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Structure and Synthesis of 3,5-Dimethyl-*N*-nitro-1*H*-pyrazole-1-carboxamidine

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Abstract—A new approach to the synthesis of 3,5-dimethyl-*N*-nitro-1*H*-pyrazole-1-carboxamidine was developed based on condensing 1-amino-2-nitroguanidine with pentane-2,4-dione under alkaline catalysis. The known method of its preparation in the presence of acetic acid was improved. The structure of 3,5-dimethyl-*N*-nitro-1*H*-pyrazole-1-carboxamidine was characterized by NMR, IR spectroscopy and X-ray diffraction analysis.

Keywords: 1-amino-2-nitroguanidine, 3,5-dimethyl-*N*-nitro-1*H*-pyrazol-1-carboxy-amidine

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In recent decades, much attention is paid to research in the chemistry of guanidine derivatives. This is due to the biological activity of compounds containing guanidine fragment [1], and to the prospect of the use of its derivatives in the organic synthesis. A large number of linear and heterocyclic compounds has been synthesized on the basis of 1-amino-2-nitroguanidine. Thus, 3,5-dimethyl-*N*-nitro-1*H*-pyrazole-1-carboxamidine is used as protective group in the synthesis of aliphatic polyamines (spermidines) involved in the cellular metabolism [2] and also as a carrier of nitroguanidine moiety in the synthesis of substituted amino nitroguanidines [3]. Compared with other protecting groups like *N*,*N*'-bis-Boc-1-pyrazole-1-carboxamidine and *N*,*N*'-bis-Boc-*N*'-triflylguanidine, the synthesis of 3,5-dimethyl-*N*-nitro-1*H*-pyrazole-1-carboxamidine is more convenient and simple (no use of inert atmosphere), and its yield is significantly superior to that of analogs [3].

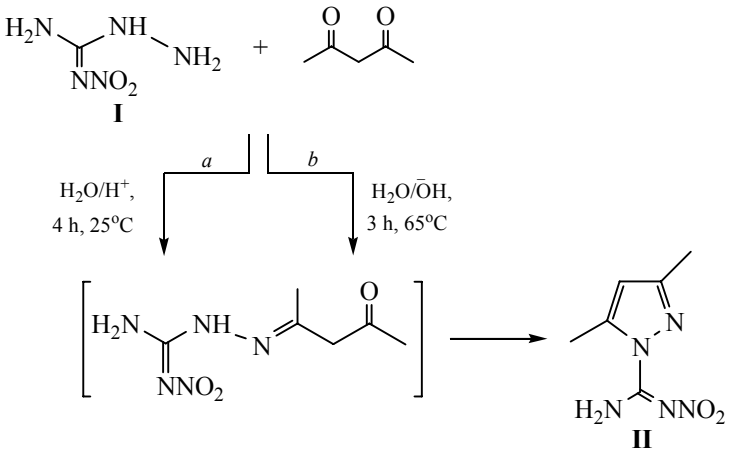
According to the literature data, the synthesis of 3,5-dimethyl-*N*-nitro-1*H*-pyrazole-1-carboxamidine involves a classical reaction of 1-amino-2-nitroguanidine with an excess of a dicarbonyl compound (pentane-2,4-dione) under acid catalysis (acetic acid [2–5]). Scott et al. [4] detected the formation of linear osazone along with the target heterocycle, which leads to a decrease in the yield of the desired 3,5-dimethyl-*N*-nitro-1*H*-pyrazole-1-carboxamidine. In [2–5] the reaction time was from 7 to 12 h, and the used temperature varied from 4 to 25°C; the heterocycle was obtained with a maximum yield of 80% at room temperature within 7 h [2].

