan Kiem District, Ha Noi, Viet Nam.

E-mail: tankzordang@gmail.com

ABSTRACT: Amantadine hydrochloride (1) is an antiviral drug currently used to treat certain influenza infections (type A). It is also used as an anti-dyskinetic agent to treat Parkinson's disease. Several methods for the preparation of amantadine hydrochloride (1) were reported, these procedures started from adamantane (2), using procedure four reaction steps to obtain amantadine hydrochloride with an overall yield of 46-58%. In this article, we present a convenient two-step procedure for the synthesis of 1 from 1-bromoadamantane (3) and acetylamide in the presence of sulfuric acid *via* N-(1-adamantyl) acetamide (4) in one-pot with an overall yield of 74%. The procedure was also optimized to reduce the use of toxic reagents and solvents to make it to safer and more environmentally friendly. The procedure can be considered as more suitable for large-scale production of amantadine hydrochloride. The structure of the obtained amantadine hydrochloride was confirmed by MS, IR, ^{1}H-NMR and ^{13}C-NMR.

INTRODUCTION: Amantadine hydrochloride (1-amino-adamantane hydrochloride) (1) is an antiviral drug, which was used to treat certain influenza infections type A. It is also used as an anti-dyskinetic agent to treat Parkinson's disease [1]. The antiviral activity of amantadine hydrochloride was first reported in 1964 by M. L. Davies *et al.* [2]. It was first approved by FDA in 1966 for use in the prevention of respiratory infections caused by influenza A2 virus strains. Amantadine was also used to prevent the high risk of Asian influenza virus infection and against influenza A [3].

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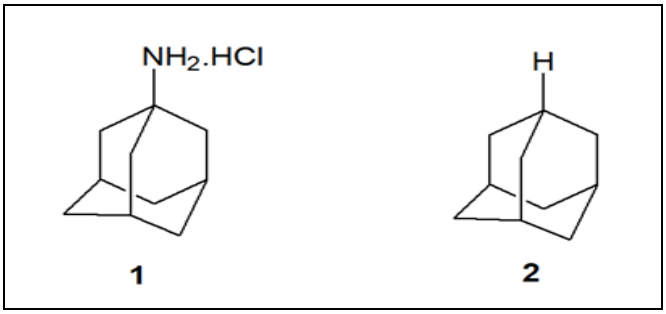

FIG. 1: STRUCTURE OF AMANTADINE HYDRO-CHLORIDE (1) AND ADAMANTANE (2)

There have been several publications about the synthesis of amantadine (5) and amantadine hydrochloride (1) using different raw materials such as adamantane (2) 4-10, 1-bromoadamantane (3) [11, 15,] 1-adamantanecarboxylic acid [16,] 1-adamantano [17, 18,] 1-adamantyl-magnesium bromide 19-21 and tetra hydro dicyclopentadiene [22]. Several groups reported the synthesis of amantadine hydrochloride (1) in four steps from adamantane (2) 4, 6. Firstly, compound 2 was brominated or nitroxylated to yield 1-bromo-adamantane (3a) or 1-adamantyl nitrate (3b). In the next step, 3a or 3b was converted to N-(1-adamantyl) acetamide (4) in the presence of sulfuric acid and acetonitrile by Ritter-style reaction, followed by treatment of 4 with NaOH and polyethylene glycol (PEG) at reflux conditions (240-250 °C) for 10-15 h and then extraction with diethyl ether to yield amantadine (5). The last step, compound 5 was formed into 1 by anhydrous HCl in ether solution. The overall yield of these procedures varies from 46 to 58% **Fig. 1** [4, 6].

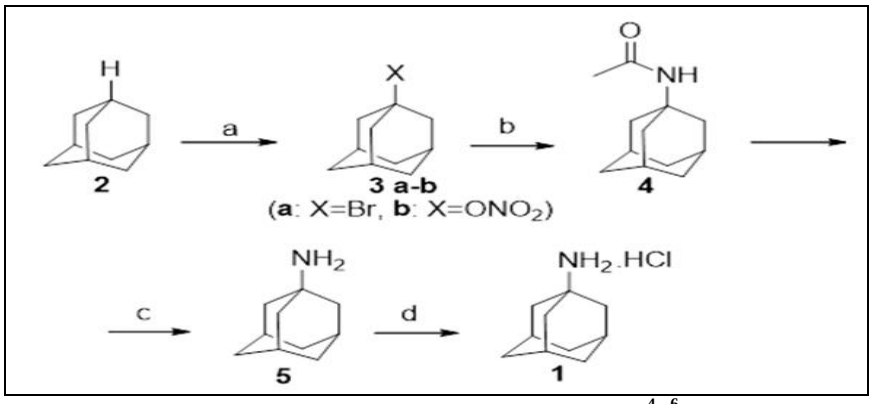

FIG. 2: FOUR-STEP SYNTHESIS OF AMANTADINE HYDROCHLORIDE [4, 6] REAGENTS AND CONDITIONS: A) Br_2/reflux; B) H_2SO_4/CH_3CN/reflux/5-15h/benzene extraction; C) NaOH/DEG/reflux/5-10h/ether extraction; D) anhydrous HCl/ether

To make these procedures suitable for large-scale production of amantadine hydrochloride, several issues should be addressed. Firstly, the bromination or nitroxylation of 2 steps afford 3 is carried out under reflux of liquid bromine or fuming nitric acid, which can lead to the emission of toxic bromine or NO_2 vapor. The second step was a conversion of 3 to 4 with Ritter-type reaction by acetonitrile in the presence of sulfuric acid. To isolation of 4, benzene was used as the solvent for extraction of compound 4, which is toxic.

The solvent used in the hydrolysis step, diethylene glycol (DEG), which is also poisonous when heated to 240-250 °C for 15 h, with sodium hydroxide, decomposes exothermic to release explosive hydrogen gas and emits acrid smoke with irritating fumes [23]. Finally, ether was used as a solvent for extraction of amantadine base (5) and its subsequent acidification of 5 into amantadine hydrochloride (1) by anhydrous HCl in ether 4, 5, 6, 11, because of the highly inflammable nature of ether and its tendency to form peroxides, using ether for large-scale production of amantadine hydrochloride is a matter of concern. In this article, we report the method for synthesis of amantadine hydrochloride (1) from 1-bromoadamantane (3) through a key intermediate 4 in only two steps.

MATERIALS AND METHODS: General procedures: All of the commercially available solvents and reagents were used without further purification. The ^{1}H-NMR and ^{13}C-NMR spectra were measured in $CDCl_3$ on Bruker-AV500 spectrometer; the chemical shifts are reported in 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 spectrum (70eV) was recorded on Auto Spec Primer spectrometer. The melting points were measured on Stuart, SMP-10 apparatus and were uncorrected. Analytical thin-layer chromatography (TLC) ware carried out on Merck pre-coated aluminum silica gel sheets (Kieselgel 60F-254). The reagents and solvents were used without further purification.

