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Reaction of 3,3-disubstituted 1-chloromethoxy-1-triazene 2-oxides with tetramethylammonium hydroxide

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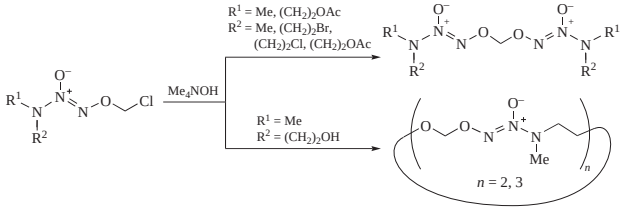
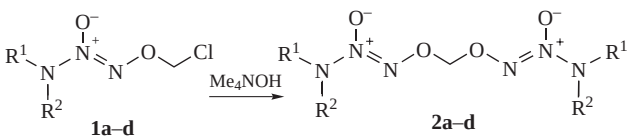
The reaction of 3,3-disubstituted 1-chloromethoxy-1-triazene 2-oxides with tetramethylammonium hydroxide results in corresponding [methylenebis(oxy)]bis(1-triazene 2-oxides). Treatment of 1-chloromethoxy-3-(2-hydroxyethyl)-3-methyl-1-triazene 2-oxide with Me_4NOH gives 16- and 24-membered intermolecular cyclization products.



Nitrogen monoxide NO is one of the versatile required regulators of cellular metabolism functions in living organisms. To date, a broad range of various compounds that can serve as nitrogen monoxide generators in mammal organisms are reported.[1] On the other hand, intense search for new compounds capable of generating nitrogen monoxide is underway.[2–7] In this context, derivatives of 1-alkoxy-1-triazene 2-oxides which have become known rather recently[8] deserve attention. Some of them are undergoing in-depth biological or preclinical studies as means against diseases of the cardiovascular system, kidneys, pulmonary insufficiency, oncological diseases, and diabetes.[9–11]

Previously,[12–14] we described the synthesis of new alkoxytriazene oxide derivatives, [methylenebis(oxy)]bis(3,3-dialkyl-1-triazene 2-oxides), *i.e.*, compounds incorporating two oxytriazene oxide moieties linked through a methylene unit, which are of interest as potential nitrogen monoxide donors. One method involved the alkylation of sodium salts of 1-hydroxy-3,3-dialkyl-1-triazene 2-oxides with chloromethyl ethers of 1-oxy-3,3-dialkyl-1-triazene 2-oxides,[12–14] the other one was the reaction of salts of the same type with dibromomethane.[12] In both cases, the yields of the target compounds did not exceed 30%. In continuation, we have found that treatment of chloromethyl ethers **1a**–**d** (Scheme 1) with tetramethylammonium hydroxide affords [methylenebis(oxy)]bis(3,3-dialkyl-1-triazene 2-oxides).† The yields of products **2** considerably depend on the structure of substituents at 3-position of the chloromethyl ethers **1**. The highest yields were achieved for compounds **2a** (80%) and **2b** (68%). The presence of *N*-(2-haloethyl) substituents in chloromethyl ethers (**1c**,**d**) notably drops the yields: 17% for chloroethyl derivative **2c** and 10% for bromoethyl derivative **2d**.



1a–d **2a–d**

a $R^1 = R^2 = Me$
b $R^1 + R^2 = (CH_2CH_2)_2O$
c $R^1 = Me$, $R^2 = CH_2CH_2Cl$
d $R^1 = Me$, $R^2 = CH_2CH_2Br$

Scheme 1

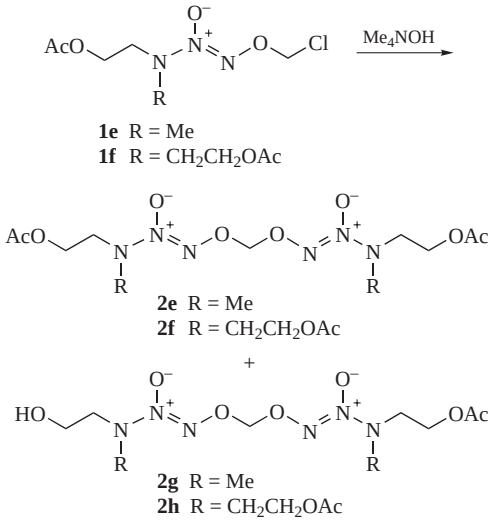
† Chloromethyl ethers **1a**,**b**,[12] **1c**–**e** and **3**,[13] **1f**[15] were synthesized using reported procedures.

