Synthesis of Unsymmetrically Substituted 4,6,10-Trihydroxy-1,4,6,10-tetraazaadamantanes via Intramolecular Cyclization of Tris(β-oximinoalkyl)amines

Artem N. Semakin, Alexey Yu. Sukhorukov,* Yulia V. Nelyubina, Sema L. Ioffe, Vladimir A. Tartakovsky

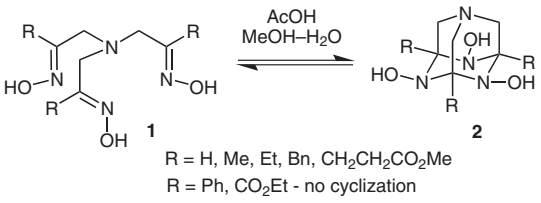
N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, Leninsky prosp. 47, 119991 Moscow, Russian Federation
Fax +7(499)1355328; E-mail: sukhorukov@server.ioc.ac.ru

Received 30 December 2011; revised 8 February 2012

Abstract: The cyclotrimerization of oximino groups in unsymmetrically substituted tris(β-oximinoalkyl)amines was studied. A general approach to the synthesis of 4,6,10-trihydroxy-1,4,6,10-tetraazaadamantanes containing different substituents at bridgehead carbon atoms was developed from available aliphatic nitro compounds.

Key words: cyclization, heterocycles, amines, oximes, adamantanes

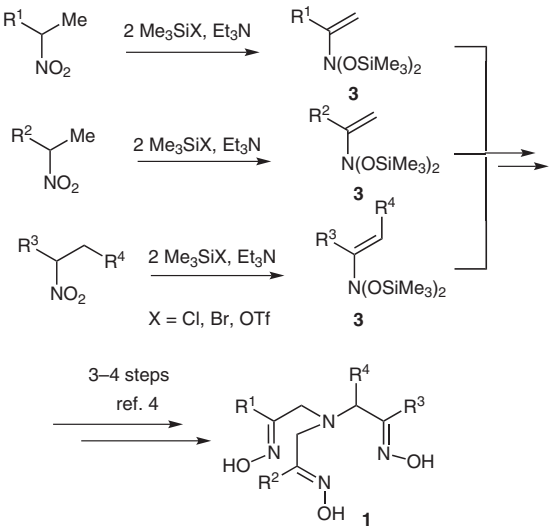
1,4,6,10-Tetraazaadamantane is a structural isomer of the well-known 1,3,5,7-tetraazaadamantane (urotropin), which is widely applied in various fields of science and industry.[1] Although 1,4,6,10-tetraazaadamantane itself has not yet been obtained, the synthesis of its derivatives **2** by an unusual intramolecular cyclization of tris(β-oximinoalkyl)amines **1** was recently reported (Scheme 1).[2]



Scheme 1 Cyclization of symmetrical tris-oximes **1**

However, according to this procedure, only symmetrically substituted 1,4,6,10-tetraazaadamantanes **2** possessing all equal substituents R in bridgehead positions could be obtained, because only symmetrically substituted tris-oximes **1** were available until recently. Furthermore, the reversible cyclization of **1** into **2** is sensitive to the nature of the substituent R. Thus, whereas the cyclization of tris-oximes **1** with R = H or alkyl to 1,4,6,10-tetraazaadamantanes **2** proceeds smoothly, formation of the corresponding adamantanes from tris-oximes **1** with R = Ph or CO_2Et was not observed.[2] Clearly, for a more detailed study of the effects of the substituent on the equilibrium between **1** and **2** it would be beneficial to explore the cyclization of 'mixed' tris-oximes **1** containing substituents that favor or disfavor the transformation into tetraazaadamantanes **2**. Furthermore, the successful realization of the cyclization of unsymmetrically substituted tris-oximes **1** will provide access to a large library of 1,4,6,10-tetraazaadamantanes so that their properties and, in particular, their biological activity, can be explored.[3] Recently, unsymmetrically substituted tris-oximes **1** became available using a strategy that involved the silylation of aliphatic nitro compounds (Scheme 2).[4] According to this approach, tris-oximes **1** containing two or three different oximinoalkyl groups are assembled in several steps from two or three different *N*,*N*-bis(siloxy)enamines **3**. The latter enamines are obtained by double silylation of the corresponding nitro compounds.[5]

In the present work, the cyclotrimerization of oximino groups in unsymmetrically substituted tris-oximes **1** to give 1,4,6,10-tetraazaadamantanes **2** was studied.

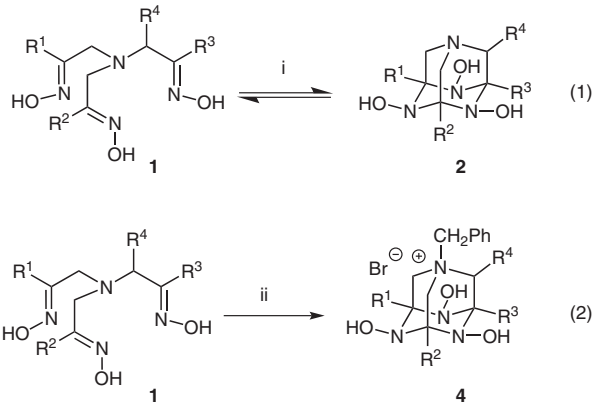


Scheme 2 Synthesis of unsymmetrically substituted tris-oximes **1**

A series of 'unsymmetrical' tris-oximes **1a–l** obtained by a known method[4] were chosen as model objects to study the cyclotrimerization reaction (Scheme 3 and Table 1). Tris-oximes **1a** and **1b** partially underwent cyclization to the corresponding tetraazaadamantanes **2a** and **2b** at room temperature.[4] Other tris-oximes **1c–l** were stable and did not cyclize to tetraazaadamantanes **2** spontaneously. However, in the presence of acetic acid (see Scheme 3, equation 1 and Table 1, procedure 1) most of the tris-oximes **1** produced the corresponding tetraazaadamantanes **2**, which were isolated in good yields in some cases (products **2a–e**). For tris-oxime **1f**, the formation of tetraazaadamantane **2f** was detected in trace amounts by ^1H

SYNTHESIS 2012, 44, 1095–1101
Advanced online publication: 05.03.2012
DOI: 10.1055/s-0031-1289735; Art ID: T119911SS

NMR analysis (Table 1, entry 6). No cyclization of tris-oximes **1h–j** was observed under these conditions (Table 1, entries 8–10).



