

Synthesis and study of organic nitrates of the heterofunctional series

2.* Synthesis and structure of

4,4-dihydroxymethyl-2-(3-pyridyl)-2-oxazoline dinitrate

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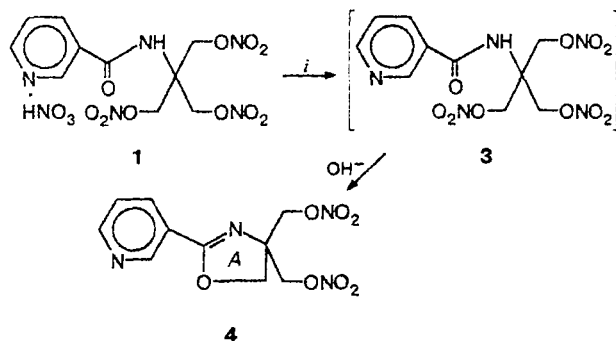
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The first representative of organic nitrates of the oxazoline series, 4,4-dihydroxymethyl-2-(3-pyridyl)-2-oxazoline dinitrate, was synthesized by the reaction of *N*-nicotinoyltri(hydroxymethyl)aminomethane trinitrate hydronitrate (**1**) with a solution of KOH in alcohol. The reactivities of compound **1** and *N*-nicotinylethanolamine nitrate (nicorandil) in the reaction of intramolecular heterocyclization were compared. The structure of the compound synthesized has been established by X-ray diffraction analysis.

Key words: *N*-nicotinoyltri(hydroxymethyl)aminomethane trinitrate hydronitrate, 4,4-dihydroxymethyl-2-(3-pyridyl)-2-oxazoline dinitrate, *N*-nicotinylethanolamine nitrate (nicorandil), reactivity, intramolecular heterocyclization, X-ray diffraction analysis.

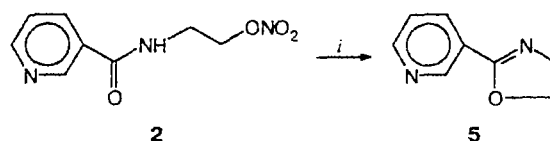
Previously,¹ we have synthesized *N*-nicotinoyltri(hydroxymethyl)aminomethane trinitrate hydronitrate (**1**), studied its properties, and demonstrated that the NO₃⁻ anion can be replaced by Cl⁻. This work was undertaken as part of continuing studies of this analog of the highly efficient antianginal drug nicorandil (*N*-nicotinylethanolamine nitrate, **2**).²

It was demonstrated that under mild conditions, free base **3**, which was isolated from salt **1**, underwent intramolecular heterocyclization to form 4,4-dihydroxymethyl-2-(3-pyridyl)-2-oxazoline dinitrate (**4**). Compound **4** is the first representative of organic nitrates of the oxazoline series.



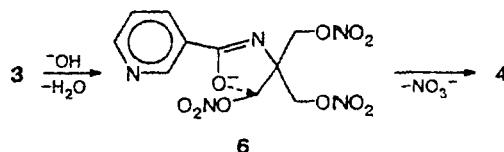
i. OH⁻, 18–20 °C, 15 min

Unsubstituted 2-(3-pyridyl)-2-oxazoline (**5**) was prepared from compound **2** under the action of NaOH in substantially more drastic conditions.³



i. OH⁻ (20-fold excess), 60 °C, 5 h

This is attributable to the fact that compound **3** contains a larger number of electron-withdrawing substituents that promote the formation of anion **6**,³ which is necessary for the above-mentioned conversion. In addition, all other factors being the same, the possibilities for the attack of the anionic reaction center at one of the β-carbon atoms, which were polarized by the nitrate groups, increase substantially:



The structure and composition of product **4** were established by elemental analysis, spectroscopic methods, and X-ray diffraction analysis.

* For Part I, see Ref. 1.

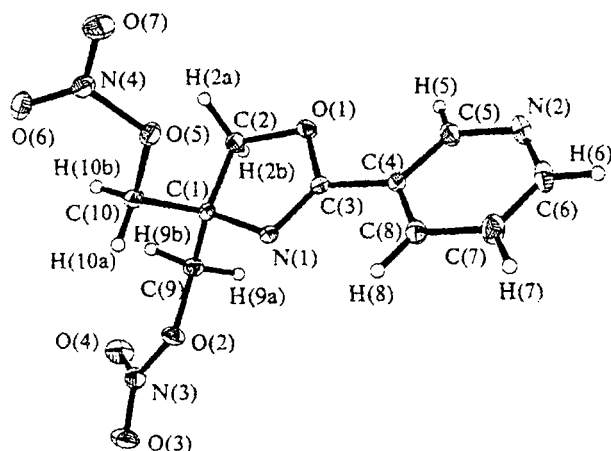


Fig. 1. Overall view of molecule 4.

