

## Unexpected Transformation of 1,2-Bis(*N*-methoxy-*N*-nitrosoamino)cycloalkanes: First Synthesis of 4,5-Dihydro-1,2,3-triazole 2-Oxides

Vadim K. Khlestkin<sup>a</sup>, Dmitrii G. Mazhukin<sup>a</sup>, Aleksei Ya. Tikhonov<sup>a</sup>, Irina Yu. Bagryanskaya<sup>a</sup>,  
 Yurii V. Gatilov<sup>a</sup>, Darkhan I. Utepbergenov<sup>b</sup>, Valery V. Khrantsov<sup>c</sup> and Leonid B. Volodarsky<sup>a\*</sup>

<sup>a</sup>Novosibirsk Institute of Organic Chemistry, Novosibirsk 630090, Russia

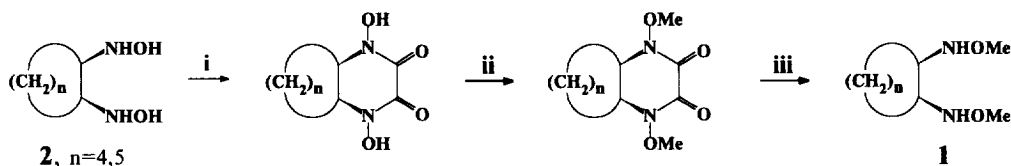
<sup>b</sup>Novosibirsk State University, Novosibirsk 630090, Russia

<sup>c</sup>Institute of Chemical Kinetics and Combustion, Novosibirsk 630090, Russia

**Abstract:** Thermolysis of 1,2-bis(*N*-methoxy-*N*-nitrosoamino)cycloalkanes in organic solvents led to 4,5-dihydro-1,2,3-triazole 2-oxides. Copyright © 1996 Elsevier Science Ltd

1,2,3-Triazole 1-oxides are well known heterocyclic compounds<sup>1</sup> whereas their 4,5-dihydro derivatives were synthesized in the last decade.<sup>2</sup> However to the best of our knowledge, there is no data on the 4,5-dihydro-1,2,3-triazole 2-oxides. We wish to report here the first synthesis of the latter compounds and their transformation into 2-hydroxy-1,2,3-triazoles.

Recently, we reported a convenient route to *cis*-1,2-bismethoxyaminocycloalkanes **1**<sup>3</sup> from *cis*-1,2-bishydroxylamines **2**<sup>4</sup> upon acylation, subsequent *O*-alkylation and then deprotection (Scheme 1).

