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A SIMPLE AND ECONOMICAL PROCEDURE FOR SYNTHESIS OF AMANTADINE HYDROCHLORIDE

Dinh Chau Phan ^{*1}, Tuan Anh Dang ¹, Huu Tung Nguyen ^{*2,3} and Binh Duong Vu ⁴

School of Chemical Engineering ¹, Hanoi University of Science and Technology, 01 Dai Co Viet Str, Hai Ba Trung District, Hanoi 100000, Vietnam.

Faculty of Pharmacy ², Phenikaa University, Hanoi 100000, Vietnam.

Phenikaa Research and Technology Institute (PRATI) ³, A & A Green Phoenix Group, 167 Hoang Ngan, Hanoi 10000, Vietnam.

Center for Drug Research & Development ⁴, Military Medical University, 160 Phung Hung str, Hadong District, Hanoi, Vietnam.

Keywords:

Amantadine hydrochloride,
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Correspondence to Author:

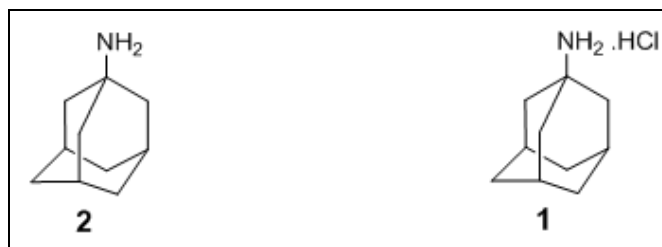
Nguyen Huu Tung

PhD/Lecturer,
Faculty of Pharmacy, Phenikaa
University, Hanoi 100000, Vietnam.

E-mail: tung.nguyenhuu@phenikaa-uni.edu.vn

ABSTRACT: Amantadine hydrochloride (1), a well-known antiviral drug, has been used to treat certain type-A influenza infections and been also medicated as an anti-dyskinetic agent for Parkinson's disease. In this paper, we report a simple and economical procedure for synthesis of amantadine hydrochloride (1) from 1-bromoadamantane (3) and urea in a one-step procedure with high yield (81%) and advantage. The structure of the obtained amantadine hydrochloride was confirmed by MS, ¹H-NMR and ¹³C-NMR spectra and its quality was validated following the United State Pharmacopeia (USP 38). In addition, the synthesis condition was optimized following parameters including reaction reagent as source of nitrogen, reaction temperature, reaction time, reagent molar-ratio, solvent and HCl concentration, successively, to archive the highest yield of amantadine hydrochloride (1) at the following certified condition: reaction temperature = 175°C; reaction time = 1.0 h; molar ratio of (urea: 1-bromo-adamantane) = (3 : 1), in diphenyl ether with ratio of (Ad-Br : Ph₂O) = 1.1 g : 1 mL), respectively.

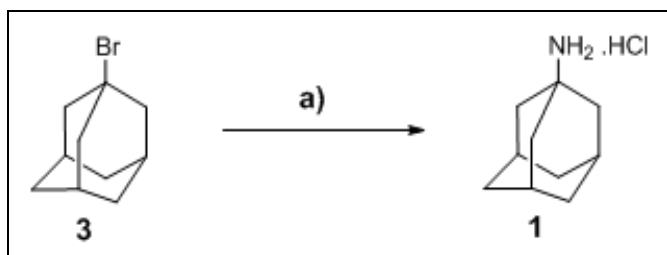
INTRODUCTION: Amantadine (2) and/or amantadine hydrochloride (1) is a well-known oral M2 inhibitor-antiviral drug, which was first reported in 1964 by M. L. Davies *et al.*, ¹ and has been approved by FDA for the treatment of certain A-type influenza such as H7N9, H5N1 and H1N1 ². This compound is also used as an anti-dyskinesia agent to treat Parkinson's disease for decades.