We first developed a method of the synthesis of 3,5-dimethyl-*N*-nitro-1*H*-pyrazole-1-carboxamidine **II** under alkaline catalysis. The reaction was carried out at 65°C for 3 h with equimolar amounts of the reactants; the yield reaches 55%. We also improved the procedure for obtaining **II** in acid catalysis conditions: slow addition of equimolar amounts of the reactants at room temperature and maintaining the reaction mixture for 4 h allowed obtaining the target compound in 88% yield. In both cases, the formation of a linear osazone was not observed (Scheme 1).

The structure of 3,5-dimethyl-*N*-nitro-1*H*-pyrazole-1-carboxamidine **II** was characterized by NMR, IR spectroscopy and X-ray diffraction data.

The ^{1}H NMR spectrum of compound **II** contained the signals of the protons of all structural fragments. In a weak field there were characteristic broadened signals of magnetically nonequivalent protons of the primary amino group (8.21, 9.08 ppm) due to the participation of one of the hydrogen atoms of the amino group in the formation of an intramolecular

Scheme 1.



hydrogen bond with the oxygen of the nitro group. The singlet of the CH proton of the pyrazole ring was observed at 6.02 ppm. In a strong field (2.23, 2.60 ppm) there were the singlets of methyl groups. The $^{13}C–\{1H\}$ NMR spectrum of **II** contained the signals at 112.73, 144.92, and 153.81 ppm belonging to the carbon atoms of the pyrazole ring. The signals of the methyl groups were recorded at 13.86 and 16.05 ppm. In a weak field (155.81 ppm) there was the signal of the carbon of nitroamidine fragment. These findings are consistent with those described in [2].

The IR spectrum of 3,5-dimethyl-*N*-nitro-1*H*-pyrazole-1-carboxamidine **II** contained a set of the strong absorption bands in the range of 1240–1622 cm^{-1}. Thus, the strong bands at 1622 and 1578 cm^{-1} can be probably attributed to the stretching vibrations of the C=N bond and bending vibrations of N–H bond, respectively. The absorption at 1408 and 1240 cm^{-1} is due to the stretching vibrations of NO_2-group [6]. In the high-frequency part of the spectrum (3332, 3448 cm^{-1}) there was absorption of stretching vibrations of the N–H bond.

According to XRD data, the nitroamidine moiety, pyrazole ring, and the methyl groups attached to the ring lie in the same plane (Fig. 1). In the nitroamidine fragment, as in other nitrimines [7], there is an intramolecular hydrogen bond between the oxygen atom of the nitro group and the amino group ($O^{12}\cdots H–N^{9}$). Also, the formation of the hydrogen bonds $O^{12}\cdots H–N^{9}\cdots O^{12A}$ makes it possible to combine adjacent molecules into

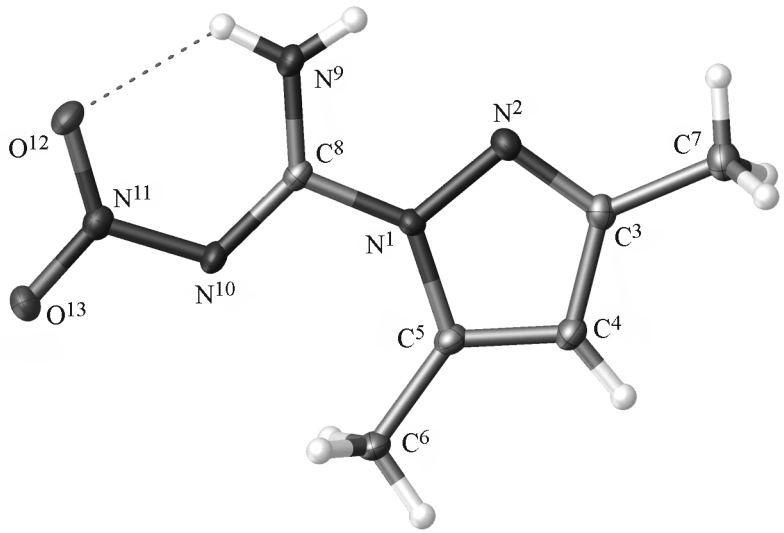


Fig. 1. General view of the molecule **II**. The thermal ellipsoids are represented at the 50% probability level.