Scheme 3 *Reagents and conditions*: (i) AcOH (3 equiv), MeOH, r.t. (procedure 1); (ii) AcOH (3 equiv), BnBr (1.5 equiv), MeOH, r.t. (procedure 2).

Previously, we demonstrated that quaternization of the bridgehead nitrogen atom in tetraazaadamantanes **2** results in a shift in the equilibrium between **1** and **2** towards the adamantane structure.[2] Therefore, the cyclization of tris-oximes **1a–l** was studied in the presence of 1.5 equivalents of benzyl bromide, which reacts with tetraazaadamantanes **2** to give the corresponding quaternary salts **4** (see Scheme 3, equation 2 and Table 1, procedure 2). The majority of tris-oximes **1** afforded the corresponding quaternary salts of tetraazaadamantanes **4** in high yields according to this protocol. However, under these conditions, tris-oximes **1h–j** produced mixtures of unidentified products in which quaternary salts of 1,4,6,10-tetraazaadamantanes **4** were not detected.

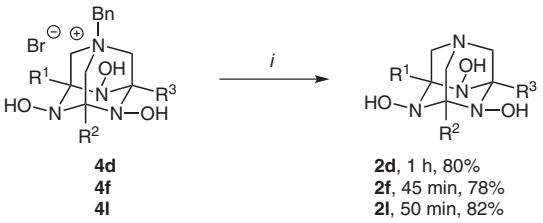
Thus, the transformation of tris-oximes **1** into quaternary salts **4** proceeds more efficiently and with higher yields than the cyclization to free tetraazaadamantane bases **2**. Interestingly, tetraazaadamantanes **2** decompose into the corresponding tris-oximes **1** quite slowly at room temperature, demonstrating their kinetic stability. Based on this observation, we developed a two-step procedure for the preparation of tetraazaadamantanes **2** from tris-oximes **1** that consists of the initial preparation of quaternary salts **4** by using procedure 2, followed by catalytic debenzylation with hydrogen over Pd/C[6] (procedure 3, Scheme 4). According to this route, product **2f**, which is practically unavailable by using procedure 1, could be obtained in good yield (cf. Scheme 4 and Table 1, entry 6).

As seen from the data presented in Table 1, the cyclization of tris-oximes **1** to adamantanes **2** is sensitive to steric effects of substituents R^1–R^3 in the oximinoalkyl fragments.

Table 1 Scope of the Cyclization

Entry	**1**	R^1	R^2	R^3	R^4	Procedure 1		Procedure 2	
						Time (%)[a]	Yield **2** (%)[b]	Time (h)	Yield **4** (%)[b]
1	**1a**	Me	Me	H	H	10	89	3	75
2	**1b**	Me	Me	H	Me	12	85	4	92
3	**1c**	Me	Me	$(CH_2)_2CO_2Me$	H	24	78	24	86
4	**1d**	Me	Me	Bn	H	48	68[c]	20	87
5	**1e**	Me	Me	CO_2Et	H	72	60[d]	25	90
6	**1f**	Me	Me	Ph	H	240	<5[e]	30	83
7	**1g**	Bn	Bn	Me	H	96	31[f]	48	88
8	**1h**	CO_2Et	CO_2Et	Me	H	240	n.r.	96	–[g]
9	**1i**	Ph	Ph	Me	H	240	n.r.	96	–[g]
10	**1j**	Ph	Ph	Bn	H	240	n.r.	96	–[g]
11	**1k**	$(CH_2)_2CO_2Me$	$(CH_2)_2CO_2Me$	Bn	H	96	24[h]	72	75
12	**1l**	Me	$(CH_2)_2CO_2Me$	Bn	H	96	32[i]	48	72

[a] The time corresponds to either the point of full consumption of tris-oxime **1** or the time after which its residual concentration remained constant (TLC analysis).
[b] Isolated yield.
[c] Conversion of **1d**: 78%.
[d] Conversion of **1e**: 75%, see ref. 2.
[e] Determined by ^{1}H NMR analysis.
[f] Conversion of **1g**: 55%.
[g] A complex mixture of unidentified products.
[h] Conversion of **1k**: 32%.
[i] Conversion of **1l**: 40%.

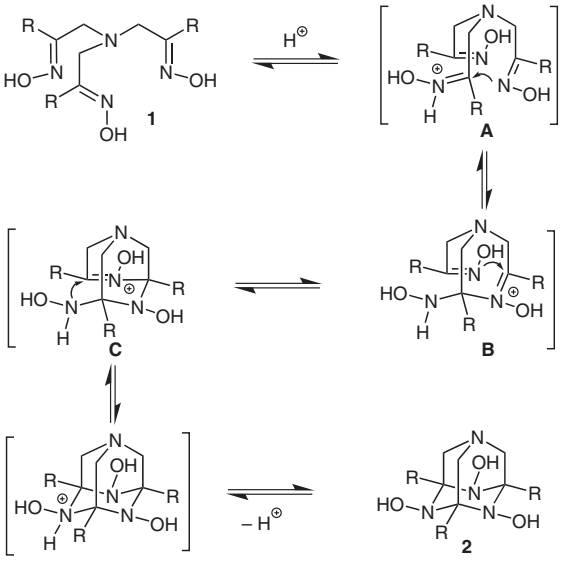


Scheme 4 *Reagents and conditions*: (i) H_2 (1 atm), Pd/C, K_2CO_3, MeOH, r.t. (procedure 3).

The smaller these substituents are, the more efficiently the intramolecular cyclotrimerization proceeds. Thus, tris-oximes **1a** and **1b**, which possess one sterically unhindered aldoxime group, enter the cyclization reaction most easily. Tris-oximes **1c–e**, which contain two methyl groups and a more bulky substituent R^3 ($CH_2CH_2CO_2Me$, Bn, or CO_2Et), produced the corresponding tetraazaadamantanes **2c–e** in high yields in the presence of acetic acid. In the series of tris-oximes **1a–f**, containing different substituents R^3 (H, $CH_2CH_2CO_2Me$, Bn, CO_2Et, or Ph) and equal substituents R^1 and R^2 (methyl group), substrate **1f** with the bulkiest R^3 group (phenyl) produced the tetraazaadamantane in the lowest yield (cf. Table 1, entries 1–6).[7] The presence of two bulky substituents R^1 and R^2 (for example, benzyl groups) in tris-oximes **1** led to a significant decrease in the yield of tetraazaadamantanes **2** under the conditions of procedure 1 (cf. Table 1, entries 4 and 7). Tris-oximes **1i** and **1j**, bearing two phenyl groups, did not cyclize to the tetraazaadamantanes at all (Table 1, entries 9 and 10). We suppose that such an effect of substituent size in the oximino group on the cyclotrimerization reaction is associated with the thermodynamic stability of tetraazaadamantanes **2**. The more sterically hindered tetraazaadamantane **2** is, the less thermodynamically preferable it is compared to the corresponding tris-oxime **1** (see also Semakin et al.[2]).