According to the data of X-ray diffraction analysis (Fig. 1, Tables 1 and 2), the five-membered heterocycle of molecule 4 is almost planar. The C(3)—C(4) bond is

shorter (1.474(3) Å) than the corresponding single bond in compound 1 (Table 3). The bond between the C(3) atom and the nitrogen atom of the new ring, C(3)—N(1), is shorter (1.266(2) Å) than the adjacent N(1)—C(1) bond (1.474(2) Å), and it is, evidently, the double bond. The bond between the C(3) atom and the oxygen atom, C(3)—O(1), is also shorter (1.358(2) Å) than the adjacent O(1)—C(2) bond (1.443(3) Å), and its length is intermediate between the lengths of the corresponding single and double bonds (Tables 2 and 3). The above-mentioned structural features are indicative of the presence of a general system of conjugated bonds in bicyclic molecule 4, which adopts the *Z* conformation. The dihedral angle between the rings is 11.9° (Fig. 1). The geometric characteristics of the CH₂ONO₂ fragments remain virtually unchanged compared to the values of the initial compound 1 (Table 3).

Experimental

The IR spectra were recorded on a Specord M82 spectrometer. The ¹H NMR spectrum was measured on a

Table 1. Atomic coordinates and equivalent isotropic temperature factors for molecule 4

| Atom | x | y | z | B _{eq} | Atom | x | y | z | B _{eq} |
|------|----------|----------|----------|-----------------|--------|-----------|-----------|-----------|-----------------|
| O(1) | 8710(1) | -3956(2) | -97(1) | 39(1) | C(6) | 9683(2) | 1734(5) | -1941(1) | 52(1) |
| O(2) | 6736(1) | 332(2) | 976(1) | 38(1) | C(7) | 8784(2) | 2618(4) | -1979(1) | 50(1) |
| O(3) | 5981(1) | 2752(3) | 1575(1) | 61(1) | C(8) | 8314(1) | 1481(3) | -1489(1) | 39(1) |
| O(4) | 6738(1) | -464(3) | 2262(1) | 59(1) | C(9) | 7419(1) | -1731(3) | 1103(1) | 36(1) |
| O(5) | 6359(1) | -5114(2) | -907(1) | 41(1) | C(10) | 6335(1) | -3929(3) | -149(1) | 34(1) |
| O(6) | 5187(1) | -7633(3) | -794(1) | 58(1) | H(2A) | 7952(17) | -6590(44) | 252(14) | 41(5) |
| O(7) | 5771(1) | -8078(3) | -1798(1) | 60(1) | H(2B) | 8550(16) | -5030(40) | 975(14) | 38(5) |
| N(1) | 7561(1) | -969(2) | -288(1) | 30(1) | H(5) | 10009(17) | -2738(49) | -669(15) | 50(6) |
| N(2) | 10141(1) | -174(4) | -1455(1) | 52(1) | H(6) | 10052(18) | 2489(44) | -2285(16) | 55(7) |
| N(3) | 6471(1) | 900(3) | 1673(1) | 40(1) | H(7) | 8447(20) | 4265(59) | -2412(19) | 69(8) |
| N(4) | 5711(1) | -7105(3) | -1183(1) | 39(1) | H(8) | 7730(19) | 2054(47) | -1514(16) | 60(7) |
| C(1) | 7340(1) | -2842(3) | 261(1) | 29(1) | H(9A) | 8021(16) | -1057(43) | 1377(14) | 37(5) |
| C(2) | 8150(1) | -4845(3) | 403(1) | 36(1) | H(9B) | 7211(15) | -2925(39) | 1447(13) | 38(5) |
| C(3) | 8296(1) | -1763(3) | -449(1) | 29(1) | H(10A) | 5861(15) | -2645(39) | -308(13) | 32(5) |
| C(4) | 8764(1) | -514(3) | -989(1) | 32(1) | H(10B) | 6169(15) | -5139(38) | 218(14) | 35(5) |
| C(5) | 9673(1) | -1267(4) | -992(1) | 41(1) | | | | | |

