SUPPORTING INFORMATION

A Simple Two-Step Procedure for Synthesis of Memantine Hydrochloride from 1,3-Dimethyladamantane

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1.1. Investigation for the effect of reaction parameters on the yield of N-formyl-1-amino-3,5-dimethyladamantane (6)

1.1.1. Effect of reaction temperature on the yield of 6

In a round-bottom flask, at 20-25 ºC 1,3-dimethyl-adamantane (2 mL, 0.01 mol) was slowly added to nitric acid (10.65 mL, 0,25 mol) over 20 min with stirring at this temperature over 1 h, then formamide (11 mL,0.27 mol) was slowly added within 0.5 h followed by heating the mixture to 75 ºC for 3.5 h. After the reaction was finished, the solution was cooled to 5-10 ºC and added to ice-cold water (20 mL), the reaction mixture was extracted with dichloromethane (40 mL). The separated organic layer was adjusted to pH 8-9 with 10% NaOH solution and then washed with chilled water, the organic layer was dried over Na_2SO_4, and then the solvent was evaporated to dryness in vacuum to give N-formyl-1-amino-3,5-dimethyl-adamantane (1.54 g, 77.44%) as an oil, which crystallized to a white solid at 10-15 ºC, m.p. 60-64 ºC. The reaction above preparation of **6** was performed the same operation as *2.1.1,* but reaction temperature 75 ºC instead of 60, 70, 75, 80, 85, 90 ºC, respectively. (**Table S1)**

Table S1. *Effect of reaction temperature and reaction time on the yield of N-formyl-1-amino-3,5-dimethyladamantane (**6**)*

No.	Temperature (ºC)	Reaction Time (h)	Compound 6		
			Weight (g)	Mp (^{0}C)	Yield (%)
1	60	7	1.24	60-65	59.64
2	70	5	1.45	61-66	69.76
3	75	3.5	1.54	62-66	77.44
4	80	3.0	1.78	60-67	85.65
5	**85**	**2.0**	**1.82**	**63-65**	**87.58**
6	90	2	1.81	60-66	87.13

Other reaction parameters. 1,3-Dimethyl-adamantane (**2**) = 0.01 mol; Reaction temperature: 60 ºC, 70 ºC, 75 ºC, 80 ºC, 85 ºC, 90 ºC; molar ratio of (compound **2**: nitric acid : formamide) = (1:12.5:13.5).

Conclusion: The reaction temperature gives the best yield of **6** was 85 ºC for 2.5 h (the yield 87.58%) (No.5, **Table S1**).

1.1.2. Effect of molar ratio between nitric acid and compound 2 on the yield of 6

*Experiment***:** The reaction preparation of **6** was performed the same operation as *1.1.1,* but the molar ratio between nitric acid and compound **6** was 7.5:1; 9:1; 10:1; 11.5:1, respectively. (**Table S2)**

Table S2. *Effect of molar ratio between nitric acid and compound **2** on the yield of N-formyl-1-amino-3,5-dimethyladamantane (**6**)*

No.	HNO_3 ml (mol)	Molar ratio of HNO_3: 2	Compound 6		
			Weight (g)	Mp (^{0}C)	Yield (%)
1	3.2 (0.075)	7.5:1	1.73	60-64	83.65
2	3.7 (0.09)	9:1	1.81	62-66	87.56
3	**4.2 (0.10)**	**10:1**	**1.91**	**63-66**	**92.10**
4	4.8 (0.113)	11.5:1	1.90	62-67	91.74

Other reaction parameters. Reaction temperature = 85 ^{o}C; Reaction time = 2.5 h;

Conclusion: The result found that using molar ratio of nitric acid:compound **2** was 10:1 got the highest yield of **6** was 92.10% (No.3, **Table S2**)

1.1.3. Effect of molar ratio between formamide and compound 2 on the yield of 6

*Experiment***:** The reaction preparation of **6** was performed the same operation as *1.1.2,* but the molar ratio between nitric acid and compound **6** was 20:1 and molar ratio between formamide and compound **2**was 5:1; 7.5:1; 9:1; 10:1, respectively. (**Table S3)**

Table S3. *Effect of molar ratio between formamide and compound **2** on the yield of N-formyl-1-amino-3,5-dimethyladamantane (**6**)*

No.	Formamide ml (mol)	Molar ratio of Formamide:2	Compound 6		
			Weight (g)	Mp (^{o}C)	Yield (%)
1	2.10 (0.05)	5:1	1.80	60-64	86.96
2	3.15 (0.075)	7.5:1	1.95	62-66	94.20
3	**3.65 (0.09)**	**9:1**	**2.02**	**63-66**	**97.58**
4	4.25 (0.10)	10:1	1.99	62-67	96.14

Other reaction parameters. Reaction temperature = 85 ^{o}C; Reaction time = 2.5 h;

Conclusion: The result found that using molar ratio of formamide:compound **2** was 9:1 got the highest yield = 97.58% (No.3, **Table S3**)

⇨ **Results.**The combination of reaction parameters found that the highest yield of N-formyl-1-amino-3,5-dimetyl adamantane were followed: 1,3-Dimethyl-adamantane (**2**) = 0.01 mol; Reaction condition: Reaction temperature = 85^{o}C; Reaction time = 2.0 h; Molar ratio of (nitric acid:formamide:1,3-dimethyl-adamantane) = (10:9:1); Yield = 97.58%.

1.2. Experimental section

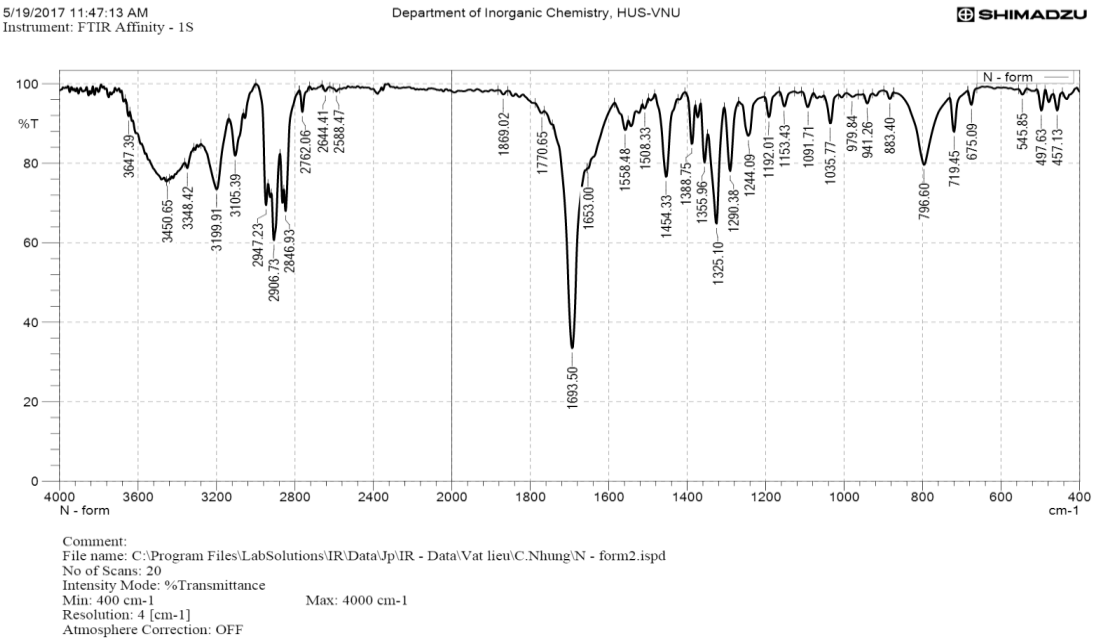
Synthesis of N-formyl-1-amino-3,5-dimethyladamantane (6)