Synthesis of N-(1-Adamantyl) Acetamide (4) from 1-Bromoadamantane[3]: To acetylamide (15 mL; 0.3 mol) at 115 °C, 1-bromoadamantane 98%

(6.6 g; 0.03 mole) was added for 0.5 h with stirring and then H_2SO_4 96% (9.6 mL; 0.18 mole) was added slowly (drop-wise) for 0.5 hat 115 °C. The mixture was heated to 125 °C and maintained at this temperature until reaction ended (3, 5 h, which was indicated by TLC; solvent: $CHCl_3$: CH_3OH: aq. NH_3 25% = 6:1:1 (v/v); visualization: iodine; detection reactions: starting material compound 3 completely was disappeared and found to be complete after this time. After the reaction was finished, the reaction mixture was cooled to room temperature and was added to ice water (75 mL), and the mixture was stirred for 1.0 h at 0-5 °C. The white solid was precipitated, filtered and washed with cool water. The obtained product was dried under vacuum, yield: 5.03 g (86.85%) compound 4, m.p: 145-149 °C (reported5149-150 °C).IR (KBr, (cm^{-1}): 3312 (NH); 2903-2849 (CH); 1647 (C=O). MS (m/z): 194.24 [M+1] +; 135.19 [M-$NHCOCH_3$]+. 1H-NMR (500 MHz, $CDCl_3$), δ (ppm): 5.31 (s, 1H, NH); 2.08 (m, 3H, CH_3); 2.01-2.00 (s, 6H, C_2, C_8, C_{10}); 1.93 (m, 3H, C_3, C5, C7); 1.69 (m, 6H, C_4, C_6, C_9). 13C-NMR (125 MHz, $CDCl_3$), δ (ppm): 169.4 (C=O); 51.9 (C1); 41.6 (C_2, C_8, C_{10}); 36.4 (C_3, C_5, C_7); 29.4 (C_4, C_6, C_9); 24.6 (CH_3).

Amantadine Hydrochloride (1) From N-(1-Adamantyl) Acetamide[4]: To a mixture of sodium hydroxide (7.2 g, 0.18 mole), water (4,5 mL) and propylene glycol (15 mL), which was stirred at room temperature for 30 min, was added N-(1-adamantyl) acetylamide (4) 5.9 g (0.03 mole). The reaction mixture was heated to 125 °C with stirring and maintained at 125-130 °C until compound 4 completely was disappeared, (7.5 h, which was indicated by TLC; solvent: $CHCl_3$: CH_3OH: aq. NH3 25%= 6:1:1 (v/v); visualization: Dragendorff reagent; compound 4 completely was disappeared and found to be complete after this time). After the reaction was terminated, the reaction mass was cooled to room temperature, and ice-cold water (40 mL) was added; the reaction mixture was extracted with dichloromethane (100 mL) for 3 times. The separated organic layer was concentrated (to 1/4 volume) and then to which was added a solution of HCl 6 N (25 mL; 0.15 mol), the reaction mixture was heated to 55-60 °C for 1 h. After cooling, the separated aqueous layer was evaporated under vacuum to give a white solid, to which was added acetone (7 mL). The mixture was stirred and heated to 50 °C for 1 h and then at 0-5 °C for 1 h. A white solid was isolated and dried under vacuum: yield 4.55 g (84.78%), amantadine hydrochloride (1), which did not melt at up to 360 °C; R_f = 0.5 ($CHCl_3$/ MeOH/ 25% aqueous NH_3= 6:1:1). MS, m/z: 152.2 [M+1]+ ; 135.2 [M-NH_2-1]+;^{1}H-NMR (500 MHz, $CDCl_3$), δ (ppm): 8.28 (br, s, 3H, NH_2.HCl), 2.15 (s, 3H, C_3-H, C_5-H, C_7-H); 2.04 (s, 6H, C_4-H_2,C_6-H_2 and C_9-H_2); 1.69 (m, 6H, C_2-H_2, C_8-H_2 and C_{10}-H_2); ^{13}C-NMR (125 MHz, $CDCl_3$), δ (ppm): 52.9 (C_1); 40.6 (C_3+C_5 and C_7); 35.4 (C_2+C_8 and C10); 29.0 (C_4+C_6 and C_9).

One-Pot Synthesis of Amantadine Hydrochloride (1) From 1-Bromoadamantane[3]: To acetylamide (600 mL; 12 mol) at 115 °C, 1-bromoadamantane (3) 98% (263 g; 1.20 mole) was added over 30 min with stirring and then 386 mL (7.2 mole) H_2SO_4 96% was added slowly (drop-wise) at 115 °C for 0.5 h. The mixture was heated to 125-130 °C and maintained at this temperature until compound 3 completely was disappeared (3, 5 h, which was indicated by TLC; solvent: $CHCl_3$: CH_3OH: aq. NH_3 25% = 6:1:1 (v/v); visualization: iodine. After the reaction was finished, the reaction mixture was cooled to room temperature and was added to ice water (2.5 L) and the mixture was stirred for 1.0 h at 0-5 °C.

The white solid was precipitated, filtered, and washed with cool water. This obtained product 4 was added to a mixture of sodium hydroxide (264 g, 6.6 mole), water (50 mL), and propylene glycol (470 mL) with stirred at room temperature for 30 min. The reaction mixture was heated to 125 °C with stirring and maintained at 125-130 °C for reaction was finished off (7, 5 h, which was indicated by TLC; solvent: $CHCl_3$: CH_3OH: aq. NH_3 25% = 6 : 1 : 1 (v/v); visualization: Drag end off reagent; detected reactions: compound 4 completely was disappeared). After the reaction was terminated, the reaction mass was cooled to room temperature and ice-cold water (1.8 mL) was added; the reaction mixture was extracted with dichloromethane (3.0 L).

The separated organic layer was concentrated (to 1/9 volume) and then to which was added a solution of HCl 6 N (1000 mL), the reaction mixture was heated to 55-60 °C for 1 h. After cooling, the separated aqueous layer was

evaporated under vacuum to give a white solid, to which was added acetone (260 mL). The mixture was stirred and heated to 50 °C for 1h and then at 0-5 °C for 1 h and a white solid was filtered and dried under vacuum: yield 165.86 g (73.61%), amantadine hydrochloride (1), which did not melt at up to 360 °C, R_f = 0.5 ($CHCl_3$/MeOH/25% aqueous NH_3= 6:1:1). Purity (GC): 99.22%, tR10.10 min;

RESULTS AND DISCUSSION: Last year we reported some methods for the preparation of amantadine hydrochloride (1) from adamantine [9, 10] in two-step or 1-bromoadamantane [14, 15] in one-step. In this article, we synthesized amantadine hydrochloride (1), from 1-bromadamantane (3) and acetylamide via N-(1-adamantyl) acetylamide (4) in two steps. Compound 4 was identified as a suitable intermediate to prepare 1. 4 was prepared from 1-bromoadamantane (3) and acetylamide and H_2SO_4 at 125 °C for 3.5 h in only one step by a Ritter-type reaction. Following 4 was treated with sodium hydroxide in a mixture of water and propylene glycol (PG) at 125-130 °C for 7.5 h to give amantadine (5). Finally, compound 5 was treated with a solution of aq. 6N HCl to obtain amantadine hydrochloride (1). Direct conversion of compound 3 into 4 is the key step in the synthesis of 1 **Fig. 2**.