Table 2. Bond lengths (d) and bond angles (ω) in molecule 4

| Bond | d/Å | Bond | d/Å | Angle | ω/deg | Angle | ω/deg |
|------------|----------|------------|----------|-----------------|----------|-----------------|----------|
| O(1)—C(2) | 1.443(3) | N(1)—C(1) | 1.474(2) | N(3)—O(2)—C(9) | 114.0(1) | N(4)—O(5)—C(10) | 114.6(1) |
| O(2)—C(9) | 1.451(2) | N(2)—C(6) | 1.340(3) | C(1)—N(1)—C(3) | 107.0(1) | C(5)—N(2)—C(6) | 116.5(2) |
| O(5)—N(4) | 1.394(2) | C(1)—C(10) | 1.518(2) | O(2)—N(3)—O(3) | 112.3(2) | O(2)—N(3)—O(4) | 118.5(2) |
| O(7)—N(4) | 1.199(2) | C(4)—C(8) | 1.383(2) | O(3)—N(3)—O(4) | 129.1(2) | O(5)—N(4)—O(6) | 118.5(2) |
| N(2)—C(5) | 1.337(3) | O(2)—N(3) | 1.398(2) | O(5)—N(4)—O(7) | 112.7(2) | O(6)—N(4)—O(7) | 128.8(2) |
| C(1)—C(9) | 1.521(2) | O(4)—N(3) | 1.194(2) | N(1)—C(1)—C(2) | 104.3(1) | N(1)—C(1)—C(9) | 111.9(1) |
| C(4)—C(5) | 1.391(3) | O(6)—N(4) | 1.202(3) | C(2)—C(1)—C(9) | 107.7(1) | N(1)—C(1)—C(10) | 110.3(1) |
| C(7)—C(8) | 1.384(3) | N(1)—C(3) | 1.266(2) | C(2)—C(1)—C(10) | 112.6(1) | C(9)—C(1)—C(10) | 110.0(1) |
| O(1)—C(3) | 1.358(2) | C(1)—C(2) | 1.551(2) | O(1)—C(2)—C(1) | 103.6(1) | O(1)—C(3)—N(1) | 118.5(2) |
| O(3)—N(3) | 1.197(2) | C(3)—C(4) | 1.474(3) | O(1)—C(3)—C(4) | 115.5(1) | N(1)—C(3)—C(4) | 125.9(1) |
| O(5)—C(10) | 1.449(2) | C(6)—C(7) | 1.377(3) | C(3)—C(4)—C(5) | 121.0(1) | C(3)—C(4)—C(8) | 120.4(2) |
| | | | | C(5)—C(4)—C(8) | 118.6(2) | N(2)—C(5)—C(4) | 123.6(2) |
| | | | | N(2)—C(6)—C(7) | 124.1(2) | C(6)—C(7)—C(8) | 118.7(2) |
| | | | | C(4)—C(8)—C(7) | 119.5(2) | O(2)—C(9)—C(1) | 108.6(1) |
| | | | | O(5)—C(10)—C(1) | 105.7(1) | | |

Table 3. Comparative geometric characteristics of the CONH(R₂*)CH₂ONO₂ fragment (the precursor of the five-membered ring *A* in compound **4**) in compound **1** and the five-membered ring *A* in compound **4** and also of the C(CH₂ONO₂)₂ fragments of compounds **1** and **4**

| Bond | $d/\text{\AA}$ | | Effect upon formation of the ring |
|--|-------------------------|-----------------------|--|
| | 1 | 4 | |
| CONH(R ₂ *)CH ₂ ONO ₂ and A | | | |
| C _{pynd} —C | 1.514 (10) | 1.474 (3) | Strengthening of the bond |
| N—C | 1.346 (10) | 1.226 (2) | Strengthening of the bond accompanied by the change in the bond order |
| O—C | 1.218 (9) | 1.358 (2) | Antibonding accompanied by the change in the bond order |
| (R ₂ *)C—CH ₂ | 1.522 (9) | 1.551 (2) | Weak antibonding |
| N—C(R ₂ *) | 1.486 (9) | 1.474 (2) | Without changes |
| C(CH ₂ ONO ₂) ₂ | | | |
| C—C(ONO ₂) | 1.521(11); 1.522(12) | 1.518(2); 1.521(2) | Without changes |
| C—ONO ₂ | 1.436(8); 1.454(10) | 1.449(2); 1.451(2) | Without changes |
| O—NO ₂ | 1.391(9); 1.419(9) | 1.394(2); 1.398(2) | Without changes |
| N=O | 1.186(8)— 1.208(9) | 1.194(2)— 1.202(3) | Without changes |

* R = CH₂ONO₂.

