Synthesis and study of organic nitrates of heterofunctional series
4.* Synthesis and some chemical properties of 4,4-bis(nitroxymethyl)-2-phenyl-2-oxazoline and -2-oxazolinium nitrate

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O-Nitration of 4,4-bis(hydroxymethyl)-2-phenyl-2-oxazoline with conc. HNO_3 in the presence of Ac_2O was found to occur without ring-opening. Hydrolysis of the reaction products gives tris(hydroxymethyl)aminomethane derivatives.

Key words: 4,4-bis(hydroxymethyl)-2-phenyl-2-oxazoline, *O*-nitration, 4,4-bis(nitroxymethyl)-2-phenyl-2-oxazolinium nitrate, 4,4-bis(nitroxymethyl)-2-phenyl-2-oxazoline, tris(hydroxymethyl)aminomethane.

Earlier,[2] we synthesized an analog of *N*-nicotinoylethanolamine *O*-nitrate, which is the active principle of nicorandil, a modern highly efficient antianginal drug,[3] *viz.*, *N*-nicotinoyltris(nitroxymethyl)aminomethane, in the form of hydronitrate and hydrochloride. This was shown[4] to undergo intramolecular cyclization in alkaline media to give 4,4-bis(nitroxymethyl)-2-(3-pyridyl)-2-oxazoline, the first representative of organic nitrates of the oxazoline series, whose structure was confirmed by X-ray diffraction analysis.

It was of interest to study the possibility of synthesis of such organic nitrates by direct *O*-nitration of the corresponding alcohols, which is the main method for the preparation of organic nitrates. The nitration of 4,4-bis(hydroxymethyl)-2-phenyl-2-oxazoline (**1**) was shown[1] to give 2-benzoyloxy-1,1-bis(nitroxymethyl)-ethylammonium nitrate (**2**) as the main reaction product (Scheme 1, reaction *a*). Probably, this compound results from hydrolytic ring-opening of 2-oxazoline in the product of *O*-nitration of diol **1**.

The aim of the present work is to check this assumption and continue the study of the possibility of obtaining organic nitrates of the oxazoline series by *O*-nitration of the corresponding alcohols with diol **1** as an example.

Results and Discussion

Diol **1** reacts with an equimolar mixture of conc. HNO_3 (free of nitrogen oxides, d_4^{20} 1.513) and Ac_2O to give 4,4-bis(nitroxymethyl)-2-phenyl-2-oxazolinium nitrate (**3**).

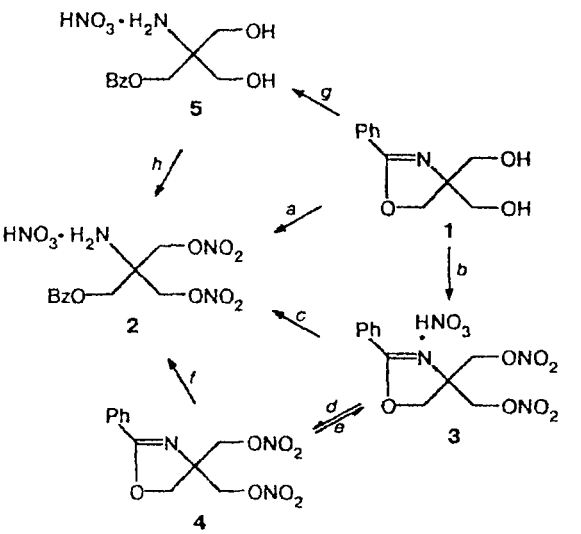
This colorless crystalline salt precipitates in the cold from a solution in CH_2Cl_2 and is stable at room temperature when stored over P_2O_5. However, it is easily hydrolyzed even upon short-term heating in the presence of traces of moisture present in Pr^iOH (which had not been specially dried) to form compound **2**. It is for this reason that recrystallization of the product of *O*-nitration of diol **1** gave mixed ester.[4]

Nitrate **3** reacts with a solution of KOH in MeOH to yield 4,4-bis(nitroxymethyl)-2-phenyl-2-oxazoline (**4**), which is converted into salt **3** upon treatment with conc. HNO_3.