In a round-bottom flask, at 20-25 °C 1,3-dimethyladamantane (11.13 mL, 9.86 g, 0.06 mol) was slowly added to nitric acid (25.25 mL, 0.6 mol) over 20 min with stirring at this temperature for 1 h, then formamide (22.5 mL, 0.54 mol) was added within 0.5 h followed by heating the mixture to 85 °C for 2 h. After reaction completion, the solution was cooled to 5-10 °C and added to ice-cold water (120 mL), the reaction mixture was extracted with dichloromethane (150 mL). The separated organic layer was adjusted to pH 8-9 with 10% NaOH solution and then washed with chilled water, the organic layer was dried over Na_2SO_4, and the solvent was evaporated to dryness in vacuum to give N-formyl-1-amino-3,5-dimethyladamantane (12.18 g, 97.91%) as an oil, which crystallized into white solid at 10-15 °C, m.p. 60-64 °C. IR (KBr), (cm^{-1}): 3450-3199 (N-H); 2947-2847 (C-H); 1693,50 (C=O). MS (m/z): 208.16$[M+1]^+$. ^{1}H-NMR (500 MHz, $CDC1_3$), δ (ppm): 8.23 (d, J=12.5 Hz, 1H, NH) 7.99 (s, 1H, CHO); 6.23 and 5.25 (br, s, 1H); 2.12-2.17 (m, 1H); 1.83 (s, 1H); 1.67-1.61 (m, 2H); 1.48-1.40 (m, 2H); 1.37-1.25 (m, 4H); 1.17-1.12 (m, 2H); 0.85-0.83 (m, 6H, $2CH_3$). ^{13}C-NMR (125 MHz, $CDC1_3$), δ (ppm): 162.3/160.3 (CHO); 53.7/52.3 (C_1) 50.5-50,3 (2C, C_2 and C_9); 47.8 (C_4); 42.7/42.5 (C_6); 42.2 (C_{10}); 40.4 (C_7); 32.5-32.4 (2C, C_3 and C_5); 30.1/30.0 (C_8); 29.9 (C_{11}); 29.8 (C_{12}).

1.3. Analytical data (IR, MS, NMR) of N-formyl-1-amino-3,5-dimethyladamantane (6)

1.3.1. IR spectrum of N-formyl-1-amino-3,5-dimethyladamantane (6)

IR (KBr), (cm^{-1}): 3450-3199 (N-H); 2947-2847 (C-H); 1693,50 (C=O).



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Min: 400 cm-1 Max: 4000 cm-1
Resolution: 4 [cm-1]
Atmosphere Correction: OFF

Figure S1. IR spectrum **6.**

1.3.2. MS spectrum of N-formyl-1-amino-3,5-dimethyladamantane (6)

MS (m/z): 208.16 $[M+1]^+$

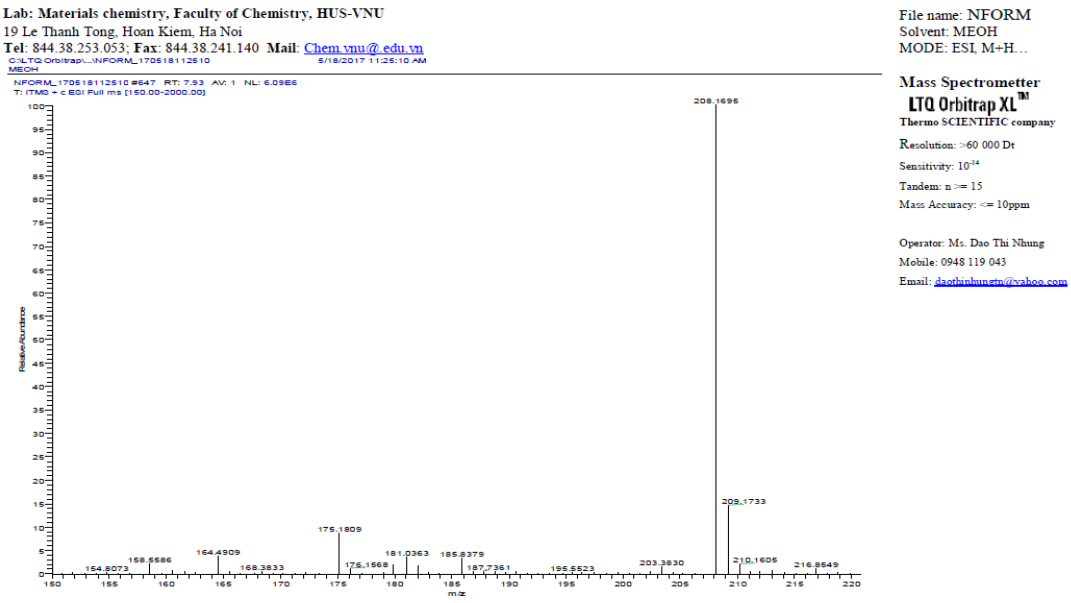
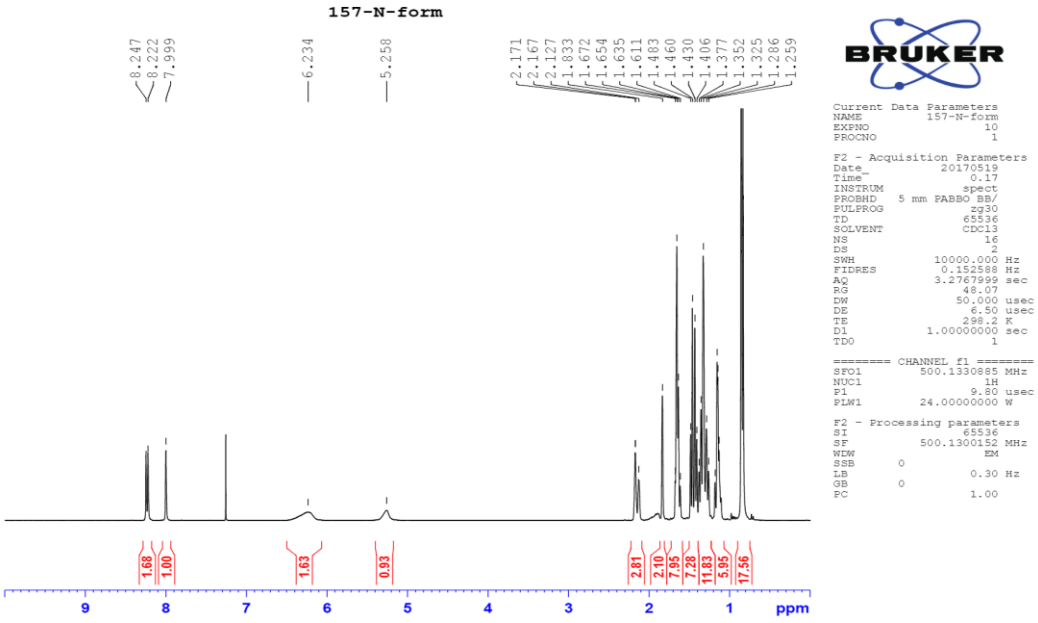
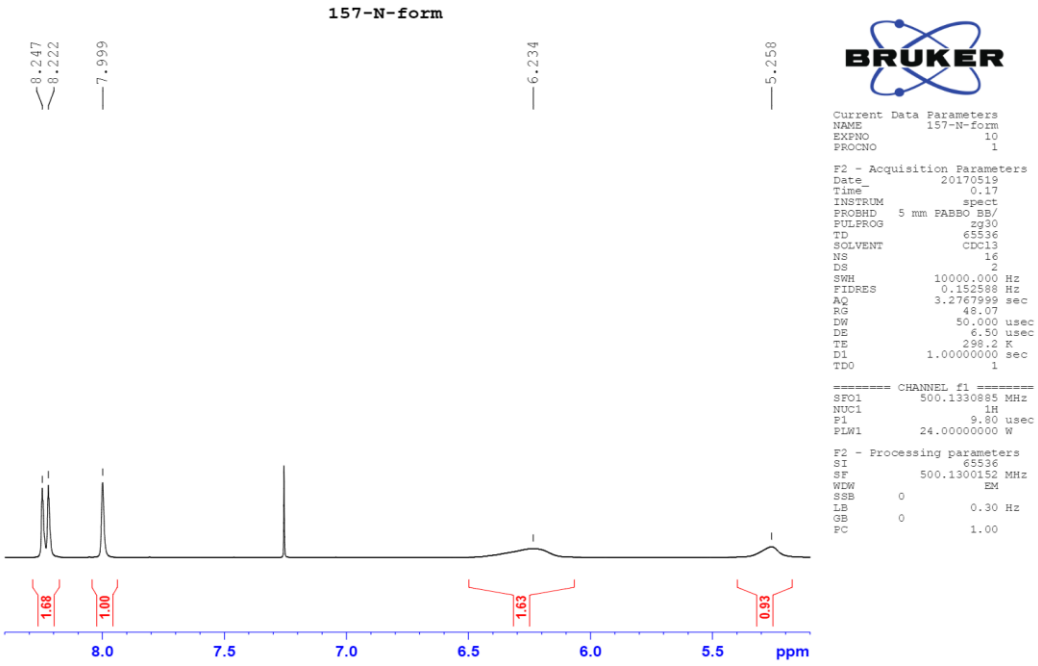