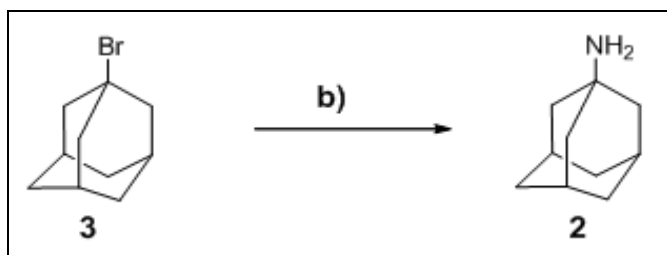
To date, the synthesis of amantadine (2) and amantadine hydrochloride (1), which is commonly in use, has been well reported in the literature by various methods and protocols from different starting materials such as 1-hydroxyadamantane, adamantyl-carboxylic, adamantyl-magnesium-bromide especial adamantane ³⁻¹⁴, 1-bromoadamantane ¹⁵⁻¹⁹.

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In this viewpoint, the principle of the amantadine synthesis is based on whether Ritter reaction/Ritter-type reaction or direct amination, whose procedures are usually from 2 to 5 steps and usually remain several disadvantages. The drawbacks include special equipment and use of potentially toxic, explosive or flammable reagents during the reaction and low yields of the intermediate and final product of 2 and 1. As well-documented methods reported the synthesis of amantadine hydrochloride (1) started from 1-bromoadamantane (3) ¹⁵⁻¹⁶ with overall low yield whether by direct amination of 3 by liquid ammonia in a closed stainless-steel bomb at a temperature of about 170 °C for 15 h (in high pressure) with the overall yield of 1 as 15% **Scheme 1** ¹⁶ or by aminating agents (Li/NH₂Cl) in an ultrasound bath to yield of 1-amino-adamantane (amantadine, 2) as 54% **Scheme 2** ¹⁷.



SCHEME 1: REAGENTS AND CONDITIONS: A) 1. ETHANOL/LIQUID NH₃/170 °C/15h; 2. NaOH/ETHER EXTRACTION/HCl GAS; 15%



SCHEME 2: REAGENTS, CONDITIONS, AND YIELD: B) 1.Li WIRE/N₂/ETHER/ULTRASOUND/NH₂Cl; 54%

These previously described amination methods are unfavorable for preparation of amantadine/amantadine hydrochloride in large-scale so that there is a need for improved preparation of amantadine hydrochloride (1) suitable for industrial application.

MATERIALS AND METHODS:

General Procedures: The ¹H-NMR and ¹³C-NMR spectra were measured in CDCl₃ on Bruker-AV500 spectrometer (Bruker Spin, Germany) and the chemical shifts are reported in ppm relative to TMS

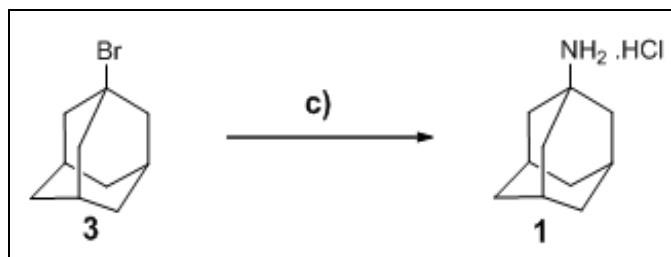
as the internal standard. The IR spectra were recorded in the solid state as KBr dispersion using a GX-Perkin Elmer spectrophotometer (USA). The mass spectrum (70 eV) was recorded on AutoSpec Primer spectrometer (Waters, USA). The melting points were measured on Stuart SMP-10 apparatus (Stuart, UK). Analytical thin layer chromatography (TLC) was carried out on Merck pre-coated aluminum silica gel sheets (Kieselgel 60F-254, Merk, Darmstadt, Germany). The reagents and solvents were used without further purification.

Synthesis of Amantadine Hydrochloride (1): In a round-bottom flask, a mixture of 1-bromoadamantane (350 g, 1.6 mol), urea (298 g, 5.0 mol), and diphenyl ether (300 mL) was heated to 175 °C for 1 h, then cooled to room temperature, to which was added mixture of water (1.0 L) and chloroform (2.0 L). The reaction mass was maintained at reflux temperature for 0.5 h and then was adjusted to pH 11-12 with 20% sodium hydroxide solution, the organic layer was separated from the aqueous, the organic layer was washed with water, and the solvent was evaporated under vacuum to remove of 3/4 volume. The remainder was added a solution of HCl 5N (2.2 L) and the reaction mass was maintained at 55-60 °C for 1 h and then to this mixture, activated carbon (15 g) was added and heated to 55-60 °C for 1h, filtration, the filtrate was cooled to room temperature, the aqueous layer was separated from the organic layer, the aqueous layer was washed with *n*-hexane (400 mL).