In the presence of benzyl bromide (procedure 2), the nature of substituents mainly influences the time required for full conversion of tris-oximes **1**. However, when tris-oxime **1** contained at least two phenyl substituents R [see Table 1, entry 10 and Scheme 1 (R = Ph)], the corresponding tetraazaadamantane salts **4** were not formed even under these conditions.

Tris-oximes **1**, possessing two (see Table 1, entry 8) or three (see Scheme 1 and Semakin et al.[2]) CO_2Et groups did not cyclize to tetraazaadamantanes **2** using either procedure 1 or 2. This fact may be explained in terms of Brønsted acid catalysis of the oxime cyclotrimerization reaction between **1** and **2** (Scheme 5). Apparently, the major role of acetic acid is the protonation of the nitrogen atom in the oximino group, with reversible generation of cation **A**.[8] The latter reacts with a nucleophilic nitrogen atom of a neighboring oximino group (Scheme 5). Two subsequent cyclizations of intermediate cations **B** and **C** furnish the tetraazaadamantane cage. The carboxyethyl group, due to its electron-withdrawing character, does not favor the generation of cation **A** because it decreases the basicity of the nitrogen atom in the oxime group. Furthermore, carboxyethyl groups destabilize cations **B** and **C** (shifting the equilibrium to the starting oxime), as well as complicate the cyclization reactions of intermediates **A** and **B** by reducing the nucleophilicity of nitrogen atom of oxime group (Scheme 5).



Scheme 5 Proposed mechanism of cyclization of tris-oximes **1**

The structures of previously unknown tetraazaadamantanes **2** and **4** were confirmed by ^1H and ^{13}C NMR spectroscopy, high-resolution mass spectrometry and elemental analysis for quaternary salts **4**. In the ^1H and ^{13}C NMR spectra of tetraazaadamantanes **2** and **4**, a broadening of signals, which is characteristic for this class of compounds, was observed.[2,4] The structure of salt **4e** was established by X-ray diffraction analysis of its hydrate obtained by crystallization of **4e** from a solution in aqueous methanol (Figure 1).[9]

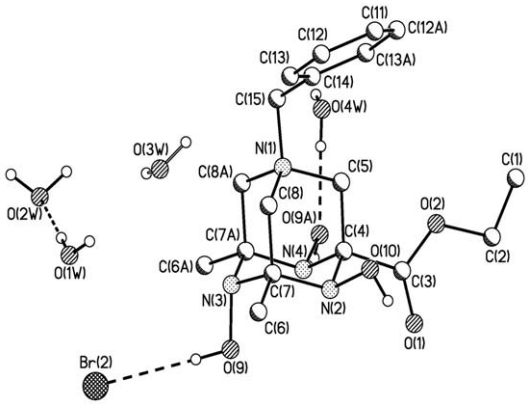


Figure 1 X-ray diffraction analysis of product 2(**4e**)·$7H_2O$[9]

Thus, tris-oximes **1**, containing two or three different oximinoalkyl fragments, were involved in the cyclotrimerization reaction leading to 1,4,6,10-tetraazaadamantanes **2**. Only tris-oximes **1** containing two (three) ester groups

or two (three) phenyl substituents connected to oximino groups (substituents R^1–R^3) do not undergo cyclization to tetraazaadamantanes **2**. Using this methodology, a wide spectra of 1,4,6,10-tetraazaadamantanes **2** and **4** containing different combinations of substituents at bridgehead positions can be obtained starting from a small set of available nitro compounds.

Analytical TLC was performed on Silufol silica gel plates; visualization was accomplished by using a solution of ninhydrin in EtOH. Flash chromatography was performed on a thin pad (20–30 mm) of silica gel 40–60 mm (Acros). MeOH was distilled over Mg. Hexane and EtOAc were distilled without drying agents. Acetic acid was twice recrystallized. The commercial reagents BnBr (Sigma–Aldrich) and palladium on activated charcoal (10% Pd/C; Sigma–Aldrich) were used as received. Tris-oximes **1a–l** were prepared according to literature procedures.[4] Catalytic hydrogenation reactions were carried out in a round-bottom flask equipped with a balloon and a magnetic stirrer.

^{1}H (300.13 MHz) and ^{13}C NMR (75.47 MHz; with complete proton decoupling) spectra were recorded at r.t. with a Bruker AM 300 NMR spectrometer; samples were dissolved in DMSO-d_6. Chemical shifts are reported in ppm relative to the residual solvent peak as internal standard.[11] Elemental analyses were performed by the Analytical Laboratory of the N.D. Zelinsky Institute of Organic Chemistry. High-resolution mass spectra were recorded with a MicroTOFF spectrometer. Melting points (uncorrected) were determined with a Kofler apparatus. Atom numberings in products **2** and **4** are shown, respectively, in Figure 2 and Figure 3. The numbers in parentheses in the characterization data refer to these atom numbers.

Adamantanes 2a–e, 2g, 2k, and 2l; General Procedure 1

AcOH (0.172 mL, 3.00 mmol) was added to a stirred solution of the corresponding tris-oxime **1** (1.00 mmol) in MeOH (5.0 mL). The reaction mixture was kept with periodic stirring at r.t. until either full conversion or constant residual concentration of tris-oxime **1** was observed (TLC analysis, time indicated in Table 1). The mixture was evaporated in vacuo at 5–20 °C. The residue was preadsorbed on silica gel and purified by flash chromatography (silica gel; EtOAc–hexane, 1:1 then EtOAc–MeOH, 3:1). Yields of target adamantanes **2** and conversions of tris-oximes **1** are presented in Table 1.

3,5-Dimethyl-1,4,6,10-tetraazatricyclo[3.3.1.1^{3,7}]decane-4,6,10-triol (2a)[4]

Yield: 192 mg (89%; procedure 1). All NMR data are in accordance with literature data for **2a**.[4]

2,5,7-Trimethyl-1,4,6,10-tetraazatricyclo[3.3.1.1^{3,7}]decane-4,6,10-triol (2b)[4]

Yield: 196 mg (85%; procedure 1). All NMR data are in accordance with literature data for **2b**.[4]

Methyl 3-{4,6,10-Trihydroxy-5,7-dimethyl-1,4,6,10-tetraazatricyclo[3.3.1.1^{3,7}]decan-3-yl}propanoate (2c)

Yield: 236 mg (78%; procedure 1); colorless solid; mp 75–86 °C; R_f = 0.35 (EtOAc–MeOH, 3:1).

