Synthesis and properties of 2-hydroxyethyl derivatives of methylene-bis(1-oxy-3,3-dialkyl-1-triazene 2-oxides)

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Synthetic approach to 2-hydroxyethyl derivatives of methylene-bis(1-oxy-3,3-dialkyl-1-triazene 2-oxides), promising NO donors, which can release NO in living organisms was developed. Some transformations of the hydroxyethyl moiety of the synthesized compounds were studied.

Key word: methylene-bis(1-oxy-1-triazene 2-oxides), hydroxyethyl derivatives, bromination, acetylation, oxidation, carbamoylation.

Nitric oxide (NO) is of critical importance as a mediator and a regulator of numerous processes in living organisms. Nitric oxide plays an essential role in cardiovascular homeostasis, *e.g.*, it is involved in such physiological functions as blood flow, respiration, thermoregulation, and metabolism. To date, a wide variety of chemical compounds capable of producing nitric oxide in mammals are known. Derivatives of guanidine and hydroxylamine, *N*-nitro derivatives, *C*-nitrates and nitrites, and some compounds of other classes were found to be the NO donors.[1] The representatives of these classes of compounds are used in pharmacology, for instance, 1-alkoxy-3,3-dialkyl-1-triazene 2-oxides. The number of publications in this field grows from year to year.[2—6] Some compounds of this type are in detailed study of biological properties or have entered preclinical trials. These compounds are of interest as medications for the treatment of cardiovascular, kidney, and lung diseases, as well as cancer, and diabetes.

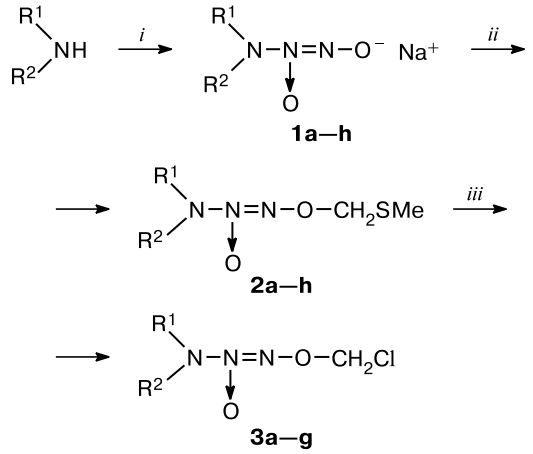
Functionalization of oxytriazene *N*-oxides can serve for widening a range of compounds with promising applications. Earlier,[7,8] we have shown the possibility to modify oxytriazene *N*-oxides.

In the previous work,[9] we have described the synthesis of a new class of potential NO donors, derivatives of 1-alkoxy-3,3-dialkyl-1-triazene 2-oxides, namely, methylene-bis(1-oxy-3,3-dilakyl-1-triazene 2-oxides).[9]

With the aim to broaden the scope of these compounds, in the present work we elaborated synthetic approaches towards similar molecules bearing 2-hydroxyethyl group as one of the alkyl substituents at 3-position and studied functionalization of 2-hydroxyethyl moiety of the synthesized compounds.

We investigated two different approaches to methylene-bis-oxytriazene 2-oxides bearing 2-hydroxyethyl moiety. Starting from sodium salts of 1-triazene 2-oxides **1a—g** *via* sulfides **2a—g**, we synthesized *O*-chloromethyl derivatives of 1-oxy-3,3-dialkyl-1-triazene 2-oxides **3a—g** (Scheme 1). Compounds **3a—g** were the starting materials for the implementation of both synthetic approaches.

Scheme 1



Compounds **1—3**	R^1	R^2	Compounds **1—3**	R^1	R^2
a	Me	Me	**e**	$(CH_2)_4$	
b	Et	Et	**f**	$(CH_2)_5$	
c	Me	Et	**g**	$(CH_2)_2O(CH_2)_2$	
d	Bn	Me	**h**	Me	CH_2CH_2OH

Reagents: *i.* NO, MeONa; *ii.* $MeSCH_2Cl$, NaI, K_2CO_3, DMF; *iii.* SO_2Cl_2, CH_2Cl_2.

The first approach involved reaction of compounds **3a—h*** with sodium salt **1h** in DMF at room temperature

* Compound **3h** was synthesized by the reaction of **2h** with SO_2Cl_2 in dichloromethane (see Schemes 1 and 3).

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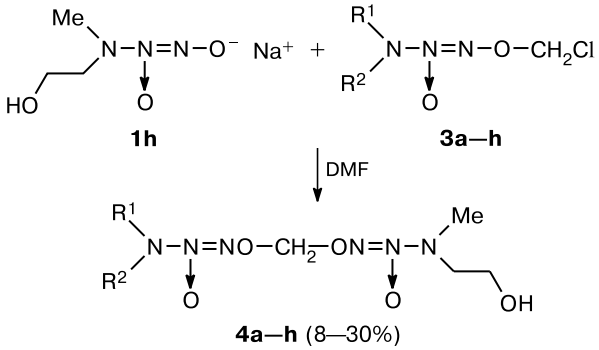
to give the target mono-hydroxyethyl derivatives of methylene-bis(oxytriazene 2-oxides) **4a**—**h** in 8—30% yields (Scheme 2).