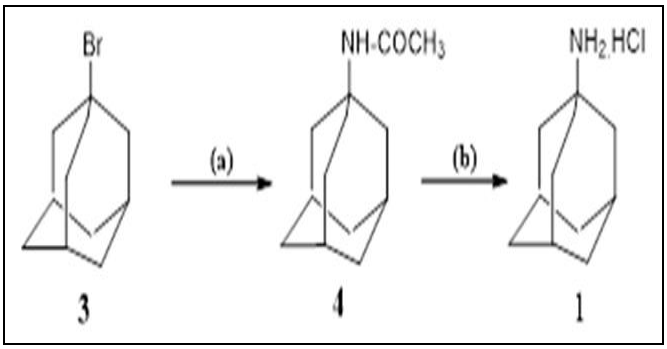

FIG. 3: TWO-STEP SYNTHESIS OF AMANTADINE HYDROCHLORIDE *REAGENTS AND CONDITIONS AND YIELDS: (A) 1.H_2SO_4, CH_3 $CONH_2$/125 °C/3.5 h; 86.85% (B) 1. NAOH/ H_20 + PG/125-130 °C/ 7, 5 h; 2, HCL 6N; 84.78%; OVERALL YIELD 74%.

In our procedure, the synthesis of amantadine hydrochloride (1) from 1-bromadamantane (3) and acetylamide (both the reagent and solvent of reaction) in the presence of sulfuric acid, the procedure was reduced to two steps. Firstly, in step (a), compound 4 was prepared in only one reaction from 1-bromo-adamantane (3) and acrylamide in the presence of H_2SO_4 96-98%, which shortened the time of reaction, isolation, and separation of 4 as well as eliminated the use of liquid bromine 3 or concentrated nitric acid 5, and we don't use benzene as a solvent for extraction of intermediate 4, unlike other procedures in the isolation of 4 from a reaction mixture, 3, 5 we were carried out only in water to precipitate the compound 4, which is more environmentally friendly.

In addition, the parameters of reaction effect on the yield of compound 4 such as reaction temperature and time **Table 1**, the molar ratio of reagents **Tables 2-3** were optimized. The result found that using the optimal molar ratio between (acetylamide: sulfuric acid: 1-bromoadamantane (3) = 10: 6: 1; reaction temperature = 125 °C, reaction temperature = 3.5 h got the highest yield of 4 (86.85%). Secondly, in hydrolysis step (b) we carried out at lower temperature for a shorter time by using NaOH in a mixture of water and propylene glycol (PE) instead of diethylene glycol (DEG)/ NaOH at 240-250 °C, which is toxic. Besides the reaction temperature and time **Table 4**, the molar ratio of NaOH: PG: H_2O: N-(1-adamantyl) acetylamide (4) **Tables 5-6** was optimized.

The result found that using a molar ratio of NaOH: PG: H_2O: 4 = (5.5: 6.78: 4.17: 1), on temperature 125-130 °C for 7.5 h to be suitable for the deacetylation of 4 into 5 (instead molar ratio of NaOH: DEG: compound 4 ware 9.7: 40: 1 on 240-250 °C /5-15 h. In the isolation of amantadine base (5) from the reaction mixture, we no use ether as a solvent but use dichloromethane. Finally, we used a solution of aqueous hydrochloride 6N to replace anhydrous HCl in ether solution for the preparation of amantadine hydrochloride, which reduced toxicity and risk of explosion and fire. In summary, **Fig. 2** presents a safe, simple, economically competitive and more environment-friendly synthesis of amantadine hydrochloride (1). Compound 1 was obtained in two steps with an overall yield of 74% (instead of four steps with an overall yield of 46-58%). Raw materials and reagents used in this procedure are inexpensive and commercially available. Each reaction step was optimized to reduce or eliminate the use of toxic reagents and solvents. Total reaction time was significantly reduced compared to conventional

methods. This procedure is safer and more economical than other reported procedures. To our best knowledge, this protocol is economically advantageous over the earlier reported synthesis owing to its high yields and the use of less expensive raw materials.

General Procedure the Synthesis of Memantin Hydrochloride:

1.1. Effect of Reaction Parameters on the Yield of N-(1-Adamantyl) Acetamide[4]:

1.1.1. Effect of Reaction Parameters on the Yield of N-(1-Adamantyl) Acetamide (4):

TABLE 1: EFFECT OF REACTION TEMPERATURE AND TIME ON THE YIELD OF N-(1-ADAMANTYL ACETAMIDE [4]

S. no.	Reaction Temperature (°C)	Reaction Time (h)*	N-(1-adamantyl)acetamide (4)		
			Weight (g)	Melting point (^{0}C)	Yield (%)
1	110	5.0	1.56	147-148	80.56
2	115	4.5	1.57	147-149	81,43
3	120	4.0	1.60	146-149	83.05
4	125	3,5	1.61	147-149	83.27
5	130	3.0	1.60	147-148	82.98

Other Reaction Parameters 1- bromoadamane: 0.01 mole; Molar ratio of (Acetamide: Sulfuric acid: Adamantane) = (15: 9: 1); * Time for reaction to finish determined by TLC;

Conclusion: The optimal reaction temperature is 125 °C, and the reaction time is 3.5 h (see No. 4 in **Table S1**.

1.1.2. Effect of Molar Ration between Acetamide and 1-Bromo-Adamantane on the Yield of N-(1-Adamantyl) Acetamide[4]:

TABLE 2: EFFECT OF MOLAR RATIO BETWEEN ACETAMIDE AND 1-BROMO-ADAMANTANE ON THE YIELD OF N-(1- ADAMANTYL) ACETAMIDE[4]

S. no.	Molar ratio of Acetamide : Ad-Br	N-(1-adamantyl)acetamide (4)		
		Weight (g)	Melting point (^{0}C)	Yield (%)
1	8 : 1	1.59	147-148	82.42
2	9 : 1	1.60	147-149	82.95
3	10 : 1	1.64	146-149	84.87
4	11 : 1	1.63	147-149	84.10
5	12 : 1	1.62	147-148	83.59

Other reaction parameters 1- bromoadamane: 0.01 mole; Reaction temperature = 125 oC, Time = 3.5 h; Molar ratio of (Acetamide : Sulfuric acid: Adamantane) = (8 :1 -15 :1) : 9 : 1.

CONCLUSION: The result found that using the molar ratio of (Acetamide: Adamantane) = (10: 1). got the highest yield of N-(1-adamantyl)acetamide (4) (see No. 3 in **Table 2**.

