Synthesis and studies of organic nitrates of the heterofunctional series
1. Synthesis and structure of *N*-nicotinoyltris(hydroxymethyl)aminomethane trinitrate hydronitrate

A. M. Korolev,[a] L. T. Eremenko,[a] L. V. Meshikhina,[a] I. L. Eremenko,[b] and S. E. Nefedov[b]*

[a] *Institute of Chemical Physics in Chernogolovka, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russian Federation. Fax: 007 (096) 515 3588. E-mail: elt@icp.ac.ru*

[b] *N. S. Kurnakov Institute of General and Inorganic Chemistry, Russian Academy of Sciences, 31 Leninsky prosp., 117907 Moscow, Russian Federation. Fax: 007 (095) 952 1279*

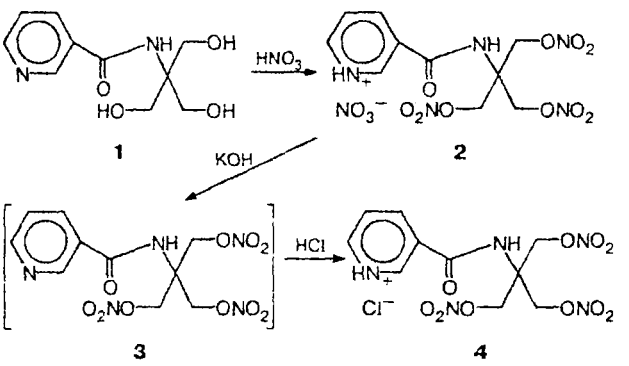
N-Nicotinoyltris(hydroxymethyl)aminomethane trinitrate hydronitrate, an analog of *N*-nicotinoylethanolamine nitrate (the active principle of the antianginal drug nicorandil), was prepared by *O*-nitration of the corresponding triol with concentrated HNO_3. The structure of the reaction product was established by X-ray structural analysis.

Key words: *N*-nicotinoyltris(hydroxymethyl)aminomethane, *N*-nicotinoyltris(hydroxymethyl)aminomethane trinitrate hydronitrate, *O*-nitration, *N*-nicotinoyltris(hydroxymethyl)aminomethane trinitrate hydrochloride, structure, X-ray structural analysis.

Progress in the chemistry of organic nitrates is increasingly associated with the synthesis of organic nitrates of the heterofunctional series. For example, *N*-nicotinoylethanolamine[1] is widely used as the active principle of the new highly efficient antianginal drug nicorandil.[2] Analogs of this compound, which contain one or two nitrate groups, have been studied.[3,4] In this work, we synthesized a new analog of nicorandil, which contains three primary nitrate groups, and studied its structure.

O-Nitration of the known[5] *N*-nicotinoyltris(hydroxymethyl)aminomethane (**1**) gave *N*-nicotinoyltris(hydroxymethyl)aminomethane trinitrate hydronitrate (**2**). We failed to isolate the corresponding free base (**3**) because of its lability. Treatment of salt **2** with an equimolar amount of KOH in EtOH and then with HCl afforded hydrochloride (**4**) (Scheme 1).

Scheme 1



The structures of salts **2** and **4** were confirmed by elemental analysis and IR and ^1H NMR spectroscopy. The structure of salt **2** was additionally established by X-ray structural analysis (Fig. 1, Tables 1—3). The molecule has the ionic structure and consists of the organic cation and the NO_3^- anion. In the crystal, ions are linked through strong hydrogen bonds (O(2A)...H(5N) 1.87(6) Å). The N—H bond in the pyridinium ring (N(5)—H(5N) 0.84(6) Å) is somewhat shorter than the corresponding bond observed in the protonated form of nicorandil (N—H 0.94(5) Å).[6] In compound **2**, the lengths of the C—N bonds at the N atom of the amide group (N(4)—C(7) and N(4)—C(6) are 1.486(9) and 1.346(7) Å, respectively) are changed only slightly compared to the corresponding parameters in nicorandil (1.458(2) and 1.338(2) Å, respectively[6]). The lengths of the C—C single bonds of these C atoms have close values and are within the normal range (C(6)—C(1), 1.514(10) Å; and C(7)—C(8—10), 1.521(11)—1.522(12) Å). It should also be noted that the presence of three bulky CH_2ONO_2 substituents (C—O(ONO_2), 1.436(9)—1.454(10) Å; O—N(NO_2), 1.358(7)—1.419(9) Å; and N—O, 1.186(8)—1.208(9) Å) at the tertiary C(7) atom results in their different arrangement with respect to other functional groups of the molecule. As a result, the O atom of one nitrate group is in the immediate vicinity of the carbonyl group (C—O, 1.218(9) Å) (see Fig. 1), which should be manifested in the chemical properties of compound **2**.

