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Unusual Intramolecular Cyclization of Tris(β-oximinoalkyl)amines. The First Synthesis of 1,4,6,10-Tetraazaadamantanes

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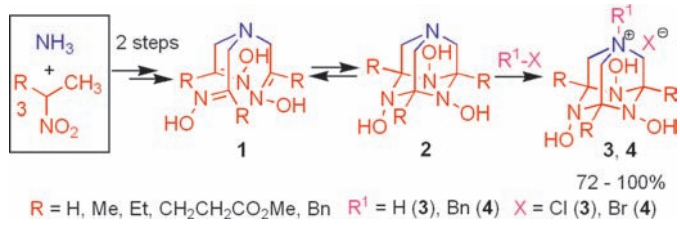
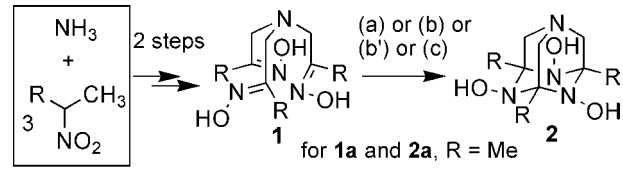
ABSTRACT



An unusual intramolecular cyclization of tris(β-oximinoalkyl)amines 1 into 4,6,10-trihydroxy-1,4,6,10-tetraazaadamantanes 2 was discovered. Compounds 2 are related to a previously unknown type of heteroadamantanes that contain the cage isomeric to urotropin. A simple three-step synthesis of tetraazaadamantanes 2 and their *N*-substituted derivatives 3 and 4 from ammonia and aliphatic nitro compounds via the intermediacy of available tris-oximes 1 was developed.

Recently, we reported a simple and efficient synthesis of tris(β-oximinoalkyl)amines **1** from secondary nitro compounds $RCH(NO_2)CH_3$ and ammonia.[1] In the course of a systematic study on the reactivity of these interesting but rather poorly explored compounds, we discovered a quite unusual intramolecular cyclization of tris-oxime **1a** (R = CH_3) to 4,6,10-trihydroxy-1,4,6,10-tetraazaadamantane **2a** (Scheme 1). Such a reaction of poly-oximes has never been observed before.[2] However, a few examples of successful cyclization of tris-imines and some other nitrogen-containing

Scheme 1. Intramolecular Cyclization of Tris-oxime **1a**



(a) - nuclephilic activation; (b), (b') - electrophilic activation
(c) - transition metal activation

derivatives of tris-carbonyl compounds of general formula $X[CH_2C(O)R]_3$ (X = AlkC or heteroatom) as well as cyclohexanes bearing three $-CH_2C(O)R$ groups in the C1, C3, and C5 positions are known. These reactions were

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(1) Semakin, A. N.; Sukhorukov, A. Yu.; Lesiv, A. V.; Khomutova, Yu. A.; Ioffe, S. L.; Lyssenko, K. A. *Synthesis* **2007**, 2862.
(2) Among closely related reactions, only two intermolecular trimerizations of oximes were reported: (a) Gardent, J. *Ann. Chim. (Paris)* **1955**, *10*, 413. (b) Sacca, A.; Freni, M. *Gazz. Chim. Ital.* **1956**, *86*, 199.

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applied to the synthesis of some heteroadamantanes[3] and other heterocage structures (wurzitanes and isowurzitanes[4]).

Tetraazaadamantane **2a** is assigned to an unknown class of 1,4,6,10-tetraazaadamantanes. The unsubstituted 1,4,6,10-tetraazaadamantane is a structural isomer of well-known 1,3,5,7-tetraazaadamantane (urotropin) that has found various applications.[5] Although the procedure for the synthesis of urotropin itself from ammonia and formaldehyde is very efficient,[5,6a] even the simplest C-substituted derivatives of urotropin are almost unknown, apparently, because of their relative thermodynamic instability.[6b,c]

From this standpoint, the synthesis of tetraazaadamantanes of type **2** could be considered as an urgent but not quite simple task. The comparison of physical and chemical properties of heteroadamantanes of types **2** and urotropin represents a fundamental interest. In addition, tetraazaadamantanes **2** or their derivatives could find some important applications like urotropin. Therefore, it seems reasonable to carry out a detailed study of the intramolecular cyclization of tris-oximes **1** in order to optimize the procedure for preparation of adamantanes **2**.[7] This study was performed using tris-oxime **1a** as a model compound.