^{1}H NMR: δ = 1.16 [s, 6 H, (7)], 1.93 [br s, 2 H, (4)], 2.38 [s, 2 H, (3)], 2.5–3.2 [br s, 6 H, (6 and 9)], 3.57 [s, 3 H, (1)], 7.6–8.2 [2 × br s, 3 H, (10 and 11)].

^{13}C NMR: δ = 21.1 (7), 27.6 and 28.4 (3 and 4), 51.5 (1), 49–63 (br, 6 and 9), 74.7 (8), 75.5 (5), 174.4 (2).

HRMS (+ve): *m/z* [M + Na]$^+$ calcd for $C_{12}H_{22}N_4O_5$: 325.1482; found: 325.1482.

3-Benzyl-5,7-dimethyl-1,4,6,10-tetraazatricyclo[3.3.1.1^{3,7}]decane-4,6,10-triol (2d)

Adamantane **2d** was obtained by procedure 1 from tris-oxime **1d** (306 mg, 1.0 mmol) and by procedure 3 from benzyl salt **4d** (119 mg, 0.25 mmol).

Yield: 68% (208 mg; procedure 1); 80% (61 mg; procedure 3); colorless oil; R_f = 0.12 (EtOAc).

^{1}H NMR: δ = 1.19 [s, 6 H, (8)], 2.3–3.2 [br, 6 H, (7 and 10)], 3.13 [s, 2 H, (5)], 7.1–7.3 [m, 5 H, (1, 2 and 3)], 7.8–8.2 [2 × br s, 3 H, (11 and 12)].

^{13}C NMR: δ = 21.3 (8), 38.5 (5), 51–60 (br, 7 and 10), 75.1 (9), 76.7 (6), 126.3, 128.0 and 131.2 (1, 2 and 3), 137.2 (4).

HRMS (+ve): *m/z* [M + H]$^+$ calcd for $C_{15}H_{23}N_4O_3$: 307.1765; found: 307.1769.

Ethyl 5,7-Dimethyl-1,4,6,10-tetraazatricyclo[3.3.1.1^{3,7}]decane-4,6,10-triol-3-carboxylate (2e)[2]

Adamantane **2e** was obtained by procedure 1 from tris-oxime **1e** (51 mg, 0.177 mmol).[2]

Yield: 60% (31 mg); white foam. All NMR data are in accordance with literature data for **2e**.[2]