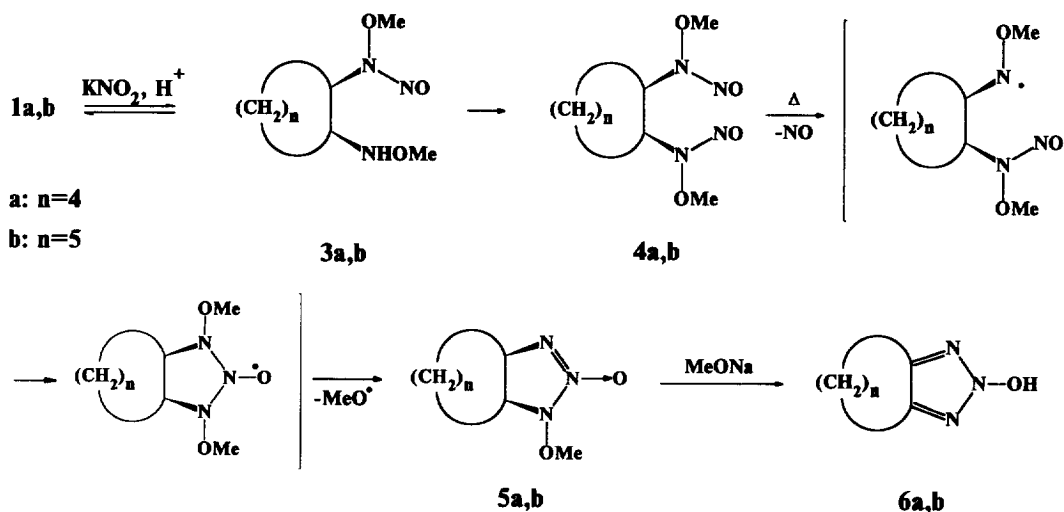


Scheme 1. i.  $(\text{COOEt})_2$ , MeOH, reflux, 3 h. ii. MeI,  $\text{K}_2\text{CO}_3$ , MeOH -  $\text{H}_2\text{O}$ , r.t., 48 h (or  $\text{CH}_2\text{N}_2$ , r.t., 15 h). iii. 6% HCl, MeOH, reflux, 7-15 h (or KOH, MeOH, reflux, 15 h).

Reaction of *cis*-1,2-bismethoxyaminocycloalkanes **1a,b** with 1 equiv  $\text{KNO}_2$  in acid media led to mononitroso derivatives **3a,b**. They were found to be unstable on isolation and easily

disproportionated to *cis*-1,2-bismethoxyaminocycloalkanes **1a,b** and *N,N'*-dinitroso derivatives **4a,b** (in accordance with TLC-data and  $^1\text{H}$  NMR spectra). The use of 2 equiv of  $\text{KNO}_2$  under the same conditions afforded *N,N'*-dinitroso derivatives **4a,b**.

Refluxing of bisnitroso compound **4a** with  $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$  and Raney nickel in methanol unexpectedly led to 4,5-dihydro-1,2,3-triazole 2-oxide **5a** instead of the desired hydrazine derivative. In the course of further study of this transformation it was shown that 2-oxide **5a** was also formed upon heating in organic solvents (acetonitrile, toluene, methanol) in the absence of both  $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$  and Raney nickel. Similar heating of 1,2-bis(*N*-methoxy-*N*-nitrosoamino)cycloheptane **4b** in methanol led to compound **5b** (Scheme 2).



Scheme 2

4,5-Dihydro-1,2,3-triazole 2-oxides **5a,b** are stable compounds with low melting points.<sup>5</sup> X-ray study of compounds **5a,b** showed the *cis*-ring fusion of triazole and cycloalkane cycles (Fig. 1).<sup>6</sup> A feature of the structure of molecules **5a,b** is an appreciable lengthening of the N(1)-N(2) bond up to 1.493(2) Å in **5a** and 1.461(6) Å in **5b** in comparison with the expected value 1.420(15) Å for N(pyr) - N(plan)<sup>7</sup> and the length 1.389(1) Å in 4-imino-5,5-dimethyl-3-phenyl-4,5-dihydro-1,2,3-triazole 1-oxide.<sup>2b</sup>

The mechanism of the formation of compounds **5** from 1,2-bis(*N*-methoxy-*N*-nitrosoamino)cycloalkanes is suggested to be of a radical type which

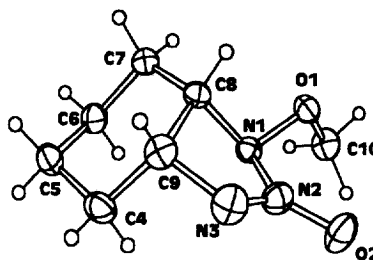


Fig. 1 The crystal structure of molecule **5a**. Selected bond length (Å) and angles (°): N(1)-N(2) 1.493(2), N(2)=N(3) 1.257(2), N(2)-O(2) 1.237(2), N(1)-O(1) 1.403(2), O(1)-N(1)-C(8) 109.7(1), O(1)-N(1)-N(2) 107.4(1), N(1)-N(2)-O(2) 117.7(1), N(3)-N(2)-O(2) 128.1(2).

