SUPPORTING INFORMATION

A SIMPLE AND ECONOMICAL PROCESS FOR PRODUCING OF AMANTADINE HYDROCHLORIDE

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1. FIGURE

**Figure S1.** Simple and economical process for producing of Amantadine hydrochloride from 1-Bromo-admantan

![Diagram of Figure S1](image)

**Figure S2.** Four-step synthesis of Amantadine hydrochloride from Adamantan or three-step from 1-Bromo-Adamantan

Reagents and conditions: (a) liquid Br$_2$ reflux; (b) CH$_3$CN/H$_2$SO$_4$/40°C/12h/ benzene extraction; (c) NaOH, Diethylenglycol, reflux,5h/ ether extraction; (d) anhydrous HCl/ ether.

![Diagram of Figure S2](image)

**Figure S3.** Two-step synthesis of Amantadine hydrochloride from 1-Bromo-admantan

Reagents and conditions: (a) /NH$_2$CHO/H$_2$SO$_4$/85°C/5.5 h; 94%; (b) aqueous HCl 19.46%/reflux /1h; 93%. Overall yield 88%.
2. GENERAL PROCEDURE FOR SYNTHESIS OF N-(ADAMANTYL) FORMAMIDE (6)

2.1. Effect of reaction parameters on the yield of N-(1-adamantyl) formamide (6)

2.1.1. Effect of reaction Temperature and Time on the yield of N-(1-adamantyl) formamide (6)

**Experiment:** At 75°C 1-bromo-adamantane (2.19 g; 0.01 mol) was added to formamide (4.5 mL; 0.11 mol) with stirring. To this mixture H₂SO₄ 96% (4.3 mL, 0.08 mol) was added dropwise, then it was heated to 75°C, 80°C, 85°C, 90°C, 100°C, 110°C, and maintained for until finished reaction until the compound 3 was disappeared (5.5 hours, which was indicated by Thin layer chromatography with solvents: methanol : CHCl₃ : aq. NH₃ 25% = 6: 1 (v/v); visualization: iodine). After reaction mixture cooled to room temperature and slowly added to ice-cold water (15 mL) and stirred at 0-5°C for 1 h. The white solid was precipitated, filtered and washed with cool water. Finally, recrystallization of raw N-(1-adamantyl)formamide from methanol-water gave 6. The obtained product was dried under vacuum, yield: Result see **Table S1**

| No. | Temperature(°C) | Time (h)* | N-(1-adamantyl) formamide (6) |
|-----|----------------|-----------|--------------------------------|
|     |                |           | Weight(g) | Melting point (°C) | Yield (%) |
| 1   | 75             | 7.5       | 1.46      | 130-131            | 81.49     |
| 2   | 80             | 6         | 1.53      | 130-132            | 85.32     |
| 3   | 85             | 5.5       | 1.62      | 131-132            | 90.48     |
| 4   | 90             | 5         | 1.62      | 130-132            | 90.48     |
| 5   | 100            | 3.5       | 1.60      | 131-132            | 89.63     |
| 6   | 110            | 2.5       | 1.58      | 130-132            | 88.45     |

Reaction parameters. *Indicated by Thin layer chromatography; 1-Bromo-adamane: 0.01 mole; Molar ratio of (formamide: nitric acid: 1-Brom-adamantane) = (11:8:1)

**Conclusion:** The optimal reaction temperature is 85°C and reaction time is 5.5 h (see No. 3 in **Table S1**)
2.1.2. Effect of molar ratio between sulfuric acid and 1-bromoadamantan on the yield of N-(1-adamantyl)formamide (6)

Experiment: The reaction synthesis of N-(1-adamantyl) formamide (6) was performed the same operation as investigation on effect of the reaction temperature on the yield of 6 above, but reaction temperature was 85°C, reaction time 5.5 h and in different the molar ratio between sulfuric acid and 1-Br-adamantane from 4:1 to 8:1 (Result see Table S2).