Translated from *Izvestiya Akademii Nauk. Seriya Khimicheskaya*, No. 12, pp. 2224—2227, December, 1997.

1066-5285/97/4612-2110$18.00

Table 1. Atomic coordinates and equivalent temperature factors for molecule **2**

Atom	x	y	z	B_{eq}
O(1)	−2767(11)	−2347(8)	−1031(3)	71(3)
O(2)	−2085(10)	−1290(8)	194(4)	64(3)
O(3)	−3257(9)	386(7)	−602(3)	45(2)
O(4)	1759(11)	5974(8)	−624(3)	69(3)
O(5)	1879(9)	7248(7)	−1664(3)	52(2)
O(6)	−389(8)	4731(6)	−1698(3)	33(2)
O(7)	1362(10)	−767(7)	−2995(3)	44(2)
O(8)	−1298(9)	−3065(8)	−3350(3)	52(2)
O(9)	−1772(8)	−859(6)	−2522(3)	40(2)
O(10)	−5862(8)	3748(7)	−1889(3)	45(2)
N(1)	−2670(11)	−1238(9)	−478(4)	49(3)
N(2)	1172(11)	6074(9)	−1292(4)	39(3)
N(3)	−430(12)	−1631(9)	−3003(3)	36(3)
N(4)	−3687(9)	2155(8)	−2491(3)	31(2)
N(5)	−7013(10)	2821(8)	−4605(3)	44(3)
C(1)	−5963(12)	3612(10)	−3262(4)	34(3)
C(2)	−636413)	5336(12)	−3331(5)	44(3)
C(3)	−7030(14)	5775(13)	−4027(5)	49(4)
C(4)	−7375(14)	4469(12)	−4680(6)	48(4)
C(5)	−6311(12)	2348(11)	−3912(4)	36(3)
C(6)	−5176(12)	3178(10)	−2474(4)	35(3)
C(7)	−2513(12)	1743(9)	−1782(4)	29(3)
C(8)	−4126(14)	529(12)	−1386(4)	38(3)
C(9)	−1479(14)	3445(10)	−1233(4)	33(3)
C(10)	−755(13)	825(10)	−2051(5)	32(3)
N(1A)	−8019(8)	−1168(7)	−5677(3)	8(2)
O(1A)	−8474(12)	−2555(12)	−6083(4)	91(4)
O(2A)	−7278(12)	192(12)	−5824(4)	81(3)
O(3A)	−8328(12)	−1265(9)	−4943(4)	85(3)
H(2)	−6197(109)	6211(93)	−2805(42)	41(20)
H(3)	−7238(112)	6797(96)	−4111(39)	35(22)
H(4)	−7589(97)	4740(83)	−5107(37)	16(19)
H(5)	−6403(109)	1036(94)	−4009(37)	34(19)
H(8A)	−5517(126)	657(92)	−1398(39)	35(21)
H(8B)	−4392(152)	−696(139)	−1662(55)	86(33)
H(9A)	−249(146)	3453(113)	−914(49)	69(29)
H(9B)	−2610(93)	4032(74)	−1012(31)	12(14)
H(10A)	245(121)	845(95)	−1661(43)	42(23)
H(10B)	277(88)	1677(71)	−2311(31)	5(15)
H(4N)	−3034(98)	2024(81)	−2910(34)	30(17)
H(5N)	−7221(97)	1994(80)	−4984(35)	27(17)

Experimental

The IR spectra were recorded on a Specord M-82 spectrometer. The ^{1}H NMR spectra were obtained on a cryogenic NMR spectrometer (294 MHz), which has been developed and built at the Institute of Chemical Physics in Chernogolovka of the Russian Academy of Sciences. Melting points were determined on a Boetius RNMK-05 instrument.

***N*-Nicotinoyltris(hydroxymethyl)aminomethane trinitrate hydronitrate (2).** Compound **1** (2.26 g, 10 mmol) was slowly added with stirring to concentrated HNO_3 (d_4^{20} 1.50—1.51) (13.5 mL, 320 mmol) at ~0 °C. The reaction mixture was stirred at this temperature for 1—1.5 h and then poured onto crushed ice. The precipitate was filtered off, washed with water, and dried. Compound **2** was obtained in a yield of 4.0 g (94.3%), m.p. 136—137 °C (from anhydrous EtOH). Found (%): C, 28.40; H, 2.90; N, 19.77. $C_{10}H_{11}N_5O_{10} \cdot HNO_3$. Calculated (%): C, 28.31; H, 2.85; N, 19.81. IR (KBr), ν/cm^{-1}: 1647, 1281, 865, 849 (ONO_2); 3274, 1670, 1559 (CONH); 1385 (NO_3^-); 2900—2600 (pyridinium); 749, 682 (3-pyridyl). ^{1}H NMR (DMSO-d_6), δ: 5.07 (s, 6 H, CH_2ONO_2); 8.10 (br.s, 1 H, NH^+); 8.11 (dd, 1 H, H-5, $^3J_{H\text{-}5—H\text{-}4}$ = 7.7 Hz, $^3J_{H\text{-}5—H\text{-}6}$ = 5.5 Hz); 8.78 (dt, 1 H, H-4, $^3J_{H\text{-}4—H\text{-}5}$ = 7.7 Hz, $^4J_{H\text{-}4—H\text{-}2}$ = $^4J_{H\text{-}4—H\text{-}6}$ ≈ 1.5 Hz); 9.08 (br.d, 1 H, H-6,