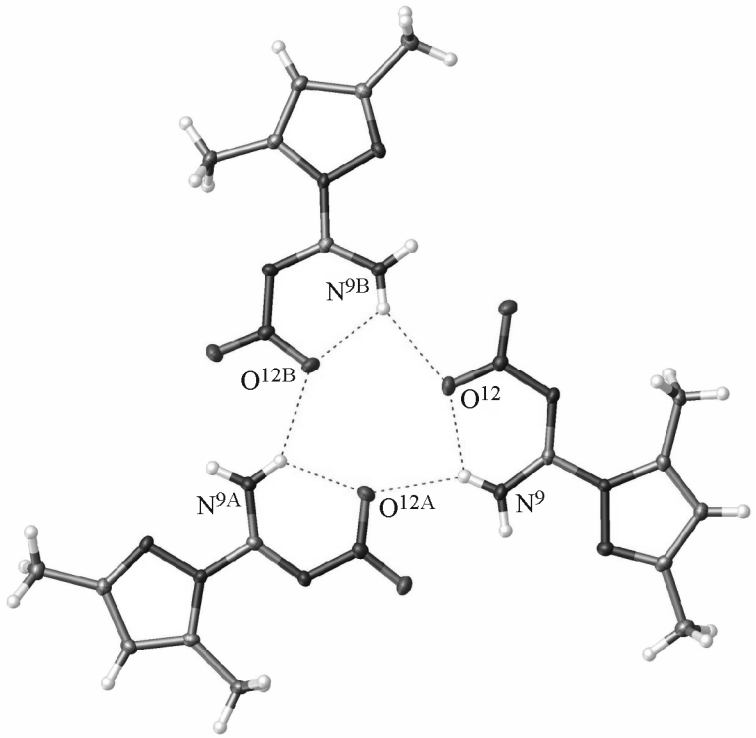


Fig. 2. Crystal structure of **II**. Merging of neighboring molecules in trimers by a system of hydrogen bonds (dashed lines) [$O^{12}\cdots N^{9}\cdots O^{12A}$].

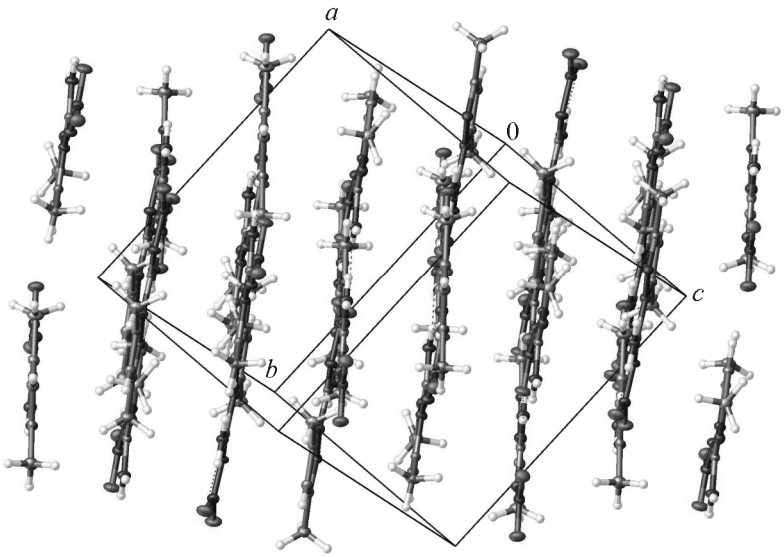


Fig. 3. Crystal packing of the molecules **II**.

trimers (Fig. 2). The latter stacked in layers parallel to the crystallographic plane (11–1) (Fig. 3).