Table S2. Effect of molar ratio between sulfuric acid and 1-Bromo-adamantane on the yield of N-(1-adamantyl)formamide (6)

| No. | Molar ratio of H₂SO₄ : Ad-Br | N-(1-adamantyl)formamide (6) | Weight (g) | Melting point (°C) | Yield (%) |
|-----|-----------------------------|-----------------------------|------------|--------------------|-----------|
| 1   | 4 : 1                       |                             | 1.34       | 129-132            | 74.84     |
| 2   | 5 : 1                       |                             | 1.62       | 130-131            | 90.25     |
| 3   | 5.5 : 1                     | 1.66                       | 131-132    | 92.86              |
| 4   | 6 : 1                       |                             | 1.66       | 130-132            | 92.86     |
| 5   | 7: 1                        |                             | 1.65       | 130-132            | 92.14     |
| 6   | 8: 1                        |                             | 1.63       | 130-131            | 90.86     |

Reaction parameters. Reaction temperature = 85°C, Time = 5.5 h; Molar ratio of (formamide: sulfuric acid: 1-Br-adamantane) = (11:4- 8: 1).

Conclusion: The result found that molar ratio of (sulfuric acid: 1-Br-adamantane) = (5.5:1) got the highest yield of N-(1-adamantyl) formamide (6) (see No. 3 in Table S2.)

2.1.3. Effect of molar ratio between formamide and 1-bromo-adamantan on the yield of N-(1-adamantyl) formamide (6)

Experiment: The reaction synthesis of 6 was performed the same operation as investigation on effect of of molar ratio between sulfuric acid and 1-Br-adamantane on the yield of N-(1-adamantyl) formamide (6) (1.1.2) above, but in different the molar ratio between formamide and 1-Br-adamantane from 7:1 to 11:1 (Result see Table S3).

Table S3. Effect of molar ratio between formamide and 1-Bromo-adamantane on the yield of N-(1-adamantyl)formamide (6)

| No. | Molar ratio of Formamide: Ad-Br | N-(1-adamantyl)formamide (6) | Weight (g) | Melting point (°C) | Yield (%) |
|-----|--------------------------------|-----------------------------|------------|--------------------|-----------|
| 1   | 7 : 1                          |                             | 1.64       | 129-132            | 91.54     |
| 2   | 8 : 1                          |                             | 1.68       | 130-131            | 93.57     |
Reaction parameters. Reaction temperature = 85°C, Time = 5.5 h;; Molar ratio of (Formamide : sulfuric acid:1-Bromo-adamantane)= (7 – 12 : 5.5: 1).

**Conclusion:** The result found that molar ratio of (formamide: 1-Br-adamantane)= (9:1). got the highest yield of N-(1-adamantyl) formamide (6) (see No. 3 in Table S3)

⇒ **Results.** The combination of reaction parameters that gives the highest yield of N-(1-adamantyl)formamide (6): Temperature =85°C; Time = 5.5 h; 1Br-damantane = 0.01mol;
Molar ratio of (formamide :sulfuric acid :1-bromo-adamantane)=(9: 5.5:1).

### 2.2. Experimental section

**Synthesis of N-(1-Adamantyl)formamide (6) :**

At 75°C 1-bromo-adamantane (66.0 g; 0.3 mol) was added to formamide (122 mL; 2.7 mol) with stirring. To this mixture, H₂SO₄96% (90 mL, 1.65 mol) was added dropwise, then it was heated to 85°C and maintained for until finished reaction( the compound 3 was disappeared) (5.5 hours, which was indicated by Thin layer chromatography with solvents: methanol : CHCl₃: aq. NH₃ 25% = 1: 6: 1 (v/v); visualization: iodine). After reaction mixture cooled to room temperature and slowly added to ice-cold water (350 mL) and stirred at 0-5°C for 1 h. The white solid was precipitated, filtered and washed with cool water. Finally, recrystallization of raw N-(1-adamantyl)formamide from methanol-water gave 50.8 (94.44%) compound 6; Purity (GC) 99.20%). Mp. 130-133°C; **IR** (KBr, cm⁻¹): 3333-3084 (N-H); 2897, 2851 (C-H); 1688 (C=O) ; 1362 (C-N); **MS, m/z:** 180,35 [M+1]⁺; 152.30 [M-CHO+1]⁺; 136.35 [M-NHCHO+1]⁺; **¹H-NMR**(500 MHz, CDCl₃), δ (ppm): 8.31 (d, J=12.3Hz, 0.67H); 8.07 (d, J= 1,7Hz, 0,33H); 6.26 (s, 0,65H); 5.35 (s, 0,35H); 2.16 (d, J=18,6 Hz, 3H), 1.88 (d, J= 2,4Hz, 2H); 1.70 (d, J= 2,2Hz, 4H), 1.69-1,65 (m, 6H); **¹³C-NMR**(125 MHz, CDCl₃), δ (ppm): 162.33; 160.42; 52.24 ; 50.79; 44.16; 41.85; 38.88; 35.26; 29.41; 29.31.