Presumably, the generation of heteroadamantanes **2**, which are related to aminals, is a reversible reaction like the synthesis of urotropin.[6a] In any case, reflux of adamantane **2a** solution in water resulted in its full conversion to tris-oxime **1a**, while on the contrary, heating of tris-oxime **1a** up to a melting point (for 20 min) or in boiling water solution (for 4−5 h), did not furnish the adamantane **2a**. This indicates that the open-chain form **1a** is more thermodynamically favored at high temperature than the cage structure **2a**, possibly due to a large contribution of an entropy factor in the position of the equilibrium **1**⇆**2**. In that case, in order to shift the equilibrium to the adamantane structure **2**, one needs to minimize the entropy contribution by reducing the reaction temperature. This effect can be attained by accelerating the cyclization of **1** using different types of additional promoting reagents (for details see the discussion of Table 1).

An alternative way for shifting the equilibrium **1**⇆**2** to the right may be the increasing of thermodynamic preference of adamantane structure **2a**, for example, by a quaternization of the nitrogen atom in the bridgehead position (see the discussions of Tables 1 and 2).

Expected effects of various factors on the rate of the process **1** → **2** and on the position of the equilibrium **1**⇆**2** are briefly discussed below.

Action of Nucleophiles (Route (a) in Scheme 1). Addition of a nucleophile to the double C,N bond of **1a** increases the nucleophilicity of the nitrogen atom of this oximino group in the reaction with a carbon atom of the neighboring oximino fragment. The formation of the adamantane cage is completed after the elimination of the nucleophile.

Action of Electrophiles (Routes b and b′ in Scheme 1). Brønsted acids (HX) and other electrophiles can promote the formation of adamantanes **2** by two different pathways. First, protonation of the nitrogen atom of the oximino group (route (b)) provides an imminium cation, which can react with the nitrogen atom of another oximino group. Two subsequent cyclizations and elimination of proton from cage ammonium cation furnish target adamantane **2a**. However, protonation of a more basic sp^3 nitrogen atom of the tris-oxime **1a** (route (b′)) leading to a corresponding ammonium cation seems to be more likely. The generation of ammonium cation increases the electrophilicity of carbon atoms of double C,N bonds due to a −*I*-effect and favors the desired cyclization process. At the same time, quaternization of the nitrogen may affect the relative disposition of reacting oximino fragments.[8] However, one should take into account a possibility of deoximation as a side reaction promoted by acids.[9]

Action of Transition-Metal Salts (Route (c) in Scheme 1). The coordination of metal ion M^{n+} with oxime groups of tris-oxime **1a** may bring oxime groups closer to each other, thereby promoting their cyclotrimerization to give target adamantane **2a**.

The isomerization of model tris-oxime **1a** into adamantane **2a** with different types of co-reagents was studied. The results are summarized in Table 1.

Positive results could be achieved with all types of reagents employed. In reactions with nucleophiles (ammonia and sulfite anion in H_2O−MeOH) the target adamantane **2a** was obtained in moderate yield (entries 1 and 4, Table 1). When more basic reagents (NaOH and NaCN) were employed (entries 2 and 3, Table 1) only traces of adamantane **2a** were detected after full conversion of initial oxime **1a**. Possibly, this could be caused by a deoximation of **1a** in alkaline media.[9]

Brønsted acids (HX) promote the formation of adamantane **2a** (or its salts **2a**·HX) as well (entries 5−7, Table 1). However, when strong acids (HCl or TFA) are employed, besides the respective salts of target adamantane **2a**·HX (yield 30−40%), complex mixtures of unidentified products and corresponding salts of hydroxylamine are generated. This result indicates that the hydrolysis of initial oxime **1a** or adamantane **2a** takes place substantially under these conditions.

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(4) (a) Nielsen, A. T.; Christian, S. L.; Moore, D. W. *J. Org. Chem.* **1987**, *52*, 1656. (b) Izumi, H.; Setokuchi, O.; Shimizu, Y. *J. Org. Chem.* **1997**, *62*, 1173. (c) Izumi, H.; Setokuchi, O.; Shimizu, Y. *J. Chem. Soc., Perkin Trans. 1* **1998**, 1925.