The aqueous layer was evaporated under vacuum to give white solid. To this white solid was added acetone (180 mL), stirred and heated at 50 °C for 30 min and then cooled and stirred for 1 h at 0-5 °C, the white solid was filtered and dried under vacuum to give amantadine hydrochloride (1) (244.45 g, 81%), which did not melt up to 360 °C, R_f = 0.50 (CHCl₃: Methanol: 25% Aqueous NH₃ = 6:1:1, v/v/v) ³.

Amantadine Hydrochloride (1): Purity (GC) 99.34%. *t_R* 10.11 min; MS: *m/z* 152.0 [M+H]⁺, 135.1 [M-NH₂]⁺; ¹H-NMR (500 MHz, CDCl₃): δ (ppm) 8.26 (br, s, 3H, NH₂.HCl), 2.14 (s, 3H), 2.04 (s, 6H), 1.68 s, 6H); ¹³C-NMR (125 MHz, CDCl₃): δ (ppm) 52.95 (C-1), 40.56 (C-3,5,7), 35.37 (C-2,8,10), 28.96 (C-4,6,9).

RESULTS AND DISCUSSION: Last year we reported the method for synthesis of amantadine hydrochloride from adamantane^{13,14} in two-step on the base Ritter-style reaction. In our current study, amantadine hydrochloride (1) was prepared from 1-bromoadamantane (3), by direct amination of 3 with urea in diphenyl ether at 175 °C for 1h to give amantadine (2), which was treated with a solution of aq. 5N hydrochloride to obtain amantadine hydrochloride (1) with a high overall yield of 81% **Scheme 3**.



SCHEME 3: REAGENTS, CONDITIONS, AND YIELD:
 C) 1. UREA/Ph₂O/175 °C/1 h; 2. HCl 5N/55-60 °C/1 h; 81%

It becomes evident that the synthesis of amantadine hydrochloride (1) in **Scheme 3** is more simple and economical than the ones reported (**Schemes 1 & 2**). Our synthesis procedure has some advantages including safety concern from high pressure and temperature in a long time (heated for 15 h on 170 °C under high pressure in a closed stainless-steel bomb) as above mentioned¹⁶. The reaction conditions were examined by screening of amination agents (including ammonium chloride,

ammonium acetate, urea, thiourea, and ammonium carbonate) and optimization of reaction parameters in no use solvent condition like reaction temperature (see Supporting Information **Table S1**), and optimization of reaction parameters in no use solvent condition like reaction temperature (see Supporting Information **Table S2**), molar ratio of reactants in no solvent (see Supporting Information **Table S3**), solvents (see Supporting Information **Table S4**), and reaction temperature and reaction time in diphenyl ether (see Supporting Information **Table S5**), solvent of quantity (see Supporting Information **Table S6**), molar ratio of reactants when reaction carry out in diphenyl ether (see Supporting Information **Table S7**) as well as concentration of HCl used in formation and purification of the final product 1 also were studied (see Supporting Information **Table S8**).

Taken together and in conclusion, amantadine hydrochloride (1) was obtained from adamantane (2) by 5N hydrochloride solution, not by its anhydrous HCl flowing through ether solution (that was avoided from high flammability and tendency to form peroxides). Thus, this procedure was relatively simple and reduced toxicity and risk of explosion and fire. Our synthesis procedure had an overall yield of 81%. To our best knowledge, this optimized protocol is simple and economically advantageous over the earlier reported synthesis owing to high yields and the use of less expensive raw materials.