The bond lengths, bond and torsion angles values are presented in Tables 1–3. The bond lengths between the atoms of the pyrazole ring (C^3–C^4, C^4–C^5, N^1–N^2, N^1–C^5, N^2–C^3) are consistent with the data for the unsubstituted pyrazole: C^3–C^4 1.410, C^4–C^5 1.369, N^1–N^2 1.366, N^1–C^5 1.357, N^2–C^3 1.329 Å [8].

EXPERIMENTAL

In this research were utilized resources of the Center for Joint Use of the Herzen Russian State

Table 1. Bond lengths in the structure of **II**

Bond	*d*, Å	Bond	*d*, Å
$O^{12A}–N^{11A}$	1.2489(19)	$N^{10B}–N^{11B}$	1.364(2)
$O^{13A}–N^{11A}$	1.2360(18)	$N^{10B}–C^{8B}$	1.338(2)
$N^{1A}–N^{2A}$	1.3821(19)	$C^{3B}–C^{4B}$	1.420(2)
$N^{1A}–C^{5A}$	1.393(2)	$C^{3B}–C^{7B}$	1.496(2)
$N^{1A}–C^{8A}$	1.398(2)	$C^{4B}–C^{5B}$	1.358(2)
$N^{2A}–C^{3A}$	1.322(2)	$C^{5B}–C^{6B}$	1.491(2)
$N^{9A}–C^{8A}$	1.307(2)	$O^{12}–N^{11}$	1.2483(18)
$N^{10A}–N^{11A}$	1.3667(19)	$O^{13}–N^{11}$	1.2372(19)
$N^{10A}–C^{8A}$	1.336(2)	$N^{1}–N^{2}$	1.387(2)
$C^{3A}–C^{4A}$	1.418(2)	$N^{1}–C^{5}$	1.396(2)
$C^{3A}–C^{7A}$	1.496(2)	$N^{1}–C^{8}$	1.394(2)
$C^{4A}–C^{5A}$	1.362(2)	$N^{2}–C^{3}$	1.320(2)
$C^{5A}–C^{6A}$	1.490(2)	$N^{9}–C^{8}$	1.311(2)
$O^{12B}–N^{11B}$	1.2478(18)	$N^{10}–N^{11}$	1.3627(19)
$O^{13B}–N^{11B}$	1.2346(18)	$N^{10}–C^{8}$	1.333(2)
$N^{1B}–N^{2B}$	1.3894(19)	$C^{3}–C^{4}$	1.415(2)
$N^{1B}–C^{5B}$	1.394(2)	$C^{3}–C^{7}$	1.498(2)
$N^{1B}–C^{8B}$	1.393(2)	$C^{4}–C^{5}$	1.360(2)
$N^{2B}–C^{3B}$	1.321(2)	$C^{5}–C^{6}$	1.490(2)
$N^{9B}–C^{8B}$	1.307(2)		