includes the formation of NO and methoxyl radicals (Scheme 2).<sup>8</sup> To support the methoxyl radical formation 5,5-dimethylpyrroline 1-oxide (DMPO) was added to a solution of compound **4a** in benzene at 40°C. The ESR spectrum of spin adduct with methoxyl radical ( $a_{\text{H}}^{\text{r}}=1.9$  G;  $a_{\text{H}}^{\text{b}}=7.0$  G;  $a_{\text{N}}=13.6$  G) was observed.<sup>9</sup> To detect NO release from the reaction mixture nitronitroxide, (5,5-dimethyl-2,4-diphenyl-4-methoxy-2-imidazoline-3-oxide 1-oxyl, NNR<sup>10</sup>) as specific spin trap for nitric oxide,<sup>11</sup> has been used.<sup>12</sup> The characteristic transformation of ESR spectrum of NNR ( $a_{\text{N1}}=a_{\text{N3}}=7.1$  G) in the ESR spectrum of iminonitroxide ( $a_{\text{N1}}=7.5$  G,  $a_{\text{N3}}=4.0$  G) formed under reaction with NO has been observed.<sup>11b</sup>

As expected, treatment of triazoline *N*-oxides **5a,b** with MeONa in methanol gave 2-hydroxy-1,2,3-triazoles **6a,b** (Scheme 2). These compounds are representatives of a rare type of 2-hydroxy-1,2,3-triazole derivatives.<sup>13</sup>

We have thus demonstrated that 4,5-dihydro-1,2,3-triazole 2-oxides can be readily prepared from 1,2-bis(*N*-methoxy-*N*-nitrosoamino)cycloalkanes accessible from 1,2-bismethoxyamines.

**Acknowledgement:** We thank the Russian Foundation for Basic Research (grant no. 93-03-04719) for financial support.

## References and Notes

- For a comprehensive review see: Godovikova, T. I.; Ignat'eva, E. L.; Khmel'nitskii, L. *I. Khim. Geterotsikl. Soedin.* **1989**, 147-156.
- (a) Zlotin, S. G.; Prokshits, O. V.; Dekaprilevich, M. O.; Luk'janov, O. A. *Mendeleev Commun.* **1992**, 131-134. (b) Zlotin, S. G.; Prokshits, O. V.; Dekaprilevich, M. O.; Yufit, D. S.; Luk'janov, O. A.; Struchkov, Yu. T. *Izv. Akad. Nauk, Ser. Khim.* **1993**, 746-751.
- Mazhukin, D. G.; Khlestkin, V. K.; Tikhonov, A. Ya.; Volodarsky, L. B. *Izv. Akad. Nauk, Ser. Khim.* **1996**, 925-929.
- Mazhukin, D. G.; Tikhonov, A. Ya.; Volodarskii, L. B.; Konovalova, E. P.; Tikhonova, L. A.; Bagryanskaya, I. Yu.; Gatilov, Yu. V. *Russ. Chem. Bull.* **1993**, *42*, 851-857.
- All new compounds gave spectroscopic and elemental analyses data in agreement with the assigned structure.
 

**4a:** 100% yield, viscous yellow oil; IR (CCl<sub>4</sub>): 1455 cm<sup>-1</sup> (N-N=O); UV (EtOH):  $\lambda_{\text{max}}$  (lg  $\epsilon$ ) 235 nm (4.00); <sup>1</sup>H NMR (200.13 MHz, CDCl<sub>3</sub>):  $\delta$  1.42 - 1.66, 1.77 - 2.11, 2.21 - 2.46 [3 m, 8H, (CH<sub>2</sub>)<sub>4</sub>], 3.79 (s, 6H, 2 MeO), 4.69 - 4.86 (m, 2H, 2 CH).

**4b:** 95% yield, viscous yellow oil; IR (CCl<sub>4</sub>): 1455 cm<sup>-1</sup> (N-N=O); UV (EtOH):  $\lambda_{\text{max}}$  (lg  $\epsilon$ ) 235 nm (3.95); <sup>1</sup>H NMR (200.13 MHz, CDCl<sub>3</sub>):  $\delta$  1.47 - 1.70, 1.84 - 2.08, 2.20 - 2.44 [3 m, 10H, (CH<sub>2</sub>)<sub>5</sub>], 3.82 (s, 6H, 2 MeO), 4.93 - 5.09 (m, 2H, 2 CH).

