Synthetic Routes to Aminotriamantanes, Topological Analogues of the Neuroprotector Memantine®

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Abstract: The amino derivatives of diamantane and triamantane, representing close topological analogues of the neuroprotective drug Memantine®, were prepared via amination of the respective carboxylic acids or alcohols.

Key words: amines, diols, drugs, hydrocarbons, medicinal chemistry

Adamantane amino derivatives play an outstanding role in the treatment of influenza and a wide spectrum of diseases of the central nervous system. However, many recent studies have shown an increase in resistance of common viruses toward adamantane-containing drugs such as amantadine and rimantadine.[2] These findings have prompted a number of studies on the preparation of the amino derivatives of other cage compounds.[3,4]

Fortunately, Memantine®[1-amino-3,5-dimethyladamantane; **1**] is still the most effective drug for combating Alzheimer's disease and it was recently considered to be the 'new hope' in the development of *N*-methyl-D-aspartate-receptor antagonists.[5] Memantine® also shows pronounced antiparkinsonian activity. The key mechanistic feature in the mechanism of action involves blocking of the NMDA-receptor channel, where **1** displays a moderate binding affinity due to its size and hydrophobicity.[5] Further development of this class of neuroprotectors should build on these two key features of the Memantine® molecule.

A number of higher adamantane analogues, i.e., diamondoids (nanodiamonds), were recently isolated from crude oil,[6] and triamantane, [121]-, [1(2)3]-, [123]tetramantanes, [1(2,3)4]pentamantane and [12312]hexamantane (cyclohexamantane), are now available in preparative quantities.[7,8] Recently, we developed a variety of methods for the selective preparation of functional derivatives of these hydrocarbons involving selective C–H substitutions as well as functional group exchanges.[1,9–15] The diamondoid derivatives have already shown some remarkable properties such as negative electron affinity and highly effective self-assembly.[16,17]

Herein, we report the preparation of hitherto unknown amino triamantanes that are geometrically and electronically related to Memantine® allowing variations in the topological and spatial characteristics of these potential neurodrugs. The computed geometries of **1**, as well as 2-amino- (**2**), 3-amino- (**3**), 4-amino-(**4**) and 9-amino triamantane (**5**), show that all these molecules have a common maximum dimension of around 5.6 Å (Figure 1). For comparison, we also prepared 1- and 4-amino diamantane (**6** and **7**, *vide infra*) as higher homologues of amantadine (1-amino adamantane), as well as diamantane diamines (**8** and **9**).[18,19,23]