General Procedure for the Synthesis of Amantadine Hydrochloride:

Effect of Reaction Parameters on the Yield of Amantadine. HCl:

TABLE S1: EFFECT OF SOURCE OF NITROGEN ON THE YIELD OF AMANTADINE. HCl (1) IN NO SOLVENT

S. no.	Source of nitrogen	AdNH ₂ .HCl		
		Weight (g)	Yield (%)	T _{nc} (°C)
1	Urea	0.33	35.16	>330 °C
2	Thiourea	0.31	32.25	> 330 °C
3	NH ₄ Cl	0.00	0.0	> 330 °C
4	(NH ₄) ₂ CO ₃	0.09	9.61	>330 °C
5	Amoni acetate	0.22	23.39	> 330 °C
6	Urethane	0.36	38.56	> 330 °C

Other Reaction Parameters: Molar ratio of source of nitrogen: Ad-Br = 3 : 1; Reaction temperature =135-140 °C; Reaction time = 4 h; Molar ratio of (Urea : 1-Br-Ad) = (3 : 1).

TABLE S2: EFFECT OF REACTION TEMPERATURE AND REACTION TIME ON THE YIELD OF 1 IN NO SOLVENT

S. no.	Reaction temperature (°C)	Reaction time (min)	Weight (g)	Yield (%)
1	130	300	0.90	31.96
2	140	150	0.99	35.16
3	155	60	1.32	46.88

4	165	45	1.35	47.94
5	175	30	1.44	51.14
6	185	30	1.38	49.11

Other Reaction Parameters: Molar ratio of (urea : Ad-Br) = (3 : 1); Temperature = 130-185 °C.

TABLE S3: EFFECT OF MOLAR RATIO BETWEEN Ad-Br AND UREA ON THE YIELD 1 IN NO SOLVENT

S. no.	Molar ratio of Urea: Ad-Br	Weight (g)	Yield (%)
1	1:1.5	0.96	34.09
2	1:2	1.14	40.48
3	1:3	1.45	51.49
4	1:4	1.39	49.35
5	1:6	1.41	50.07

Other Reaction Parameters: Time = 0.5 hours; Temperature = 175 °C.

TABLE S4: EFFECT OF SOLVENT AND REACTION TEMPERATURE AND REACTION TIME ON THE YIELD OF 1

S. no.	Solvent (mL)	Reaction temperature (°C)	Reaction time (min)	Weight (g)	Yield (%)
1	Xylene (6)	140	150	0.99	38.61
2	EtOH (9)	80	300	0.36	12.77
3	Ph ₂ O (3)	140	150	1.23	43.85
4	Ph ₂ O (3)	175	30	2.22	78.84

Other Reaction Parameters: Molar ratio of (urea : Ad-Br) = (3: 1).

TABLE S5: EFFECT OF TEMPERATURE AND REACTION TIME ON THE YIELD OF 1 IN SOLVENT Ph₂O

S. no.	Reaction temperature (°C)	Reaction time (h)	Weight (g)	Yield (%)
1	150	2.5	1.51	53.51
2	165	1.5	2.04	72.44
3	170	1.0	2.22	78.84
4	175	1.0	2.28	80.97
5	180	1.0	2.27	80.71

Other Reaction Parameters: Molar ratio of (urea : Ad-Br) = (3: 1) in Ph₂O

TABLE S6: EFFECT OF MOLAR RATIO OF UREA AND Ad-Br ON THE YIELD OF 1 IN SOLVENT Ph₂O

S. no.	Molar ratio of Urea: Ad-Br	Weight (g)	Yield (%)
1	1.5:1	1.86	66.06
2	2:1	1.90	75.71
3	2.5:1	2.21	78.47
4	3:1	2.27	80.60
5	3.5:1	2.26	80.45
6	4 : 1	2.25	79.89

Other reaction parameters: Time = 1.0 h; Temperature = 175°C, in Ph₂O

TABLE S7: EFFECT OF VOLUME OF Ph₂O SOLVENT ON THE YIELD OF 1

S. no.	Ph ₂ O (mL)	Reaction time (h)	Weight (g)	Yield (%)
1	3	0.5 h	2.22	78.84
2	3	1.0 h	2.31	81.04
3	6	1.5 h	2.29	80.54
4	9	4.5 h	2.25	78.93

Other reaction parameters: Temperature = 175 °C, Molar ratio of (Urea: Ad-Br) = (3: 1).