2,10-Dimethyl-5,7-dioxa-2,3,4,8,9,10-hexaaza-3,8-undecadiene 3,9-dioxide[12] **2a**. Base Me_4NOH (0.12 g, 0.66 mmol) was added to compound **1a** (0.1 g, 0.45 mmol) in acetonitrile (5 ml). The mixture was stirred for 5 days at room temperature. The solvent was removed by evaporation. Product **2a** (0.06 g, 83%), mp 62–63 °C, was isolated from the residue using preparative TLC ($CHCl_3$–MeOH, 9 : 1). The spectral characteristics of the product were identical to those reported previously.

1,7-Di(morpholin-4-yl)-1,2,6,7-tetraaza-3,5-dioxa-1,6-heptadiene 1,7-dioxide[12] **2b** was obtained similarly from Me_4NOH (0.071 g, 0.39 mmol) and compound **1b** (0.064 g, 0.33 mmol) in MeCN (3 ml), 20 °C, 3 h. Product **2b** (0.034 g, 68%) was isolated by preparative TLC (ethyl acetate–light petroleum, 2 : 1), colourless crystals, mp 119–121 °C (EtOH). The spectral characteristics were identical to those reported previously.

1,13-Dichloro-3,11-dimethyl-6,8-dioxa-3,4,5,9,10,11-hexaazatrideca-4,9-diene 4,10-dioxide **2c** was obtained similarly from Me_4NOH (0.08 g, 0.44 mmol) and reactant **1c** (0.038 g, 0.19 mmol) in MeCN (3 ml), 20 °C, 3.5 h. Product **2c** (0.005 g, 17%) was isolated by preparative TLC (ethyl acetate–light petroleum, 1 : 1). IR (thin layer, ν/cm^{-1}): 1502, 1440, 1257, 1067, 1024, 942. ^{1}H NMR ($CDCl_3$) δ: 3.16 (s, 6H, 2MeN), 3.69 (m, 8H, 4CH_2), 5.78 (s, 2H, OCH_2O). MS (ESI), *m*/*z*: 319.0683, 321.0654 $[M+H]^+$, 336.0948, 338.0919 $[M+NH_4]^+$, 357.0225 $[M+K]^+$ (calc. for $C_7H_{16}Cl_2N_6O_4$, *m*/*z*: 319.0676, 321.0647 $[M+H]^+$, 336.0938, 338.0910 $[M+NH_4]^+$, 357.0242 $[M+K]^+$).

1,13-Dibromo-3,11-dimethyl-6,8-dioxa-3,4,5,9,10,11-hexaazatrideca-4,9-diene 4,10-dioxide **2d** was obtained similarly from Me_4NOH (0.08 g, 0.44 mmol) and reactant **1d** (0.065 g, 0.22 mmol) in MeCN (3 ml), 20 °C, 3 h. Product **2d** (0.006 g, 11%) was isolated by preparative TLC (ethyl acetate–light petroleum, 1 : 1). IR (KBr, ν/cm^{-1}): 1501, 1440, 1257, 1234, 1066, 1024, 943. ^{1}H NMR ($CDCl_3$) δ: 3.15 (s, 6H, 2MeN), 3.50 (t, 4H, 2CH_2, *J* 6.7 Hz), 3.78 (t, 4H, 2CH_2, *J* 6.7 Hz), 5.75 (s, 2H, OCH_2O). MS (ESI), *m*/*z*: 408.9643 $[M+H]^+$, 425.9914 $[M+NH_4]^+$, 428.9487, 430.9464, 432.9442 $[M+Na]^+$, 446.9201 $[M+K]^+$ (calc. for $C_7H_{16}Br_2N_6O_4$, *m*/*z*: 408.9652 $[M+H]^+$, 425.9918 $[M+NH_4]^+$, 428.9492, 430.9472, 432.9451 $[M+Na]^+$, 446.9211 $[M+K]^+$).