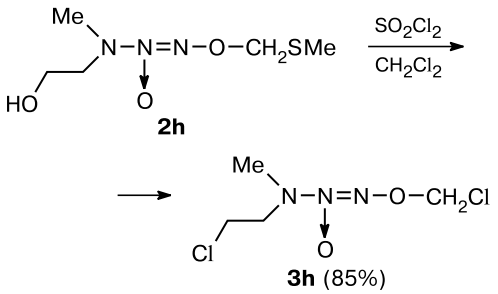
Scheme 2



Compounds **3**, **4**	R^1	R^2	Compounds **3**, **4**	R^1	R^2
a	Me	Me	**e**	$(CH_2)_4$	
b	Et	Et	**f**	$(CH_2)_5$	
c	Me	Et	**g**	$(CH_2)_2O(CH_2)_2$	
d	Bn	Me	**h**	Me	CH_2CH_2Cl

The idea of the second approach to 2-hydoxyethyl derivatives of methylene-bis-oxitriazene 2-oxides was the synthesis of hitherto unknown *O*-chloromethyl derivative of 3-(2-hydroxyethyl)-1-oxy-3-methyl-3-triazene 2-oxide. We hoped to synthesize this compound by the reaction of triazene oxide **2h** (see Scheme 1) with SO_2Cl_2 under mild conditions (20°, 1 h). However, under these conditions the reaction produces compound **3h** in high yield (85%) instead of the target expected product (Scheme 3).

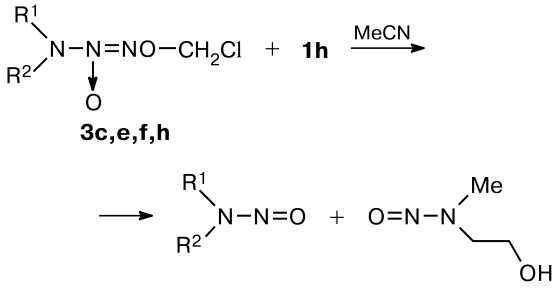
Scheme 3



All synthesized 2-hydroxyethyl derivatives of methylene-bis-oxytriazene *N*-oxides **4a**—**h** are oils. Structures of the synthesized compounds were established by IR and NMR spectroscopy and high resolution mass spectrometry. Yields of compounds **4a**—**h** did not exceed 30% due apparently to the ability of the ambidentate anion of salt **1h** to react with chloromethyl derivative following two reaction directions, only one of which afforded triazene *N*-oxides.

It is of note that the attempts to perform the reaction (see Scheme 2) in MeCN failed. Alkylation of sodium salt **1h** with chloromethyl derivatives **3c**, **3e**, **3f**, and **3h** in MeCN leads predominantly to a mixture of *N*-nitrosamine derivatives instead of target methylene-bis-triazene oxides. Apparently, MeCN favors the other center of the ambidentate anion of salt **1h** to react and subsequent decomposition of an unstable intermediate gives nitrosamines (Scheme 4).

Scheme 4



Methylene-bis(1-oxy-3,3-dialkyl-1-triazene 2-oxides) bearing the *N*-hydroxyethyl moieties **4** were found to be very convenient building blocks for the synthesis of new monofunctionalized derivatives with potential biological activity. Thus, hydroxyethyl derivatives **4a** and **4e** react with bromosuccinimide in the presence of triphenylphosphine to give the corresponding bromoethyl derivatives **5a** and **5b** in good yield (Schemes 5 and 6).

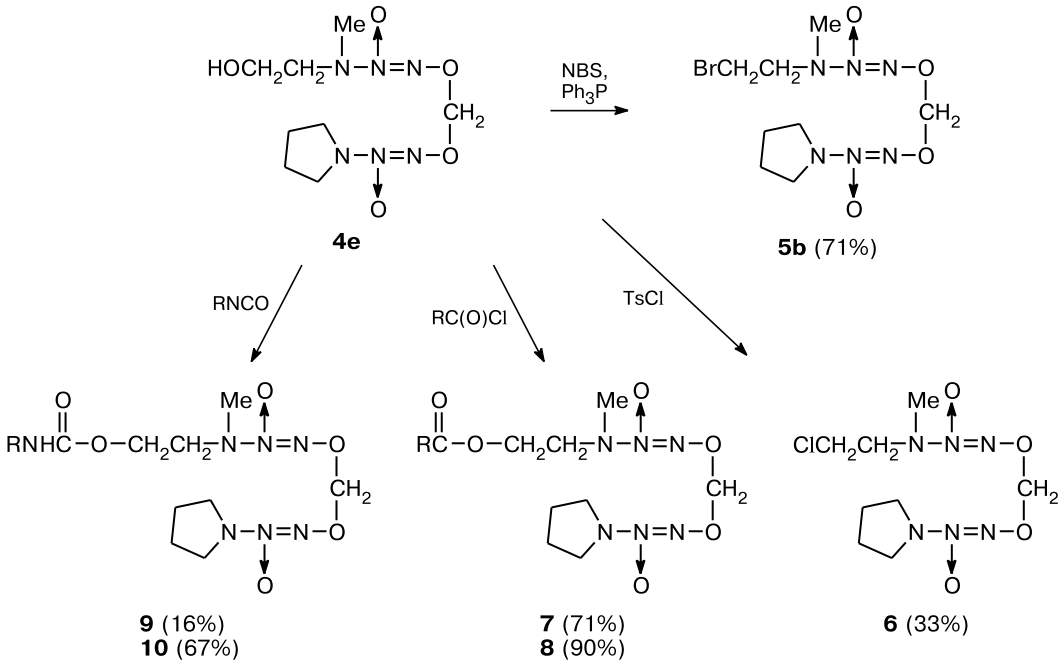
It is interesting to note that the reaction of 2-hydroxyethyl derivative **4e** with tosyl chloride does not stop at the tosylate stage and proceeds further to give chloroethyl derivative **6**.