**IR spectrum of N-(1-adamantyl) formamide (6)**

![IR spectrum of N-(1-adamantyl) formamide (6)](image_url)
**Figure S4.** Molecular structure of N-(1-adamantyl) formamide (6)

**Figure S5.** IR spectrum of N-(1-adamantyl) formamide (6)

IR (KBr): cm\(^{-1}\) 3333- 3084 (N-H); 2897-2850 (C-H); 1688 (C=O)

**MS spectrum of N-(1-adamantyl)formamide (6)**

**Figure S6.** MS spectrum of N-(1-adamantyl)formamide (6)

MS: m/z = 180.35 [M+1]\(^+\); 152.30 ; 135.27
$^1$H-NMR spectrum of $N$-(1-adamantyl)formamide (6) in CDCl$_3$

$^1$H-NMR (CDCl$_3$, 500 MHz): $\delta$ (ppm) 8.32 (d, $J=12.3$ Hz, 0.67H); 8.07 (d, $j=1.7$ Hz, 0.33H); 6.26 (s, 0.65H); 5.35 (s, 0.35H); 2.16 (d, $J=18.6$ Hz, 3H); 1.88 (d, 2.4Hz, 2H); 1.70 (d, $J=2.2$ Hz, 4H), 1.69-1.65 (m, 6H).
Figure S8. 1H-NMR spectrum of N-(1-adamantyl)formamide (6) in CDCl₃ high resolution spectrum

\[ ^{13} \text{C-NMR spectrum of } N\text{-}(1\text{-adamantyl})\text{formamide (6) in CDCl}_3 \]

\[ ^{13} \text{C-NMR (CDCl}_3, 125 \text{ MHz}): \delta \text{ (ppm): 162.33; 160.42; 52.24; 50.80; 44.16; 41.85; 36.26; 35.90; 29.41; 29.31.} \]
Figure S10. $^{13}$C-NMR spectrum of (6) in CDCl$_3$, high resolution spectrum.

GC data of the synthesized $N$-(1-adamantyl)formamide (6)
Figure S11. GC spectrum of N-(1-adamantyl)formamide (6)

Column: (5%-Phenyl)-methylpolysiloxane.
Length of 30 m, diameter of 0.32 mm, film layer of 0.25 µm.
Column temperature of 115ºC; Oven temperature of 250ºC. Injection volume: 1 µL

3. GENERAL PROCEDURE FOR THE SYNTHESIS OF AMANTADINE HYDROCHLORIDE

3.1. Effect of reaction parameters on the synthesis of amantadine hydrochloride (1)

3.1.1. Effect of concentration of HCl on the yield of amantadine.HCl (1)
A mixture of solution of hydrochloride (0.09 mole) in different concentration (36, 19.5, 15.4, 11.3, 8.9% (suitable for 9 ml HCl 36%, 18 ml HCl 19.46%, 27 ml HCl 15.37%, 36 ml HCl 11.27%, 45 ml HCl 8.90%) and N-formyl-1-amino-adamantane (6) (5.40 g, 0.03 mole) was stirred at room temperature for 10 min, and then it was heated to reflux for until the compound 6 was disappeared, which indicated by Thin layer chromatography (solvents: CHCl$_3$: methanol: 25$\%$NH$_3$ aq. = 6:1:1; visualization: Dragendorff reagent; the time needed for the reaction to go to completion was determined by the time when the starting material 6 disappeared from the Thin layer chromatography of the reaction mixture). After the reaction was finished, the reaction mixture was concentrated to dryness in vacuum, to which this reaction mass ethyl acetate (8mL) was added, the reaction mixture was heated to reflux for 0.5h and then at 5-10$\degree$C for 1h, the white solid was precipitated, filtered and washed with cooled ethyl acetate and dried under vacuum to give 1-adamantylamine hydrochloride (1), did not melted up to 360$\degree$C, $R_f=0.5$. Result see in Table S4.