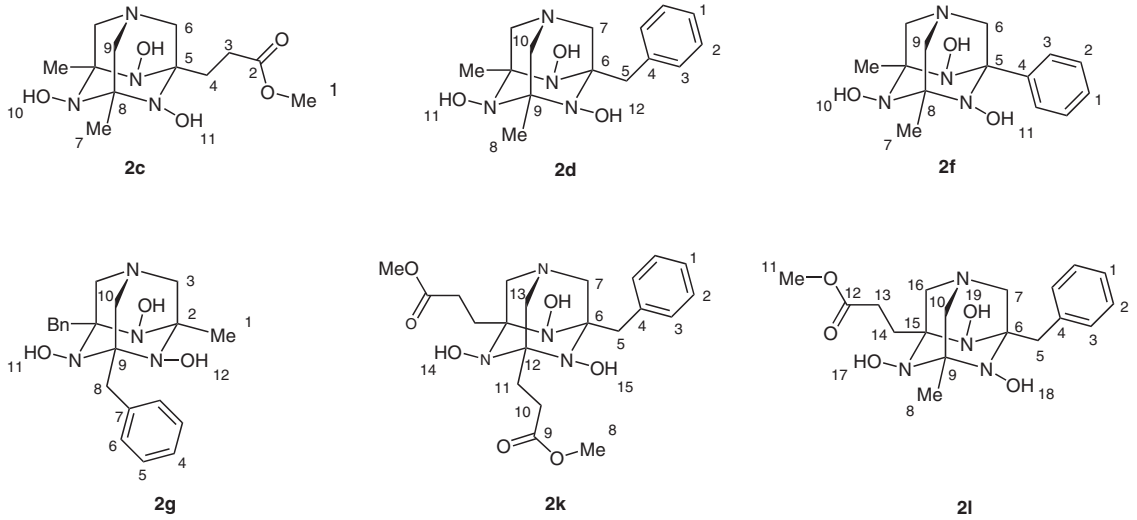


Figure 2 Atom numbering in products **2**

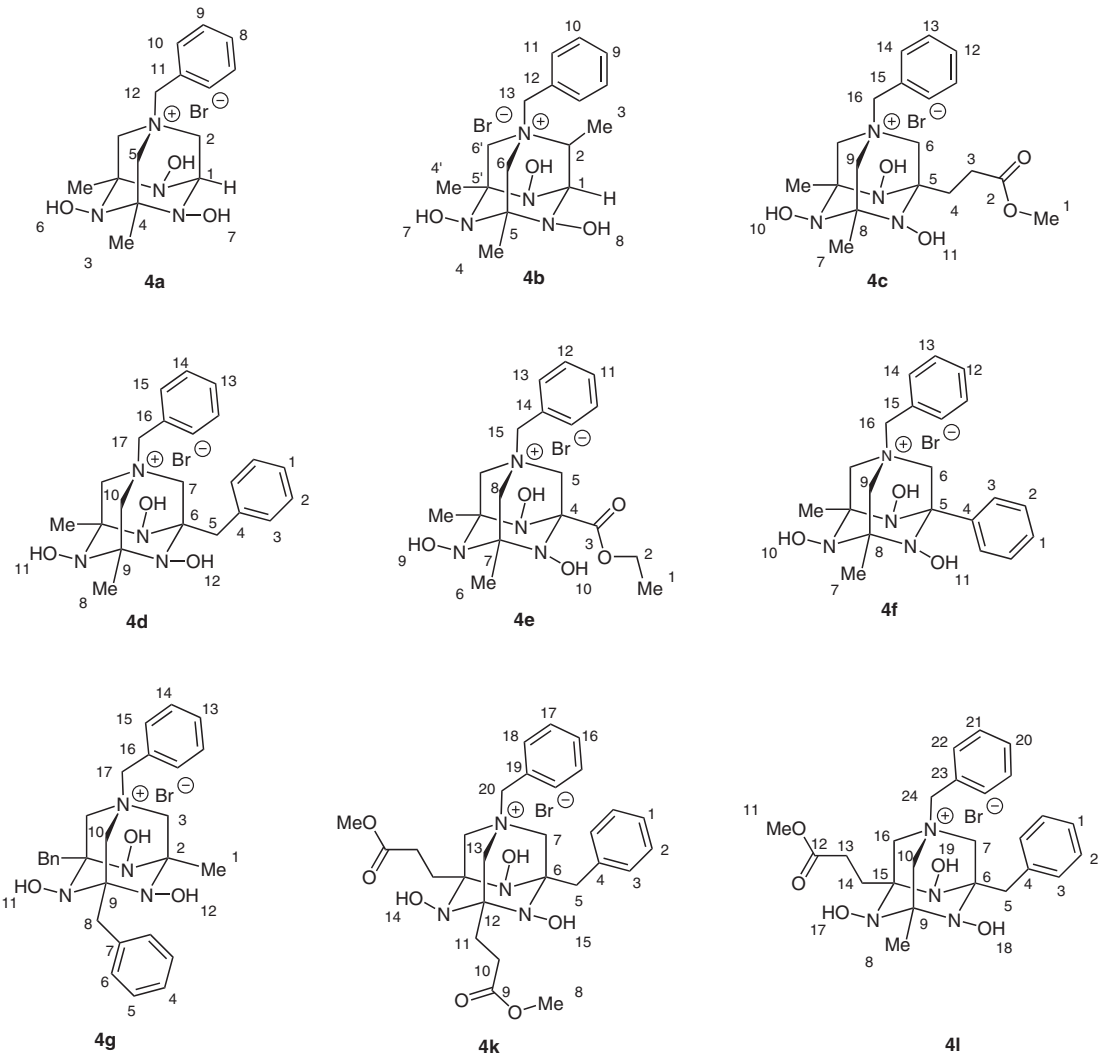


Figure 3 Atom numbering in products **4**

3,5-Dimethyl-7-phenyl-1,4,6,10-tetraazatricyclo[3.3.1.1^{3,7}]decane-4,6,10-triol (2f)

Yield: 57 mg (78%; procedure 3); white solid; mp 102–115 °C; R_f = 0.68 (EtOAc–MeOH, 3:1).

^{1}H NMR: δ = 1.28 [s, 6 H, (7)], 2.69 and 2.83 [2 × br s, 6 H, (6 and 9)], 7.1–7.4 [m, 5 H, (1, 2 and 3)], 7.98 and 8.04 [2 × s, 3 H, (10 and 11)].

^{13}C NMR: δ = 21.1 (7), 54–56 (br, 6 and 9), 75.0 and 79.0 (5 and 8), 125.7, 126.5 and 127.5 (1, 2 and 3), 140.5 (4).

HRMS (+ve): *m*/*z* [M + H]$^+$ calcd for $C_{14}H_{21}N_4O_3$: 293.1608; found: 293.1601.

3,5-Dibenzyl-7-methyl-1,4,6,10-tetraazatricyclo[3.3.1.1^{3,7}]decane-4,6,10-triol (2g)

Yield: 118 mg (31%; procedure 1); colorless oil; R_f = 0.40 (EtOAc).

^{1}H NMR: δ = 1.23 [s, 3 H, (1)], 2.5–3.9 [br m, 10 H, (3, 8 and 10)], 7.0–7.4 [m, 10 H, 4, 5 and 6], 7.8–8.0 [br s, 1 H, (11)], 8.1–8.4 [br s, 2 H, (12)].

^{13}C NMR: δ = 21.6 (1), 38.3 (8), 50–58 (br, 3 and 10), 75.7 (2), 76.9 (9), 126.3, 127.8 and 131.2 (4, 5 and 6), 137.0 (7).

HRMS (+ve): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{27}N_4O_3$: 383.2078; found: 383.2075.

Methyl 3-{5-Benzyl-4,6,10-trihydroxy-7-(3-methoxy-3-oxopropyl)-1,4,6,10-tetraazatricyclo[3.3.1.1^{3,7}]decan-3-yl}propanoate (2k)

Adamantane **2k** was obtained by procedure 1 from tris-oxime **1k** (290 mg, 0.64 mmol).

Yield: 24% (70 mg); white foam; R_f = 0.35 (EtOAc–MeOH, 3:1).

^{1}H NMR: δ = 1.7–2.1 [br s, 4 H, (11)], 2.2–2.6 [br s, 4 H, (10)], 2.9–3.8 [br m, 8 H, (5, 7 and 13)], 3.57 [s, 6 H, (8)], 7.1–7.4 [m, 5 H, (1, 2 and 3)], 7.9–8.2 [br s, 3 H, (14 and 15)].

^{13}C NMR: δ = 27.5 and 28.8 (10 and 11), 38.3 (5), 49–55 (br, 7 and 13), 51.6 (8), 74.0 (12), 76.7 (6), 126.4, 127.9 and 131.2 (1, 2 and 3), 137.0 (4), 174.4 (9).

HRMS (+ve): *m*/*z* [M + H]$^+$ calcd for $C_{21}H_{31}N_4O_7$: 451.2187; found: 451.2182.

Methyl 3-{5-Benzyl-4,6,10-trihydroxy-7-methyl-1,4,6,10-tetraazatricyclo[3.3.1.1^{3,7}]decan-3-yl}propanoate (2l)

Adamantane **2l** was obtained by procedure 1 from tris-oxime **1l** (150 mg, 0.39 mmol) and by procedure 3 from benzyl salt **4l** (38 mg, 0.069 mmol).

Yield: 32% (47 mg; Procedure 1); 82% (22 mg, Procedure 3); white amorphous solid; R_f = 0.32 (EtOAc).

^{1}H NMR: δ = 1.19 [s, 3 H, (8)], 2.2–2.6 [br s, 4 H, (13 and 14)], 2.7–3.6 [3 × br, 8 H, (5, 7, 10 and 16)], 3.58 [s, 3 H, (11)], 7.0–7.4 [m, 5 H, (1, 2 and 3)], 7.7–8.2 [2 × br, 3 H, (17, 18 and 19)].

^{13}C NMR: δ = 20.9 (8), 27.3 and 28.5 (13 and 14), 37.9 (5), 51.2 (11), 50–60 (br, 7, 10 and 16), 74.8, 75.5 and 76.2 (6, 9 and 15), 125.9, 127.5 and 130.8 (1, 2 and 3), 136.7 (4), 174.0 (12).