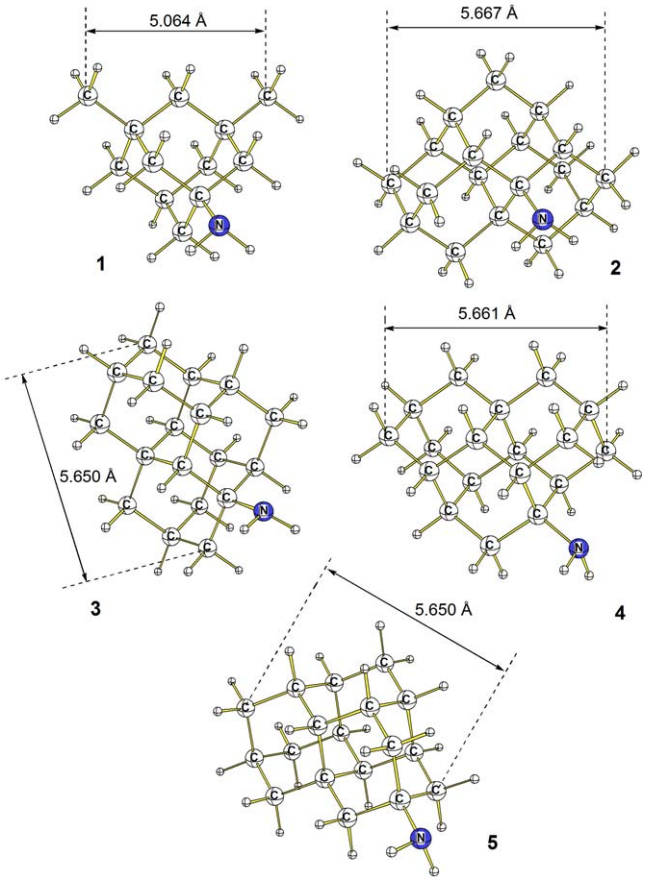

Figure 1 The key spatial dimensions of Memantine® (**1**), 2-amino- (**2**), 3-amino- (**3**), 4-amino- (**4**), and 9-amino triamantane (**5**) computed at the B3LYP/6-31+G(d) level of theory

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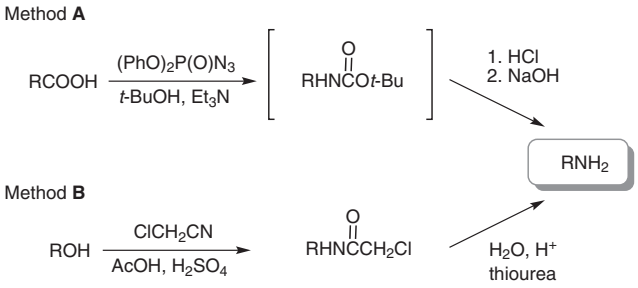
For the preparation of the amino derivatives we utilized two alternative procedures shown in Scheme 1: (a) the reaction of the respective carboxylic acids with diphenylphosphoryl azide[20] followed by hydrolysis (method A) and (b) acid-catalyzed exchange of the hydroxyl group of the respective diamondoid alcohol with chloroacetonitrile followed by cleavage of the chloroacetamide thus formed[21] (method B).



Scheme 1 The two alternative approaches used for the preparation of diamondoid amino derivatives

As starting compounds for method A we used the diamondoid carboxylic acids prepared as described previously through the carboxylation of the respective diamondoid derivatives.[22] Method B, applied to the readily available alcohols,[12] gave mono- (**6** and **7**) as well as diamines (**8** and **9**)[23,18] in high preparative yields with complete conservation of the substitution pattern (Figure 2). The X-ray crystal structures of intermediate chloroacetamides **14** and **16** are shown in Figure 3. These routes offer a convenient alternative to the existing synthetic approach to amino diamantanes based on the reaction of the respective bromo-derivatives with nitrogen trichloride[24] or through the Ritter reaction, which gives hydrolytically stable acetamides.[25] It is also safer and operationally superior to the method of Davis and Nissan (starting from the bromides utilizing a large excess of $TMSN_3$ and $SnCl_2$) because it does not involve potentially hazardous (and expensive) chemicals.[26]

As we described previously,[12] all possible *tertiary* hydroxy derivatives form through the nitroxylation/hydrolysis of triamantane. Method B gave the 2-, 3-, 4-, and 9-amino triamantanes (**2**–**5**) via the cleavage of the respective chloroacetamides (**11**–**13**) in high preparative yields (Figure 2). The only exception is the most sterically hindered acetamide **10**, which gave amine **2** in very low yield.

In summary, we have obtained a number of diamondoid amines in good yields from their respective acids and alcohols. Testing of the neurophysiological activities of these structural analogues of Memantine® is currently underway.