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(7) An alternative scheme for the synthesis of **2**, an intermolecular condensation $NH_3 + 3NH_2OH + 3\ RCOCH_2LG \rightarrow$ **2** (LG = leaving group) similar to a known synthesis of urotropin[6] seems to be quite problematic because it is a multicomponent reaction proceeding via many reversible transformations of very unstable intermediates.

(8) According to the X-ray data, oximino fragments of tris-oxime **1a** are remote from each other in the crystal: Goldcamp, M. J.; Krause Bauer, J. A.; Baldwin, M. J. *Acta Crystallogr. Sect. E: Struct. Rep. Online* **2002**, *E58*, 1354.

(9) Corsaro, A.; Chiaccio, U.; Pictara, V. *Synthesis* **2001**, 1903.

Table 1. Intramolecular Cyclization of Tris-oxime **1a** under Action of Various Activating Reagents

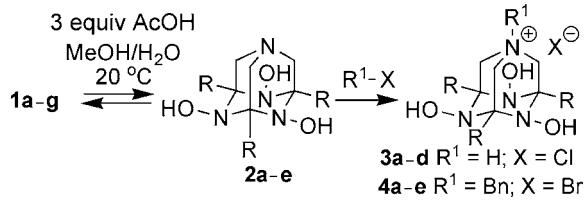
no.	reagent; conditions	amount of reagent (equiv)	time (h)	yield of **2a** (%)
1	NH_3; MeOH/H_2O, 60 °C	~150	4.0	65[a]
2	NaOH; MeOH/H_2O, 60 °C	1.0	2.5	traces[b,c]
3	NaCN; MeOH/H_2O, 60 °C	0.3	3.0	0[c]
4	Na_2SO_3; MeOH/H_2O, 20 °C	1.0	48	34[a,d]
5	HCl; MeOH/H_2O, 20 °C	1.0	0.3	30[b,e]
6	TFA; MeOH/H_2O, 20 °C	1.0	0.3	40[b,f]
7	**AcOH; MeOH/H_2O, 20 °C**	**3.0**	**24**	**95**[a]
8	$NiCl_2$; H_2O, 20 °C	1.0	48	0[g]
9	$CuCl_2$; H_2O, 20 °C	1.0	1.0	0[g]
10	$ZnCl_2$; H_2O, 20 °C	1.0	1.0	0[g]
11	$FeCl_3$; H_2O, 20 °C	1.0	1.0	0[g]
12	$CoCl_2$; H_2O, 20 °C	1.0	72	26[a,e,h]
13	$CoCl_2$; 1 equiv HCl, H_2O, 20 °C	0.05	0.5	80[a,e]
14	$NiCl_2$; HCl/H_2O, 20 °C	1.0	1.0	0[g]

[a] On isolated product. [b] From ^{1}H NMR spectra with internal standard. [c] Complex mixtures of products were obtained. [d] Conversion of **1a** ~60%. [e] Product **2a**·HCl (**3a**). [f] Product **2a**·TFA. [g] Only stable metallo-complexes of tris-oxime **1a** were identified. [h] Possibly, HCl is generated due to a partial hydrolysis of $CoCl_2$.

Reactions of transition-metal salts with tris-oxime **1a** usually led to an instantaneous and quantitative formation of stable metallo-complexes.[10] However, in the case of $CoCl_2$ (entry 12, Table 1) a small amount of adamantane salt **2a**·HCl (**3a**) was isolated by crystallization from the reaction mixture. Optimization allowed us to realize the synthesis of **3a** on a preparative scale by using a catalytic amount of $CoCl_2$ and 1 equiv of HCl (entry 13, Table 1). It is noteworthy that the above-mentioned process is the first example of azomethine cyclotrimerization successfully catalyzed by a transition-metal compound.

Thus, the simplest and most convenient procedure for the cyclization **1a** → **2a** is the treatment of tris-oxime **1a** with 3 equiv of acetic acid in aqueous methanol media at ambient temperature (entry 7, Table 1). This procedure was used for the cyclization of a series of "symmetrically-substituted" tris-oximes **1b**−**g**, bearing substituents with different steric and electronic demands at the oximino group (Scheme 2, Table 2).