TABLE S8: EFFECT OF HCL CONCENTRATION ON THE YIELD OF 1 IN SALT FORMATION

S. no.	Concentration of HCl	Weight (g)	Yield (%)
1	2N	1.85	66.06
2	5N	2.29	80.54
3	12N	2.30	80.97

Other reaction parameters: Time = 1.0 h; Temperature = 175°C, Molar ratio of (Urea: Ad-Br) = (3: 1).

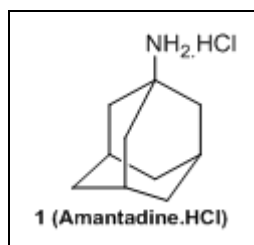
Results: The combination of reaction parameters that gives the highest yield of amantadine hydrochloride (1): Reaction temperature = 175 °C;

Reaction time = 1.0 h; Molar ratio of (urea: 1-bromo-adamantane) = (3 : 1), in diphenyl ether with ratio of (Ad-Br : Ph₂O) = 1.1g : 1mL).

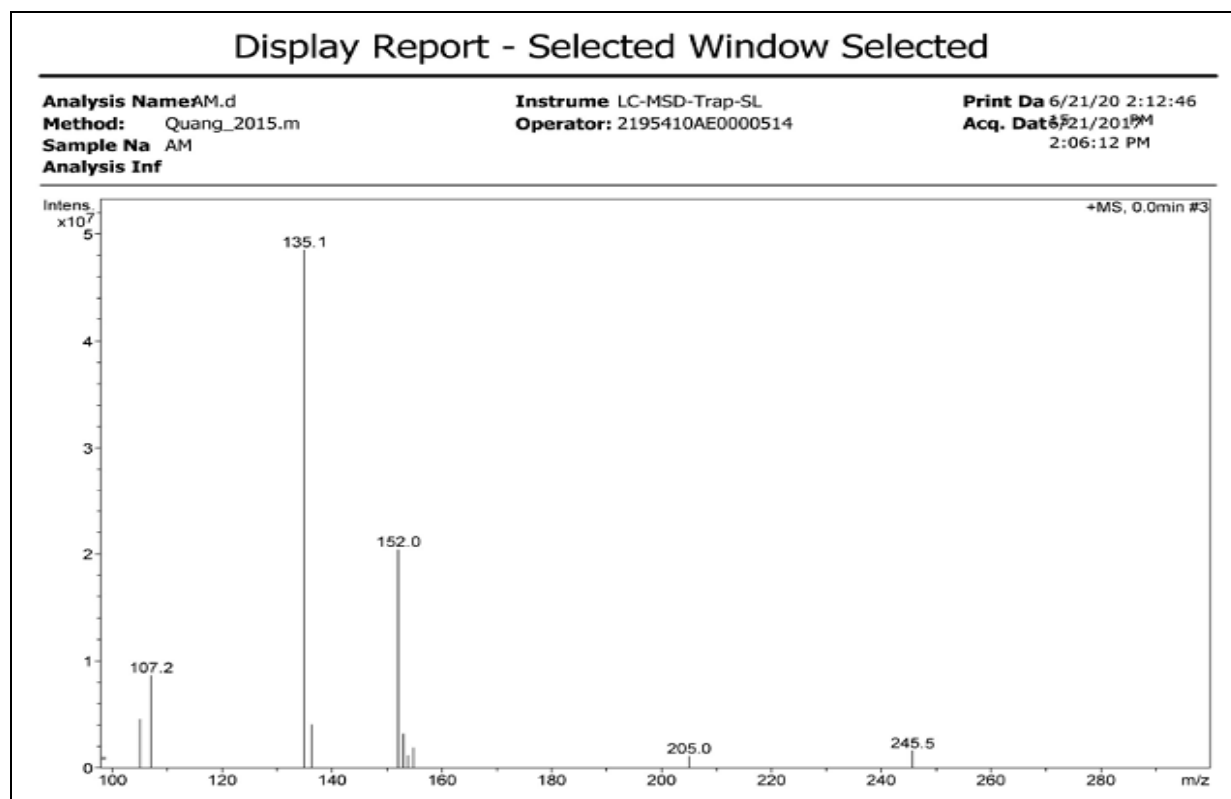
Experimental Section:

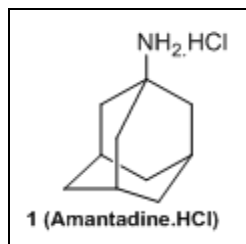
Amantadine Hydrochloride (1): In a round-bottom flask, a mixture of 1-bromo-adamantane (350 g, 1.6 mol), urea (298 g, 4.8 mol), and diphenyl ether (300 mL) was heated to 175 °C for 1 h, then cooled to room temperature, to which was added mixture of water (1.0 L) and chloroform (2.0 L). The reaction mass was maintained at reflux temperature for 0.5 h and then was adjusted to pH 11-12 with 20% sodium hydroxide solution, the organic layer was separated from the aqueous, the organic layer was washed with water, and the solvent was evaporated under vacuum to remove of 3/4 volume. To remainder was added a solution of HCl 5N (2.2 L) and the reaction mass was maintained at 55-60 °C for 1 h and then to this mixture activated carbon (15g) were added and heated to 55-60 °C for 1 h, filtration, the filtrate

was cooled to room temperature, the aqueous layer was separated from the organic layer, the aqueous layer was washed with n-hexane (400 mL). The aqueous layer was evaporated under vacuum to give white solid. To this white solid was added acetone (180 mL), stirred and heated at 50 °C for 30 min and then cooled and stirred for 1 h at 0-5 °C, the white solid was filtered and dried under vacuum to give amantadine hydrochloride (1) (244.45 g, 81%), which did not melt up to 360 °C^{3c}, $R_f = 0.5$ (CHCl₃: methanol: 25% NH₃ aqua = 6:1:1, Purity (GC) 99.34%. t_R 10.11 min; MS, m/z : 152.0 [M+H]⁺; 135.1 [M-NH₂]⁺; ¹H-NMR (500 MHz, CDCl₃), δ (ppm): 8.26 (br, s, 3H, NH₂.HCl), 2.14 (s, 3H, H-3, H-5, C₇-H); 2.04 (s, 6H, H-4,6,9); 1.68 (s, 6H, H-2,8,10); ¹³C-NMR (125 MHz, CDCl₃), δ (ppm): 52.95 (C-1), 40.56 (C-3,5,7), 35.37 (C-2,8,10), 28.96 (C-4,6,9).

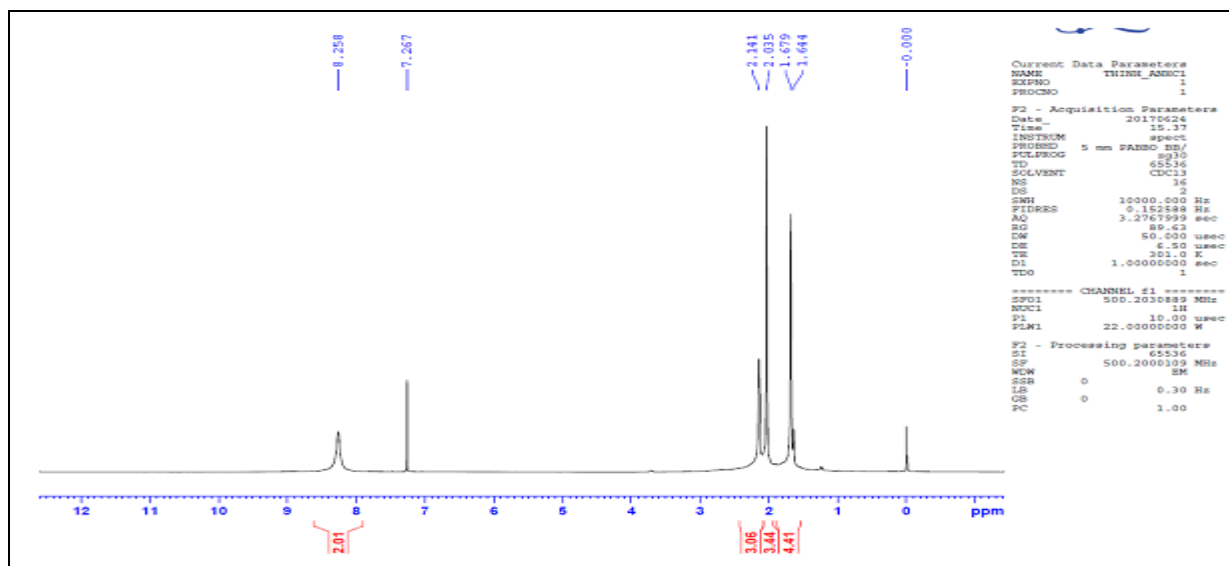
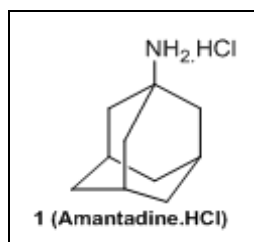
MS Spectrum of Amantadine Hydrochloride (1):