Figure S2.MS spectrum of **6**.

1.3.3. ^{1}H-NMR spectrum of N-formyl-1-amino-3,5-dimethyladamantane (6)

^{1}H-NMR (500 MHz, $CDCl_3$), δ (ppm): 8.23 (d, J=12.5 Hz, 1H, NH) 7.99 (s, 1H, CHO); 6.23 and 5.25 (br, s, 1H); 2.12-2.17 (m, 1H); 1.83 (s, 1H); 1.67-1.61 (m, 2H); 1.48-1.40 (m, 2H); 1.37-1.25 (m, 4H); 1.17-1.12 (m, 2H); 0.85-0.83 (m, 6H, $2CH_3$).





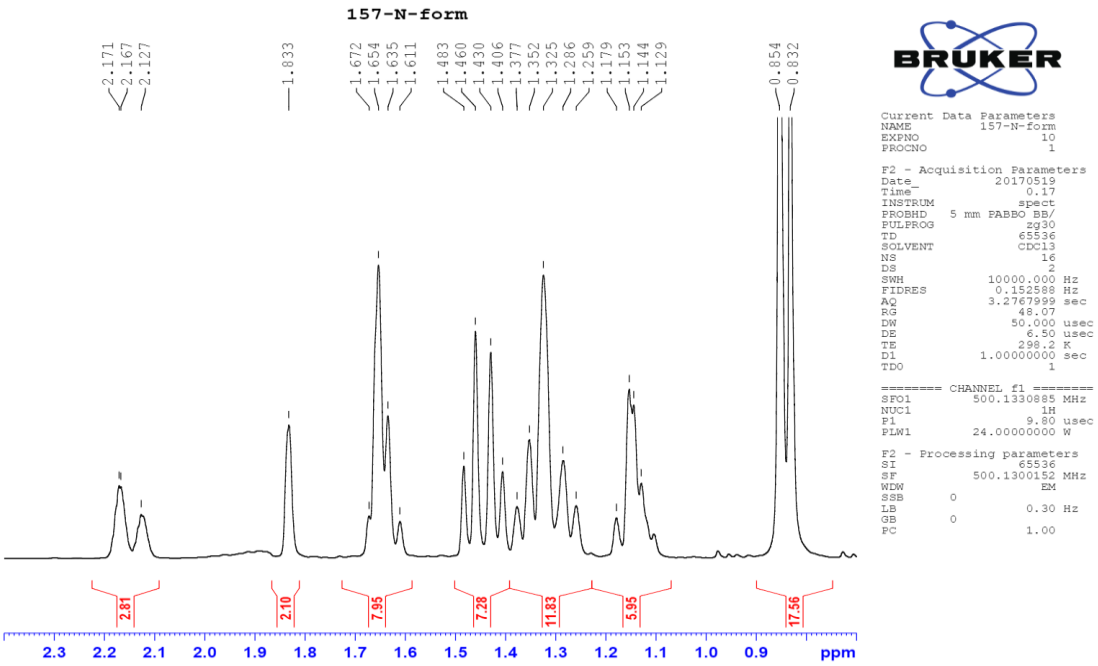


Figure S3. ^{1}H-NMR spectrum of **6.**

1.3.4. ^{13}C-NMR spectrum of N-formyl-1-amino-3,5-dimethyladamantane (6)

^{13}C-NMR (125 MHz, $CDCl_3$), δ (ppm): 162.3/160.3(CHO); 53.7/52.3(C_1) 50.5-50.3(2C, C_2 and C_9); 47.8 (C_4); 42.7/42.5(C_6); 42.2(C_{10}); 40.4 (C_7); 32.5-32.4 (2C, C_3 and C_5); 30.1/30.0 (C_8); 29.9 (C_{11}); 29.8 (C_{12}).