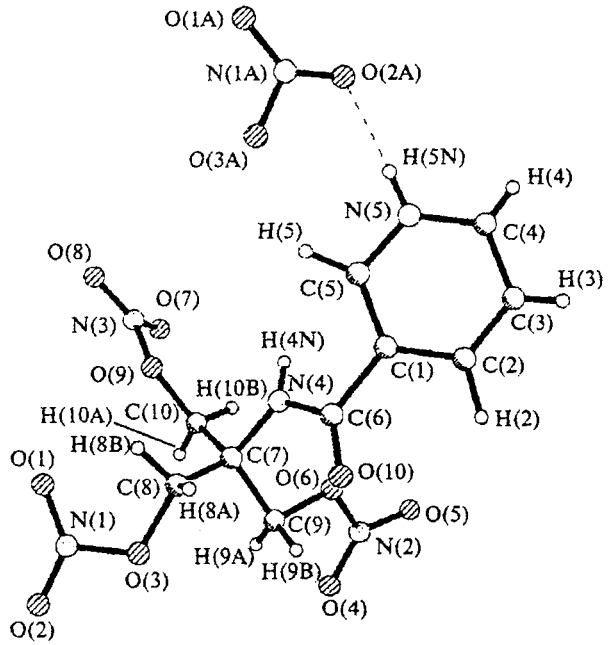


Fig. 1. Overall view of molecule **2**.

Table 2. Bond lengths (d) in molecule **2**

Bond	d/Å	Bond	d/Å
O(1)—N(1)	1.192(9)	O(2)—N(1)	1.206(10)
O(3)—N(1)	1.391(9)	O(3)—C(8)	1.454(10)
O(4)—N(2)	1.208(9)	O(5)—N(2)	1.206(9)
O(6)—N(2)	1.358(7)	O(6)—C(9)	1.450(9)
O(7)—N(3)	1.208(9)	O(8)—N(3)	1.186(8)
O(9)—N(3)	1.419(9)	O(9)—C(10)	1.436(8)
O(10)—C(6)	1.218(9)	N(4)—C(6)	1.346(10)
N(4)—C(7)	1.486(9)	N(4)—H(4N)	0.883(64)
N(5)—C(4)	1.335(12)	N(5)—C(5)	1.363(10)
N(5)—H(5N)	0.839(58)	C(1)—C(2)	1.398(12)
C(1)—C(5)	1.369(10)	C(1)—C(6)	1.514(10)
C(2)—C(3)	1.350(13)	C(2)—H(2)	1.052(67)
C(3)—C(4)	1.391(13)	C(3)—H(3)	0.839(79)
C(4)—H(4)	0.802(67)	C(5)—H(5)	0.979(71)
C(7)—C(8)	1.521(11)	C(7)—C(9)	1.522(9)
C(7)—C(10)	1.522(12)	C(8)—H(8A)	0.918(83)
C(8)—H(8B)	0.971(100)	C(9)—H(9A)	0.926(88)
C(9)—H(9B)	1.000(63)	C(10)—H(10A)	0.889(73)
C(10)—H(10B)	1.012(55)	N(1A)—O(1A)	1.167(9)
N(1A)—O(2A)	1.119(10)	N(1A)—O(3A)	1.323(9)