Acid chlorides smoothly acetylate the hydroxy group of 2-hydroxyethyl derivatives of methylene-bis(oxytriazene oxides) producing the corresponding products **7** and **8** in high yields (70—90%) (see Scheme 5).

This concerns also the reactions of 2-hydroxyethyl derivatives of methylene-bis(oxytriazene oxides) with aromatic and heterocyclic isocyanates affording the corresponding urethane derivatives **9** and **10** (see Scheme 5). However, in this case the reaction outcome strongly depends on the nature of the substituent in the starting isocyanate (the yields of the target product varied from 16 to 67%).

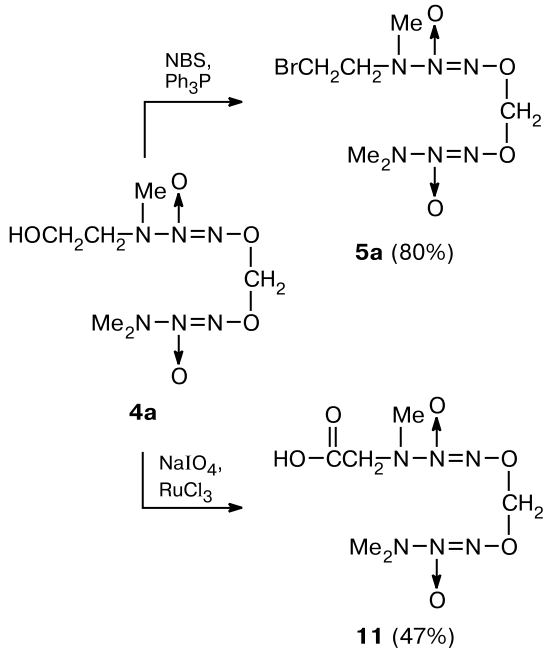
In all mentioned reactions, the ethylene unit of the hydroxyethyl substituent retains. Using compound **4a** as an example, we demonstrated that oxidation of compounds **4** with sodium periodate in the presence of $RuCl_3$ results in conversion of hydroxymethyl moiety to carbonyl group while other sensitive bonds remain unchanged. Oxidation

Scheme 5



R = Me (**7**), CH_2Cl (**8**), Ph (**9**), 3-pyridyl (**10**)

Scheme 6



of **4a** produces the corresponding product **11** in 47% yield (see Scheme 6).

In summary, the studied reactions may be useful in rational synthesis of functionalized methylene-bis(oxytriazene *N*-oxides), which in turn may be of interest as convenient building blocks in the synthesis of compounds possessing valuable pharmacological properties.

Experimental

The reaction course was monitored by TLC using precoated Silufol UV-254 plates. IR spectra were recorded with a Bruker ALPHA-T spectrophotometer. NMR spectra were run on a Bruker AM-300 instrument. High resolution electrospray ionization mass spectrometry was performed with a Bruker micrOTOF II instrument. Melting points were measured on Kofler apparatus. Sodium salts **1a**—**e**,**g** and thiomethyl (**2a**—**e**,**g**) and chloromethyl (**3a**—**e**,**g**) triazene oxide derivatives were synthesized by the known procedures.[9] Compounds **3f** and **3h** were obtained similarly.

1-Hydroxy-(3,3-pentamethylene)-1-triazene 2-oxide sodium salt (1f)[10]. A 500 mL three-neck flask equipped with a mechanical stirrer, a condenser, a ground sleeve stirrer gland, and a gas inlet adapter was charged with piperidine (10 g, 11.6 mL, 0.119 mol), 25% MeONa in MeOH (24 mL), diethyl ether (200 mL), and methanol (40 mL). Nitric oxide was passed through a vigorously stirred reaction mixture for 8 h maintaining the NO overpressure of 13—20 mm Hg. Thick residue formed was collected by filtration, washed with diethyl ether, dried first on air and then under oil pump vacuum to give the target sodium salt **1f** in the yield of 9 g (45%). ^{1}H NMR (D_2O), δ: 1.45 (m, 2 H, CH_2); 1.70 (m, 4 H, 2 CH_2); 3.00 (m, 4 H, 2 CH_2).

1-Hydroxy-[3-(2-hydroxyethyl)-3-methyl]-1-triazene 2-oxide sodium salt (1h)[11] was synthesized as described above from 2-hydroxyethyl-1-methylamine (15 g, 0.2 mol). Nitric oxide was passed for 16 h, then the liquid was decanted, and the syrupy precipitate was dissolved in minimum amount of MeOH and the

solution was diluted with EtOAc. The precipitate was collected by filtration, washed with diethyl ether (2×100 mL), and dried *in vacuo* to give the title product **1h** in the yield of 18.3 g (58%). ^{1}H NMR (D_2O), δ: 2.70 (s, 3 H, CH_3N); 3.00 (t, 2 H, CH_2N, J = 5.0 Hz); 3.50 (t, 2 H, CH_2O, J = 5.0 Hz).