**Table S4. Effect of concentration of HCl and reaction time on the yield of amantadine.HCl (1)**

| No. | Concentration of HCl ml (%) | Time (min) | Weight(g) | Yield (%) | Melting point (0$\degree$C) |
|-----|-----------------------------|------------|-----------|-----------|---------------------------|
| 1   | 9-(36)                      | 90         | 5.13      | 91.07     | >360                      |
| 2   | 18-(19.46)                  | 60         | 5.21      | 92.49     | >360                      |
| 3   | 27-(15.37)                  | 85         | 5.14      | 91.25     | >360                      |
| 4   | 36-(11.27)                  | 95         | 5.05      | 89.65     | >360                      |
| 5   | 45-(8.90)                   | 120        | 4.89      | 86.81     | >360                      |

Reaction parameters: $N$-(1-adamantyl) formamide (6) = 0.03 mol; Molar ratio of (hydrochloric acid: $N$-(1-adamantyl) formamide (6)) = (3: 1); Reaction temperature = 100$\degree$C (reflux). The concentration of HCl were 36%, 19.46%, 15.37%, 11.27%, and 8.90%)

**Conclusion:** The optimal concentration of HCl was 19.46% and reaction time is 60 min, got the highest yield of amantadine hydrochloride (1) (92.49%) (see No. 2 in Table S4).

3.1.2. Effect of molar ratio of HCl: compound 6 on the yield of amantadine.HCl
Experiment: The reaction synthesis of 1 was performed the same operation as investigation on effect of concentration of HCl on the yield of amantadine. HCl (1) above, but HCl concentration was 19.46% and in different the molar ratio between HCl and N-(1-adamantyl) formamide (6) 2:1, 2.5:1, 3.0:1, 3.5:1 and 4.0: 1. Result see Table S5.

Table S5. Effect of molar ration of HCl: N(1-adamantyl) formamide on the yield of amantadine.HCl

| No. | Molar ratio of HCl: N(1-adamantyl) formamide | Weight(g) | Melting point (°C) | Yield (%) |
|-----|---------------------------------------------|-----------|--------------------|----------|
| 1   | 2.0 : 1                                     | 5.02      | > 360°C           | 89.13    |
| 2   | 2.5 : 1                                     | 5.17      | > 360°C           | 91.78    |
| 3   | 3.0 : 1                                     | 5.23      | > 360°C           | 92.84    |
| 4   | 3.5 : 1                                     | 5.25      | > 360°C           | 93.21    |
| 5   | 4.0:1                                       | 5.24      | > 360°C           | 93.02    |

Reaction parameters:; HCl solution = Aqueous solution HCl 19.46%, ; Reaction temperature = 100°C (reflux); Reaction time = 60 minutes; Molar ratio between HCl and N-(1-adamantyl) formamide (6) 2:1, 2.5:1, 3.0:1, 3.5:1 and 4.0: 1

Conclusion: The result found that molar ratio of (HCl: N-(1-adamantyl) formamide (6)) = (3.5 :1). got the highest yield of Amantadine.HCl (1) (93.21%) (see No.4 in Table S5).

⇒ Results. N-(1-adamantyl)formamide (6); The combination of reaction parameters that gives the highest yield of amantadine. HCl: Temperature = 100°C; Time = 60 minutes; Concentration of Solution HCl= 19.19.46%; Molar ratio of (HCl: N-(1-adamantyl) formamide = (3.5:1).

3.2. Experimental section

Synthesis of Amantadine hydrochloride (1):

A mixture of, solution of hydrochloride 19.46% (180 mL 1.05 mole) and N-formyl-1-amino-adamantane(6) (53.79 g, 0.3 mole) was stirred at room temperature for 10 min, and then it was heated to reflux for until the compound 6 was disappeared (1 h, which was indicated by Thin
layer chromatography (solvents: CHCl₃: methanol: 25%NH₃ aq. = 6:1:1; visualization: Dragendorff reagent). After reaction finish, the reaction mixture was extracted with dichloromethane (100mL). The separated aqueous layer was evaporated under vacuum to give a white solid, to which was added acetone (35 mL), stirred at 50°C for 1 h and then at 0-5°C for additional 1 h, the white solid was precipitated, filtered and washed with cooled acetone and dried under vacuum to give 246.67g amantadine hydrochlorid (I), (93.17%); mp 360°C; Rf = 0.5 (CHCl₃: methanol: 25%NH₃ aq. = 6:1:1), did not melt up to 360°C (from ethanol as described previously);