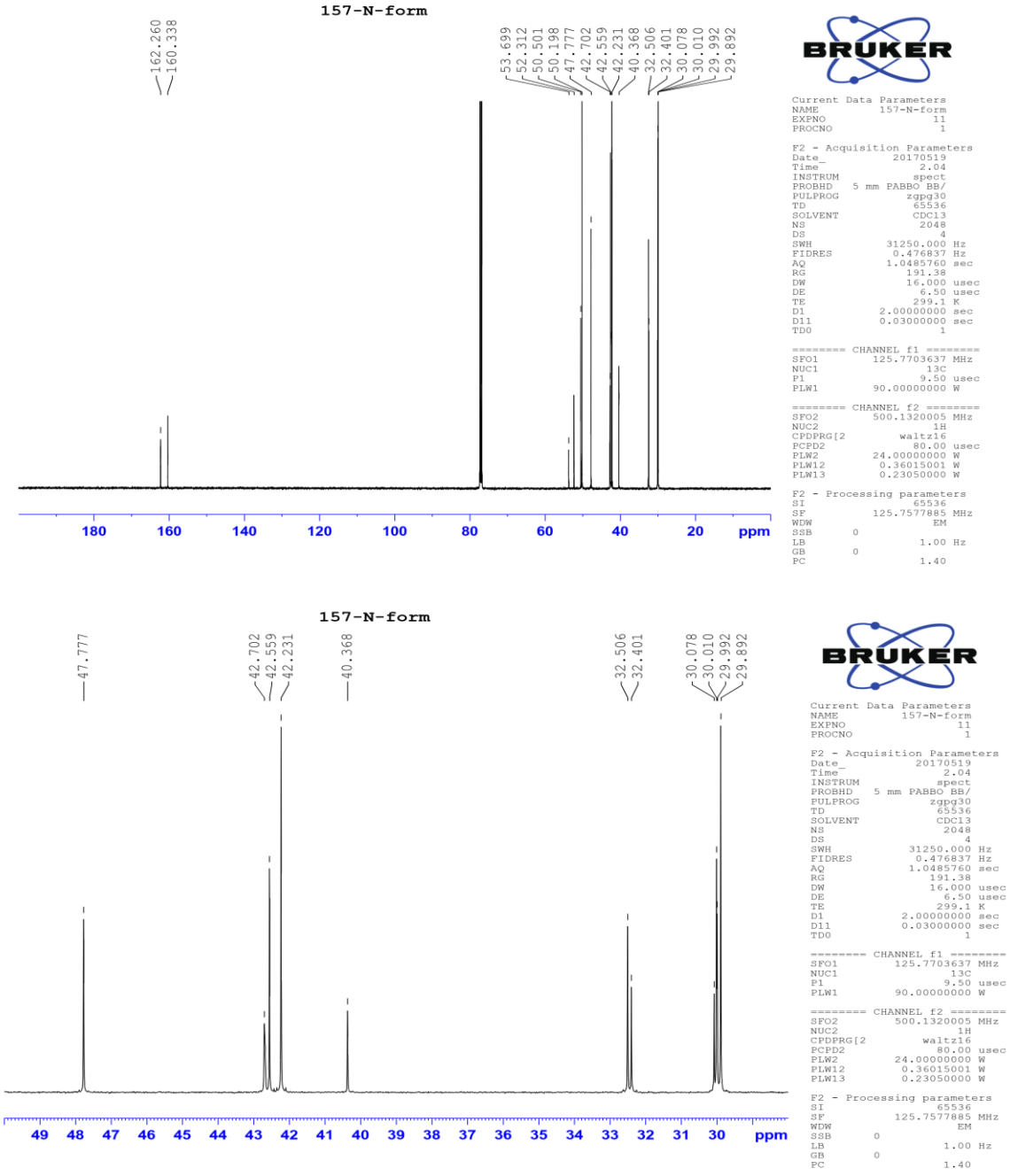


Figure S4. ^{1}H-NMR spectrum of **6.**

2.GENERAL PROCEDURE FOR THE SYNTHESIS OF MEMANTINE HYDROCHLORIDE (1)

2.1.Effect of reaction parameters on the synthesis of memantine hydrochloride (1) from N-formyl-1-amino-3,5-dimethyladamantane(6)

2.1.1. Effect of solvent type on the yield of memantine hydrochloride (1)

Experiment: In a round-bottom flask, a mixture 18 mL water, 36% hydrochloride solutions (21 mL, 0.24 mol) and N-formyl-1-amino-3,5-dimethyl adamantane (**6**) (6.55 g, 0.03 mol) was stirred for 10 min, and then was heated to reflux until the reaction was finished off (the compound **6**was consumed). The reaction mixture was concentrated to a half volume of solvent under vacuum. To this solution, n-hexane (10 mL) was added, the reaction mixture was heated to reflux for 0.5 h. The reaction was cooled to 5-10 ^{o}C for 1 h, whereupon a white solid was separated. The solid was filtered and washed with cooled ethyl acetate to obtain a white solid, which was further recrystallized from a mixture of ethanol and ethyl acetate and dried under vacuum to give memantine hydrochloride (**1**), which was melted at 290 ^{o}C and sublimated at 300 ^{o}C (**Table S4)**

Table S4. *Effect of solvent type on the yield of memantine hydrochloride(1)*

No.	Solvent type (ml)	Reaction Temperature/ reaction time (^{o}C/h)	Memantine hydrochloride(1)		
			Weight (g)	Mp & Sp (^{0}C)	Yield (%)
1	**H_2O (18)**	**100-103/1**	**5.19**	**290-300**	**80.45**
2	95% C_2H_5OH (18)	80-85/3	4.83	290-300	74.56
3	CH_3OH (18)	70-75/2.5	4.68	290-300	72.47

Other reaction parameters. 36% HCl; Molar ratio of (HCl:compound **6**) = (8:1).

Conclusion: The result found that using water as a solvent got the highest yield (No.1, **Table S4**)

2.1.2. Effect of reaction time on the yield of memantine hydrochloride (1)

Experiment: The reaction preparation of **1** was performed the same operation as 2*.1.1,* but reaction temperature 75, 80, 90, 100, and reaction time was 2.5, 2, 1.5, 1 h, respectively. (**Table S5)**

Table S5. *Effect of reaction time on the yield of memantine hydrochloride (1)*

No.	Reaction time (°C)	Reaction time (h)	Memantine hydrochloride(1)		
			Weight (g)	Mp & Sp (°C)	Yield (%)
1	75	2.5	5.10	290-300	78.81
2	80	2.0	5.13	290-300	79.15
3	90	1.5	5.16	290-300	79.93
4	**100**	**1.0**	**5.22**	**290-301**	**80.58**

Other reaction parameters.Solvent = water. Molar ratio of (HCl:compound **6**) = (8:1).

Conclusion: The reaction temperature gives the best yield of **1** was 100 °C for 1 h (No.4, **Table S5**).

2.1.3. Effect of molar ratio between HCl and compound 6 on the yield of memantine hydrochloride (1)

Experiment: The reaction preparation of **1** was performed the same operation as 2*.1.2,* but molar ratio between HCl and compound **6** was 6:1, 7.2:1, 8.4:1, 9.6:1, 10.8:1, respectively. (**Table S6)**

Table S6. *Effect of molar ratio between HCl and compound* ***6****on the yield of memantine hydrochloride (1)*

No.	HCl 36% ml (mol)	Molar ratio of HCl:6	Memantine hydrochloride(1)		
			Weight (g)	Mp & Sp (^{0}C)	Yield (%)
1	15(0.180)	6.0:1	5.22	290-300	80.45
2	18(0.216)	7.2:1	5.37	290-300	82.98

3	**21(0.252)**	**8.4:1**	**5.43**	**290-300**	**83.57**
4	24(0.288)	9.6:1	5.34	290-300	82.52
5	27(0.324)	10.8:1	5.16	290-300	79.74

Other reaction parameters.Solvent = water. Molar ratio of (HCl:compound **6**) = (6:1, 7.2:1, 8.4:1, 9.6:1 and 10.8:1).

Conclusion: The molar ratio between HCl and compound **6** gives the best yield of **1** was 8.4:1 (see No.4 in **Table S6**).

2.1.4. Effect of solvent volume on the yield of memantine hydrochloride(1)

*Experiment***:** The reaction preparation of **1** was performed the same operation as 2*.1.3,* but solvent (water) volume was 6, 9, 12, 15, 18, 21, 24 mL, respectively. (**Table S7)**

Table S7. *Effect of solvent volume on the yield of memantine hydrochloride (1)*

No.	**Water volume (ml)**	**HCl concentration N**	**Memantine hydrochloride(1)**		
			Weight (g)	**Mp & Sp (^{0}C)**	**Yield (%)**
1	6	10.50	5.22	290-300	80.25
2	9	9.33	5.30	290-300	81.86
3	12	8.40	5.37	290-300	82.98
4	15	7.64	5.43	290-300	83.87
5	**18**	**6.46**	**5.49**	**290-300**	**84.85**
6	21	6.0	5.47	290-300	84.46
7	24	5.5	5.36	290-300	82.75

Other reaction parameters. Solvent = water. Reaction time = 1h. Molar ratio of (HCl : compound **6**) = (8.4:1).