Synthesis of thio derivatives 2f,h (general procedure). To a suspension of K_2CO_3 (0.01 mol) and NaI (0.001 mol) in DMF (5 mL) cooled to 0 °C, chloromethyl methyl sulfide (0.025 mol) was added dropwise with stirring. The reaction mixture was stirred at 0 °C for 10 min, then the corresponding salt **1f**,**h** (0.02 mol) was added. The cooling was removed and the reaction mixture was stirred 8 h, diluted with ethyl acetate (60 mL), and washed with water (3×20 mL). The organic layer was dried and the solvent was removed *in vacuo*. Preparative TLC of the residue afforded the target compounds **2f**,**h**.

1-[(Methylthio)methoxy]-3,3-pentamethylene-1-triazene 2-oxide (2f)[12]. Preparative TLC (elution with MeOH—$CHCl_3$, 1 : 15) afforded the title product in the yield of 25%. Oil. IR (neat), ν/cm^{-1}: 2942, 2856, 1497, 1443, 1223, 981. ^{1}H NMR ($CDCl_3$), δ: 1.50 (m, 2 H, CH_2(4)); 1.75 (m, 4 H, C(3)H_2, C(5)H_2); 2.30 (s, 3 H, CH_3S); 3.40 (t, 4 H, C(2)H_2, C(6)H_2, J = 5.5 Hz); 5.25 (s, 2 H, CH_2S).

3-(2-Hydroxyethyl)-3-methyl-1-[(methylthio)methoxy]-1-triazene 2-oxide (2h). Preparative TLC (elution with MeOH—$CHCl_3$, 1 : 20) afforded the title product in the yield of 39%. IR (neat), ν/cm^{-1}: 3437, 2926, 1496, 1440, 1389, 1255, 1095, 1053, 981, 693. ^{1}H NMR ($CDCl_3$), δ: 2.25 (s, 4 H, OH and CH_3S); 3.10 (s, 3 H, CH_3N); 3.45 (t, 2 H, CH_2, J = 5.0 Hz); 3.80 (t, 2 H, CH_2, J = 5.0 Hz); 5.75 (s, 2 H, CH_2).

Synthesis of chloromethoxy-1-triazene 2-oxides 3f,h (general procedure). To a stirred solution of the corresponding sulfide **2** (0.02 mol) in dichloromethane (40 mL), SO_2Cl_2 (2.83 g, 0.021 mol) was added dropwise at 0 °C. After warming up to room temperature, the reaction mixture was kept for 1 h. The solvent was removed *in vacuo*, purification of the residue by preparative TLC (elution with MeOH—$CHCl_3$, 1 : 25) afforded the title products **3f**,**h**.

1-Chloromethoxy-3,3-(pentamethylene)-1-triazene 2-oxide (3f)[12]. Yield 96%. Oil. IR (neat), ν/cm^{-1}: 2946, 2857, 1499, 1445, 1323, 1227, 1086, 1018, 937, 918, 688. ^{1}H NMR ($CDCl_3$), δ: 1.50 (m, 2 H, C(4)H_2); 1.75 (m, 4 H, C(3)H_2, C(5)H_2); 3.50 (t, 4 H, C(2)H_2, C(6)H_2, J = 5.5 Hz); 5.85 (s, 2 H, CH_2Cl).

3-(Chloroethyl)-1-chloromethoxy-3-methyl-1-triazene 2-oxide (3h). Yield 85%. Oil. IR (neat), ν/cm^{-1}: 2975, 2928, 1502, 1440, 1321, 1254, 1078, 1023, 941, 681. ^{1}H NMR ($CDCl_3$), δ: 3.20 (s, 3 H, CH_3N); 3.80 (m, 4 H, 2 CH_2); 5.90 (s, 2 H, CH_2). MS (ESI), *m/z*: 202.0156 [M + H]$^+$, 223.9967 [M + Na]$^+$, 239.9706 [M + K]$^+$. $C_4H_9Cl_2N_3O_2$. Calculated: 202.0145 [M + H]$^+$, 223.9964 [M + Na]$^+$, 239.9703 [M + K]$^+$.

3-Methyl-10-(pyrrolidin-1-yl)-6,8-dioxa-3,4,5,9,10-pentaazadeca-4,9-dien-1-ol 4,10-dioxide (4e). To a suspension of Na-salt **1h** (0.152 g, 0.97 mmol) and Na_2CO_3 (0.103 g, 0.97 mmol) in DMF (2 mL) cooled to 0 °C, a solution of chloride **3e** (0.174 g, 0.97 mmol) in DMF (1 mL) was added. The reaction mixture was stirred at 20 °C for 7 h, kept at room temperature for 16 h, diluted with water (10 mL), and extracted with ethyl acetate (4×5 mL). The combined organic layers were washed with water (3×1 mL), dried with $MgSO_4$, and the solvent was removed *in vacuo*. Purification of the residue by preparative TLC (elution with ethyl acetate—hexane, 2 : 1) afforded compound **4e** in the yield of 0.081 g (30%), viscous oil. IR (neat), ν/cm^{-1}: 3474, 2963, 2883, 1490, 1275, 1025, 936. ^{1}H NMR ($CDCl_3$), δ: 1.95 (m, 4 H, 2 CH_2); 2.30 (br.s, 1 H, OH), 3.12 (s, 3 H, NCH_3); 3.51, 3.72 (both t, 2 H each, 2 CH_2, J = 5.0 Hz); 3.60 (t, 4 H, 2 CH_2, J = 6.5 Hz); 5.74 (s, 2 H, OCH_2O). ^{14}N NMR ($CDCl_3$), δ: −50.54, −53.24. MS (ESI), *m/z*: 279.1423 [M + H]$^+$, 296.1688 [M + NH_4]$^+$, 301.1244 [M + Na]$^+$, 317.0976 [M + K]$^+$. $C_8H_{18}N_6O_5$. Calculated: 279.1411 [M + H]$^+$, 296.1677 [M + NH_4]$^+$, 301.1231 [M + Na]$^+$, 317.0970 [M + K]$^+$.