**MS**,

m/z: 152.22 [M+1]+; 135.20 [M-NH₂]+; **¹H-NMR** (500 MHz, CDCl₃), δ (ppm): 8.31 (br, s, 3H, NH₂.HCl), 2.17 (s, 3H, C₃-H, C₅-H, C₇-H); 2.06 (s, 6H, C₄-H₂,C₆-H₂ và C₉-H₂); 1.70 (s, 6H, C₂-H₂, C₈-H₂ và C₁₀-H₂); **¹³C-NMR** (125 MHz, CDCl₃), δ (ppm): 52.9 (C₁); 40.6 (C₃+C₅ và C₇); 35.4 (C₂+C₈ và C₁₀); 28.9 (C₄+C₆ và C₉) (PL 20).

**MS spectrum of amantadine hydrochloride (1)**

![MS spectrum of amantadine hydrochloride (1)](image)

**Figure S15.** Molecular structure of amantadine hydrochloride (1)

![MS spectrum of amantadine hydrochloride (1)](image)

**Figure S16.** MS spectrum of amantadine hydrochloride (1)
MS: $m/z = 152.22\ [M+1]^+,$ 135.20 [M-NH$_2$-1]$^+.$

$^1$H-NMR spectrum of amantadine hydrochloride (1) in CDCl$_3$

$^1$H-NMR (CDCl$_3$, 500 MHz): $\delta$ 8.31 (br, s, 3H), 2.17 (s, 3H), 2.06 (s, 6H); 1.70 (s, 6H).

$^{13}$C-NMR spectrum of amantadine hydrochloride (1) in CDCl$_3$

Figure S17. $^1$H-NMR spectrum of amantadine hydrochloride (1) in CDCl$_3$
4. One-pot procedure for synthesis of amantadine hydrochloride

Procedure: Synthesis of \textit{N-}(1-Adamantyl)formamide (6)

At 75°C 1-bromo-adamantane (330 g; 1.5 mol) was added to formamide (610 mL; 13.5 mol) with stirring. To this mixture, H\textsubscript{2}SO\textsubscript{4} 96% (450 mL, 8.25 mol) was added dropwise, then it was heated to 85°C and maintained for until finished reaction (the compound 3 was disappeared) (5.5 hours, which was indicated by Thin layer chromatography with solvents: methanol : CHCl\textsubscript{3} : aq. NH\textsubscript{3} 25% = 1: 6: 1 (v/v); visualization: iodine). After reaction mixture cooled to room temperature and slowly added to ice-cold water (1750 mL) and stirred at 0-5°C for 1 h. The white solid was precipitated, filtered and washed with cool water, then filtered by suction until achieve dryness. The this obtained crude product 6 was added to solution of hydrochloride 19.46% (990 mL, 5.25 mole) and stirred at room temperture for 10 min, and then it was heated to reflux for until the compound 6 was disappeared (1 h, which was indicated by Thin layer chromatography (solvents: CHCl\textsubscript{3} : methanol: 25%NH\textsubscript{3} aq. = 6:1:1; visualization: Dragendorff reagent). After reaction finish, the reaction mixture was extracted with dichloromethane (450mL). The separated aqueous layer was evaporated under vacuum to give a white solid, to which was added acetone (165 mL), stirred at 50°C for 1 h and then at 0-5°C for additional 1h, the white solid was precipitated, filtered and washed with cooled acetone and dried under vacuum to give 247.67 g amantadine hydrochlorid (I), (87.94%), purity (GC): 99.221%, t\textsubscript{R10.10} min; R\textsubscript{f}=0.5 (CHCl\textsubscript{3} : methanol: 25%NH\textsubscript{3} aq. = 6:1:1), did not melted up to 360°C.

\textbf{GC data of the synthesized amantadine hydrochloride (1)}

GC condition: FID Detector, temperature of 250°C

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

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

Injection volume: 1 µl.
Figure S19. Gas Chromatography data of the synthesized amantadine hydrochloride (1)