HRMS (+ve): *m*/*z* $[M + H]^+$ calcd for $C_{18}H_{27}N_4O_5$: 379.1976; found: 379.1974.

Quaternary Salts of 1,4,6,10-Tetraazaadamantanes 4a–g, 4k, 4l; General Procedure 2

AcOH (0.172 mL, 3.00 mmol) and benzyl bromide (257 mg, 1.50 mmol) were consecutively added to a stirred solution of the corresponding tris-oxime **1** (1.00 mmol) in MeOH (5.0 mL). The reaction mixture was kept at r.t. with periodic stirring until full consumption of starting material was observed (TLC analysis, see Table 1). The reaction mixture was evaporated and the residual solid was washed with EtOAc and dried in vacuo to give pure quaternary salts **4** (for analytical purposes, samples were recrystallized from Et_2O–MeOH or Et_2O–acetone). Yields of products **4** are presented in Table 1.

1-Benzyl-4,6,10-trihydroxy-3,5-dimethyl-4,6,10-triaza-1-azoniatricyclo[3.3.1.1^{3,7}]decane bromide (4a)

Yield: 290 mg (75%); white solid; mp 236–238 °C.

^{1}H NMR: δ = 1.23 [s, 6 H, (3)], 3.43 [br s, 4 H, (5)], 3.56 [br s, 2 H, (2)], 4.28 [s, 1 H, (1)], 4.67 [s, 2 H, (12)], 7.5–7.7 [m, 5 H, (8, 9 and 10)], 8.4–9.2 [br s, 3 H, (6 and 7)].

^{13}C NMR: δ = 20.1 (3), 49–58 (2 × br, 2 and 5), 67.3 (12), 74.4 and 74.9 (1 and 4), 126.0 (11), 129.0, 130.5 and 133.1 (8, 9 and 10).

HRMS (+ve): *m*/*z* calcd for $C_{15}H_{23}N_4O_3^+$: 307.1765; found: 307.1761.

Anal. Calcd for $C_{15}H_{23}N_4O_3Br$: C, 46.52; H, 5.99; N, 14.47. Found: C, 46.01; H, 6.49; N, 13.97.

1-Benzyl-4,6,10-trihydroxy-2,5,7-trimethyl-4,6,10-triaza-1-azoniatricyclo[3.3.1.1^{3,7}]decane bromide (4b)

Yield: 369 mg (92%); white solid; mp 167–173 °C (dec.).

^{1}H NMR (COSY, HSQC): δ = 1.14 and 1.23 [2 × s, 6 H, (4 and 4′)], 1.64 [d, *J* = 6.4 Hz, 3 H, (3)], 3.03 and 3.52 [2 × d, *J* = 12.0 Hz, 2 H, (6)], 3.25 and 3.79 [2 × d, *J* = 12.6 Hz, 2 H, (6′)], 4.21 [br s, 2 H, (1 and 2)], 4.52 and 4.60 [2 × d, *J* = 12.6 Hz, 2 H, (13)], 7.4–7.7 [m, 5 H, (9, 10 and 11)], 8.47, 8.64 and 8.99 [3 × s, 3 H, (7 and 8)].

^{13}C NMR (HSQC): δ = 12.2 (3), 20.5 and 20.7 (4 and 4′), 50-55 (br, 6 and 6′), 58-61 (br, 2), 64.3 (13), 74.9 and 76.9 (5 and 5′), 79.2 (1), 126.7 (12), 129.4, 130.9 and 133.6 (9, 10 and 11).

HRMS (+ve): *m*/*z* calcd for $C_{16}H_{25}N_4O_3^+$: 321.1921; found: 321.1916.

Anal. Calcd for $C_{16}H_{25}BrN_4O_3$: C, 47.89; H, 6.28; N, 13.96. Found: C, 47.52; H, 6.80; N, 13.55.

1-Benzyl-4,6,10-trihydroxy-3-(3-methoxy-3-oxopropyl)-5,7-dimethyl-1,4,6,10-tetraazatricyclo[3.3.1.1^{3,7}]decan-1-ium Bromide (4c)

Yield: 407 mg (86%); white solid; mp 201–206 °C (dec.).

^{1}H NMR: δ = 1.22 [s, 6 H, (7)], 1.86 [br s, 2 H, (4)], 2.53 [br s, 2 H, (3)], 3.38 [br s, 6 H, (6 and 9)], 3.58 [s, 3 H, (1)], 4.65 [s, 2 H, (16)], 7.4–7.7 [m, 5 H, (12, 13 and 14)], 8.4–9.0 [br s, 3 H, (10 and 11)].

^{13}C NMR: δ = 21.1 (7), 26.4 and 27.6 (2 × br, 3 and 4), 51.7 (1), 53–57 (br, 6 and 9), 67.9 (16), 75.7 (br, 8), 77.3 (br, 5), 126.4 (15), 129.4, 130.9 and 133.6 (12, 13 and 14), 174.0 (2).

HRMS (+ve): *m*/*z* calcd for $C_{19}H_{29}N_4O_5^+$: 393.2132; found: 393.2128.

Anal. Calcd for $C_{19}H_{29}BrN_4O_5$: C, 48.21; H, 6.18; N, 11.84. Found: C, 47.80; H, 6.29; N, 11.67.

1,3-Dibenzyl-4,6,10-trihydroxy-5,7-dimethyl- 1,4,6,10-tetraazatricyclo[3.3.1.1^{3,7}]decan-1-ium Bromide (4d)

Yield: 415 mg (87%); white solid; mp 218–225 °C (dec.).

^{1}H NMR: δ = 1.26 [s, 6 H, (8)], 3.15, 3.29 and 3.38 [3 × s br, 8 H, (5, 7 and 10)], 4.58 [s, 2 H, (17)], 7.15–7.35 and 7.40–7.55 [2 × m, 10 H, (1, 2, 3, 13, 14, 15)], 8.5–9.2 [br s, 3 H, (11 and 12)].

^{13}C NMR: δ = 21.3 (8), 38.5 (5), 50-57 (br, 7 and 10), 67.9 (17), 76.5 (9), 77.7 (6), 126.3 (16), 127.1, 128.4, 129.3, 130.9, 131.3 and 133.5 (1, 2, 3, 13, 14 and 15), 135.1 (4).

