Formation of Isomeric 3-Azabicyclo[3.3.1]nonanes in a Reaction of 1-(2-Hydroxyethoxy)-2,4-dinitrobenzene with Sodium Borohydride, Formaldehyde, and Methylamine

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Abstract—Anionic hydride adduct of 1-(2-hydroxyethoxy)-2,4-dinitrobenzene was brought into a double Mannich condensation with formaldehyde and methylamine to furnish a mixture of isomeric 3-azabicyclo[3.3.1]nonanes: 3-methyl-6-(2-hydroxyethoxy)-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene and 3-methyl-6,6-ethylenedioxy-1,7-dinitro-3-azabicyclo[3.3.1]nonane. By means of NMR spectroscopy, X-ray diffraction analysis, and quantum chemistry (PM3) we demonstrated that the spirocyclic isomer had *chair-chair* conformation with diequatorial orientation of substituents in positions *3* and *7*.

A large number of physiologically active compounds was found among derivatives of 3-azabicyclo[3.3.1]-nonane [1–3], and consequently the extension of this class compounds and the study of their properties remain urgent. In continuation of our research on the synthesis of polyfunctional derivatives of 3-azabicyclo[3.3.1]nonane from aromatic nitro compounds [4–7] we carried out reactions of 1-(2-hydroxyethoxy)-2,4-dinitrobenzene in succession with sodium borohydride, formaldehyde, and methylamine hydrochloride. It was established that alongside the expected reaction product, 3-methyl-6-(2-hydroxyethoxy)-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene (**I**), formed its spirocyclic isomer which was isolated from the reaction mixture and identified as 3-methyl-6,6-ethylenedioxy-1,7-dinitro-3-azabicyclo[3.3.1]nonane (**II**) (Scheme 1). The separation of the isomers was performed by column chromatography on silica gel using eluents of different polarity.

The structure of isomeric bicyclononanes **I** and **II** was proved by IR, ^{1}H and ^{13}C NMR spectroscopy, and also by elemental analysis. In the IR spectrum of compound **I** alongside the absorption of the nitro groups (1342, 1374, and 1528 cm^{-1}) a broad band was observed belonging to absorption of the OH group in the region 3347 cm^{-1}, and also a band from vibrations of the C=C bond at 1663 cm^{-1} lacking in the spectrum of compound **II**.

The comparison of data from Tables 1 and 2 reveals that the characteristics of the ^{1}H and ^{13}C NMR spectra of compounds **I** and **II** are quite different. The signals in the ^{1}H NMR spectra were assigned using two-dimensional homonuclear spectroscopy COSY; the assignments of signals in the ^{13}C NMR spectra were performed with the aid of 2D heteronuclear ^{1}H–^{13}C spectroscopy HSQC [correlation by constants J(^{1}H, ^{13}C) through one bond, assignment of the signals of the protonated carbon atoms] and HMBC [correlation by J(^{1}H,[13]C) through two and
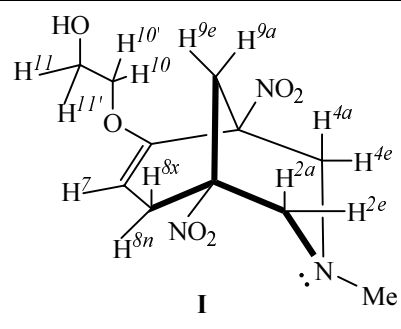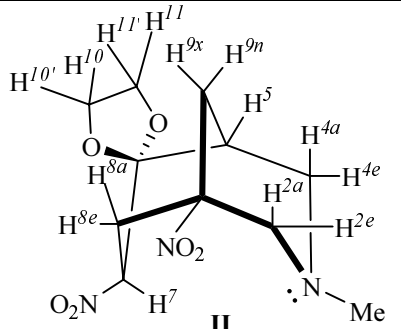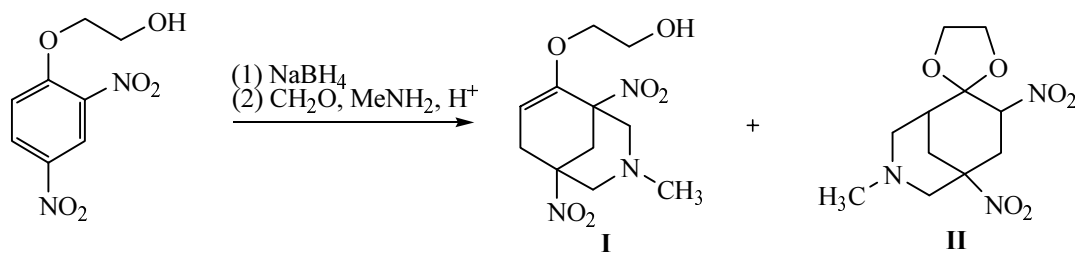
Scheme 1.