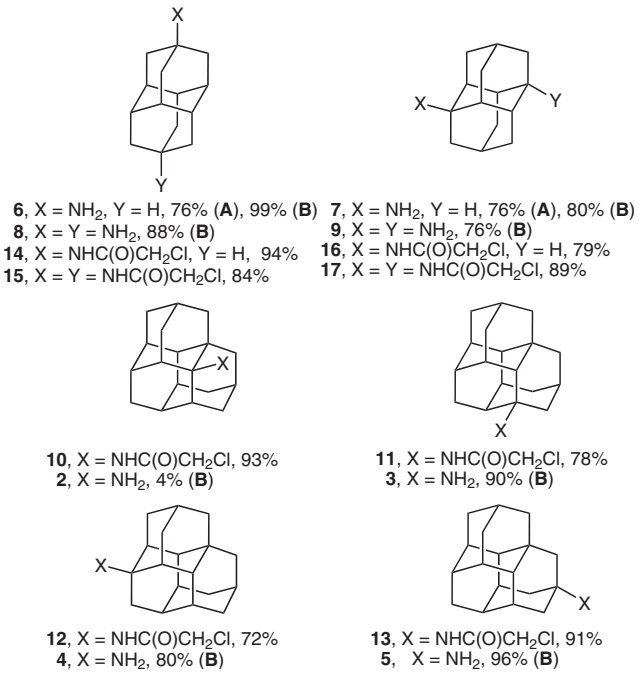


Figure 2 The structures and preparative yields of compounds **2**–**17**

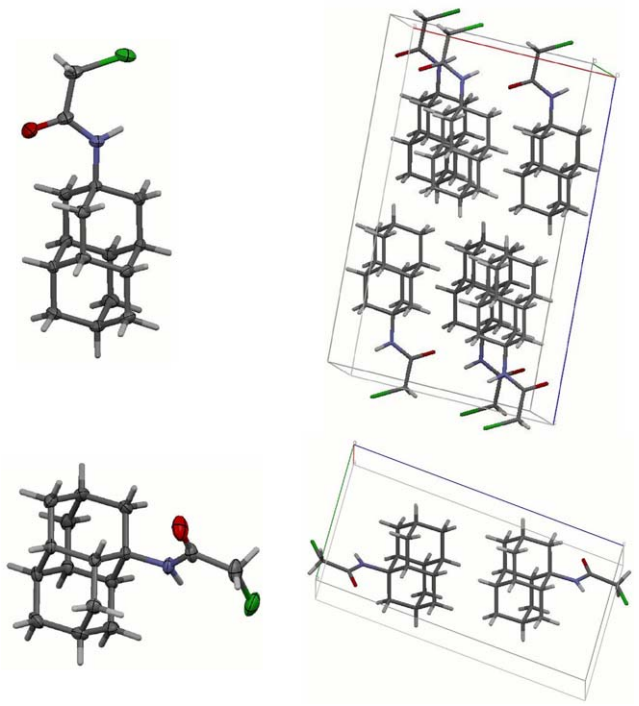


Figure 3 The X-ray crystal structures and crystal packing of chloroacetamides **14** and **16**[27]

NMR: Bruker Avance II spectrometers operating at 400.130 and 200.13 MHz (^{1}H NMR) and 100.613 and 50.32 MHz (^{13}C NMR) and an Avance II spectrometer at 600.130 MHz (^{1}H NMR) and 150.903 MHz (^{13}C NMR); internal standard = Me_4Si. GC–MS: HP5890 GC instrument with an H5971A mass-selective detector; HP GC–MS capillary column 50 m × 0.2 mm, Ultra 1, silicone, 80–205 °C. All compounds showed adequate IR and DEPT ^{13}C NMR spectra.

Method A; General Procedure

A mixture of the chosen diamondoid carboxylic acid (1 mmol), Et_3N (0.14 mL, 1 mmol) and diphenylphosphoryl azide (275 mg, 1 mmol; Acros) and *t*-BuOH (2 mL) was stirred for 12 h, quenched with aq $NaHCO_3$, extracted with $CHCl_3$, and dried over Na_2SO_4.