Conclusion: The solvent (water) volume gives the best yield of **1** was 18 ml (No.5, **Table S7**)

⇨ **Results.**The optimal parameters of reaction for the highest yield of memantine hydrochloride were followed: Compound **6** (0.03 mol); 36% HCl (25 ml, 0.288 mol); Molar ratio of (HCl:compound **6**) = (8.4:1); water (18 mL); Temperature = 100-104 ^{o}C; Reaction time = 1.0 h.

2.2. Experimental section

In a round-bottom flask, a mixture of water (36 mL), solution of 36% hydrochloride (45 mL, 0.51 mol) and N-formyl-1-amino-3,5-dimethyladamantane (12.44 g, 0.06 mol) were stirred for 10 min, followed by heating to reflux for 1 h. The reaction mixture was concentrated to half volume of the solvent under vacuum. To this solution, n-hexane (20 mL) was added, the reaction mixture was heated to reflux for 0.5 h. The reaction was cooled to 5-10 °C for 1 h, whereupon a white solid was separated. The solid was filtered and washed with cooled ethyl acetate to obtain a white solid, which was further recrystallized from a mixture of ethanol and ethyl acetate (5:4, v/v) and dried under vacuum to give memantine hydrochloride (**1**) (10.97 g, 84.74%), which was melted at 290 ºC and sublimated at 300 °C (literature[17] m.p. 290-295 ºC). IR (KBr), (cm^{-1}): 3441 (N-H); 2943, 2901 (CH); 1364 (C-N); MS, m/z: 180.17 $[M\text{-}HC1+1]^+$. ^{1}H-NMR (500 MHz, $CDCI_3$), δ (ppm): 8.34 (s, 3H, NH_2.HCl); 2.20 (m, 1H); 1.89 (s, 2H); 1.74 (d, J=11.5, 2H); 1.68 (d, J=11.5, 2H); 1.42 (d, J=12.5, 2H); 1.31 (d, J=12.5 2H); 1.22 (d, J=12.5Hz, IH); 1.16 (d, J=12.5Hz, IH); 0.86 (s, 6H, $2CH_3$. ^{13}C-NMR (125 MHz, $CDC1_3$), δ (ppm): 54.4 (C_1); 49.8 (2C, C_2 and C_9); 46.4 (C_4); 41.8 (2C, C_6 and C_{10}); 39.2 (C_7); 32.6 (C_3 and C_5); 29.8 (C_8); 29.6 (2C, C_{11} and C_{12}).

2.3. Analytical data (IR, MS, NMR) of Memantine Hydrochloride

2.3.1. IR spectrum of Memantine Hydrochloride

IR (KBr), (cm^{-1}): 3406 (N-H); 2988, 2901 (CH); 1361 (C-N);

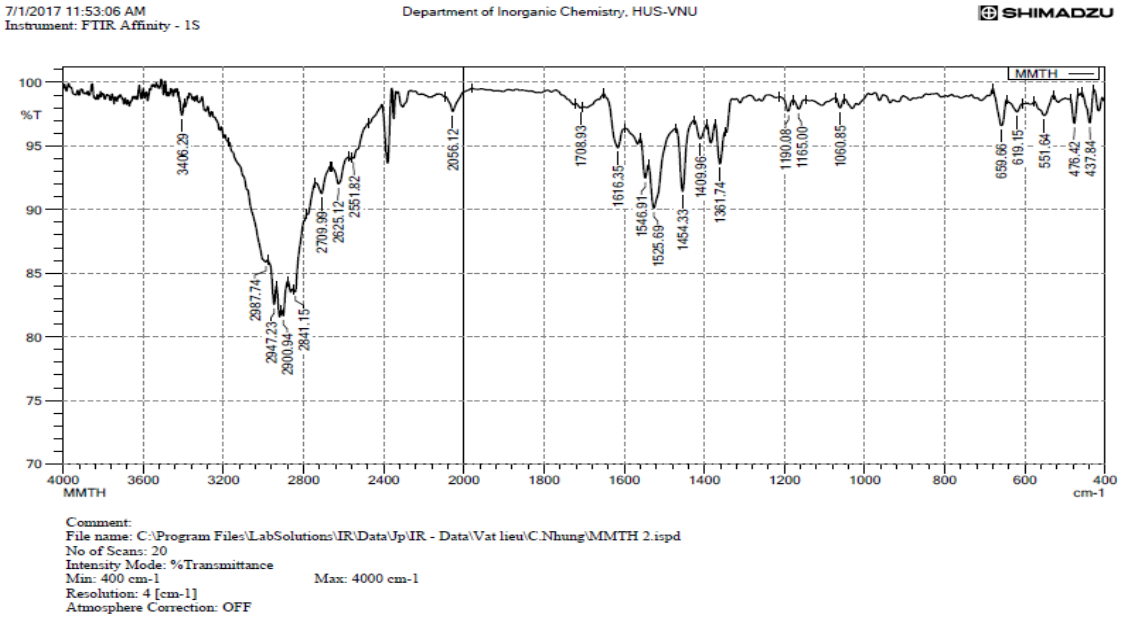


Figure S5. IR spectrum of Memantine Hydrochloride.

2.3.2. MS spectrum of Memantine Hydrochloride

MS, m/z: 180.17 $[M- HCl+1]^+$

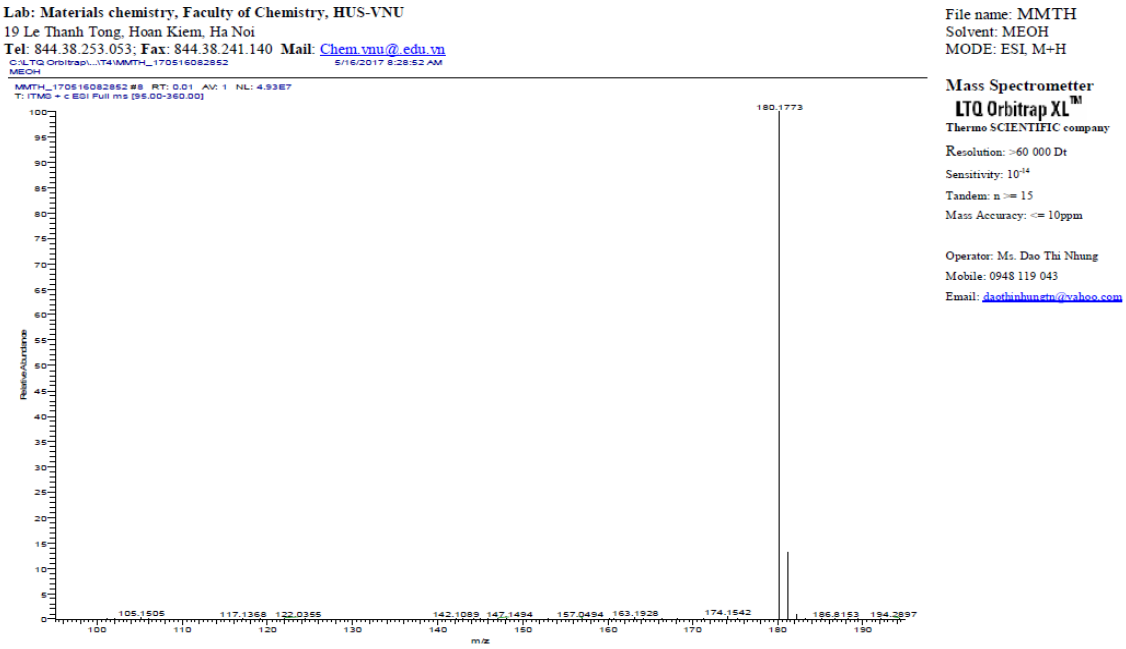


Figure S6. MS spectrum of Memantine Hydrochloride.