Table 2. Bond angles in the structure of **II**

Angle	ω, deg	Angle	ω, deg
$N^{2A}N^{1A}C^{5A}$	111.84(13)	$N^{2B}C^{3B}C^{7B}$	121.32(16)
$N^{2A}N^{1A}C^{8A}$	117.48(14)	$C^{4B}C^{3B}C^{7B}$	127.23(16)
$C^{5A}N^{1A}C^{8A}$	130.68(15)	$C^{5B}C^{4B}C^{3B}$	106.97(15)
$C^{3A}N^{2A}N^{1A}$	104.49(14)	$N^{1B}C^{5B}C^{6B}$	125.66(16)
$C^{8A}N^{10A}N^{11A}$	117.92(15)	$C^{4B}C^{5B}N^{1B}$	105.50(15)
$O^{12A}N^{11A}N^{10A}$	122.97(14)	$C^{4B}C^{5B}C^{6B}$	128.83(16)
$O^{13A}N^{11A}O^{12A}$	122.35(14)	$N^{9B}C^{8B}N^{1B}$	116.05(15)
$O^{13A}N^{11A}N^{10A}$	114.68(14)	$N^{9B}C^{8B}N^{10B}$	131.28(17)
$N^{2A}C^{3A}C^{4A}$	111.62(15)	$N^{10B}C^{8B}N^{1B}$	112.67(14)
$N^{2A}C^{3A}C^{7A}$	121.17(16)	$N^{2}N^{1}C^{5}$	111.54(14)
$C^{4A}C^{3A}C^{7A}$	127.20(16)	$N^{2}N^{1}C^{8}$	117.79(14)
$C^{5A}C^{4A}C^{3A}$	106.73(16)	$C^{8}N^{1}C^{5}$	130.65(15)
$N^{1A}C^{5A}C^{6A}$	125.99(15)	$C^{3}N^{2}N^{1}$	104.60(14)
$C^{4A}C^{5A}N^{1A}$	105.30(15)	$C^{8}N^{10}N^{11}$	118.13(14)
$C^{4A}C^{5A}C^{6A}$	128.70(16)	$O^{12}N^{11}N^{10}$	123.13(15)
$N^{9A}C^{8A}N^{1A}$	115.93(15)	$O^{13}N^{11}O^{12}$	122.09(14)
$N^{9A}C^{8A}N^{10A}$	131.41(16)	$O^{13}N^{11}N^{10}$	114.78(14)
$N^{10A}C^{8A}N^{1A}$	112.66(15)	$N^{2}C^{3}C^{4}$	111.56(16)
$N^{2B}N^{1B}C^{5B}$	111.48(14)	$N^{2}C^{3}C^{7}$	121.45(16)
$N^{2B}N^{1B}C^{8B}$	117.67(14)	$C^{4}C^{3}C^{7}$	126.98(16)
$C^{8B}N^{1B}C^{5B}$	130.83(14)	$C^{5}C^{4}C^{3}$	107.07(15)
$C^{3B}N^{2B}N^{1B}$	104.60(14)	$N^{1}C^{5}C^{6}$	126.06(16)
$C^{8B}N^{10B}N^{11B}$	117.86(14)	$C^{4}C^{5}N^{1}$	105.23(16)
$O^{12B}N^{11B}N^{10B}$	123.13(14)	$C^{4}C^{5}C^{6}$	128.70(16)
$O^{13B}N^{11B}O^{12B}$	122.02(15)	$N^{9}C^{8}N^{1}$	115.75(16)
$O^{13B}N^{11B}N^{10B}$	114.85(14)	$N^{9}C^{8}N^{10}$	131.35(16)
$N^{2B}C^{3B}C^{4B}$	111.44(15)	$N^{10}C^{8}N^{1}$	112.90(14)

Pedagogical University. X-Ray studies were performed in the X-ray Diffraction Centre of St. Petersburg State University.

NMR spectra ($CDCl_3$) were recorded on a Jeol ECX400A instrument operating at 399.78 (^1H) and 100.52 (^{13}C) MHz using the residual signals of undeuterated solvent as internal reference. IR spectra (chloroform) were obtained on a Shimadzu IRPrestige-21 FTIR spectrometer.

XRD studies were performed on a single-crystal diffractometer Agilent Technologies Excalibur Eos equipped with a CCD detector. Measurements were performed at 100 K using monochromated MoK_α-irradiation. The unit cell parameters (Table 4) were refined by the least squares method based on the 10439 reflections with 2θ in the range of 5.52°–55.00°. The structure was solved by the direct method and refined to R_1 0.047 (wR_2 0.096) for 4262 independent reflections with $|F_0| \geq 4\sigma_F$ using SHELXL-97 [9] and OLEX2 [10] software. The correction for extinction was made by CrysAlisPro program [11]. Positions of the hydrogen atoms were calculated with use of SHELX package. The crystallographic data were deposited at Cambridge Crystallographic Data Center (CCDC 1,037,784).

Synthesis of starting 1-amino-2-nitroguanidine **I** was performed as described in [12].