Compounds **4a—g,h** were synthesized similarly.

2,10-Dimethyl-5,7-dioxa-2,3,4,8,9,10-hexaazadodeca-3,8-dien-12-ol 3,9-dioxide (4a). Yield 20%. Oil. IR (neat), ν/cm^{-1}: 3477, 2920, 1498, 1265, 1024, 939. ^{1}H NMR ($CDCl_3$), δ: 3.10 (s, 6 H, $N(CH_3)_2$); 3.15 (s, 3 H, NCH_3); 3.55 (t, 2 H, $HOCH_2$, J = 5.0 Hz); 3.80 (t, 2 H, NCH_2, J = 5.0 Hz); 5.70 (s, 2 H, OCH_2O). ^{14}N NMR ($CDCl_3$), δ: −49.62. MS (ESI), *m/z*: 253.1259 [M + H]$^+$; 275.1083 [M + Na]$^+$; 291.0825 [M + K]$^+$. $C_6H_{16}N_6O_5$. Calculated: 253.1255 [M + H]$^+$; 275.1074 [M + Na]$^+$, 291.0814 [M + K]$^+$.

11-Ethyl-3-methyl-6,8-dioxa-3,4,5,9,10,11-hexaazatrideca-4,9-dien-1-ol 4,10-dioxide (4b). Yield 9%. Oil. IR (neat), ν/cm^{-1}: 3484, 2978, 2939, 2878, 1499, 1463, 1390, 1243, 1068, 1026, 947. ^{1}H NMR ($CDCl_3$), δ: 1.10 (t, 6 H, 2 CH_3C, J = 7.1 Hz); 2.40 (br.s, 1 H, OH); 3.10 (s, 3 H, CH_3N); 3.20 (q, 4 H, 2 CCH_2N, J = 7.1 Hz); 3.50 (t, 2 H, CH_2, J = 5.0 Hz); 3.75 (t, 2 H, CH_2, J = 5.0 Hz); 5.80 (s, 2 H, OCH_2O). ^{14}N NMR ($CDCl_3$), δ: −54.63. MS (ESI), *m/z*: 303.1394 [M + Na]$^+$, 319.1129 [M + K]$^+$. $C_8H_{20}N_6O_5$. Calculated: 303.1387 [M + Na]$^+$, 319.1127 [M + K]$^+$.

3,11-Dimethyl-6,8-dioxa-3,4,5,9,10,11-hexaazatrideca-4,9-dien-1-ol-4,10 dioxide (4c). Yield 17%. Oil. IR (neat), ν/cm^{-1}: 3458, 2971, 2931, 2877, 1496, 1496, 1259, 1041, 944. ^{1}H NMR ($CDCl_3$), δ: 1.10 (t, 6 H, 2 CH_3C, J = 7.1 Hz); 2.35 (br.s, 1 H, OH); 3.00 (s, 3 H, CH_3N); 3.11 (s, 3 H, CH_3N); 3.48 (q, 4 H, 2 CCH_2N, J = 7.1 Hz); 3.51 (t, 2 H, CH_2, J = 5.0 Hz); 3.78 (t, 2 H, CH_2, J = 5.0 Hz); 5.75 (s, 2 H, OCH_2O). ^{14}N NMR ($CDCl_3$), δ: −52.64. MS (ESI), *m/z*: 284.1676 [M + NH_4]$^+$, 289.1233 [M + Na]$^+$, 305.0971 [M + K]$^+$. $C_7H_{18}N_6O_5$. Calculated: 284.1677 [M + NH_4]$^+$, 289.1231 [M + Na]$^+$, 305.0970 [M + K]$^+$.

2,10-Dimethyl-1-phenyl-5,7-dioxa-2,3,4,8,9,10-hexaazadodeca-3,8-dien-12-ol-3,9 dioxide (4d). Yield 17%. Oil. IR (neat), ν/cm^{-1}: 3441, 2925, 1496, 1229, 1064, 1024, 939. ^{1}H NMR ($CDCl_3$), δ: 2.50 (s, 1 H, OH); 2.95 (s, 3 H, NCH_3); 3.10 (s, 3 H, NCH_3); 3.50 (t, 2 H, $HOCH_2$, J = 5.0 Hz); 3.75 (t, 2 H, NCH_2, J = 5.0 Hz); 4.55 (s, 2 H, NCH_2Ph); 5.70 (s, 2 H, OCH_2O); 7.30 (s, 5 H, Ph). MS (ESI), *m/z*: 351.1385 [M + Na]$^+$; 367.1117 [M + K]$^+$. $C_{12}H_{20}N_6O_5$. Calculated: 351.1387 [M + Na]$^+$; 367.1127 [M + K]$^+$.