2.3.3. [1]H-NMR spectrum of Memantine Hydrochloride

[1]H-NMR (500 MHz, $CDCl_3$), δ (ppm): 8.34 (s, 3H, NH_2.HCl); 2.20 (m, 1H, C_7-H); 1.89 (s, 2H); 1.74 (d, J=11.5, 2H); 1.68 (d, J=11.5, 2H); 1.42 (d, J=12.5, 2H); 1.31 (d, J=12.5 2H); 1.22 (d, J=12.5Hz, 1H,); 1.16 (d, J=12.5Hz, 1H); 0.86 (s, 6H, $2CH_3$)

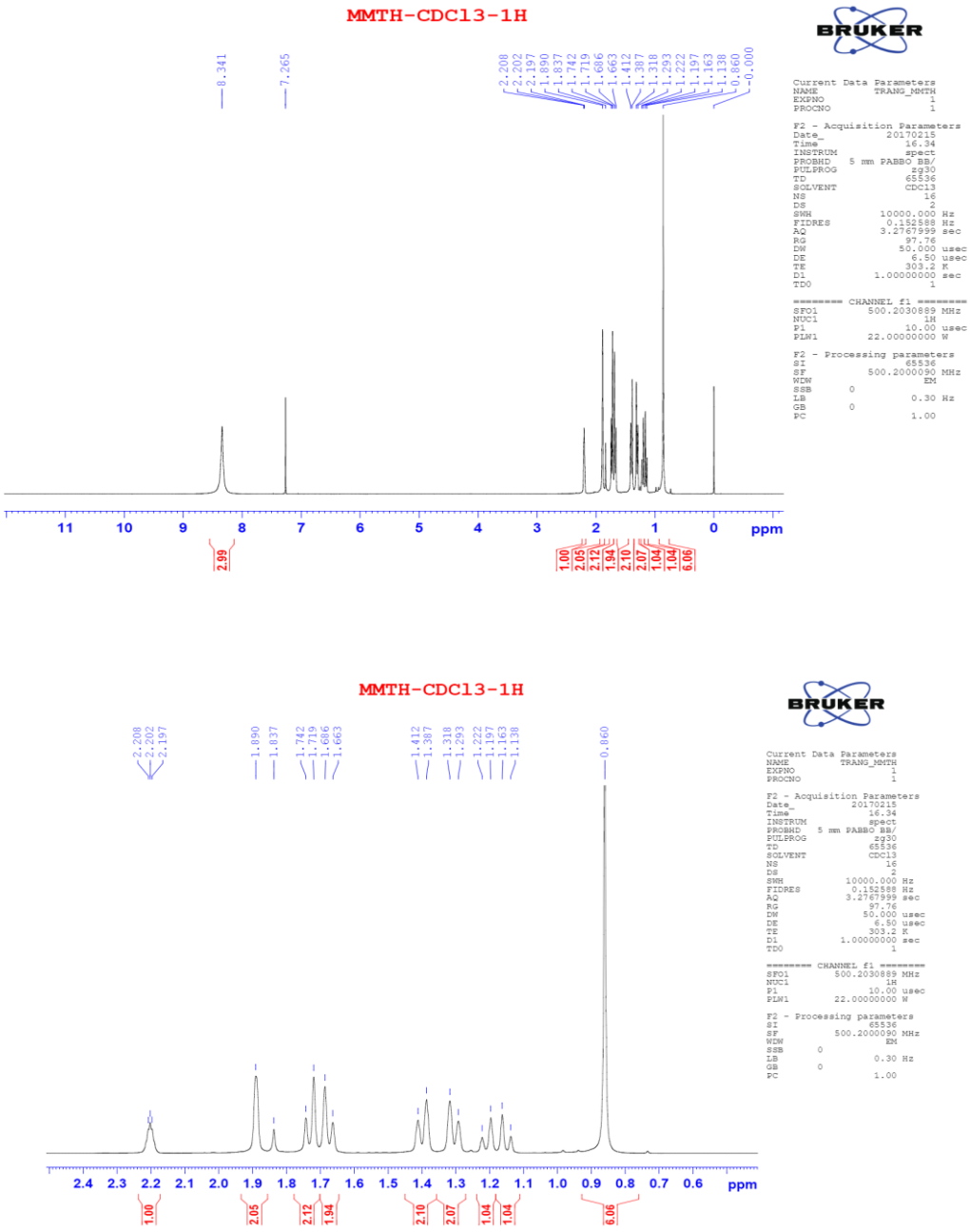


Figure S7. [1]H-NMR spectrum of Memantine Hydrochloride

2.3.4. ^{13}C-NMR spectrum of Memantine Hydrochloride

^{13}C-NMR (125 MHz, $CDCl_3$), δ (ppm): 54.4 (C_1); 49.8 (2C, C_2 and C_9); 46.4 (C_4); 41.8 (2C, C_6 and C_{10}); 39.2 (C_7); 32.6 (C_3 and C_5); 29.8 (C_8); 29.6 (2C, C_{11} and C_{12}).