Table 1. ^{1}H NMR spectra of 3-methyl-6-(2-hydroxyethoxy)-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene (**I**) and 3-methyl-6,6-ethylenedioxy-1,7-dinitro-3-azabicyclo[3.3.1]nonane (**II**), δ, ppm (*J*, Hz)[a]

Atom no.		
	I	**II**
H$^{2\varepsilon}$	3.26 d ($^2J_{e,a}$ 10.0)	3.28 d ($^2J_{e,a}$ 10.6)
H^{2a}	2.41 d ($^2J_{a,e}$ 10.0)	2.44 d ($^2J_{a,e}$ 10.6)
H$^{4\varepsilon}$	3.22 d ($^2J_{e,a}$ 9.6)	2.05 d.d ($^2J_{e,a}$ 11.6, $^4J_{4e,9x}$ 2.9)
H^{4a}	2.47 d ($^2J_{a,e}$ 9.6)	2.90 d ($^2J_{a,e}$ 11.6)
H^5	–	2.22 m ($W_{1/2}$ 2.69)
H^7	4.98 d.d ($^3J_{7,8x}$ 4.5, $^3J_{7,8n}$ 3.2)	5.945 d.d ($^3J_{7,8a}$ 11.5, $^3J_{7,8e}$ 7.0)
H^{8n} (H$^{8\varepsilon}$)	2.87 d.d ($^2J_{n,x}$ 16.5, $^3J_{8n,7}$ 3.2)	2.81 d.d.d ($^2J_{e,a}$ 12.5, $^3J_{8e,7}$ 6.9, $^4J_{8e,9n}$ 2.9)
H^{8x} (H^{8a})	2.68 d.d ($^2J_{x,n}$ 16.5, $^3J_{8x,7}$ 4.5)	2.79 d ($^2J_{a,e}$ 12.5)
H$^{9\varepsilon}$ (H^{9x})	3.05 d ($^2J_{e,a}$ 10.9)	2.425 d ($^2J_{x,n}$ 12.4)
H^{9a} (H^{9n})	2.63 d ($^2J_{a,e}$ 10.9)	2.02 d.d ($^2J_{n,x}$ 12.4, $^4J_{9n,8e}$ 2.9)
H$^{10,10'}$	3.67 m	3.945 m, 3.88 m[b]
H$^{11,11'}$	3.51 m	3.945 m, 3.78 m[b]
NSH$_3$	2.34 s	2.25 s
OH	4.65 т ($^3J_{OH,11}$ 5.2)	–

[a] X = *exo*, n = *endo.* [b] The positions of these values should be probably interchanged.

Table 2. ^{13}C NMR spectra (δ, ppm) and correlation peaks in HMBC spectra of 3-methyl-6-(2-hydroxyethoxy)-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene (**I**) and 3-methyl-6,6-ethylenedioxy-1,7-dinitro-3-azabicyclo[3.3.1]nonane (**II**)[a]