1.1.3. Effect of Molar Ration between Sulfuric Acid and 1-Bromo-Adamantane on the Yield of N-(1-Adamantyl) Acetamide[4]:

TABLE 3: EFFECT OF MOLAR RATIO BETWEEN SULFURIC ACID AND ADAMANTANE ON THE YIELD OF N-(1- ADAMANTYL) ACETAMIDE[4]

S. no.	Molar ratio of H_2SO_4 : Ad-Br	N-(1-adamantyl)acetamide (4)		
		Weight (g)	Melting point (^{0}C)	Yield (%)
1	4.0 : 1	1.56	147-148	80.76
2	5.0 : 1	1.63	147-149	84.10
3	5.5 :1	1.66	146-149	85.79
4	6.0 :1	1.69	146-149	86.85
5	6.5:1	1.67	147-149	86.34
6	7.0: 1	1.66	147-148	85.78
7	8.0: 1	1.65	146-149	**85.24**

Other reaction parameters 1- bromo- adamane: 0.01 mole; Reaction temperature = 125 °C, Time = 3.5 h; Molar ratio of (Acetamide: Sulfuric acid: 1-bromo-adamantane) = 10: (4 :1- 8:1) : 1);

CONCLUSION: The result found that using the molar ratio of (Sulfuric acid: 1-bromoadamantane) = (6: 1) got the highest yield of N-(1-adamantyl) acetamide (4) (see No. 4 in **Table 3**.

Results: The combination of reaction parameters that gives the highest yield of N-(1-adamantyl) acetamide (4): Temperature = 125 °C; Time = 3.5 h; 1-bromo-damantane = 0.01 mol; Molar ratio of (Acetamide: Sulfuric acid: Adamantane) = (10: 6: 1). Yield = 86.85%

1.1.4. Experimental Section: Synthesis of N-(1-Adamantyl)acetamide (4) :To acetylamide (15 mL; 0.3 mol) at 115 °C, 1-bromoadamantane 98% (6.6 g; 0.03 mole) was added for 0.5 h with stirring and then H_2SO_4 96% (9.6 mL; 0.18 mole) was added slowly (drop-wise) at 115 °C for 0.5 h .

The mixture was heated to 125 °C and maintained at this temperature for until reaction was finished off (3,5 h, which was indicated by TLC; solvent: $CHCl_3$: CH_3OH: aq. NH_3 25% = 6 : 1 : 1 (v/v); visualization : iodine; detection reactions: starting material compound 3 completely was disappeared and found to be complete after this time). After the reaction was finished, the reaction mixture was cooled to room temperature and was added to ice water (75 mL) and the mixture was stirred for 1.0 h at 0-5 °C.

The white solid was precipiated, filtered and washed with cool water. The obtained product was dried under vacuum, yield: 5.03 g (86.85%) compound 4, m.p: 145-149 °C (reported5 149-1500C).IR (KBr, (cm^{-1}): 3312 (NH); 2903-2849 (CH); 1647 (C=O). MS (m/z): 194.24 [M+1] +; 135.19 [M-$NHCOCH_3$] +. ^{1}H-NMR (500 MHz, $CDCl_3$), δ (ppm): 5.31 (s, ^{1}H, NH); 2.08 (m, 3H, CH_3); 2.01-2.00 (s, 6H, C_2, C_8, C_{10}); 1.93 (m, 3H, C_3, C_5, C_7); 1.69 (m, 6H, C_4, C_6, C_9). ^{13}C-NMR (125 MHz, $CDCl_3$), δ (ppm): 169.4 (C=O); 51.9 (C_1); 41.6 (C_2, C_8, C_{10}); 36.4 (C_3, C_5, C_7); 29.4 (C_4, C_6, C_9); 24.6 (CH_3).

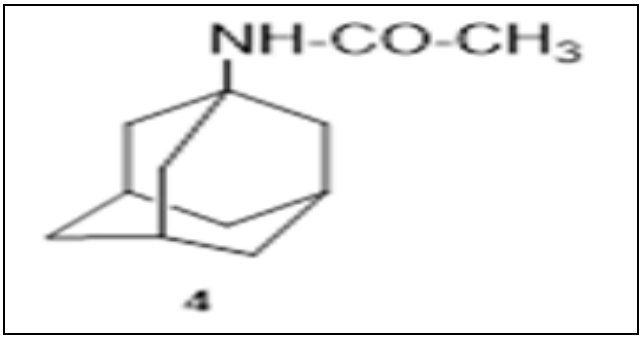

FIG. 4: IR SPECTRUM OF N-(1-ADAMANTYL) ACETAMIDE (4)

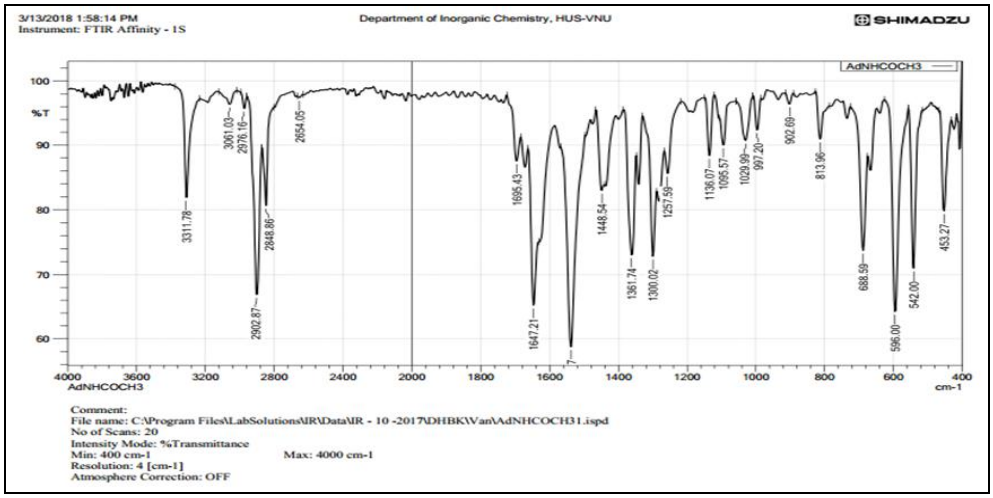

FIG. 5: IR (KBR): CM-1 3312 (N-H); 2903-2849 (C-H); 1695 (C=O).

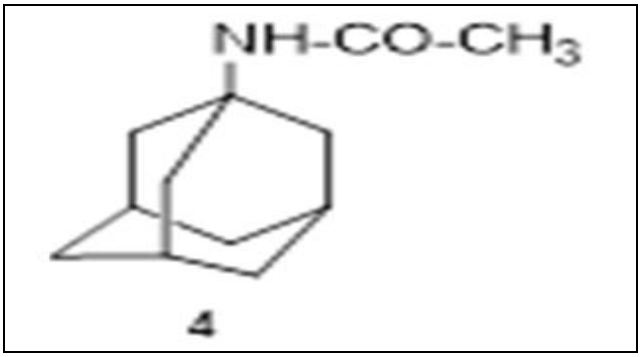

FIG. 6: MS SPECTRUM OF N-(1-ADAMANTYL) ACETAMIDE (4)