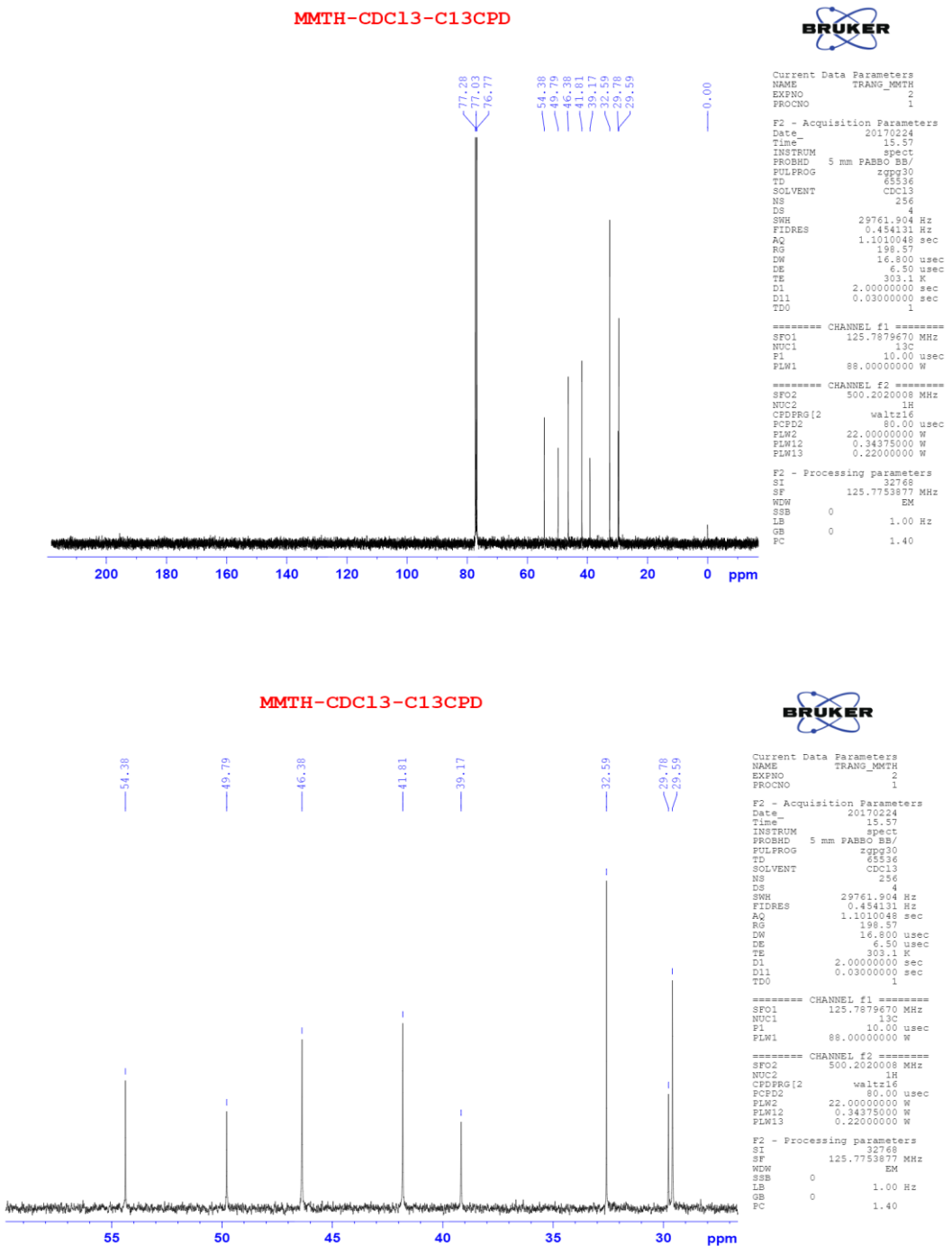


Figure S8. ^{13}C-NMR spectrum of Memantine Hydrochloride

3. THE SAFETY STUDIES

Sample preparation:

Sample 1. 1 mL 1,3-dimethyl-adamantane

Sample A. 1.24 ml 1-3 dimethyl-adamantane and 2.25 ml formamide

Sample B. 1.24 mL 1-3 dimethyl-adamantane and 2.52 mL acid nitric

Sample C.1.24 ml 1-3 dimethyl-adamantane, 2.25 ml formamide and 2.52 mL acid nitric