MS: $m/z = 152.0$ [M + 1]⁺, 135.1 [M - NH₂ - 1]⁺.

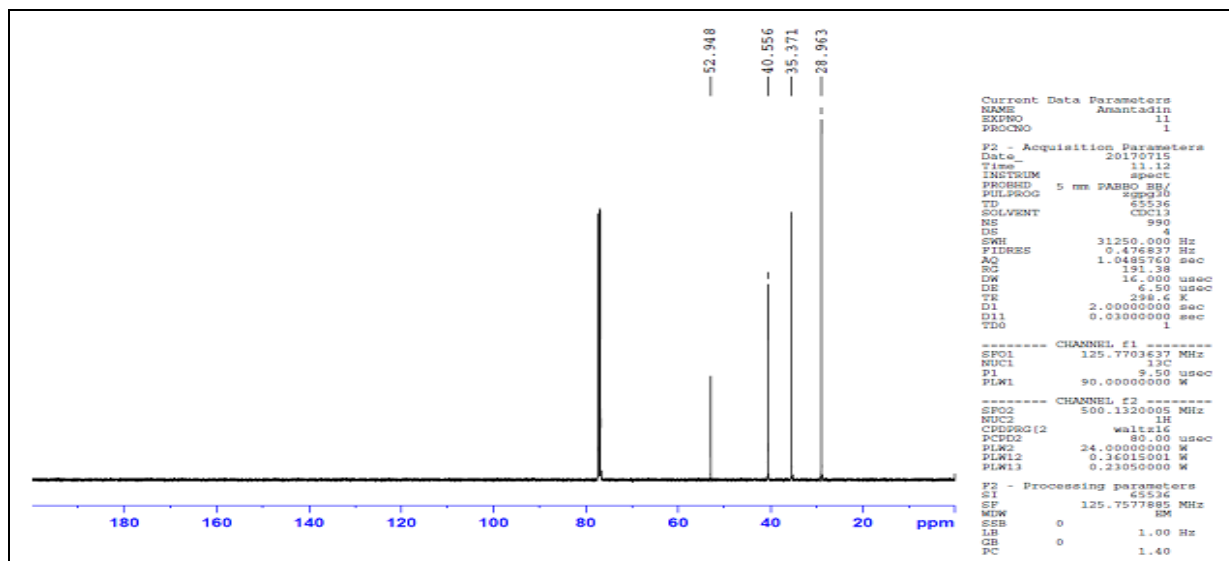


¹H-NMR Spectrum of Amantadine Hydrochloride (1) in CDCl₃:

¹H-NMR (CDCl₃, 500 MHz): δ 8.26 (br, s, 3H), 2.14 (s, 3H), 2.04 (s, 6H); 1.68 (s, 6H).

**¹³C-NMR Spectrum of Amantadine Hydrochloride (1) in CDCl₃:**

¹³C-NMR (CDCl₃, 125 MHz): δ 52.95, 40.56, 35.37, 28.96



TLC of Standard Amantadine HCl (A), Synthesized Amantadine HCl (B), and a Mixture of these two Reagents (C):

Method: Silica gel Aluminium Art 5562 DC – Alurolle Kieselgel 60 F254 (Merck).