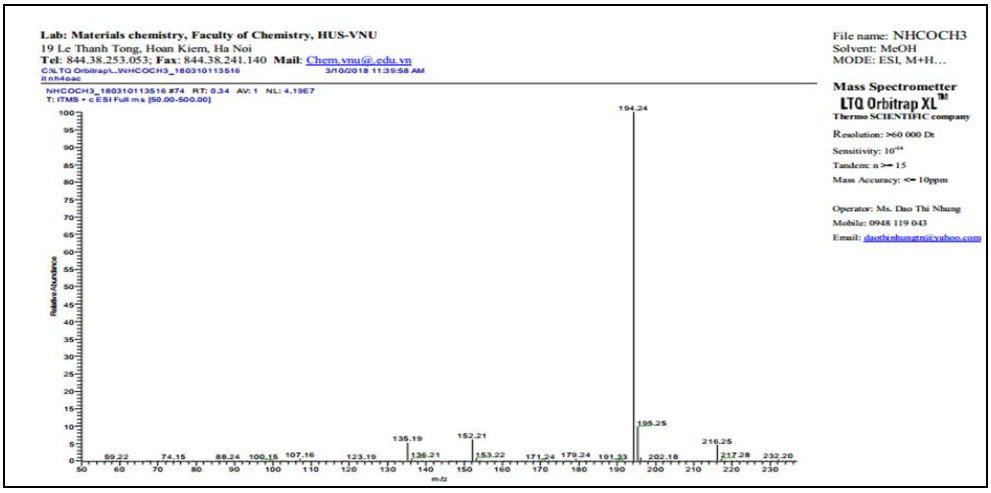

FIG. 7: MS: M/Z = 194.24 [M+1]+; 135.19 [M-NHCOCH3]

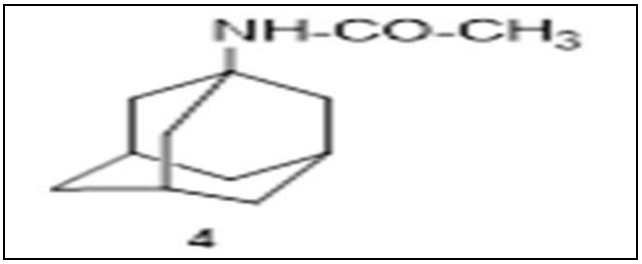

FIG. 8: 1H-NMR SPECTRUM OF N-(1-ADAMANTYL) ACETAMIDE (4) IN CDCL3

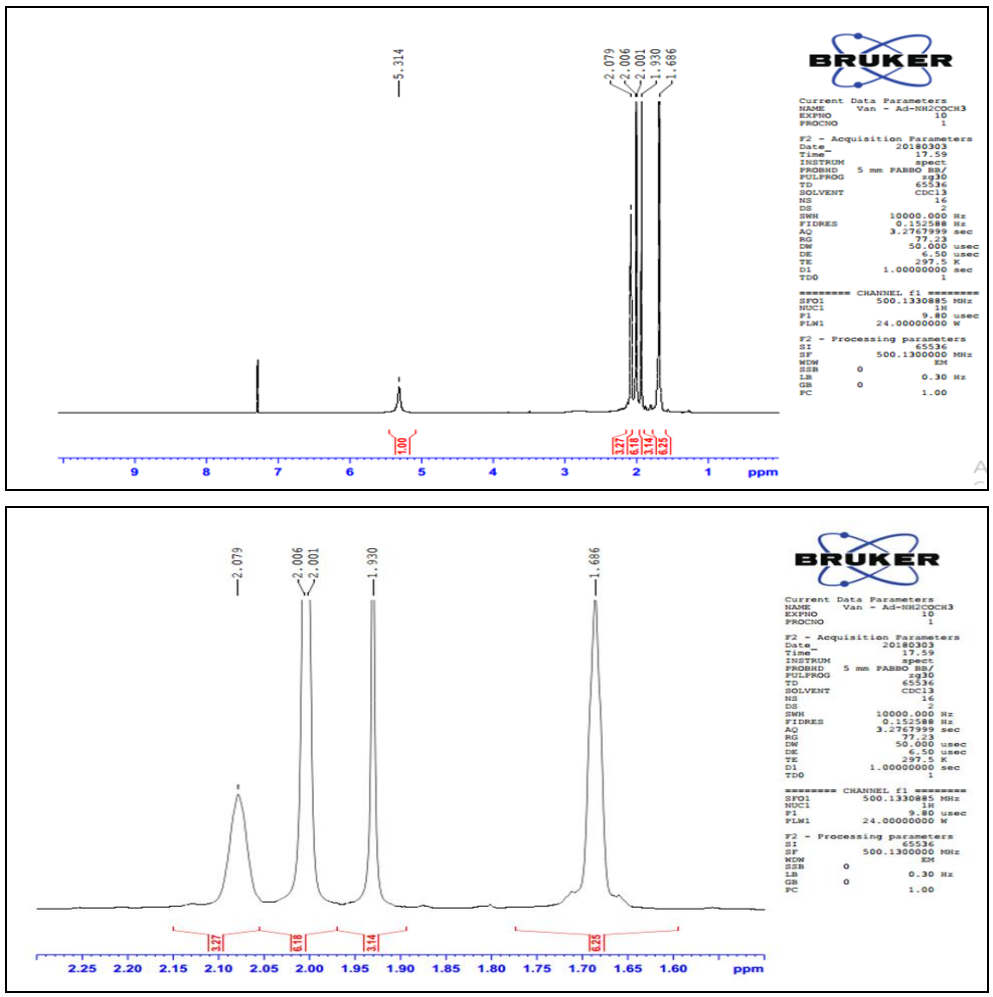

FIG. 9: 1H-NMR (CDCL3, 500 MHZ): Δ (PPM) 5.31 (S, 1H, NH); 2.08 (M, 3H, CH3); 2.01-2.00 (S, 6H, C2, C8, C10); 1.93 (M, 3H, C3, C5, C7); 1.69 (6H, C4, C6, C9).