3-Methyl-10-(piperidin-1-yl)-6,8-dioxa-3,4,5,9,10-pentaazadeca-4,9-dien-1-ol-4,10 dioxide (4f). Yield 16%. Oil. IR (neat), ν/cm^{-1}: 3474, 2944, 2859, 1498, 1445, 1227, 1171, 1069, 1035, 1018, 939. ^{1}H NMR ($CDCl_3$), δ: 1.50 (m, 2 H, C(4)H_2, J = 7.1 Hz); 1.75 (m, 4 H, 2 CH_2); 2.60 (br.s, 1 H, OH); 3.10 (s, 3 H, CH_3N); 3.40 (t, 4 H, 2 CH_2, J = 7.1 Hz); 3.50 (t, 2 H, CH_2, J = 5.0 Hz); 3.75 (t, 2 H, CH_2, J = 5.0 Hz); 5.85 (s, 2 H, OCH_2O). ^{14}N NMR ($CDCl_3$), δ: −53.45. MS (ESI), *m/z*: 315.1396 [M + Na]$^+$, 331.1137 [M + K]$^+$. $C_9H_{20}N_6O_5$. Calculated: 315.1387 [M + Na]$^+$, 331.1127 [M + K]$^+$.

8-Methyl-1-(morpholin-4-yl)-3,5-dioxa-1,2,6,7,8-pentaazadeca-1,6-dien-10-ol 1,7-dioxide (4g). Yield 12%. Oil. IR (neat), ν/cm^{-1}: 3387, 2939, 2885, 1504, 1443, 1334, 1286, 1176, 1068, 948, 666. ^{1}H NMR ($CDCl_3$), δ: 2.00 (br.s, 1 H, OH); 3.15 (s, 3 H,

CH_3); 3.50 (m, 6 H, 3 CH_2); 3.80 (m, 6 H, 3 CH_2); 5.80 (s, 2 H, OCH_2O). ^{14}N NMR ($CDCl_3$), δ: −55.45. MS (ESI), *m/z*: 295.1375 $[M + H]^+$, 312.1634 $[M + NH_4]^+$, 317.1188 $[M + Na]^+$, 333.0927 $[M + K]^+$. $C_8H_{18}N_6O_6$. Calculated: 295.1361 $[M + H]^+$, 312.1626 $[M + NH_4]^+$, 317.1180 $[M + Na]^+$, 333.0919 $[M + K]^+$.

13-Chloro-3,11-dimethyl-6,8-dioxa-3,4,5,9,10,11-hexaazatrideca-4,9-dien-1-ol 4,10-dioxide (4h). Yield 13%. Oil. IR (neat), ν/cm^{-1}: 3476, 2965, 2928, 1499, 1464, 1442, 1259, 1171, 1067, 1024, 941. ^1H NMR ($CDCl_3$), δ: 2.20 (br.s, 1 H, OH); 3.10 (s, 3 H, CH_3(OH)); 3.20 (s, 3 H, CH_3(Cl)); 3.50 (t, 2 H, CH_2N, *J* = 5.0 Hz); 3.70 (m, 4 H, 2 CH_2Cl); 3.80 (t, 2 H, CH_2O, *J* = 5.0 Hz); 5.75 (s, 2 H, OCH_2O). ^{14}N NMR ($CDCl_3$), δ: −54.11. MS (ESI), *m/z*: 323.0841, 325.0812 $[M + Na]^+$, 339.0583, 341.0556 $[M + K]^+$. $C_7H_{17}ClN_6O_5$. Calculated: 323.0841, 325.0812 $[M + Na]^+$, 339.0581, 341.0552 $[M + K]^+$

Alkylation of salt 1h in MeCN. To a suspension of Na-salt **1h** (0.152 g, 0.97 mmol) and Na_2CO_3 (0.103 g, 0.97 mmol) in anhydrous MeCN (5 mL) cooled to 0 °C, a solution of chloride **3e** (0.174 g, 0.97 mmol) in anhydrous MeCN (2 mL) was added. The reaction mixture was stirred at 20 °C for 7 h, the precipitate was filtered off, and the filtrate was concentrated *in vacuo*. Preparative TLC of the residue (elution with ethyl acetate—hexane, 2 : 1) afforded nitrosopyrrolidine (0.081 g, ~30%) and *N*-(2-hydroxyethyl)-*N*-methyl-*N*-nitrosamine (~20%). ^1H NMR spectra of the synthesized compounds are in agreement with the published data.[13,14] Compound **1h** reacts similarly with chlorides **3c**,**f**,**h** to give the corresponding nitrosamines with physico-chemical characteristics analogous to those of the previously synthesized compounds.[13,15,16].

1-Bromo-3-methyl-10-(pyrrolidin-1-yl)-6,8-dioxa-3,4,5,9,10-pentaazadeca-4,9-diene 4,10-dioxide (5b). To a stirred solution of compound **4e** (0.045 g, 0.16 mmol) in CH_2Cl_2 (3 mL), triphenylphosphine Ph_3P (0.064 g, 0.24 mmol) was added followed by portionwise addition of *N*-bromosuccinimide (0.044 g, 0.25 mmol). The reaction mixture was stirred for 4 h at 20 °C and then kept for 16 h at room temperature. Preparative TLC (elution with $CHCl_3$) afforded compound **5e** in the yield of 0.039 g (71%); oily substance, which solidified on cooling in hexane. M.p. 59—60 °C. IR (KBr), ν/cm^{-1}: 2973, 2879, 1497, 1280, 1036, 945. ^1H NMR ($CDCl_3$), δ: 1.95 (m, 4 H, 2 CH_2); 3.12 (s, 3 H, NCH_3); 3.51, 3.72 (both t, 2 H each, 2 CH_2, *J* = 5.0 Hz); 3.60 (t, 4 H, 2 CH_2, *J* = 6.5 Hz); 5.74 (s, 2 H, OCH_2O). MS (ESI), *m/z*: 358.0839 $[M + NH_4]^+$, 363.0391 $[M + Na]^+$. $C_8H_{17}BrN_6O_4$. Calculated: 358.0839 $[M + NH_4]^+$; 363.0387 $[M + Na]^+$.