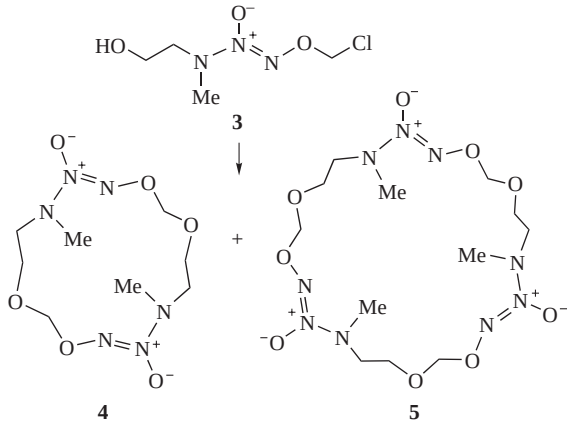
Scheme 2

The reaction of interest proceeds ambiguously in the case of acetoxy derivatives **1e**,**f** (Scheme 2).‡ Their treatment with Me_4NOH led to the corresponding diacetate **2e** or tetraacetate **2f**. However, the process is acompanied by hydrolysis of one acetyl group to give monoacetate **2g** or triacetate **2h**, respectively. The ratio of the products strongly depends on the reaction temperature. At room temperature, compounds **2e** and **2f** are formed in 35 and 24% yields, while the yields of **2g** and **2h** are 26 and 31%, respectively. Lowering the reaction temperature to 0 °C slows down the hydrolysis, and the yields of **2e** and **2f** increase to 56%, whereas those of **2g** and **2h** decrease to 10%.

The formation of symmetric compounds **2** can probably be explained by conversion of chloromethyl ethers **1a**–**f** into the corresponding salts of hydroxytriazene oxides under the reaction conditions, followed by their reactions with the remaining chloromethyl ether.

The similar reaction of 3-(2-hydroxyethyl)-3-methyl-1-chloromethoxy-1-triazene 2-oxide **3** takes a quite different route (Scheme 3).§ In this case, intermolecular condensation is followed by cyclization to give the first representatives of oxytriazene *N*-oxides **4**, **5** of two new chemotypes, namely, 16- and 24-membered heterocycles that incorporate two (compound **4)** or three (compound **5**) 1-oxytriazene 2-oxide structural moieties in the ring. The yields of compounds **4** and **5** were 37 and 3%, respectively. Their structures were determined from spectral data and elemental analysis, and confirmed by X-ray single crystal analysis for compound **4** (Figure 1).¶

In summary, we have developed a new method for the synthesis of [methylenebis(oxy)]bis(3,3-dialkyl-1-triazene 2-oxides), including previously unknown ones, that allows one to prepare target products in higher yields as compared to the methods



Scheme 3

‡ *1,13-Diacetoxy-3,11-dimethyl-6,8-dioxa-3,4,5,9,10,11-hexaazatrideca-4,9-dien-13-ol 4,10-dioxide* **2e** and *1-acetoxy-3,11-dimethyl-6,8-dioxa-3,4,5,9,10,11-hexaazatrideca-4,9-dien-13-ol 4,10-dioxide*[14] **2g**.

Method A. Base Me_4NOH (0.036 g, 0.2 mmol) was added with stirring to a solution of compound **1e** (0.038 g, 0.17 mmol) in dry MeCN (3 ml), and the mixture was stirred at 20 °C for 1 h, then the solvent was removed *in vacuo*. Compounds **2e** (0.007 g, 35%) and **2g** (0.007 g, 26%) were isolated as an oil from the residue by preparative TLC with ethyl acetate as the eluent.

Method B. Base Me_4NOH (0.029 g, 0.16 mmol) was added with stirring and ice cooling to a solution of compound **1e** (0.031 g, 0.14 mmol) in dry MeCN (3 ml), the cooling was removed, the reaction mixture was allowed to heat up (~15 min) and stirred at 20 °C for 2 h, then the solvent was removed *in vacuo*. Products **2e** (0.014 g, 56%) and **2g** (0.002 g, 9%) were isolated from the residue by preparative TLC with ethyl acetate as the eluent.