The residue after evaporation was dissolved in MeOH and stored in a flow of anhydrous HCl. Evaporation of MeOH, washing of the resulting hydrochloride with Et_2O, neutralization with 10% NaOH, extraction with Et_2O, and drying over Na_2SO_4, gave the pure amines **6** and **7**, whose spectral data were identical to those of standard samples.[22,24]

Method B; General Procedure

A solution of the respective diamondoid alcohol (1 mmol) in a mixture of AcOH (1.7 mL, 30 mmol), $ClCH_2CN$ (0.4 mL, 6.3 mmol) and concd H_2SO_4 (0.5 mL, 9.4 mmol) was stirred at r.t. for 20 h. The reaction mixture was poured onto ice and extracted with $CHCl_3$. Evaporation of the extracts gave the chloroacetamide, which was dissolved in a mixture of EtOH (0.8 mL, 13.7 mmol), thiourea (20 mg, 0.26 mmol) and AcOH (0.3 mL, 5.2 mmol) and heated at 95 °C for 20 h. The mixture was neutralized with 10% NaOH, extracted with $CHCl_3$, and dried over Na_2SO_4. Evaporation gave amines **2**–**5**, which were purified through their hydrochlorides as described in Method A.

2-Aminotriamantane (2)

Colorless solid; mp 236–239 °C.

^{1}H NMR (400 MHz, CD_3OD): δ = 2.15–2.10 (m, 2 H), 1.90–1.87 (m, 2 H), 1.86–1.81 (m, 2 H), 1.81–1.71 (m, 7 H), 1.70–1.64 (m, 4 H), 1.56–1.51 (m, 4 H), 1.08–1.04 (m, 2 H).

^{13}C NMR (100 MHz, CD_3OD): δ = 56.0 (C), 50.5 (CH), 44.2 (CH), 40.1 (CH_2), 39.9 (CH), 39.8 (CH), 39.6 (CH_2), 39.3 (CH_2), 38.2 (C), 33.5 (CH_2), 28.9 (CH).

MS (EI): *m*/*z* (%) = 255, 239, 238 (100), 197, 167, 129, 128.

HRMS: *m*/*z* calcd for $C_{18}H_{25}N$: 255.1987; found: 255.1968.

3-Aminotriamantane (3)

Colorless solid; mp 206–210 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.06–1.93 (m, 3 H), 1.85–1.78 (m, 1 H), 1.77–1.70 (m, 2 H), 1.68–1.50 (m, 9 H), 1.47–1.30 (m, 6 H), 1.28–1.15 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 52.8 (CH), 51.1 (C), 46.7 (CH_2), 46.1 (CH), 45.1 (CH_2), 44.7 (CH_2), 41.5 (CH), 39.1 (CH), 37.9 (CH_2), 37.7 (CH_2), 37.6 (CH_2), 37.5 (CH), 34.9 (C), 34.8 (CH), 33.2 (CH_2), 32.1 (CH), 29.7 (CH), 27.6 (CH).

MS (EI): *m*/*z* (%) = 255, 239, 238 (100), 167, 128.

HRMS: *m*/*z* calcd for $C_{18}H_{25}N$: 255.1987; found: 255.1992.

4-Aminotriamantane (4)

Colorless solid; mp 207–209 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.09–2.01 (m, 2 H), 1.85–1.75 (m, 3 H), 1.72–1.65 (m, 6 H), 1.60–1.55 (m, 2 H), 1.51–1.37 (m, 8 H), 1.31–1.26 (m, 2 H), 1.25–1.21 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 49.2 (C), 48.4 (CH), 47.1 (CH_2), 45.5 (CH_2), 44.8 (CH_2), 44.1 (CH), 39.3 (CH), 37.9 (CH), 37.5 (CH_2), 32.9 (C), 32.7 (CH_2), 27.6 (CH), 27.3 (CH).

MS (EI): *m*/*z* (%) = 255, 238 (100), 181, 167, 142, 130, 129, 91.

HRMS: *m*/*z* calcd for $C_{18}H_{25}N$: 255.1987; found: 55.1933.

