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

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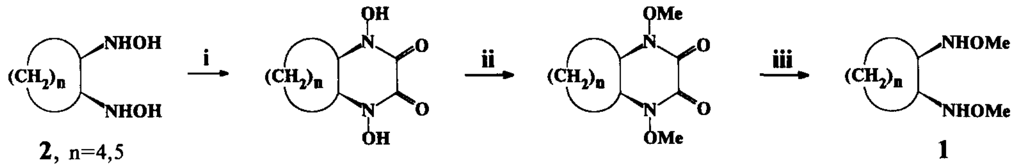
Abstract: Thermolysis of 1,2-bis(*N*-methoxy-*N*-nitrosoamino)cycloalkanes in organic solvents led to 4,5-dihydro-1,2,3-triazole 2-oxides.

1,2,3-Triazole 1-oxides are well known heterocyclic compounds[1] whereas their 4,5-dihydro derivatives were synthesized in the last decade.[2] 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.

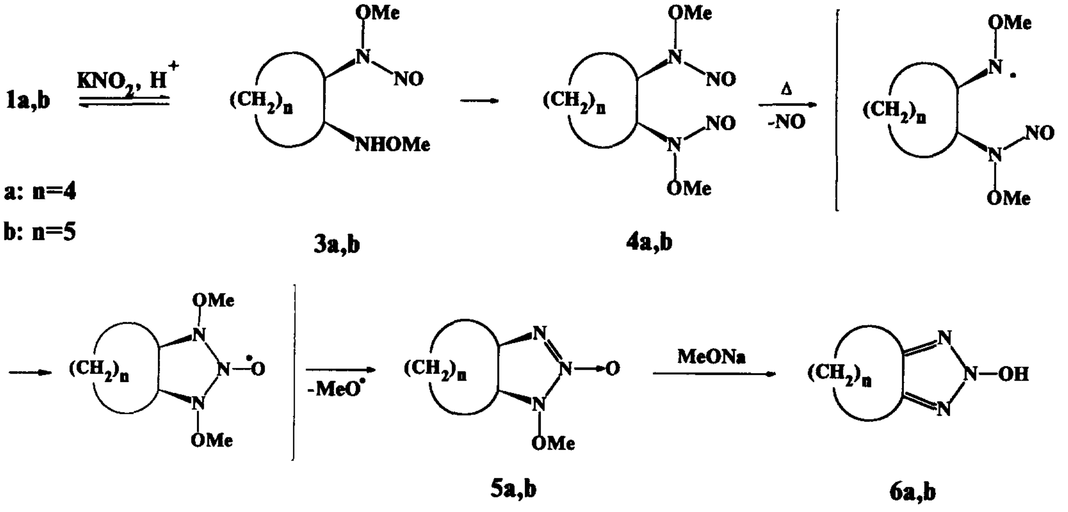
Recently, we reported a convenient route to *cis*-1,2-bismethoxyaminocycloalkanes **1**[3] from *cis*-1,2-bishydroxylamines **2**[4] upon acylation, subsequent *O*-alkylation and then deprotection (Scheme **1**).



Scheme **1**. **i**. $(COOEt)_2$, MeOH, reflux, 3 h. **ii**. MeI, K_2CO_3, MeOH - H_2O, r.t.,48 h (or CH_2N_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 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}H NMR spectra). The use of 2 equiv of KNO_2 under the same conditions afforded *N,N'*-dinitroso derivatives **4a,b**.

Refluxing of bisnitroso compound **4a** with $NH_2NH_2{\cdot}H_2O$ 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 $NH_2NH_2{\cdot}H_2O$ 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.[5] X-ray study of compounds **5a,b** showed the *cis*-ring fusion of triazole and cycloalkane cycles (Fig. 1).[6] 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)[7] and the length 1.389(1) Å in 4-imino-5,5-dimethyl-3-phenyl-4,5-dihydro-1,2,3-triazole 1-oxide.[2b]

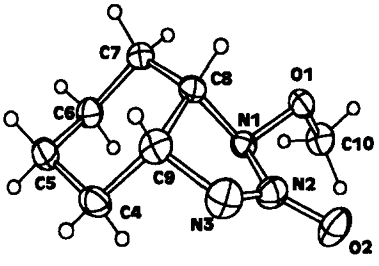


Fig. 1 The crystal structure of molecule **5a**. Selected bond length (Å) and angles (°): N(1)-N(2) 1.493(2), N(2)=N(3) 1.257(2), N(2)-O(2) 1.237(2), N(1)-O(1) 1.403(2), O(1)-N(1)-C(8) 109.7(1), O(1)-N(1)-N(2) 107.4(1), N(1)-N(2)-O(2) 117.7(1), N(3)-N(2)-O(2) 128.1(2).