3,5-Dimethyl-*N*-nitro-1*H*-pyrazole-1-carboxamidine (II). *a*. *Under acid catalysis conditions*. Pentane-2,3-dione (0.43 mL, 0.0042 mol) and a catalytic amount of acetic acid were added dropwise to a solution of 0.5 g (0.0042 mol) of 1-amino-2-nitroguanidine in 10 mL of water. The reaction mixture was stirred at 25°C for 4 h. The resulting precipitate was filtered off, washed successively with water, ethanol, and diethyl ether, and dried in air. Yield 0.68 g (88%), mp 112–113°C (*i*-PrOH) {mp 127–128°C (EtOH) [2]}. Found N, %: 38.25. $C_6H_9N_5O_2$. Calculated N, %: 38.32.

The synthesis by the literature method [2] provided compound **II** in a 80% yield , as described; however, its melting point was 112–113°C, not 127–128°C as indicated in [2]. The mixed test with the sample

Table 3. Torsion angles in the structure of **II**

Angle	τ, deg	Angle	τ, deg
$N^{1A}N^{2A}C^{3A}C^{4A}$	0.41(19)	$C^{3B}C^{4B}C^{5B}C^{6B}$	178.60(17)
$N^{1A}N^{2A}C^{3A}C^{7A}$	–179.19(15)	$C^{5B}N^{1B}N^{2B}C^{3B}$	–0.36(18)
$N^{2A}N^{1A}C^{5A}C^{4A}$	0.96(19)	$C^{5B}N^{1B}C^{8B}N^{9B}$	–178.50(17)
$N^{2A}N^{1A}C^{5A}C^{6A}$	–178.52(16)	$C^{5B}N^{1B}C^{8B}N^{10B}$	0.8(3)
$N^{2A}N^{1A}C^{8A}N^{9A}$	3.2(2)	$C^{7B}C^{3B}C^{4B}C^{5B}$	–179.35(17)
$N^{2A}N^{1A}C^{8A}N^{10A}$	–176.96(14)	$C^{8B}N^{1B}N^{2B}C^{3B}$	178.51(15)
$N^{2A}C^{3A}C^{4A}C^{5A}$	0.2(2)	$C^{8B}N^{1B}C^{5B}C^{4B}$	–178.18(17)
$N^{11A}N^{10A}C^{8A}N^{1A}$	176.25(14)	$C^{8B}N^{1B}C^{5B}C^{6B}$	2.8(3)
$N^{11A}N^{10A}C^{8A}N^{9A}$	–3.9(3)	$C^{8B}N^{10B}N^{11B}O^{12B}$	–5.4(2)
$C^{3A}C^{4A}C^{5A}N^{1A}$	–0.66(19)	$C^{8B}N^{10B}N^{11B}O^{13B}$	174.98(15)
$C^{3A}C^{4A}C^{5A}C^{6A}$	178.80(18)	$N^{1}N^{2}C^{3}C^{4}$	–0.11(19)
$C^{5A}N^{1A}N^{2A}C^{3A}$	–0.85(18)	$N^{1}N^{2}C^{3}C^{7}$	178.79(16)
$C^{5A}N^{1A}C^{8A}N^{9A}$	–176.24(17)	$N^{2}N^{1}C^{5}C^{4}$	–0.1(2)
$C^{5A}N^{1A}C^{8A}N^{10A}$	3.6(3)	$N^{2}N^{1}C^{5}C^{6}$	–179.52(17)
$C^{7A}C^{3A}C^{4A}C^{5A}$	179.74(17)	$N^{2}N^{1}C^{8}N^{9}$	–1.4(2)
$C^{8A}N^{1A}N^{2A}C^{3A}$	179.63(15)	$N^{2}N^{1}C^{8}N^{10}$	177.70(14)
$C^{8A}N^{1A}C^{5A}C^{4A}$	–179.60(17)	$N^{2}C^{3}C^{4}C^{5}$	0.0(2)
$C^{8A}N^{1A}C^{5A}C^{6A}$	0.9(3)	$N^{11}N^{10}C^{8}N^{1}$	177.42(14)
$C^{8A}N^{10A}N^{11A}O^{12A}$	–2.1(2)	$N^{11}N^{10}C^{8}N^{9}$	–3.7(3)
$C^{8A}N^{10A}N^{11A}O^{13A}$	178.62(15)	$C^{3}C^{4}C^{5}N^{1}$	0.0(2)
$N^{1B}N^{2B}C^{3B}C^{4B}$	0.08(19)	$C^{3}C^{4}C^{5}C^{6}$	179.44(18)
$N^{1B}N^{2B}C^{3B}C^{7B}$	179.68(15)	$C^{5}N^{1}N^{2}C^{3}$	0.13(19)
$N^{2B}N^{1B}C^{5B}C^{4B}$	0.49(19)	$C^{5}N^{1}C^{8}N^{9}$	176.97(16)
$N^{2B}N^{1B}C^{5B}C^{6B}$	–178.57(16)	$C^{5}N^{1}C^{8}N^{10}$	–3.9(3)
$N^{2B}N^{1B}C^{8B}N^{9B}$	2.9(2)	$C^{7}C^{3}C^{4}C^{5}$	–178.77(17)
$N^{2B}N^{1B}C^{8B}N^{10B}$	–177.79(14)	$C^{8}N^{1}N^{2}C^{3}$	178.81(15)
$N^{2B}C^{3B}C^{4B}C^{5B}$	0.2(2)	$C^{8}N^{1}C^{5}C^{4}$	–178.56(17)
$N1^{1B}N^{10B}C^{8B}N^{1B}$	178.85(14)	$C^{8}N^{1}C^{5}C^{6}$	2.0(3)
$N^{11B}N^{10B}C^{8B}N^{9B}$	–2.0(3)	$C^{8}N^{10}N^{11}O^{12}$	1.6(2)
$C^{3B}C^{4B}C^{5B}N^{1B}$	–0.41(19)	$C^{8}N^{10}N^{11}O^{13}$	–178.38(16)