HRMS (+ve): *m*/*z* calcd for $C_{22}H_{29}N_4O_3^+$: 397.2234; found: 397.2235.

Anal. Calcd for $C_{22}H_{29}BrN_4O_3$: C, 55.35; H, 6.12; N, 11.74. Found: C, 55.14; H, 6.30; N, 11.64.

1-Benzyl-3-(ethoxycarbonyl)-4,6,10-trihydroxy-5,7-dimethyl-1,4,6,10-tetraazatricyclo[3.3.1.1^{3,7}]decan-1-ium Bromide (4e)

Yield: 413 mg (90%); white solid; mp 195–207 °C (dec.).

^{1}H NMR: δ = 1.23 [br s, 9 H, (1 and 6)], 3.3–3.4 [br m, 2 H, (5)], 3.5–3.7 [br m, 4 H, (8)], 4.15 [q, *J* = 7.0 Hz, 2 H, (2)], 4.76 [s, 2 H, (15)] 7.5–7.7 [m, 5 H, (11, 12 and 13)], 8.0–8.5 [br s, 1 H, (9)], 9.1–9.3 [br s, 2 H, (10)].

^{13}C NMR: δ = 14.3 (1), 20.2 (6), 45.9 (br, 5), 55.5 (br, 8), 59.8 (2), 68.1 (15), 76.0 (7), 83.9 (4), 126.3 (14), 129.5, 131.0 and 136.6 (11, 12 and 13), 166.8 (3).

HRMS (+ve): *m*/*z* calcd for $C_{18}H_{27}N_4O_5^+$: 379.1976; found: 379.1981.

Salt **4e** was recrystallized from MeOH–H_2O to give crystalline 2(**4e**)·7H_2O that was suitable for X-ray diffraction analysis (Figure 1).[9]

1-Benzyl-4,6,10-trihydroxy-5,7-dimethyl-3-phenyl-1,4,6,10-tetraazatricyclo[3.3.1.1^{3,7}]decan-1-ium Bromide (4f)

Yield: 384 mg (83%); white solid; mp 234–239 °C (dec.).

^{1}H NMR: δ = 1.28 [s, 6 H, (7)], 3.62 [br s, 4 H, (9)], 3.93 [br s, 2 H, (6)], 4.79 [s, 2 H, (16)], 7.2–7.8 [m, 10 H, (1, 2, 3, 12, 13 and 14)], 8.2–8.7 [br s, 3 H, (10 and 11)].

^{13}C NMR: δ = 21.1 (7), 47–50 (br, 6), 54–57 (br, 9), 68.5 (16), 76.2 (8), 79.6 (5), 126.5 (15), 128.0, 128.3, 129.5, 131.0 and 133.7 (1, 2, 3, 4, 12, 13 and 14).

HRMS (+ve): *m*/*z* calcd for $C_{21}H_{27}N_4O_3^+$: 383.2078; found: 383.2076.

Anal. Calcd for $C_{21}H_{27}BrN_4O_3$: C, 54.43; H, 5.87; N, 12.09. Found: C, 54.92; H, 6.03; N, 11.84.

1,3,5-Tribenzyl-4,6,10-trihydroxy-7-methyl-1,4,6,10-tetraazatricyclo[3.3.1.1^{3,7}]decan-1-ium Bromide (4g)

Yield: 487 mg (88%); white solid; mp 233–241 °C (dec.).

^{1}H NMR: δ = 1.32 [s, 3 H, (1)], 2.5–4.0 [3 × br s, 10 H, (3, 8 and 10)], 4.53 [s, 2 H, (17)], 7.1–7.6 [m, 15 H, (4, 5, 6, 13, 14 and 15)], 7.9–8.6 [br s, 1 H, (11)], 8.8–9.2 [br s, 2 H, (12)].

^{13}C NMR: δ = 21.5 (1), 38.4 (8), 50–57 (br, 3 and 10), 67.5 (17), 76–78 [br, (2 and 9)], 126.2 (16), 127.1, 128.3, 129.2, 130.8, 131.2 and 133.3 (4, 5, 6, 13, 14 and 15), 134.8 (7).

HRMS (+ve): *m*/*z* calcd for $C_{28}H_{33}N_4O_3^+$: 473.2547; found: 473.2531.

Anal. Calcd for $C_{28}H_{33}BrN_4O_3$: C, 60.76; H, 6.01; N, 10.12. Found: C, 60.83; H, 6.04; N, 9.84.

1,3-Dibenzyl-4,6,10-trihydroxy-5,7-bis(3-methoxy-3-oxopropyl)-1,4,6,10-tetraazatricyclo[3.3.1.1^{3,7}]decan-1-ium Bromide (4k)

Benzyl salt **4k** was obtained from tris-oxime **1k** (290 mg, 0.64 mmol).

Yield: 75% (298 mg); white solid; mp 115–123 °C.

^{1}H NMR: δ = 1.88 [br s, 4 H, (11)], 2.57 [br s, 4 H, (10)], 2.9–3.6 [3 × br s, 8 H, (5, 7 and 13)], 3.6 [s, 6 H, (8)], 4.56 [s, 2 H, (20)], 7.18–7.36 and 7.40–7.55 [2 × m, 10 H, (1, 2, 3, 16, 17 and 18)], 8.7–9.0 [br s, 3 H, (14 and 15)].

^{13}C NMR: δ = 25.9 and 27.4 (2 × br, 10 and 11), 37.7 (5), 50–57 (br, 7 and 13), 51.3 (8), 67.8 (20), 76.4 (br, 6), 77.2 (br, 12), 126.7 (19), 125.8, 128.0, 128.9, 130.5, 130.75 and 133.1 (1, 2, 3, 16, 17 and 18), 134.5 (4), 173.5 (9).

HRMS (+ve): *m*/*z* calcd for $C_{28}H_{37}N_4O_7^+$: 541.2657; found: 541.2655.

1,3-Dibenzyl-4,6,10-trihydroxy-5-(3-methoxy-3-oxopropyl)-7-methyl-1,4,6,10- tetraazatricyclo[3.3.1.1^{3,7}]decan-1-ium Bromide (4l)

Benzyl salt **4l** was obtained from tris-oxime **1l** (110 mg, 0.29 mmol).

Yield: 72% (115 mg); white solid; mp 207–210 °C (dec.).