9-Aminotriamantane (5)

Colorless solid; mp 193–194 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.83–1.79 (m, 1 H), 1.78–1.74 (m, 2 H), 1.73–1.59 (m, 9 H), 1.58–1.43 (m, 7 H), 1.36–1.31 (m, 2 H), 1.29–1.25 (m, 2 H), 1.14–1.09 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 53.7 (CH_2), 47.3 (C), 46.3 (CH_2), 44.7 (CH), 44.0 (CH_2), 38.6 (CH), 37.8 (CH_2), 37.7 (CH_2), 37.5 (CH), 34.9 (CH), 34.8 (C), 34.0 (CH), 27.3 (CH).

MS (EI): *m*/*z* (%) = 255 (100), 240, 239, 197, 183, 144, 106, 91.

HRMS: *m*/*z* calcd for $C_{18}H_{25}N$: 255.1987; found: 255.1989.

***N*-Chloroacetyltriamantane-2-amine (10)**

Colorless solid; mp 164–166 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.67 (br s, 1 H), 4.00 (s, 2 H), 2.67–2.61 (m, 2 H), 1.91–1.54 (m, 17 H), 1.49–1.42 (m, 2 H), 1.15–1.08 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 163.9 (C=O), 60.9 (C–N), 49.2 (CH), 43.4 (CH_2), 39.5 (CH_2), 39.7 (CH_2), 38.3 (CH_2), 38.1 (CH), 37.6 (CH), 36.7 (CH), 35.6 (C), 32.7 (CH_2), 27.0 (CH).

MS (EI): *m*/*z* (%) = 331, 239, 238 (100), 197, 167, 129, 128, 91.

HRMS: *m*/*z* calcd for $C_{20}H_{26}ClNO$: 331.1703; found: 331.1668.

***N*-Chloroacetyltriamantane-3-amine (11)**

Colorless solid; mp 146–147 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.31 (br s, 1 H), 3.94 (s, 2 H), 2.16–2.11 (m, 1 H), 2.08–2.04 (m, 2 H), 2.03–1.97 (m, 1 H), 1.94–1.80 (m, 5 H), 1.77–1.56 (m, 8 H), 1.47–1.40 (m, 2 H), 1.38–1.28 (m, 3 H), 1.25–1.19 (m, 1 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3 (C=O), 57. 2 (C–N), 47.9 (CH), 46.1 (CH), 44.6 (CH_2), 44.4 (CH_2), 43.1 (CH_2), 41.1 (CH_2), 38.8 (CH), 37.6 (CH_2), 37.5 (CH_2), 37.4 (CH), 37.0 (CH_2), 36.8 (CH), 34.9 (C), 34.2 (CH), 33.2 (CH_2), 32.4 (CH), 29.1 (CH), 27.4 (CH).

MS (EI): *m*/*z* (%) = 331, 295, 282, 239, 238 (100), 167, 129, 128, 91.

HRMS: *m*/*z* calcd for $C_{20}H_{26}ClNO$: 331.1703; found: 331.1697.

***N*-Chloroacetyltriamantane-4-amine (12)**

Colorless solid; mp 147–149 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.36 (br s, 1 H), 3.96 (s, 2 H), 2.19–2.13 (m, 2 H), 2.03–1.98 (m, 2 H), 1.96–1.88 (m, 2 H), 1.86–1.79 (m, 3 H), 1.78–1.74 (m, 2 H), 1.74–1.60 (m, 6 H), 1.54–1.45 (m, 2 H), 1.33–1.25 (m, 4 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.4 (C=O), 47.7 (CH), 45.2 (CH_2), 44.6 (CH_2), 43.1 (CH_2), 41.4 (CH_2), 39.4 (CH), 37.5 (CH), 37.3 (C), 37.2 (CH), 37.0 (CH_2), 33.2 (C), 32.8 (CH_2), 27.4 (CH), 26.8 (CH).

MS (EI): *m*/*z* (%) = 331, 282, 239, 238 (100), 167, 142, 129, 85, 84, 83.

HRMS: *m*/*z* calcd for $C_{20}H_{26}ClNO$: 331.1703; found: 331.1720.