Table 4. Crystallographic data of compound **II**

Parameter	Value
Empirical formula	$C_6H_9N_5O_2$
Crystal system	Triclinic
a, Å	8.5457(7)
b, Å	11.8721(8)
c, Å	12.6530(7)
α, deg	105.533(5)
β, deg	93.338(6)
γ, deg	92.345(6)
V, Å^3	1232.61(14)
M	183.18
Space group	*P*-1
μ, cm^{-1}	0.116
T, K	100(2)
Z	6
d_{calc}, g/cm	1.481
Crystal size, mm^3	0.32×0.24×0.15
Radiation	MoK_α
Reflections collected	10439
Independent reflections	5663
2θ range, deg	5.52–55.00
Reflections with $\|F_0\| \geq 4\sigma_F$	4262
R_{int}	0.0263
R_σ	0.0521
R_1 ($\|F_0\| \geq 4\sigma_F$)	0.0475
wR_2 ($\|F_0\| \geq 4\sigma_F$)	0.0961
R_1 (all data)	0.0698
wR_2 (all data)	0.1067
S	1.037
r_{min}, r_{max}, *e*/Å^3	–0.307, 0.248

obtained via the method *a* did not show any depression of the melting point.

b. Under alkaline catalysis conditions. Pentane-2,3-dione (0.43 mL, 0.0042 mol) was added dropwise to a solution of 0.5 g (0.0042 mol) of 1-amino-2-nitroguanidine and 0.23 g (0.0042 mol) of potassium hydroxide in 10 mL of water. The reaction mixture was heated to 65°C and stirred for 3 h, then cooled to 18–20°C. The precipitate was filtered off, washed in succession with water, ethanol, and diethyl ether, and dried in air. Yield 0.42 g (55%), mp 112–113°C (EtOH) {mp 127–128°C (EtOH) [2]}. The mixed test with the sample obtained via the method *a* did not show any depression of the melting point.

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