**5a:** 86% yield, m.p. 56 - 58°C (hexane); IR (CCl<sub>4</sub>): 1580 cm<sup>-1</sup> (N=N→O); UV (EtOH):  $\lambda_{\text{max}}$  (lg  $\epsilon$ ) 218 nm (3.88); <sup>1</sup>H NMR (200.13 MHz, CDCl<sub>3</sub>):  $\delta$  1.10 - 2.20 [m, 8H, (CH<sub>2</sub>)<sub>4</sub>], 3.42 - 3.71 (m, 1H, 4-H or 5-H), 3.81 - 4.11 (m, 1H, 4-H or 5-H), 3.97 (s, 3H, MeO); <sup>13</sup>C NMR (50.32 MHz, CDCl<sub>3</sub>):  $\delta$  20.1, 22.1, 26.7 [3t, (CH<sub>2</sub>)<sub>4</sub>], 60.4 (d, CH), 62.4 (d, CH), 64.6 (q, MeO); MS: m/z (% relative intensity) 171 (0.8, M<sup>+</sup>), 127 (17.1), 96 (23.5), 86 (100.0); calcd for C<sub>7</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub> m/z 171.1008, measured m/z 171.1000.

**5b:** 63% yield, m.p. 50 - 51°C (hexane); IR (KBr): 1555 cm<sup>-1</sup> (N=N→O); UV (EtOH):  $\lambda_{\text{max}}$  (lg  $\epsilon$ ) 221 nm (3.80); <sup>1</sup>H NMR (200.13 MHz, CDCl<sub>3</sub>):  $\delta$  1.16 - 2.17 [m, 10H,

(CH<sub>2</sub>)<sub>5</sub>], 3.67 (ddd, 1H, J= 5.5, 9.0, 9.0 Hz, 4-H or 5-H), 3.96 (s, 3H, MeO), 4.13 (ddd, 1H, J= 3.0, 9.0, 9.0 Hz, 4-H or 5-H); <sup>13</sup>C NMR (50.32 MHz, CDCl<sub>3</sub>): δ 23.6, 26.5, 27.0, 28.2, 30.8 [5t, (CH<sub>2</sub>)<sub>5</sub>], 64.7 (q, OMe), 65.1 (d, CH), 67.7 (d, CH).

**6a**: 84% yield, m.p. 128 - 130°C (EtOAc-hexane); UV (EtOH): λ<sub>max</sub> (lg ε) 239 nm (3.83); <sup>1</sup>H NMR (200.13 MHz, (CD<sub>3</sub>)<sub>2</sub>SO): δ 1.70 - 1.90, 2.35 - 2.90 [2m, 8H, (CH<sub>2</sub>)<sub>4</sub>], 13.30 (br s, 1H, NOH); <sup>13</sup>C NMR (50.32 MHz, (CD<sub>3</sub>)<sub>2</sub>SO): δ 20.3, 22.2 [2t, (CH<sub>2</sub>)<sub>4</sub>], 137.7 (s, C=N).

**6b**: 65% yield, m.p. 101 - 103°C (EtOAc-hexane); UV (EtOH): λ<sub>max</sub> (lg ε) 236 nm (3.88); <sup>1</sup>H NMR (200.13 MHz, (CD<sub>3</sub>)<sub>2</sub>SO): δ 1.50 - 1.90 [m, 6H, (CH<sub>2</sub>)<sub>3</sub>], 2.52 - 2.73 (m, 4H, 2 CH<sub>2</sub>), 13.17 (s, 1H, NOH); <sup>13</sup>C NMR (50.32 MHz, (CD<sub>3</sub>)<sub>2</sub>SO): δ 25.9, 27.2, 30.6 [3t, (CH<sub>2</sub>)<sub>5</sub>], 141.9 (s, C=N).