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 includes the formation of NO and methoxyl radicals (Scheme 2).[8] 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^{γ}_{H}=1.9 G; a^{β}_{H}=7.0 G; a_N=13.6 G) was observed.[9] To detect NO release from the reaction mixture nitronylnitroxide, (5,5-dimethyl-2,4-diphenyl-4-methoxy-2-imidazoline-3-oxide 1-oxyl, NNR[10]) as specific spin trap for nitric oxide,[11] has been used.[12] The characteristic transformation of ESR spectrum of NNR (a_{N1}= a_{N3}=7.1 G) in the ESR spectrum of iminonitroxide (a_{N1}=7.5 G, a_{N3}=4.0 G) formed under reaction with NO has been observed.[11b]

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.[13]

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.

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5. All new compounds gave spectroscopic and elemental analyses data in agreement with the assigned structure.
   4a: 100% yield, viscous yellow oil; IR (CCl_4): 1455 cm^{-1} (N-N=O); UV (EtOH): λ_{max} (lg ε) 235 nm (4.00); ^1H NMR (200.13 MHz, $CDCl_3$): δ 1.42 - 1.66, 1.77 - 2.11, 2.21 - 2.46 [3 m, 8H, $(CH_2)_4$], 3.79 (s, 6H, 2 MeO), 4.69 - 4.86 (m, 2H, 2 CH).
   4b: 95% yield, viscous yellow oil; IR (CCl_4): 1455 cm^{-1} (N-N=O); UV (EtOH): λ_{max} (lg ε) 235 nm (3.95); ^1H NMR (200.13 MHz, $CDCl_3$): δ 1.47 - 1.70, 1.84 - 2.08, 2.20 - 2.44 [3 m, 10H, $(CH_2)_5$], 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_4): 1580 cm^{-1} (N=N→O); UV (EtOH): λ_{max} (lg ε) 218 nm (3.88); ^1H NMR (200.13 MHz, $CDCl_3$): δ 1.10 - 2.20 [m, 8H, $(CH_2)_4$], 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); ^{13}C NMR (50.32 MHz, $CDCl_3$): δ 20.1, 22.1, 26.7 [3t, $(CH_2)_4$], 60.4 (d, CH), 62.4 (d, CH), 64.6 (q, MeO); MS: m/z (% relative intensity) 171 (0.8, M^+), 127 (17.1), 96 (23.5), 86 (100.0); calcd for $C_7H_{13}N_3O_2$ m/z 171.1008, measured m/z 171.1000.
   5b: 63% yield, m.p. 50 - 51°C (hexane); IR (KBr): 1555 cm^{-1} (N=N→O); UV (EtOH): λ_{max} (lg ε) 221 nm (3.80); ^1H NMR (200.13 MHz, $CDCl_3$): δ 1.16 - 2.17 [m, 10H,

$(CH_2)_5]$, 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); ^{13}C NMR (50.32 MHz, CD Cl_3): δ 23.6, 26.5, 27.0, 28.2, 30.8 [5t, $(CH_2)_5$], 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_{max} (lg ε) 239 nm (3.83); ^1H NMR (200.13 MHz, $(CD_3)_2SO$): δ 1.70 - 1.90, 2.35 - 2.90 [2m, 8H, $(CH_2)_4$], 13.30 (br s, 1H, NOH); ^{13}C NMR (50.32 MHz, $(CD_3)_2SO$): δ 20.3, 22.2 [2t, $(CH_2)_4$], 137.7 (s, C=N).

6b: 65% yield, m.p. 101 - 103°C (EtOAc-hexane); UV (EtOH): λ_{max} (lg ε) 236 nm (3.88); ^1H NMR (200.13 MHz, $(CD_3)_2SO$): δ 1.50 - 1.90 [m, 6H, $(CH_2)_3$], 2.52 - 2.73 (m, 4H, 2 CH_2), 13.17 (s, 1H, NOH); ^{13}C NMR (50.32 MHz, $(CD_3)_2SO$): δ 25.9, 27.2, 30.6 [3t, $(CH_2)_5$], 141.9 (s, C=N).

6. X-ray analysis of **5a**: $C_7H_{13}N_3O_2$, M=171.20 g mol^{-1}, 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, ß=103.14(2)°, V=861.3(2) Å^3, T=296(2) K, D_{cal}=1.320 g cm^{-3}, μ=8.20 cm^{-1}, Z=4, monoclinic, space group $P2_1/n$, Syntex $P2_1$ diffractometer, scan mode θ-2θ (2θ < 130°), 1464 independent evaporation corrected reflections, an analytical correction for absorption applied, H atoms refined isotropically, wR_2=0.1191 and S=1.055 for all independent reflections (R=0.0428 for 1284 observed reflections [$I > 2\sigma_I$], SHELXL-93).
X-ray analysis of **5b**: $C_8H_{15}N_3O_2$, M=185.23 g mol^{-1}, 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, ß=93.42(3)°, V=984.0(7) Å^3, T=298(2) K, D_{cal}=1.250 g cm^{-3}, μ=7.54 cm^{-1}, Z=4, monoclinic, space group $P2_1/c$, 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_{iso}, wR_2=0.1971 and S=1.030 for all independent reflections (R=0.0700 for 607 observed reflections [$I > 2\sigma_I$], SHELXL-93). Atomic coordinates of compounds **5a,b** have been deposited at the Cambridge Crystallographic Data Centre.
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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.
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