For **2e**: oil. IR (thin layer, ν/cm^{-1}): 1741 (CO), 1504, 1448, 1232, 1045, 1024, 940. ^{1}H NMR ($CDCl_3$) δ: 2.10 (s, 6H, 2MeCO), 3.16 (s, 6H, 2MeN), 3.70 (t, 4H, 2CH_2, *J* 7.4 Hz), 4.28 (t, 4H, 2CH_2, *J* 7.4 Hz), 5.78 (s, 2H, OCH_2O). MS (ESI), *m*/*z*: 367.1563 $[M+H]^+$, 384.1827 $[M+NH_4]^+$, 389.1378 $[M+Na]^+$, 405.1118 $[M+K]^+$ (calc. for $C_{11}H_{22}N_6O_8$, *m*/*z*: 367.1572 $[M+H]^+$, 384.1837 $[M+NH_4]^+$, 389.1391 $[M+Na]^+$, 405.1131 $[M+K]^+$).

For **2g**: oil, the spectral characteristics were identical to those reported previously.

1,3,11,13-Tetraacetoxy-6,8-dioxa-3,4,5,9,10,11-hexaazatrideca-4,9-dien-13-ol 4,10-dioxide[16] **2f** and *1,3,11-triacetoxy-6,8-dioxa-3,4,5,9,10,11-hexaazatrideca-4,9-dien-13-ol 4,10-dioxide* **2h**.

Method A. Base Me_4NOH (0.015 g, 0.083 mmol) was added with stirring to a solution of reactant **1f** (0.02 g, 0.07 mmol) in dry MeCN (2 ml), and the mixture was stirred at 20 °C for 3 h 20 min, then the solvent was removed *in vacuo*. Products **2f** (0.004 g, 24%) and **2h** (0.005 g, 31%) were isolated as oils by preparative TLC with ethyl acetate as the eluent.

Method B. Base Me_4NOH (0.04 g, 0.22 mmol) was added with stirring and ice cooling to a solution of reactant **1f** (0.05 g, 0.17 mmol) in dry MeCN (4 ml), the cooling was removed, the mixture was allowed to heat up (~15 min) and stirred at 20 °C for 5 h, then the solvent was removed *in vacuo*. Products **2f** (0.024 g, 56%) and **2h** (0.004 g, 10%) were isolated by preparative TLC with ethyl acetate as the eluent.

For **2f**: oil, the spectral characteristics were identical to those reported previously.

For **2h**, oil. ^{1}H NMR ($CDCl_3$,) δ: 2.10 (s, 9H, 3MeCO), 3.58 (t, 2H, CH_2), 3.70 (t, 6H, 3CH_2, *J* 5 Hz), 3.80 (t, 2H, CH_2), 4.30 (t, 6H, 3CH_2, *J* 5 Hz), 5.79 (s, 2H, OCH_2O). MS (ESI), *m*/*z*: 469.1871 $[M+H]^+$, 486.2139 $[M+NH_4]^+$, 491.1693 $[M+Na]^+$, 507.1435 $[M+K]^+$ (calc. for $C_{15}H_{28}N_6O_{11}$, *m*/*z*: 469.1889 $[M+H]^+$, 486.2154 $[M+NH_4]^+$, 491.1708 $[M+Na]^+$, 507.1448 $[M+K]^+$).

§ *4,12-Dimethyl-1,7,9,15-tetraoxa-2,3,4,10,11,12-hexaazacyclohexadeca-2,10-diene 3,11-dioxide* **4** and *4,12,20-trimethyl-1,7,9,15,17,23-hexaoxa-2,3,4,10,11,12,18,19,20-nonaazacyclotetracosa-2,10,18-triene 3,11,19-trioxide* **5**. Base Me_4NOH (0.15 g, 0.83 mmol) was added in small portions, with stirring and ice cooling, to a solution of compound **3** (0.128 g, 0.7 mmol) in dry MeCN (7 ml), and the mixture was stirred for 70 min with ice water cooling, then the solvent was removed *in vacuo*. Products **4** (0.038 g, 37%) and **5** (0.003 g, 3%) were isolated by preparative TLC with ethyl acetate as the eluent.