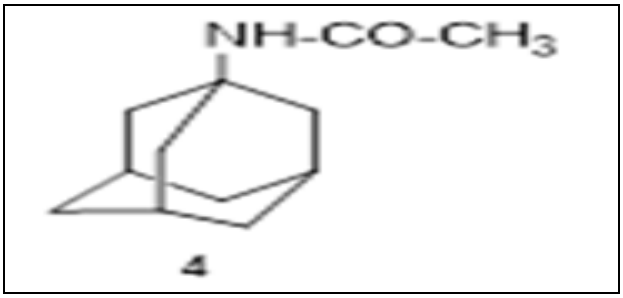

FIG. 10: 13C-NMR SPECTRUM OF N-(1-ADAMANTYL) ACETAMIDE (4) IN CDCL3

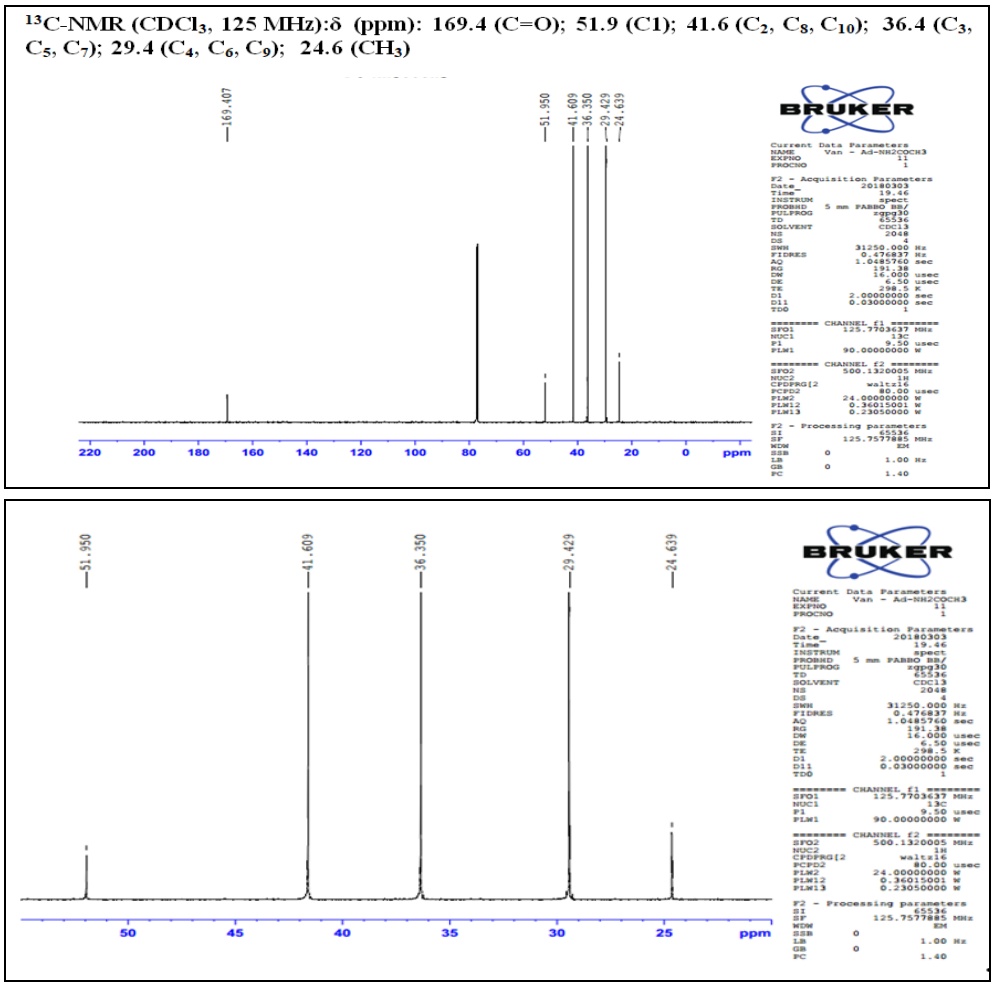

FIG. 11: 13C-NMR (CDCL3, 125 MHZ):Δ (PPM): 169.4 (C=O); 51.9 (C1); 41.6 (C2, C8, C10); 36.4 (C3, C5, C7); 29.4 (C4, C6, C9); 24.6 (CH3)

1.2. Effect of Reaction Parameters on the Synthesis of Amantadine Hydrochloride (1):

1.2.1. Effect of Reaction Temperature and Reaction Time on the Yield of Amantadine Hydrochloride (1):

TABLE 4: EFFECT REACTION OF TEMPERATURE AND TIME ON THE YIELD OF AMANTADINE HCL (1)

S. no	Reaction Temperature (°C)	Reaction Time (h)	Amantadine Hydrochloride (1)		
			Weight (g)	Melting point (^{0}C)	Yield (%)
1	150	4,5	3.73	> 360	66.23
2	140	6.5	4.24	> 360	75.24
3	130	7.5	4.44	> 360	78.76
4	125	8	4.39	> 360	78.15
5	120	10	4.25	> 360	75.49
6	110	15	3.84	> 360	68.20

Other reaction parameters N-(1-adamantyl)acetamide (4): 0.03 mole; * Time for reaction to finish determined by TLC;

Conclusion: The optimal reaction temperature is 130 °C, and reaction time is 7.5 h (see No. 4 in **Table 4.**

1.2.2. Effect of Molar Ratio between Sodium Hydroxyde and N-(1-Adamantyl) Acetamide (4) on the Yield of Amantadine Hydrochloride:

TABLE 5: EFFECT OF THE MOLAR RATIO OF NAOH TO N-(1-ADAMANTYL) ACETAMIDE (4) ON THE YIELD OF AMANTADINE HCl (1)

S. no.	Molar ratio of NaOH: Compound 4	Amantadine Hydrochloride (1)		
		Weight (g)	Melting point (^{0}C)	Yield (%)
1	4.0 :1	4.47	> 360	79.34
2	4.5 : 1	4.51	> 360	80.12
3	5.0 : 1	4.55	> 360	80.86
4	5.5 : 1	4.60	> 360	81.78
5	6.0 : 1	4.57	> 360	81.12
6	6.5 :1	4.56	> 360	80.95

Other reaction parameters N-(1-adamantyl) acetamide (4): 0.03 mole; * Time for reaction to finish determined by TLC; Reaction temperature = 130 °C; reaction time : 7.5 h.

Conclusion: The result found that using the molar ratio of (sodium hydroxyde: N-(1-adamantyl) acetamide (4) = (5.5:1). got the highest yield of 1(see No. 4 **Table 6**.

1.2.3. Effect of Weight Ratio Between Propylene Glycol (PG) and N-(1-Adamantyl) Acetamide (4) on The Yield of Amantadine Hydrochloride:

TABLE 6: EFFECT OF THE WEIGHT RATIO OF PG TO N-(1-ADAMANTYL) ACETAMIDE (4) ON THE YIELDS OF AMANTADINE. HCL (1

S. no.	Weight ratio of PG : Compound 4 (W/W)	Amantadine Hydrochloride (1)		
		Weight (g)	Melting point (^{0}C)	Yield (%)
1	1.6 : 1	4.48	> 360	79.53
2	1.8 : 1	4.52	> 360	80.36
3	2.0 : 1	4.66	> 360	82.78
4	2.2 : 1	4.68	> 360	83.12
5	2.4 :1	4.77	> 360	84.65
6	2.8 :1	4.74	> 360	84.18
7	3.0 :1	4.70	> 360	83.54.

Other reaction parameters N-(1-adamantyl) acetamide (4): 0.03 mole; * Time for reaction to finish determined by TLC; Reaction temperature = 130 °C; reaction time : 7.5 h;

Conclusion: The result found that using Weigh ratio of propylen glycol (PG) and compound 4 = 2.4:1 got the highest yield of 1 (see No. 5 in **Table 6**.

Results: The combination of reaction parameters that gives the highest yield of amantadine. HCl: Temperature = 130 °C; Time = 7.5 h; Molar ratio of (NaOH: N-(1-adamantyl) acetamide (4) = (5.5:1) and Weigh ratio (PG: water: (1-adamantyl) acetamide) = 2.4: 0.42:1. Yield = 84.65%.