^{1}H NMR: δ = 1.23 [s, 3 H, (8)], 1.89 [br s, 2 H, (14)], 2.59 [br s, 2 H, (13)], 2.8–3.5 [4 × br s, 8 H, (5, 7, 10 and 16)], 3.60 [s, 3 H, (11)], 4.54 [s, 2 H, (24)], 7.18–7.35 and 7.40–7.55 [2 × m, 10 H, (1, 2, 3, 20, 21 and 22)], 7.9–9.2 [br s, 3 H, (17, 18 and 19)].

^{13}C NMR: δ = 21.2 (8), 26.4 and 27.6 (13 and 14), 38.3 (5), 51.7 (11), 50–57 and 58–62 (2 × br; 7, 10 and 16), 68.1 (24), 76-79 (br; 6, 9 and 15), 126.2 (23), 127.1, 128.4, 128.5, 129.3, 130.9 and 133.5 (1, 2, 3, 20, 21 and 22), 134.2 (4), 174.0 (12).

HRMS (+ve): *m*/*z* calcd for $C_{25}H_{33}N_4O_5^+$: 469.2445; found: 469.2440.

Anal. Calcd for $C_{25}H_{33}BrN_4O_5$: C, 54.65; H, 6.05; N, 10.20. Found: C, 54.36; H, 5.74; N, 10.00.

Debenzylation of Quaternary Tetraazaadamantane Salts 4d, 4f and 4l; General Procedure 3

Palladium on activated charcoal (10%, 100 mg) and anhydrous K_2CO_3 (34 mg, 0.25 mmol) were added to a stirred solution of *N*-benzyl adamantane **4d**, **4f** or **4l** (0.25 mmol) in MeOH (6 mL) under argon. The reaction mixture was hydrogenated with H_2 (1 atm) at r.t. for 1 h (**4d**), 45 min (**4f**), or 50 min (**4l**). The resulting solution was filtered through Celite and the filtrate was evaporated at 35 °C in vacuo. The residue was preadsorbed on silica gel and purified by flash chromatography (silica gel; EtOAc–hexane, 3:1→EtOAc) to give pure adamantanes **2d**, **2f** or **2l**.

Primary Data for this article are available online at http://www.thieme-connect.com/ejournals/toc/synthesis and can be cited using the following DOI: 10.4125/pd0026th.

Acknowledgment

We are grateful for financial support from RFBR (grant 09-03-00676a), Council for Grants of the President of Russian Federation (grant MK-1361.2011.3) and RAS Presidium program 7P.

References

(1) For application of urotropin, see, for example: (a) Seneca, H.; Peer, P. *Med. Times* **1969**, *97*, 243. (b) Salamone, J. S. *Polymeric Material Encyclopedia*; CRC Press: New York, **1996**, 5036.

(2) Semakin, A. N.; Sukhorukov, A. Yu.; Lesiv, A. V.; Ioffe, S. L.; Lyssenko, K. A.; Nelyubina, Yu. V.; Tartakovsky, V. A. *Org. Lett.* **2009**, *11*, 4072.

(3) For application of 1,4,6,10-tetraazaadamantanes in the design of water-soluble bioactive molecules, see: Tolbin, A. Yu.; Sukhorukov, A. Yu.; Ioffe, S. L.; Lobach, O. A.; Nosik, D. N.; Tomilova, L. G. *Mendeleev Commun.* **2010**, *1*, 25.

(4) Semakin, A. N.; Sukhorukov, A. Yu.; Ioffe, S. L.; Tartakovsky, V. A. *Synthesis* **2011**, 1403.

(5) (a) Ioffe, S. L. In *Nitrile Oxides, Nitrones and Nitronates in Organic Synthesis*; Feuer, H., Ed.; Wiley Interscience: Hoboken, **2008**, 604. (b) Dilman, A. D.; Tishkov, A. A.; Lyapkalo, I. M.; Ioffe, S. L.; Strelenko, Yu. A.; Tartakovsky, V. A. *Synthesis* **1998**, 181. (c) Dilman, A. D.; Tishkov, A. A.; Lyapkalo, I. M.; Ioffe, S. L.; Kachala, V. V.; Strelenko, Yu. A.; Tartakovsky, V. A. *J. Chem. Soc., Perkin Trans. 1* **2000**, 2926.

(6) Bernier, D.; Blake, A.; Woodward, S. *J. Org. Chem.* **2008**, *73*, 4229.

(7) For the relative steric size of different substituents, see: Meyer, A. Y. *J. Chem. Soc., Perkin Trans. 2* **1986**, 1567.

(8) An additional role of acetic acid may involve quaternization of the bridgehead nitrogen atom in tetraazaadamantanes **2**, which shifts the equilibrium between **1** and **2** towards **2**.[2]

(9) X-ray data for 2(**4e**)·7H_2O: Empirical formula: $C_{36}H_{68}Br_2N_8O_{17}$; M = 1044.80; triclinic; space group $P\bar{1}$; *T* = 103 K; *a* = 8.4154(6), *b* = 10.0049(7), *c* = 14.4240(11) Å, *α* = 87.414(2), *β* = 86.468(2), *γ* = 83.935(3)°; V = 1204.43(15) Å^3; Z = 1; d_{calc} = 1.440 gcm^{-3}; $\mu(Mo_{K\alpha})$ = 17.57 cm^{-1}; F(000) = 546. Intensities of 13428 reflections were measured with a Bruker SMART APEX2 CCD diffractometer [$\lambda(Mo_{K\alpha})$ = 0.71072Å, ω-scans, 2θ<58°], and 6386 independent reflections [R_{int} = 0.0342] were used in further refinement. The structure was solved by direct methods and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. The hydrogen atoms of OH groups and those of water molecules were found in difference Fourier synthesis. The H(C) atom positions were calculated. All hydrogen atoms were refined in the isotropic approximation within the riding model. For 2(**4e**)·7H_2O, the refinement converged to *wR*2 = 0.0840 and GOF = 1.002 for all the independent reflections (*R*1 = 0.0494 was calculated against F for 3820 observed reflections with $I>2\sigma(I)$). All calculations were performed using SHELXTL PLUS 5.0.[10] CCDC-843973 contains the supplementary crystallographic data for 2(**4e**)·7 H_2O. These data can be obtained free of charge via http://www.ccdc.cam.ac.uk/conts/retrieving.html (or from the CCDC, 12 Union Road, Cambridge, CB21EZ, UK; or deposit@ccdc.cam.ac.uk).

(10) Sheldrick, G. M. *Acta Crystallogr., Sect. A: Found. Crystallogr.* **2008**, *64*, 112.

(11) Gotlieb, H. E.; Korlyar, V.; Nudelman, A. *J. Org. Chem.* **1997**, *62*, 7512.