Scheme 2. Intramolecular Cyclization and Quaternization of Tris-oximes **1a**−**g**



We believe that under conditions pointed in Scheme 2, the equilibrium **1**⇆**2** is achieved. The target adamantanes **2** and initial tris-oximes **1** are separated by liquid chromatography followed by NMR control. The position of equilibrium strongly depends on the substituent R. For tris-oximes **1a**, **1b**, and **1d** the equilibrium is shifted to the corresponding adamantanes **2**. On the contrary, no evidence of adamantane structure is observed in ^{1}H NMR spectra of reaction mixtures for entries 5−7 in Table 2. Adamantanes **2a**,**b** can be isolated from the respective reaction mixtures as individual compounds.

Table 2. Cyclization of Tris-oximes **1a**−**g** to the Corresponding Azaadamantane Derivatives **2**−**4**

			time (h)			yield (%)		
no.	**1**	R	**1**→**2**	**1**→**3**	**1**→**4**	**2**	**3**[a]	**4**[a]
1	**a**	Me	24	24	24	95[a]	100	94
2	**b**	H	4.0	4.0	24	89[a]	80	72
3	**c**	Et	72	24	24	35[b]	86	94
4	**d**	$(CH_2)_2CO_2Me$	72	24	24	59[c]	78	95
5	**e**	Bn	72	24	48	n.r.	[d]	89
6	**f**	Ph	72	48	48	n.r.	[d]	n.r.
7	**g**	CO_2Et	72	48	48	n.r.	[d]	n.r.

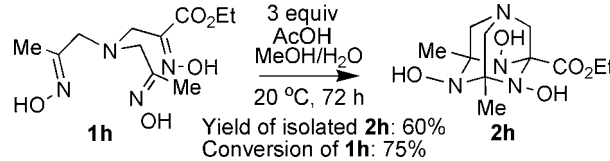
[a] On isolated product. [b] Recovery of **1c**: 55%; isolated product **2c** contains ~20% of **1c** (NMR). [c] Recovery of **1d**: 36%; isolated product **2d** contains ~10% of **1d** (NMR). [d] Only products of decomposition of **1**. n.r. = no reaction.

Evidently, quaternization of the nitrogen atom in the bridgehead position of adamantanes **2** by means of protonation (salts **3**) or benzylation (salts **4**) significantly stabilizes the adamantane cage and, accordingly, allows the equilibrium to shift to adamantanes. The procedure for the synthesis of salts **3** includes treatment of the solution of initial tris-oxime **1** in aqueous methanol with AcOH for the time indicated in Table 2 followed by addition of 1 equiv of HCl (transformation **1** → **3**). The target salts **3a**−**d** were isolated in high yields. However, under these conditions oximes **1e**−**g** gave only complex mixtures, possibly, consisting of tris-oxime salts and the products of their deoximation.

Under the conditions of the synthesis of *N*-benzyl salts **4** deoximation cannot occur, and therefore, BnBr is added just after the acetic acid. Interestingly, adamantane **4e** could be obtained using this procedure too (entry 5, Table 2), but no cyclization of tris-oximes **1f** and **1g** was observed.[11]

Using the method illustrated in Schemes 1 and 2 only "symmetrically substituted" adamantanes **2** bearing three identical substituents R can be synthesized. The example of tris-oxime **1h** demonstrates that the cyclization of tris-oximes **1** → **2** has more general scope (Scheme 3). However, the lack of convenient approaches to the synthesis of "unsymmetrically substi-

Scheme 3. Synthesis of "Unsymmetrically Substituted" Adamantane **2h** from Tris-oxime **1h**



tuted" tris-oximes (similar to **1h**) makes a systematic study of their intramolecular cyclization difficult at the moment.[12]

The presence of heteroadamantane cage in compounds **2**−**4** was established by X-ray diffraction analysis of adamantane **2a** derivatives: tartrate **5a** tetrahydrate and benzyl salt **4a** dihydrate (Figure 1).

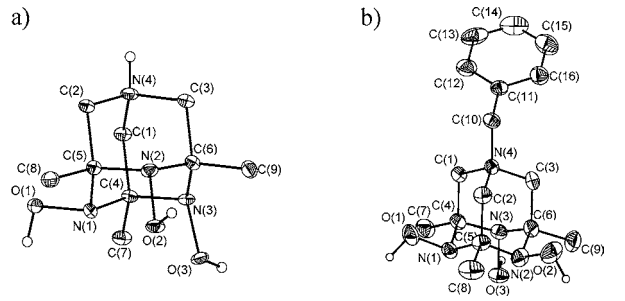


Figure 1. General view of azaadamatane cation in the crystals of tartrate **5a** tetrahydrate (a) and bromide **4a** dihydrate (b) in the representation of atoms via thermal ellipsoids (p = 50%).