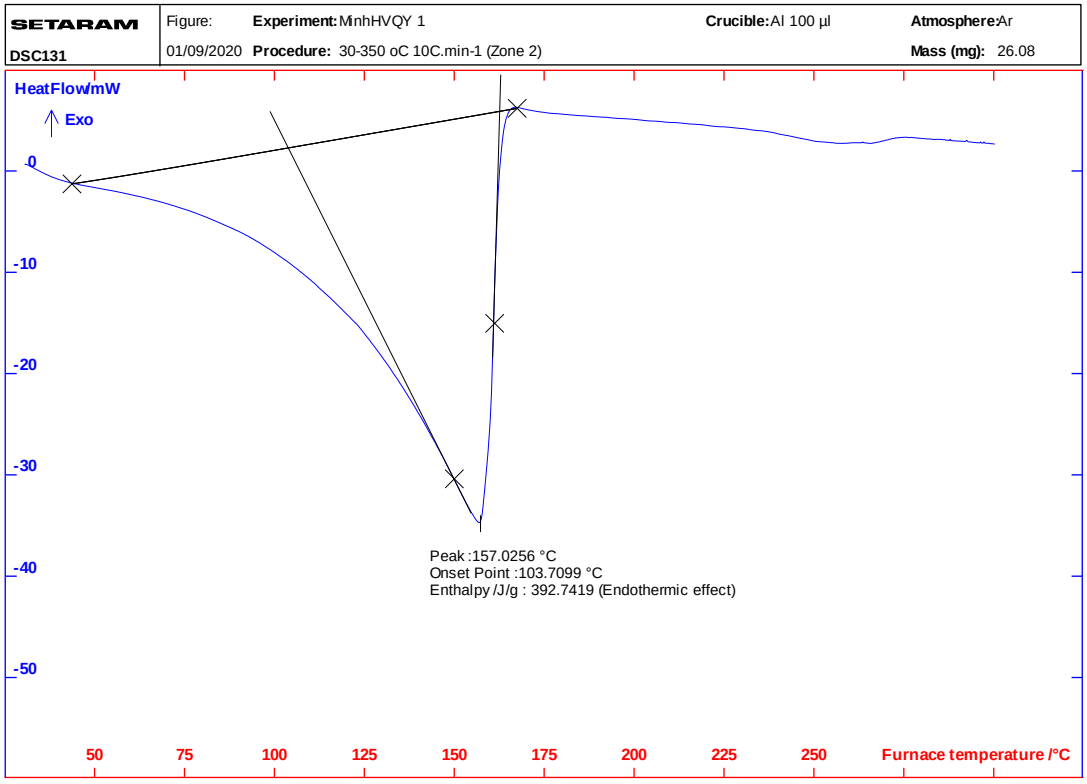


Figure S9. The DSC measurement result of sample 1

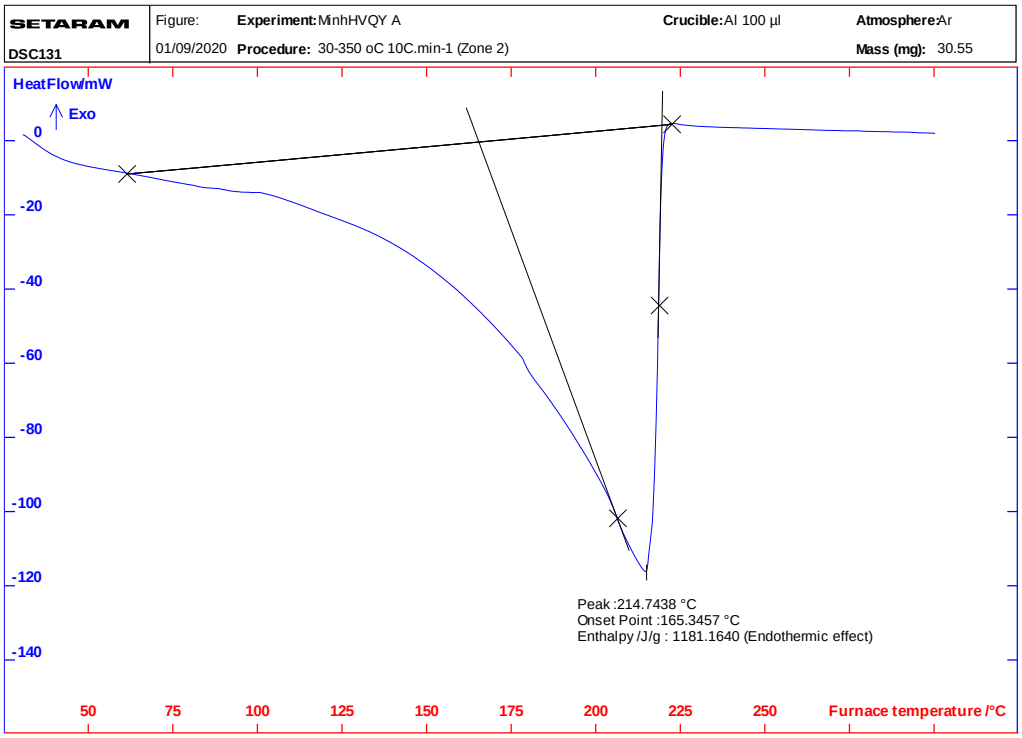


Figure S10. The DSC measurement result of sample A

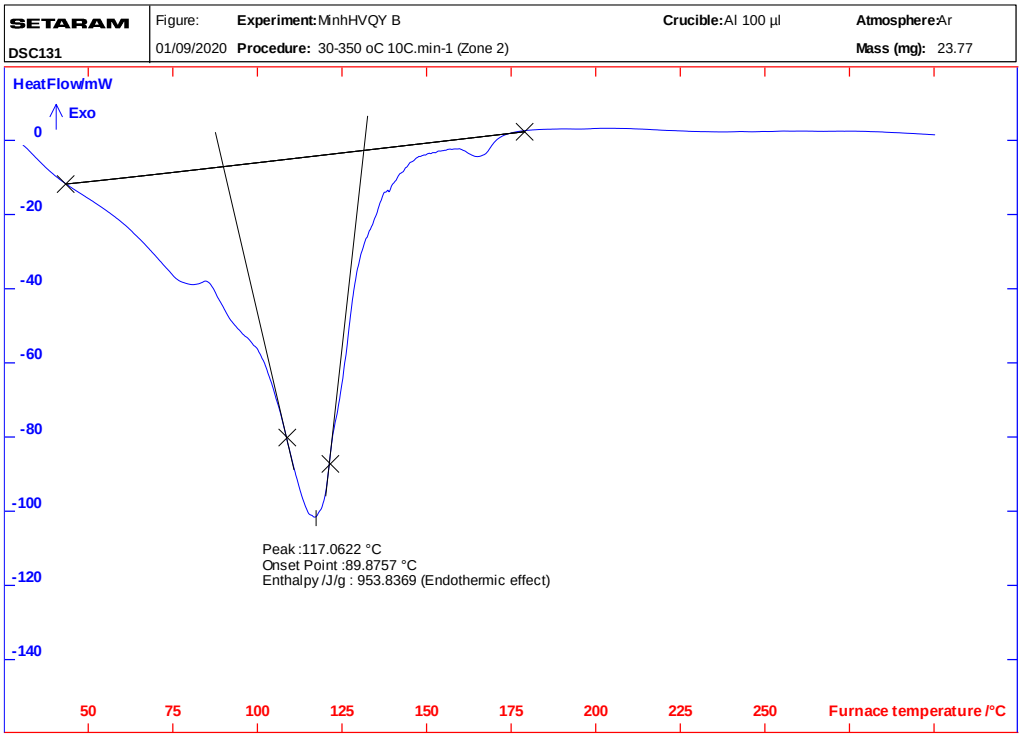


Figure S11. The DSC measurement result of sample B

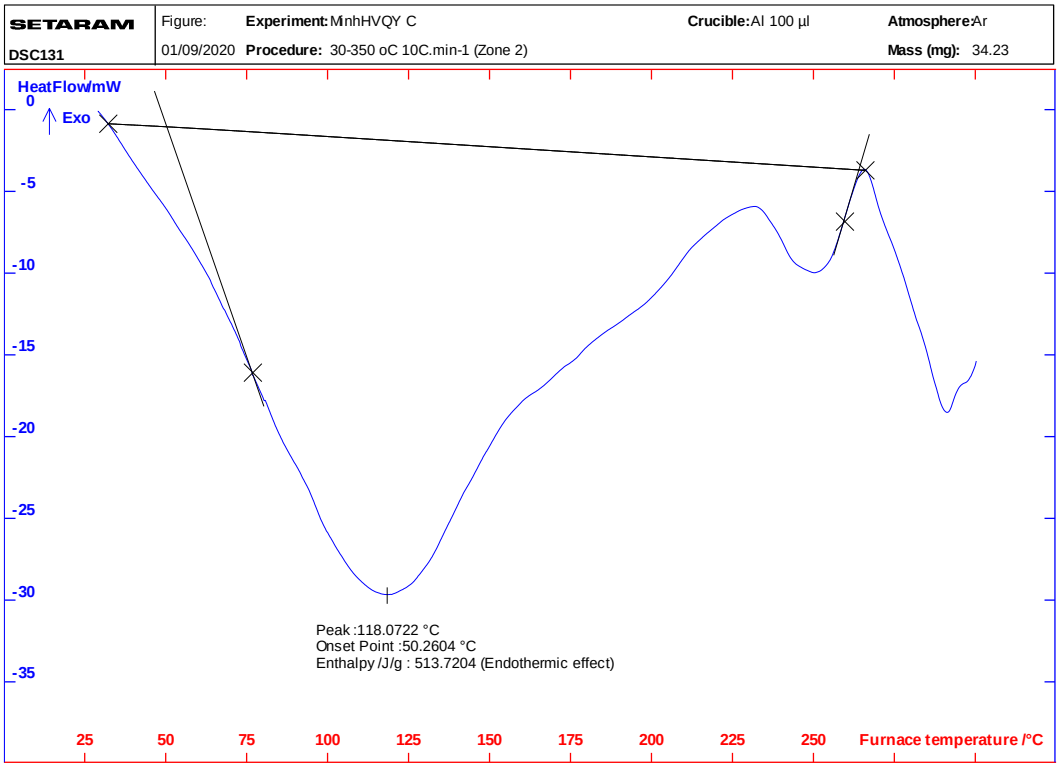


Figure S12. The DSC measurement result of sample C

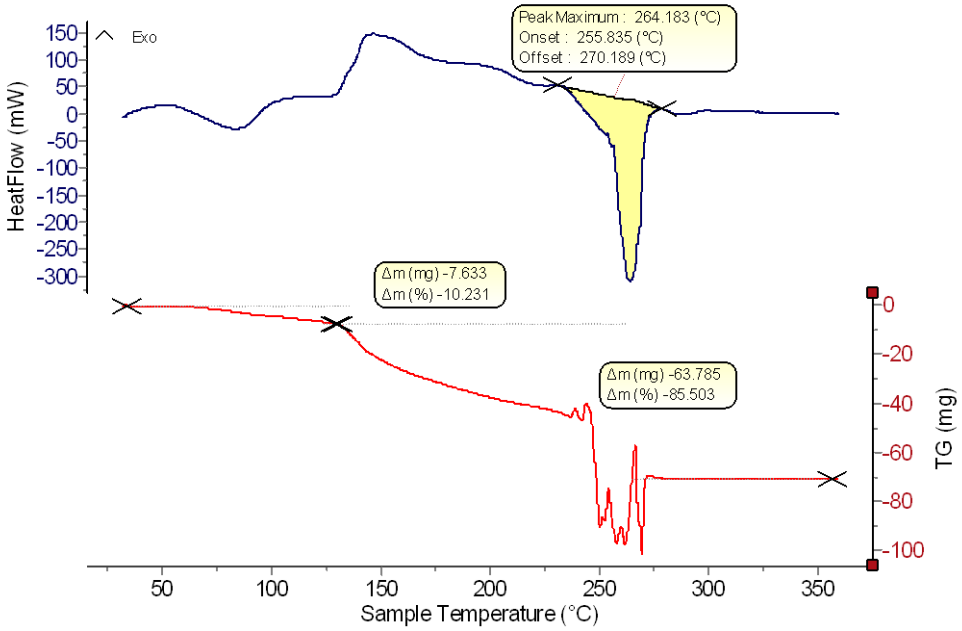


Figure S13. The ARC study of sample C

⇨ **Conclusion:**

The DSC results showed that, when heating in the area from room temperature to 300 °C, only the endothermic effect corresponding to the evaporation of the liquid is accompanied by decomposition at high temperature, no effect appears exothermic decomposition.

The ARC study of sample C also illustrated that this reaction still has an exothermic effect at 150 °C but decomposes more smoothly.

Therefore, it can be concluded that it is safe and not explosive.