***N*-Chloroacetyltriamantane-9-amine (13)**

Colorless solid; mp 128–131 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.20 (br s, 1 H), 3.90 (s, 2 H), 2.00–1.91 (m, 4 H), 1.86–1.79 (m, 3 H), 1.74–1.56 (m, 12 H), 1.48–1.43 (m, 2 H), 1.33–1.29 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.7 (C), 52.4 (C), 48.4 (CH_2), 45.6 (CH), 44.7 (CH_2), 42.9 (CH_2), 41.6 (CH_2), 39.1 (CH), 37.9 (CH), 37.6 (CH_2), 37.4 (CH_2), 34.8 (CH), 34.7 (C), 34.0 (CH), 37.1 (CH).

MS (EI): *m*/*z* (%) = 331, 296, 282, 256, 239, 238 (100), 167, 142, 91.

HRMS: *m*/*z* calcd for $C_{20}H_{26}ClNO$: 331.1703; found: 331.1684.

***N*-Chloroacetyldiamantane-4-amine (14)**

Colorless solid; mp 166 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.24 (br s, 1 H), 3.95 (s, 2 H), 2.04–1.99 (m, 6 H), 1.93 (br s, 3 H), 1.85–1.74 (m, 10 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.8 (C=O), 51.3 (C), 43.0 (CH_2), 41.8 (CH_2), 38.5 (CH), 37.3 (CH_2), 36.4 (CH), 25.5 (CH).

HRMS: *m*/*z* calcd for $C_{16}H_{22}ClNO$: 279.1390; found: 279.1391.

Anal. Calcd for $C_{16}H_{22}ClNO$: C, 68.68; H, 7.93; N, 5.01. Found: C, 68.48; H, 7.85; N, 4.79.

Bis(*N*-chloroacetyl)diamantane-4,9-diamine (15)
Colorless solid; mp 292–293 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.69 (s, 2 H), 3.95 (s, 4 H), 1.91 (s, 12 H), 1.82 (s, 6 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 165.0 (C=O), 49.7 (C), 43.4 (CH_2), 40.3 (CH_2), 36.9 (CH).

HRMS: *m*/*z* calcd for $C_{18}H_{24}Cl_2N_2O_2$: 370.1215; found: 370.1190.

***N*-Chloroacetyldiamantane-1-amine (16)**
Colorless solid; mp 125 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.40 (br s, 1 H), 3.99 (s, 2 H), 2.25 (s, 2 H), 2.10–1.91 (m, 7 H), 1.83–1.62 (m, 8 H), 1.59–1.50 (m, 2 H).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 164.3 (C=O), 56.6 (C), 43.1 (CH_2), 41.2 (CH_2), 39.0 (CH), 38.7 (CH), 38.0 (CH_2), 37.2 (CH_2), 36.9 (CH), 32.7 (CH_2), 28.5 (CH), 24.9 (CH).

HRMS: *m*/*z* calcd for $C_{16}H_{22}ClNO$: 279.1390; found: 279.1391.

Anal. Calcd for $C_{16}H_{22}ClNO$: C, 68.68; H, 7.93; N, 5.01. Found: C, 68.62; H, 7.96; N, 4.97.

Bis(*N*-chloroacetyl)diamantane-1,6-diamine (17)
Colorless solid; mp 313 °C (dec.).

^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.60 (s, 2 H), 4.01 (s, 4 H), 2.36 (br s, 4 H), 1.99–1.81 (m, 10 H), 1.40–1.31 (m, 4 H).

^{13}C NMR (100 MHz, DMSO-d_6): δ = 164.9 (C=O), 54.8 (C), 43.5 (CH_2), 41.0 (CH_2), 39.0 (CH), 31.4 (CH_2), 27.1 (CH).

HRMS: *m*/*z* calcd for $C_{18}H_{24}Cl_2N_2O_2$: 370.1215; found: 370.1185.

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(27) The structures have been deposited in the Cambridge Crystallographic Data Centre and can be retrieved using the following numbers: CCDC 701883 (**14**) and 701884 (**16**).