Tables 4. Crystallographic parameters for compound **4**

| Characteristics | Value |
|---------------------------------------|--|
| Formula | C ₁₀ H ₁₀ N ₄ O ₇ |
| Space group | P2 ₁ /n |
| a/Å | 14.622(3) |
| b/Å | 5.315(2) |
| c/Å | 17.051(3) |
| α/deg | 90 |
| β/deg | 109.29(2) |
| γ/deg | 90 |
| V/Å ³ | 1250.9(6) |
| Z | 4 |
| ρ _{calc} /g cm ⁻³ | 1.584 |
| Radiation | MoKα |
| (λ/Å) | 0.71073 |
| μ/cm ⁻¹ | 1.37 |
| θ-2θ scanning range/deg | 3–54 |
| Number of measured reflections | 2719 |
| Number of reflections with I > 4.0σ | 2260 |
| Weighting scheme | w ⁻¹ = σ ² (F) + 0.0059(F ²) |
| R | 0.046 |
| R _w | 0.058 |

cryogenic NMR spectrometer (¹H, 294 MHz), which has been developed and built at the Institute of Chemical Physics in Chernogolovka, Russian Academy of Sciences. Melting temperatures were determined on a Boetius RNMK-05 instrument.

Synthesis of 4,4-dihydroxymethyl-2-(3-pyridyl)-2-oxazoline dinitrate (4**).** A solution of KOH (335 mg, 6 mmol) in alcohol (1.75 mL) was added with stirring to a solution of compound **1** (850 mg, 2 mmol) in MeOH (80 mL) at 18–20 °C. The reaction mixture was stirred for 15 min. The residue that formed was filtered off, and the filtrate was concentrated to dryness. The residue was washed with water and dried. Compound **4** was obtained as colorless crystals in a yield of 583 mg (97.6%), m.p. 95.5–96 °C (from anhydrous EtOH). Found (%): C, 40.36; H, 3.30; N, 18.88. C₁₀H₁₀N₄O₇. Calculated (%): C, 40.28; H, 3.38; N, 18.79. IR (KBr), ν/cm⁻¹: 1649, 1283, 866 (ONO₂); 1630, 1089 (2-oxazoline ring); 1552, 1578, 1487, 1417, 741, 717 (3-pyridyl). ¹H NMR (CD₃CN), δ: 4.48 (s, 2 H, OCH₂); 4.70 (m, 4 H, CH₂ONO₂, the AB type, Δν = 9.6; |²J_{gem}| = 10.5 Hz); 7.45 (dd, 1 H, CH(5), ³J_{CH(5)–CH(4)} = 7.9 Hz, ³J_{CH(5)–CH(6)} = 5.1 Hz); 8.16 (dt, 1 H, CH(4), ³J_{CH(4)–CH(5)} ≈ 7.9 Hz, ⁴J_{CH(4)–CH(2)} ≈ ⁴J_{CH(4)–CH(6)} ≈ 1.5 Hz); 8.71 (br.d, 1 H, CH(6)); 9.03 (br.s, 1 H, CH(2)).

X-ray diffraction analysis. A single crystal was prepared by slow concentration of a solution of compound **4** in CH₂Cl₂. The experimental X-ray data were collected on an automated four-circle Siemens R3 v/m diffractometer at –20 °C. The structure was solved by the direct method. The positions of all nonhydrogen atoms were revealed. The positional and thermal parameters of the nonhydrogen atoms were refined first isotropically and then anisotropically by the full-matrix least-squares method. At this stage, the positions of the H atoms were located from the difference Fourier synthesis and then refined isotropically. No absorption correction was applied because of the low value of the coefficient. All calculations were carried out on a 486 DX-2 computer using the SHELXTL PLUS program package (PC Version).⁴ The crystallographic parameters of the compound and the selected details of the refinement are given in Table 4. The atomic coordinates are listed in Table 1. The principal geometric characteristics of molecule **4** are given in Table 2. The comparative characteristics of compounds **1** and **4** are listed in Table 3.

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