When treated with dilute HNO_3, base **4**, as under the action of water on salt **3**, undergoes opening of the 2-oxazoline ring to give the same compound **2**.

Mixed ester **2** was also obtained by an independent synthesis. First, diol **1** was treated with dilute HNO_3 to

Scheme 1



Reagents: *a*. HNO_3—Ac_2O, H_2O[1]; *b*, *h*. HNO_3—Ac_2O; *c*. H_2O+Pr^iOH; *d*. KOH+EtOH; *e*. HNO_3; *f*, *g*. H_2O+HNO_3.

* For Part 3, see Ref. 1.

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give 2-benzoyloxy-1,1-bis(hydroxymethyl)ethylammonium nitrate (5), which was then *O*-nitrated to give compound 2.

Thus, we showed that, in principle, the synthesis of nitroxymethyl-2-oxazolines is possible in both basic[4] and acidic media.

Experimental

IR spectra were recorded on a Specord M-82 spectrometer. ^{1}H NMR spectra were recorded on a cryogenic spectrometer (294 MHz) designed and manufactured in the Institute of Problems of Chemical Physics, Russian Academy of Sciences. Melting points were measured on a Boetius RNMK-05 instrument.

4,4-Bis(nitroxymethyl)-2-phenyl-2-oxazolinium nitrate (3). *A.* Compound **1** (0.83 g, 4 mmol) was added with stirring at −20 to −10 °C to a mixture of conc. HNO_3 (d_4^{20} 1.513) (1.0 mL, 24 mmol) and Ac_2O (2.3 mL, 24 mmol) in 4 mL of CH_2Cl_2. After 2 h, crystalline product **3** that formed was filtered off and washed with CH_2Cl_2. Yield 1.17 g (81%), m.p. 135—136 °C. Found (%): C, 36.72; H, 3.43; N, 15.49. $C_{11}H_{11}N_3O_7 \cdot HNO_3$. Calculated (%): C, 36.68; H, 3.36; N, 15.55. IR (KBr), ν/cm^{-1}: 1650, 1280, 860 (ONO_2); 1630, 1125 (2-oxazoline ring); 1380 (NO_3^-); 1600, 1580, 1500, 1410, 700 (Ph). ^{1}H NMR (DMSO-d_6), δ: 4.49 (s, 2 H, OCH_2); 4.78 (s, 4 H, CH_2ONO_2); 7.50 (m, 2 H, *m*-H(Ph)); 7.59 (m, 1 H, *p*-H(Ph)); 7.85 (m, 2 H, *o*-H(Ph)); ~8.7 (br.s, 1 H, NH^+).

B. A solution of conc. HNO_3 (d_4^{20} 1.513) (15.8 mg, 0.25 mmol) in CH_2Cl_2 was added with stirring at ~ −20 °C to a solution of dinitrate **4** (74.5 mg, 0.25 mmol) in 0.5 mL of CH_2Cl_2. The reaction mixture was stirred for 5 min, and then crystalline product **3** that formed was filtered off and washed with CH_2Cl_2. Yield 81.3 mg (90%), m.p. 135—136 °C. The melting point of a mixture with compound **3** obtained by method *A* was not depressed. The corresponding IR spectra are also identical.

4,4-Bis(nitroxymethyl)-2-phenyl-2-oxazoline (4). A solution of KOH (61 mg, 1.1 mmol) in 0.3 mL of methanol was added with stirring at 0 °C to a solution of salt **3** (361 mg, 1 mmol) in 10 mL of MeOH. After stirring for 20 min, the precipitate that formed was filtered off, and the filtrate was concentrated to dryness. The reaction products were extracted from the residue with ether, and the ethereal solution was dried with $MgSO_4$. The solvent was removed to give compound **4** (286 mg, 96%), m.p. 40—41 °C (from EtOH). Found (%): C, 4.50; H, 3.85; N, 13.87. $C_{11}H_{11}N_3O_7$. Calculated (%): C, 4.45; H, 3.73; N, 14.14. IR (dichloroethane), ν/cm^{-1}: 1648, 1280, 845 (ONO_2); 1635, 1065 (2-oxazoline ring); 1599, 1579, 1494, 700 (Ph). ^{1}H NMR (CD_2Cl_2), δ: 4.39 (s, 2 H, OCH_2); 4.67 (m, 4 H, CH_2ONO_2, AB-system, Δν=16.5; $^2J_{gem}$=10.0 Hz); 7.43 (m, 2 H, *m*-H(Ph)); 7.51 (m, 1 H, *p*-H(Ph); 7.91 (m, 2 H, *o*-H(Ph)).