Solvent System: chloroform: methanol (9:1).

Visualization Reagents: Dragendorff reagent.

Samples for TLC: Synthesized amantadine HCl, reference amantadine HCl, and a mixture of these two reagents. The chemicals were dissolved in dichloromethane (0.1g/1ml).

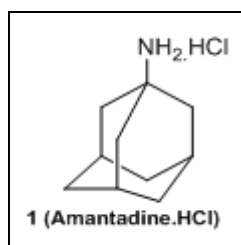
Triple small spots of each solution were applied to a TLC plate. The plate was dried shortly in a vacuum chamber at room temperature. Development and visualization of TLC were performed following the above conditions.

Results: Three red spots on the TLC plate have the same R_f value, indicating that they could be the same compound.



FIG. S2: TLC OF AMANTADINE HCl. (A) STANDARD AMANTADINE HCl, (B) SYNTHESIZED AMANTADINE HCl, (C) A MIXTURE OF THE TWO REAGENTS.

GC Data of the Synthesized Amantadine Hydrochloride (1):



GC condition: FID Detector, the temperature of 250°C

Column: (5%-Phenyl)-methylpolysiloxane, length of 30 m, the diameter of 0.32 mm, film layer of 0.25 μ m.

Column temperature of 115 °C; Oven temperature of 250 °C.

Injection Volume: 1 μ l

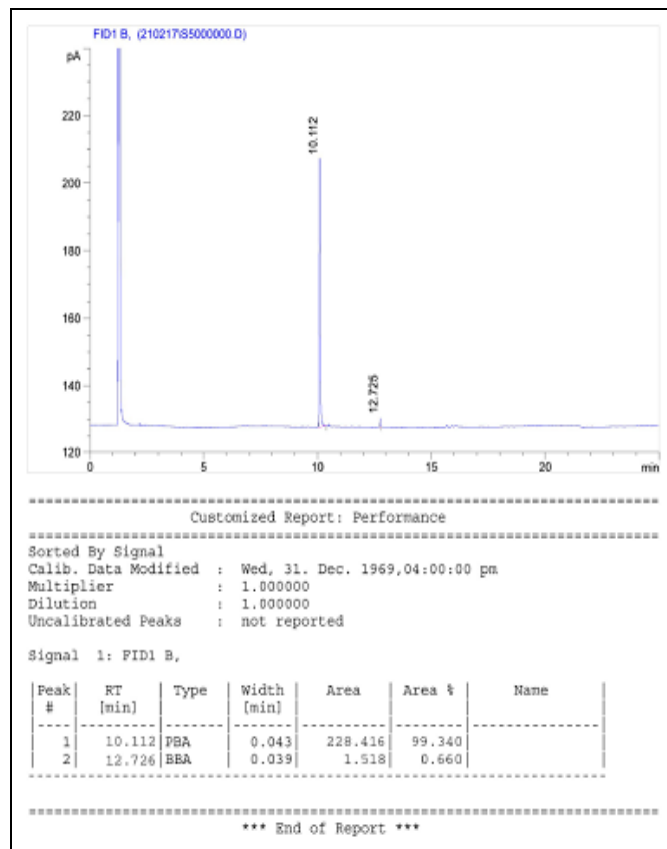


FIG. S3: GC CHROMATOGRAM OF THE SYNTHESIZED AMANTADINE HYDROCHLORIDE (1)

CONCLUSION: Taken together and in conclusion, amantadine hydrochloride (1) was obtained from adamantine (2) by 5N hydrochloride solution, not by its anhydrous HCl flowing through ether solution (that was avoided from high flammability and tendency to form peroxides). Thus, this procedure was relatively simple and reduced toxicity and risk of explosion and fire. Our synthesis procedure had the overall yield of 81%.

To our best knowledge, this optimized protocol is simple and economically advantageous over the earlier reported synthesis owing to high yields and the use of less expensive raw materials.

SUPPORTING INFORMATION: Experimental details; MS, ¹H-NMR, ¹³C-NMR spectra and GC data of amantadine hydrochloride. This material is available free of charge *via* the internet.

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CONFLICT OF INTEREST: Nil

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