6. X-ray analysis of **5a**: C<sub>7</sub>H<sub>13</sub>N<sub>3</sub>O<sub>2</sub>, M=171.20 g mol<sup>-1</sup>, colorless volatile crystals sealed in polyethylene capillary, crystal size 0.65 x 0.50 x 0.20 mm, a=10.899(2), b=6.489(1), c=12.506(2) Å, β=103.14(2)°, V=861.3(2) Å<sup>3</sup>, T=296(2) K, D<sub>cal</sub>=1.320 g cm<sup>-3</sup>, μ=8.20 cm<sup>-1</sup>, Z=4, monoclinic, space group P2<sub>1</sub>/n, Syntex P2<sub>1</sub> diffractometer, scan mode θ-2θ (2θ < 130°), 1464 independent evaporation corrected reflections, an analytical correction for absorption applied, H atoms refined isotropically, wR<sub>2</sub>=0.1191 and S=1.055 for all independent reflections (R=0.0428 for 1284 observed reflections [I > 2σ<sub>I</sub>], SHELXL-93). X-ray analysis of **5b**: C<sub>8</sub>H<sub>15</sub>N<sub>3</sub>O<sub>2</sub>, M=185.23 g mol<sup>-1</sup>, colorless volatile crystals sealed in polyethylene capillary, crystal size 0.50 x 0.45 x 0.15 mm, a=7.978(4), b=9.476(4), c=13.039(4) Å, β=93.42(3)°, V=984.0(7) Å<sup>3</sup>, T=298(2) K, D<sub>cal</sub>=1.250 g cm<sup>-3</sup>, μ=7.54 cm<sup>-1</sup>, Z=4, monoclinic, space group P2<sub>1</sub>/c, λ=1.54178 Å, scan mode θ-2θ (2θ < 114°), 1139 independent reflections, an analytical correction for absorption and correction for evaporation applied, H atoms were placed geometrically with free U<sub>iso</sub>, wR<sub>2</sub>=0.1971 and S=1.030 for all independent reflections (R=0.0700 for 607 observed reflections [I > 2σ<sub>I</sub>], SHELXL-93). Atomic coordinates of compounds **5a,b** have been deposited at the Cambridge Crystallographic Data Centre.
7. Allen, F.H.; Kennard, O.; Watson, D.G.; Brammer, L.; Orpen, A.G.; Taylor, R. *J. Chem. Soc. Perkin Trans. II*. **1987**, N 12, S1-S9.
8. Kano, K.; Anselme, J.-P. *J. Org. Chem.* **1993**, *58*, 1564-1567.
9. (a) Buettner, G. R. *Free Rad. Biol. Med.* **1987**, *3*, 259-303. (b) Janzen, E. G., Liu, J. I.-P. *J. Mag. Resonance*, **1973**, *9*, 510-512.
10. Grigor'ev, I. A.; Kirilyuk, I. A.; Starichenko, V. F.; Volodarsky, L. B. *Izv. Akad. Nauk SSSR, Ser. Khim.* **1989**, 1624-1630.
11. (a) Joseph, J.; Kalyanaraman, B.; Hyde, J. S. *Biochem. Biophys. Res. Commun.* **1993**, *192*, 926-934. (b) Woldman, Ya. Yu.; Khramtsov, V. V.; Grigor'ev, I. A.; Kirilyuk, I. A.; Utepbergenov, D. I. *Biochem. Biophys. Res. Commun.* **1994**, *202*, 195-203.
12. The reaction was carried out under continuous bubbling of argon through the boiling acetonitrile solution of **4a**. The stream of argon with formed NO gas was inserted into acetonitrile solution of NNR.
13. Kishida, H; Shudo, A.; Sakamoto, N.; Fujimoto, H.; Umeda K *Japan Patent* 05,222,006, **1993**; *Chem. Abstr.* **1994**, *120*, 25611j.