1.2.4. Experimental Section:

Synthesis of Amantadine Hydrochloride(1): To a mixture of sodium hydroxide (7.2 g, 0.18 mole), water (4,5 mL) and propylene glycol (15 mL), which was stirred at room temperature for 30 min, was added N-(1-adamantyl) acetamide (4) 5.9 g, (0.03 mole) was added. The reaction mixture was heated to 125 °C with stirring and maintained at 125-130 °C until compound 4 completely was disappeared, (7.5 h, which was indicated by TLC; solvent: $CHCl_3$: CH_3OH: aq. NH_3 25% = 6:1:1 (v/v); visualization: Dragendorff reagent; compound 4 completely was disappeared and found to be complete after this time). After the reaction was terminated, the reaction mass was cooled to room temperature, and ice-cold water (40 mL) was added; the reaction mixture was extracted with dichloromethane (100mL) for 3 times. The separated organic layer was concentrated (to 1/4 volume) and then to which was added a solution of HCl 6 N (25 mL, 0.15 mol), the reaction mixture was heated to 55-60 °C for 1 h. After cooling, the separated aqueous layer was evaporated under vacuum to give a white solid, to which was added acetone (7 mL). The mixture was stirred and heated to 50 °C for 1h and then at 0-5 °C for 1 h and a white solid was isolated and dried under vacuum:

yield 4.55 g (84.78%), amantadine hydrochloride (1), which did not melt at up to 360 °C; MS, m/z: 152.2 [M+1]+ ; 135.2 [M-NH_2-1]+;^{1}H-NMR (500 MHz, $CDCl_3$), δ (ppm): 8.28 (Br, s, 3H, NH_2.HCl), 2.15 (s, 3H, C_3-H, C_5-H, C_7-H); 2.04 (s, 6H, C_4-H_2,C_6-H_2 and C_9-H_2); 1.69 (m, 6H, C_2-H_2, C_8-H_2 and C_{10}-H_2); 13C-NMR (125 MHz, $CDCl_3$), δ (ppm): 52.9 (C_1); 40.6 (C_3+C_5 and C_7); 35.4 (C_2+C_8 and C_{10}); 29.0 (C_4+C_6 and C_9).

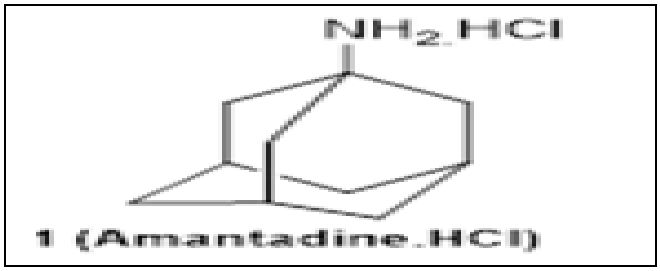

FIG. 12: MS SPECTRUM OF AMANTADINE HYDROCHLORIDE (1)

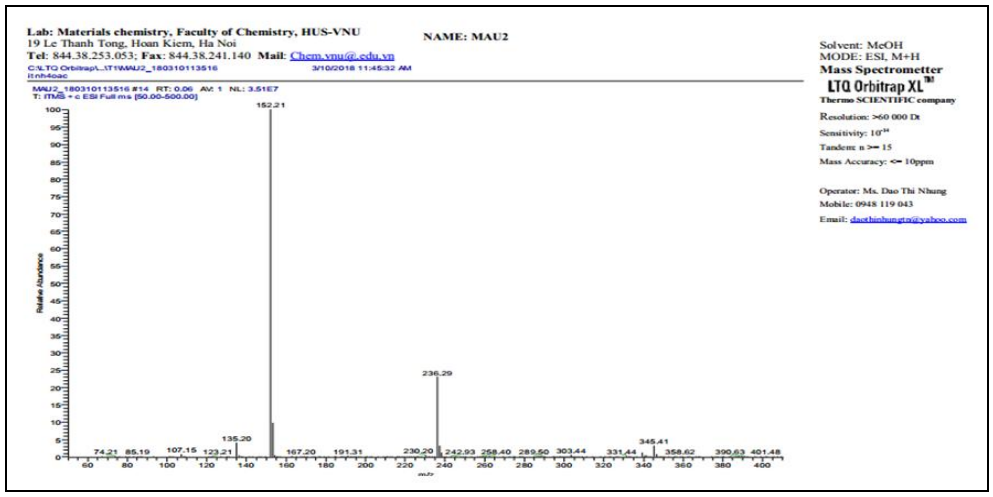

FIG. 13: MS: M/Z = 152.2 [M +1] +, 135.2 [M-NH2-1]+

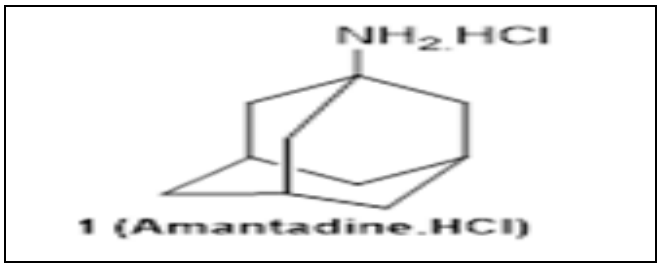

FIG. 14: 1H-NMR (CDCL3, 500 MHZ): Δ 8.28 (BR, S, 3H), 2.15 (S, 3H), 2.04 (S, 6H); 1.71 (S, 6H)

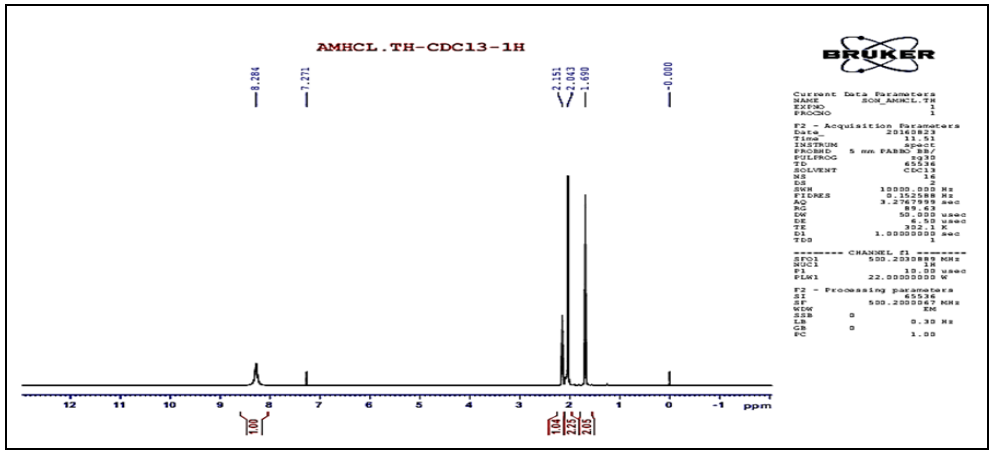

FIG. 15: 13C-NMR SPECTRUM OF AMANTADINE HYDROCHLORIDE (1) IN CDCL3:

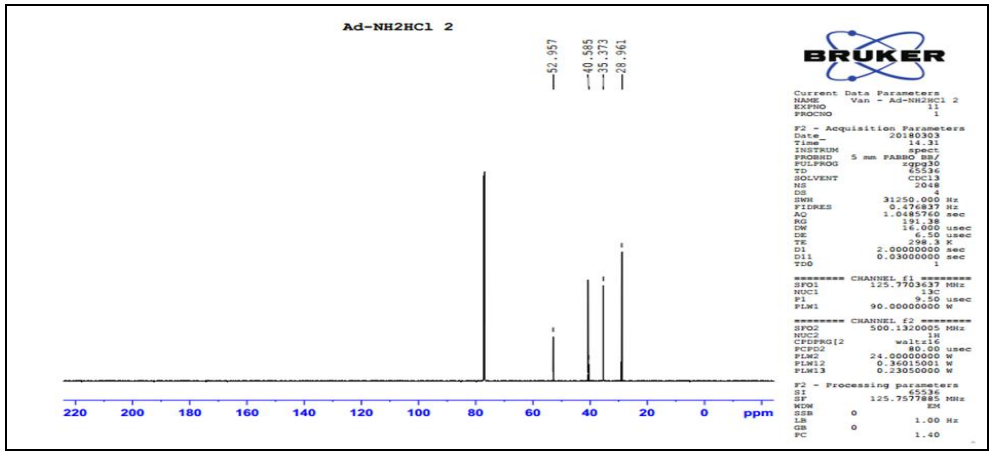

FIG. 16: 13C-NMR (CDCL3, 125 MHZ): Δ 52.9, 40.6, 35.4, 29.0.

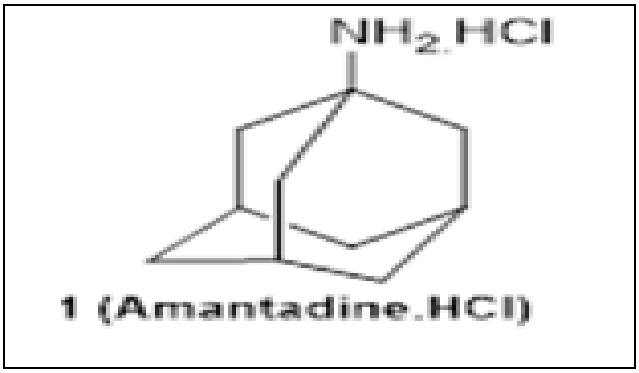

FIG. 17: GC DATA OF THE SYNTHESIZED AMANTADINE HYDROCHLORIDE (1):

GC Condition: FID Detector, temperature of 250 ºC

Column: (5%-Phenyl)-methylpolysiloxane, length of 30 m, diameter of 0.32 mm, film layer of 0.25 µm. Column temperature of 115 ºC; Oven temperature of 250 ºC

Injection Volume: 1 µl.

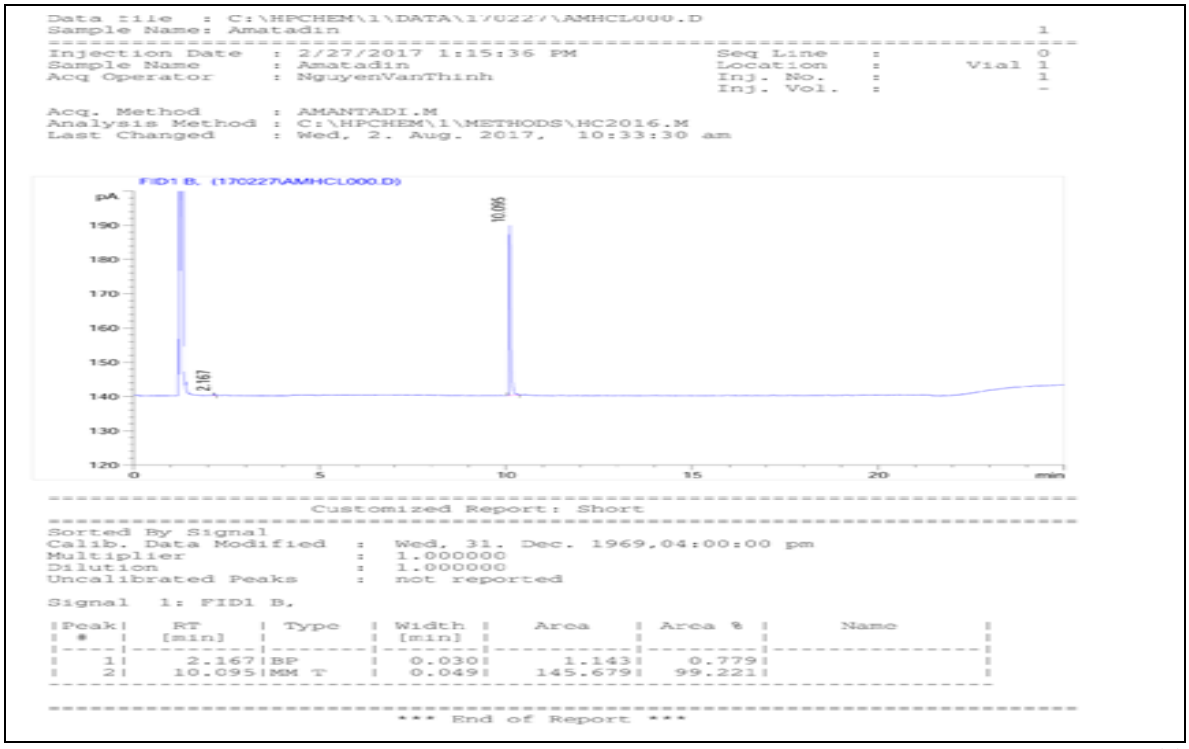

FIG. 18: GC CHROMATOGRAM OF THE SYNTHESIZED AMANTADINE HYDROCHLORIDE (1)

CONCLUSION: A simple, economical two-step process for the synthesis of amantadine hydrochloride (1), from 1-bromoadamantane (3), acetylamide with an overall efficiency of 74% was provided. Previous methods for synthesis of 1 in volved three to five reaction steps with an overall yield of 46-58%. Our process has only two steps: In the first step, we use the one-pot process to prepare N- (1-adamantyl) acetamide (4) directly from 1-bromoadamantan (3), avoiding or reducing use of toxic chemicals such as liquid bromine and organic solvents for intermediate extraction [4]. In the final step, our reaction is performed at lower temperatures in a shorter time because we use NaOH in water and propylene glycol (PG) at 125-130 °C for 7.5 h to produce amantadine (5), instead of diethylene glycol (DEG) / NaOH at 240-250 °C for 15 h, very toxic, after that, the conversion of 5 to amantadine hydrochloride (1) is performed by using 6N aqueous hydrochloride acid instead for anhydrous hydrochloride in ether solution, reducing toxicity and risk of fire. Each reaction step was optimized to reduce or eliminate the use of toxic reagents and solvents and total reaction time was significantly reduced compared to conventional methods. This procedure is safer and more economical and industrially than other reported procedures and can be considered more suitable for large-scale production of amantadine hydrochloride. To our best knowledge, this protocol is economically advantageous over the earlier reported synthesis owing to its high yields and the use of less expensive raw materials.

Author Contributions: The manuscript was written with contributions from all authors. All authors have given approval to the final version of the manuscript.

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CONFLICTS OF INTEREST: Nil

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