1-Bromo-3,11-dimethyl-6,8-dioxa-3,4,5,9,10,11-hexaazadodeca-4,9-diene 4,10-dioxide (5a) was synthesized similarly to compound **5b** in 80% yield. Oil. IR (neat), ν/cm^{-1}: 2917, 1501, 1262, 1024, 940. ^1H NMR ($CDCl_3$), δ: 3.05 (s, 6 H, $N(CH_3)_2$); 3.15 (s, 3 H, NCH_3); 3.45 (t, 2 H, $BrCH_2$, *J* = 6.0 Hz); 3.75 (t, 2 H, NCH_2, *J* = 6.0 Hz); 5.70 (s, 2 H, OCH_2O). MS (ESI), *m/z*: 332.0668, 334.0653 $[M + NH_4]^+$; 337.0223, 339.0205 $[M + Na]^+$; 352.9958, 354.9941 $[M + K]^+$. $C_6H_{15}BrN_6O_4$. Calculated: 332.0676, 334.0656 $[M + NH_4]^+$; 337.0230, 339.0210 $[M + Na]^+$; 352.9970, 354.9950 $[M + K]^+$.

1-Chloro-3-methyl-10-(pyrrolidin-1-yl)-6,8-dioxa-3,4,5,9,10-pentaazadeca-4,9-diene 4,10-dioxide (6). A solution of compound **4e** (0.03 g, 0.1 mmol) and tosyl chloride (0.02 g, 0.1 mmol) in MeCN (2 mL) was refluxed for 8 h. Preparative TLC (elution with ethyl acetate—hexane, 2 : 1) afforded compound **6** in the yield of 0.006 g (33%); oily substance, which solidified on cooling in hexane. M.p. 41—45 °C. IR (KBr), ν/cm^{-1}: 2973, 2879, 1497, 1280, 1036, 945. ^1H NMR ($CDCl_3$), δ: 1.98 (m, 4 H, 2 CH_2); 3.18 (s, 3 H, NCH_3); 3.68 (m, 4 H, 2 CH_2); 3.60 (t, 4 H, 2 CH_2, *J* = 6.5 Hz); 5.73 (s, 2 H, OCH_2O). Found (%): C, 32.64; H, 5.90; N, 27.85. $C_8H_{17}ClN_6O_4$. Calculated (%): C, 32.38; H, 5.77; N 28.32.

1-Acetoxy-3-methyl-10-(pyrrolidin-1-yl)-6,8-dioxa-3,4,5,9,10-pentaazadeca-4,9-diene 4,10-dioxide (7). To a solution of compound **4e** (0.056 g, 0.2 mmol) in MeCN (2 mL), acetyl chloride (0.1 mL, 0.11 g, 1.4 mmol) was added. The reaction mixture was kept at 20 °C for 24 h. Preparative TLC (elution with ethyl acetate—hexane, 1 : 1) afforded compound **7** in the yield of 0.046 g (71%); oily substance, which solidified on cooling in hexane. M.p. 44—46 °C. IR (KBr), ν/cm^{-1}: 2958, 2877, 1732, 1498, 1233, 1040, 937. ^1H NMR ($CDCl_3$), δ: 1.95 (m, 4 H, 2 CH_2); 2.05 (s, 3 H, CH_3); 3.13 (s, 3 H, NCH_3); 3.59 (t, 4 H, 2 CH_2, *J* = 6.5 Hz); 3.68, 4.26 (both t, 2 H each, 2 CH_2, *J* = 5.0 Hz); 5.73 (s, 2 H, OCH_2O). MS (ESI), *m/z*: 321.1520 $[M + H]^+$; 343.1337 $[M + Na]^+$. $C_{10}H_{20}N_6O_6$. Calculated: 321.1517 $[M + H]^+$; 343.1337 $[M + Na]^+$.

3-Methyl-10-(pyrrolidin-1-yl)-6,8-dioxa-3,4,5,9,10-pentaazadeca-4,9-dien-1-chloroacetoxy 4,10-dioxide (8). To a solution of compound **4e** (0.06 g, 0.22 mmol) in MeCN (2 mL), chloroacetyl chloride (0.06 mL, 0.085 g, 0.75 mmol) was added. The reaction mixture was kept at 20 °C for 24 h. Preparative TLC (elution with ethyl acetate—hexane, 2 : 1) afforded compound **8** in the yield of 0.069 g (90%); oily substance, which crystallized on cooling in hexane. M.p. 58—61 °C (from hexane). Found (%): C, 34.18; H, 5.367; N, 23.34. $C_{10}H_{19}ClN_6O_6$. Calculated (%): C, 33.85; H, 5.35; N, 23.69. IR (KBr), ν/cm^{-1}: 2962, 2879, 1763, 1491, 1193, 1039, 937. ^1H NMR ($CDCl_3$), δ: 1.95 (m, 4 H, 2 CH_2); 3.12 (s, 3 H, NCH_3); 3.53 (t, 4 H, 2 CH_2, *J* = 6.5 Hz); 3.68, 4.36 (both t, 2 H each, 2 CH_2, *J* = 5.0 Hz); 4.03 (s, 2 H, $ClCH_2$); 5.73 (s, 2 H, OCH_2O).