2-Benzoyloxy-1,1-bis(nitroxymethyl)ethylammonium nitrate (2). *A.* Salt **3** (1.26 g, 3.5 mmol) in 6 mL of Pr^iOH which had not been specially dried was stirred at 80 °C for a few minutes until the reaction mixture became homogeneous. Then, it was cooled to −20 °C and left for ~10 h. The crystalline product that formed was filtered off and washed with CH_2Cl_2 to give compound **2** (1.18 g, 89%), m.p. 141—142.5 °C (Pr^nOH). The melting point of a mixture with the sample obtained earlier[1] from compound **1** was not depressed. The corresponding IR spectra are also identical.

B. 56.7% HNO_3 (0.05 mL, 0.6 mmol) was added with stirring at −20 °C to a solution of compound **4** (74.5 mg, 0.25 mmol) in 0.2 mL of acetone. The reaction mixture was stirred for 5 h and left for ~10 h. Then, CH_2Cl_2 (1 mL) was added, and the precipitate that formed was washed with CH_2Cl_2. Yield 90.6 mg (95.5%), m.p. 141—142.5 °C (Pr^nOH). The melting point of a mixture with the sample obtained earlier[1] was not depressed. The corresponding IR spectra are also identical.

C. Compound **5** (72 mg, 0.25 mmol) was added with stirring at −20 to −10 °C to a mixture of conc. HNO_3 (d_4^{20} 1.513) (0.05 mL, 1.2 mmol) and Ac_2O (0.11 mL, 1.2 mmol) in 0.25 mL of CH_2Cl_2. After 1 h, CH_2Cl_2 (1 mL) was added, and crystalline product **2** that formed was filtered off and washed with CH_2Cl_2. Yield 85 mg (90%), m.p. 141—142.5 °C (Pr^nOH). The melting point of a mixture with the sample obtained earlier[1] was not depressed. The corresponding IR spectra are also identical.

2-Benzoyloxy-1,1-bis(hydroxymethyl)ethylammonium nitrate (5). 56.7% HNO_3 (0.2 mL, 2.4 mmol) was added to a solution of compound **1** (207 mg, 1 mmol) in 10 mL of acetone. The reaction mixture was stirred at −20 °C for 8 h and left for 2 days. The resulting solution was diluted with ether, and the precipitate that formed was filtered off. An additional amount of the product was obtained upon removal of part of the solvent from the filtrate. Yield 272 mg (94%), m.p. 150—151 °C (anhydrous EtOH). Found (%): C, 45.60; H, 5.53; N, 9.86. $C_{11}H_{15}NO_4 \cdot HNO_3$. Calculated (%): C, 45.83; H, 5.60; N, 9.72. IR (KBr), ν/cm^{-1}: 3538, 3456, 1020 (OH); 3065, 2960, 2945 (NH_3^+); 1720, 1275, 1115 (COO); 1385 (NO_3^-); 1600, 1505, 1450, 705 (Ph). ^{1}H NMR (CD_3CN), δ: ~2.35 (br.s, 2 H, 2 OH); 3.80 (s, 4 H, 2 CH_2OH); 4.45 (s, 2 H, OCH_2); ~7.44 (br.s, 3 H, $NH_2 \cdot HNO_3$); 7.52 (m, 2 H, *m*-H(Ph)); 7.64 (m, 1 H, *p*-H(Ph)); 8.09 (m, 2 H, *o*-H(Ph)).

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