Compound **4**: mp 176–179 °C (EtOH). ^{1}H NMR ($CDCl_3$) δ: 3.15 (s, 6H, 2MeN), 3.65 (t, 4H, 2CH_2, *J* 4.5 Hz), 3.80 (t, 4H, 2CH_2, *J* 4.5 Hz), 5.24 (s, 4H, 2CH_2). MS (ESI), *m*/*z*: 295.1367 $[M+H]^+$, 312.1630 $[M+NH_4]^+$, 317.1178 $[M+Na]^+$, 333.0914 $[M+K]^+$ (calc. for $C_8H_{18}N_6O_6$, *m*/*z*: 295.1361 $[M+H]^+$, 312.1626 $[M+NH_4]^+$, 317.1180 $[M+Na]^+$, 333.0919 $[M+K]^+$). Found (%): C, 32.58; H, 6.16; N, 28.39. Calc. for $C_8H_{18}N_6O_6$ (%): C, 32.65; H, 6.17; N, 28.56.

Compound **5**: ^{1}H NMR ($CDCl_3$) δ: 3.10 (s, 9H, 3MeN), 3.61 (t, 6H, 3CH_2, *J* 4.9 Hz), 3.90 (t, 6H, 3CH_2, *J* 4.9 Hz), 5.26 (s, 6H, 3CH_2). MS (ESI), *m*/*z*: 442.2007 $[M+H]^+$, 459.2279 $[M+NH_4]^+$, 464.1828 $[M+Na]^+$, 480.1567 $[M+K]^+$ (calc. for $C_{12}H_{27}N_9O_9$, *m*/*z*: 442.2004 $[M+H]^+$, 459.2270 $[M+NH_4]^+$, 464.1824 $[M+Na]^+$, 480.1563 $[M+K]^+$).

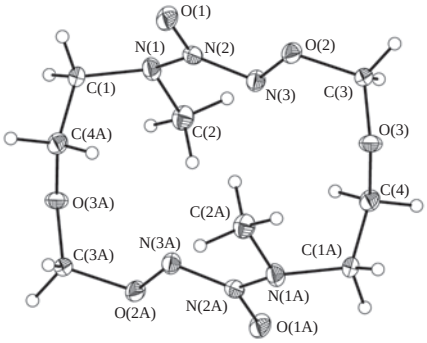


Figure 1 General view of compound **4** in representation of atoms *via* thermal ellipsoids at 50% probability level. In a crystal, the molecule occupies a special position, *viz*., the inversion centre.

reported previously. The first two representatives of cyclic analogues have been obtained.

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¶ *Crystallographic data*. Crystals of **4** ($C_8H_{18}N_6O_6$, M = 294.28) are triclinic, space group $P\bar{1}$, at 120 K: a = 6.5565(13), b = 7.0088(14) and c = 7.1970(14) Å, α = 74.562(4), β = 86.138(4), γ = 84.836(4)°, V = = 317.17(11) Å^3, Z = 1 (Z' = 1/2), d_{calc} = 1.541 g cm^{-3}, μ(MoKα) = = 1.31 cm^{-1}, F(000) = 156. Intensities of 3948 reflections were measured with a Bruker APEX2 DUO CCD diffractometer [λ(MoKα) = 0.71072 Å, ω-scans, 2θ < 58°], and 1686 independent reflections (R_{int} = 0.0269) were used in further refinement. The structure was solved by direct method and refined by the full-matrix least-squares technique against F^2 in the anisotropic-isotropic approximation. The positions of hydrogen atoms were calculated, and they were refined in the isotropic approximation within the riding model. The refinement converged to wR_2 = 0.1018 and GOF = 1.035 for all the independent reflections [R_1 = 0.0391 was calculated against F for 1411 observed reflections with $I > 2\sigma(I)$]. All calculations were performed using SHELXTL PLUS 5.0.[17]

CCDC 1545076 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre *via* http://www.ccdc.cam.ac.uk.

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