According to the X-ray data the adamantane moieties in **5a·4H$_2$O** and **4a·2H$_2$O** correspond to two conformers with equatorial-axial-axial and equatorial-equatorial-axial dispositions of hydroxyl groups. Examination of the geometry of the tetraazaadamantane moiety in both crystalline salts revealed the marked distinction between C−N bonds in the triazine cycle (1.469(4)−1.499(4) Å in **5a·4H$_2$O** and 1.462(5)−1.501(5) Å in **4a·2H$_2$O**). It is the systematic shortening of N2−C5 and N3−C4 bonds (1.469(4) and 1.479(4) Å) in **5a·4H$_2$O** and N3−C4 and N3−C6 ones (1.462(5) and 1.466(4) Å) in **4a·2H$_2$O**. Moreover, some of the C−C bonds also appear to be elongated. This is, apparently, indicative of the competitive anomeric interactions $lp_{eq}(N)\rightarrow\sigma^*(C-N)$ and $lp_{ax}(N)\rightarrow\sigma^*(C-C)$,[13] i.e., of the charge transfer from the lone pairs of nitrogen atoms to the σ^* orbitals of above-mentioned C−N and/or C−C bonds. The latter agrees with the results of the quantum-chemical calculations for all of the four isomers of **2a** (see the Supporting Information). Thus, the geometry of the tetraazaadamantane cage is mainly governed by the stereoelectronic interactions rather than steric reasons.

The brutto-formulas of stable individual products **2a**,**h**, **3a**−**d**, and **4a**−**e** were confirmed by the elemental analysis data.[14] The NMR spectra of adamantanes **2a**−**d**,**h** and their derivatives **3a**−**d** and **4a**−**e** have some characteristic features. The signals of atoms of adamantane cage and atoms connected to them with one or two bonds are shifted to higher field and appreciably widened in comparison to the corresponding signals of tris-oximes **1**. Such widening should be due to exchange processes with a barrier of 10−15 kcal/mol that may be the slow inversion of nitrogen atoms in bridge positions and/or the restricted rotation around N−O bonds.[15] According to DFT calculations of four possible conformers of adamantane **2a**, the most stable are those found in crystals of derivatives **4a·2H$_2$O** and **5a·4H$_2$O**. Conformers with equatorial-axial-axial and equatorial-equatorial-axial OH groups are energetically almost equal, while the difference in energy between these conformers and those with all axial (equatorial) OH groups is 1.1 kcal/mol (3.4 kcal/mol). However, low solubility of adamantanes **2**−**4** in most of organic solvents makes a detailed study of the stereodynamic processes in these objects problematic.[16]

Thus, a novel reaction of intramolecular cyclization of tris(β-oximinoalkyl)amines, which leads to previously unknown 4,6,10-trihydroxy-1,4,6,10-tetraazaadamantanes **2** possessing a heteroadamantane cage isomeric to urotropin, was discovered and studied. This reaction was used as a key stage in a three-step synthesis of adamantanes **2**−**4** from ammonia and available aliphatic nitro compounds.

Acknowledgment. We are grateful for the support of the Russian Foundation for Basic Research (Grant No. 09-03-00676-a).

Supporting Information Available: Experimental procedures, characterization data of products, DFT calculations, and X-ray crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(10) For generation of such complexes, see ref 1 and works cited therein.

(11) Formation of salts **3** and **4**, of course, may proceed via quaternization of sp3 nitrogen atom in initial tris-oximes **1**.

(12) Our strategy for the synthesis of "unsymmetrical" tris-oximes **1** from aliphatic nitro compounds will be published in the near future.

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(14) The brutto-formula of **2b** was indirectly confirmed by elemental analysis of its derivatives **3b** and **4b**.

(15) Raban, M.; Kost D. In *Acyclic Organonitrogen Stereodynamics*; Lambert, J. B., Takeuchi Y., Eds.; VCH Publishers: New York, 1991; pp 57−88.

(16) The problems of stereodynamics in adamantanes **2** as well as the equilibrium **1**⇆**2** will be discussed in a separate publication.