Table 3. Bond angles (ω) in molecule **2**

Angle	ω/deg	Angle	ω/deg	Angle	ω/deg
N(1)—O(3)—C(8)	117.2(6)	N(4)—C(7)—C(8)	107.0(6)	C(4)—N(5)—C(5)	123.0(7)
N(3)—O(9)—C(10)	114.6(5)	C(8)—C(7)—C(9)	110.1(6)	C(2)—C(1)—C(6)	119.7(6)
O(1)—N(1)—O(3)	117.6(7)	C(8)—C(7)—C(10)	113.2(7)	C(1)—C(2)—C(3)	121.1(8)
O(4)—N(2)—O(5)	126.5(6)	O(3)—C(8)—C(7)	111.2(6)	N(5)—C(4)—C(3)	119.1(9)
O(5)—N(2)—O(6)	114.3(6)	O(9)—C(10)—C(7)	107.3(6)	O(10)—C(6)—N(4)	124.8(7)
O(7)—N(3)—O(9)	117.0(6)	O(1A)—N(1A)—O(3A)	114.7(7)	N(4)—C(6)—C(1)	114.3(6)
C(6)—N(4)—C(7)	123.6(6)	N(2)—O(6)—C(9)	114.8(5)	N(4)—C(7)—C(9)	111.5(6)
C(2)—C(1)—C(5)	118.7(7)	O(1)—N(1)—O(2)	129.2(8)	N(4)—C(7)—C(10)	106.7(6)
C(5)—C(1)—C(6)	121.6(7)	O(2)—N(1)—O(3)	113.1(6)	C(9)—C(7)—C(10)	108.3(6)
C(2)—C(3)—C(4)	119.2(9)	O(4)—N(2)—O(8)	119.1(6)	O(6)—C(9)—C(7)	106.9(5)
N(5)—C(5)—C(1)	118.9(8)	O(7)—N(3)—O(8)	130.7(8)	O(1A)—N(1A)—O(2A)	128.1(7)
O(10)—C(6)—C(1)	120.9(7)	O(8)—N(3)—O(9)	112.3(6)	O(2A)—N(1A)—O(3A)	117.0(6)

Table 4. Crystallographic parameters for compound **2**

Parameter	Characteristics
Formula	$C_{10}H_{12}N_6O_{13}$
Space group	$P\bar{1}$
a/Å	6.437(6)
b/Å	7.586(7)
c/Å	17.464(15)
α/deg	96.71(2)
β/deg	95.42(2)
γ/deg	101.28(2)
V/Å^3	7824.5(13)
Z	2
ρ_{calc}/g cm^{-3}	1.709
Radiation	Mo-Kα (λ = 0.71073 Å)
μ/cm^{-1}	1.61
θ-2θ scanning range/deg	3—54
Number of measured reflections	3998
Number of reflections with $I > 4.0\sigma$	1354
Weighting scheme	$w^{-1} = \sigma^2F + 0.0026F^2$
R	0.070
R_w	0.086

$^3J_{H\text{-}6—H\text{-}5}$ = 5.5 Hz); 9.13 (s, 1 H, CONH); 9.22 (br.d, 1 H, H-2, $^4J_{H\text{-}2—H\text{-}4} \approx 1.5$ Hz).

***N*-Nicotinoyltris(hydroxymethyl)aminomethane trinitrate hydrochloride (4).** A solution of KOH (0.140 g, 2.5 mmol) in EtOH (0.75 mL) was added with stirring to a solution of salt **2** (1.060 g, 2.5 mmol) in MeOH (100 mL). After 15 min, the solution was concentrated to dryness. The residue was washed with water, dried *in vacuo*, and dissolved in MeOH (17 mL). Then 34% HCl (0.3 mL, 3.3 mmol) was added with stirring to the reaction mixture. Concentration *in vacuo* gave compound **4** in a yield of 0.974 g (98%), m.p. 126—127 °C (from anhydrous EtOH). Found (%): C, 29.92; H, 3.08; N, 17.78; Cl, 9.16. $C_{10}H_{11}N_5O_{10} \cdot HCl$. Calculated (%): C, 30.20; H, 3.04; N, 17.61; Cl, 8.91. IR (KBr), ν/cm^{-1}: 1637, 1283, 851 (ONO_2); 3199, 1688, 1544 (CONH); 2570 (pyridinium); 743, 677 (3-pyridyl). ^{1}H NMR (DMSO-d_6), δ: 5.07 (s, 6 H, CH_2ONO_2); 8.13 (br.dd, 1 H, H-5, $^3J_{H\text{-}5—H\text{-}6}$ = 5.5 Hz, $^3J_{H\text{-}5—H\text{-}4}$ = 7.7 Hz); 8.38 (br.s, 1 H, NH^+); 8.93 (br.d, 1 H, H-4, $^3J_{H\text{-}4—H\text{-}5}$ = 7.7 Hz); 9.10 (br.s, 1 H, H-6); 9.29 (br.s, 1 H, H-2); 9.59 (s, 1 H, CONH).

X-ray structural analysis. Single crystals suitable for X-ray structural analysis were prepared by slow concentration of a solution of compound **2** in a MeOH—CH_2Cl_2 mixture. 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 direct methods, which allowed us to reveal all nonhydrogen atoms. 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 corrections were made 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).[7] The crystallographic parameters of the compound and selected details are given in Table 4. The principal geometric characteristics of molecule **2** are listed in Tables 2 and 3.

We thank G. V. Lagodzinskaya for measuring the ^{1}H NMR spectra and for helpful discussions.

This work was financially supported by the International Scientific and Technology Center (Project No. 123-94).

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Received April 30, 1997