3-Methyl-10-(pyrrolidin-1-yl)-6,8-dioxa-3,4,5,9,10-pentaazadeca-4,9-diene-1-phenylcarbamoyl 4,10-dioxide (9). A stirred solution of compound **4e** (0.031 g, 0.11 mmol) and phenyl isocyanate (0.012 mL, 0.013 g, 0.11 mmol) in toluene (1 mL) was heated at 100 °C for 11 h. The reaction mixture was diluted with benzene (4 mL), washed with water (2 mL), dried with $MgSO_4$, and the solvent was removed *in vacuo*. Preparative TLC (elution with ethyl acetate—hexane, 1 : 1) of the residue afforded product **9** in the yield of 0.007 g (16%), oil. IR (neat), ν/cm^{-1}: 3318, 2960, 2924, 1732, 1501, 1221, 1026, 938. ^1H NMR ($CDCl_3$), δ: 1.96 (m, 4 H, 2 CH_2); 3.14 (s, 3 H, NCH_3); 3.60 (t, 4 H, 2 CH_2, *J* = 6.5 Hz); 3.75, 4.48 (both t, 2 H each, 2 CH_2, *J* = 5.0 Hz); 5.74 (s, 2 H, OCH_2O); 7.25—7.45 (m, 6 H C_6H_5 and NH). MS (ESI), *m/z*: 420.1605 $[M + Na]^+$; 436.1347 $[M + K]^+$. $C_{15}H_{23}N_7O_6$. Calculated: 420.1602 $[M + Na]^+$, 436.1341 $[M + K]^+$.

3-Methyl-10-(pyrrolidin-1-yl)-6,8-dioxa-3,4,5,9,10-pentaazadeca-4,9-diene-1-(pyridin-3-yl)carbamoyl 4,10-dioxide (10). A solution of nicotinic acid azide (0.018 g, 0.13 mmol) in toluene (1 mL) was heated at 100 °C for 1.5 h until complete consumption of the starting azide (TLC monitoring). The reaction mixture was cooled to room temperature and treated with a solution of compound **4e** (0.015 g, 0.05 mmol) in toluene (1 mL). After 16 h at room temperature (20 °C), the mixture was diluted with benzene (4 mL), washed with water (2 mL), dried with $MgSO_4$, and the solvent was removed *in vacuo*. Washing of the residue with diethyl ether afforded product **10** in the yield of 0.014 g (67%). M.p. 100—105 °C. IR (KBr), ν/cm^{-1}: 3433, 2967,

2882, 1724, 1482, 1227, 1030, 941. ^{1}H NMR ($CDCl_3$), δ: 1.98 (m, 4 H, 2 CH_2); 3.18 (s, 3 H, CH_3); 3.60 (t, 4 H, 2 CH_2, J = 6.5 Hz); 3.75, 4.60 (both t, 2 H each, 2 CH_2, J = 5.0 Hz); 5.74 (s, 2 H, OCH_2O); 7.65 (br.s, 1 H, NH); 7.22 (m, 1 H, CH); 8.00 (d, 1 H, CH, J = 7.8 Hz); 8.30 (d, 1 H, CH, J = 4.5 Hz); 8.60 (d, 1 H, CH, J = 2.2 Hz). Found (%): C, 42.68; H, 5.49; N, 27.69. $C_{14}H_{22}N_8O_6$. Calculated (%): C, 42.21; H, 5.57; N, 28.13.

2,10-Dimethyl-5,7-dioxa-2,3,4,8,9,10-hexaazadodeca-3,8-diene-12-carboxylic acid 3,9-dioxide (11). To a solution of compound **4a** (0.1 g, 0.4 mmol) in a mixture of MeCN (0.4 mL), ethyl acetate (0.4 mL), and water (0.6 mL), sodium periodate $NaIO_4$ (0.4 g, 1.9 mmol) was added followed by addition of a catalytic amount of $RuCl_3$ with stirring. A suspension was stirred at 20 °C for 2 h, the precipitate was filtered off, the filtrate was diluted with ethyl acetate (1.5 mL) and water (1.5 mL), extracted with CH_2Cl_2 (4×10 mL). The organic layer was dried with $MgSO_4$ and the solvent was removed *in vacuo*. Preparative TLC (elution with CH_2Cl_2—MeOH, 10 : 1) of the residue afforded product **11** in the yield of 0.05 g (47%). M.p. 106—110 °C. IR (KBr), ν/cm^{-1}: 3173—2926, 1749, 1501, 1267, 1025, 940. ^{1}H NMR ($CDCl_3$), δ: 3.05 (s, 6 H, $N(CH_3)_2$); 3.25 (s, 3 H, NCH_3); 4.25 (s, 2 H, CH_2); 5.70 (s, 2 H, OCH_2O); 9.26 (br.s, 1 H, COOH). MS (ESI), *m/z*: 284.1321 $[M + NH_4]^+$; 289.0872 $[M + Na]^+$; 305.0611 $[M + K]^+$. $C_7H_{16}N_6O_7$. Calculated: 284.1313 $[M + NH_4]^+$; 289.0867 $[M + Na]^+$; 305.0606 $[M + K]^+$.

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