Atom no.	(**I**)	HMBC	(**II**)	HMBC
C^1	83.9	H^{2e}, H^{2a}, H^7, H^{8n}, H^{9e}, H^{9a}	84.1	H^{2e}, H^{2a}, H^{8e}, H^{8a}, H^{9x}, H^{9n}
C^2	62.7	NMe, H^{4e}, H^{8n}, H^{9e}	60.9	NMe, H^{4a}, H^{8e}, H^{8a}
C^4	55.95	NMe, H^{2e}, H^{9e}, H^{9a}	53.3	NMe, H^{2e}, H^{9x}
C^5	86.8	H^{4e}, H^{4a}, H^{9e}, H^{9a}	39.5	H^{4e}, H^{4a}
C^6	147.95	H^{4a}, H^{8n}, H^{9a}, H^{10}	107.6	H^{4e}, H^{10}, H^{11}
C^7	97.05	H^{8n}, H^{8x}	83.6	H^{8e}, H^{8a}
C^8	33.9	H^{2a}, H^{9a}	35.3	H^{2e}, H^{2a}, H^7, H^{9n}
C^9	37.6	H^{2e}, H^{2a}, H^{4e}, H^{4a}	33.0	H^{2e}, H^{2a}, H^{4a}
C^{10}	69.7	–	64.9[b]	–
C^{11}	58.9	–	65.1[b]	–
NCH$_3$	44.45	H^{4a}	44.7	–

[a] x = *exo*, n = *endo.* [b] The positions of these values should be probably interchanged.

three bonds, assignment of the signals of quaternary carbon atoms].

As the initial point for assignment in the carbon spectrum we selected the protons of the CH$_3$N group. In the HMBC spectrum of compounds **I** and **II** these protons have correlation peaks with C^2 and C^4 atoms by the constants through three bonds. The distinguishing between the signals of C^2 and C^4 atoms is facilitated by the

existence of large constants through three bonds ($J_{2,8}$ and $J_{7,6}$) revealed due to the corresponding correlation peaks in the HMBC spectrum (Table 2). Note that in keeping with the chemical shifts the C^6 atom in compound **I** (δ 147.95 ppm) represents an sp^2-hybridized carbon with no hydrogen linked thereto, the signal of C^8 (δ 33.8 ppm) belongs to a methyl group. In compound **II** the atom C^8 (δ 35.3 ppm) corresponds to the CH_2 group of the cyclohexane fragment, and the atom C^6 (δ 107.6 ppm) is a quaternary sp^3-hybridized carbon atom with two electron-withdrawing substituents (oxygen atoms). Signals of H^7 protons in the COSY spectra of both compounds are found because of the presence of coupling constants with protons H^8. The chemical shifts of C^7 atoms revealed from the HSQC spectra show that in compound **I** this atom is the sp^2 carbon in the =CH group (δ 97.05 ppm), and in compound **II** it included in a CH group being an sp^3 carbon (δ 83.6 ppm) possessing an electron-withdrawing substituent (NO_2).

Hence the ^1H and ^{13}C NMR spectra of isomer **I** contain a set of signals characteristic of the spectra of previously described 6-substituted 1,5-dinitro derivatives of 3-azabicyclo[3.3.1]non-6-enes [4–7]. In the ^1H NMR spectrum the attention is engaged by the hydroxy group signal appearing as a weakly resolved triplet at δ 4.65 ppm [$^2J_{OH,H^{11}}$ 5.2 Hz]. Besides the spectral data obtained are well consistent with the results of X-ray diffraction studies of this type compounds [4–6, 8] which have demonstrated that the cyclohexene ring exists in the *sofa* conformation, and the piperidine ring in the *chair* conformation with the equatorial orientation of the substituent at the heteroatom.

It is well known [9] that in the saturated 3-azabicyclo[3.3.1]nonanes the carbo- and heterocyclic fragments of the molecules may be present in the *chair* or *boat* form whose combination provides four principal conformations. Compound **II** contains in its structure chiral centers (atoms C^1, N^3, C^5, and C^7) and therefore each conformation may exist as several diastereomers. Inasmuch as the rings are rigidly fused the substituents in the nodal positions *1* and *5* can assume only equatorial orientation, whereas the configurations of atoms N^3 and C^7 in the stereoisomers can vary. However the ^1H and ^{13}C NMR spectra of bicyclononane **II** contain a single set of signals indicating that the compound forms as an only stereoisomer.

The data obtained on chemical shifts δ_C and δ_H and on the coupling constants not only permitted assignment of the signals in the NMR spectra of compound **II**

(Tables 1 and 2) but also allowed a conclusion that the compound under study existed in solution mainly in the *chair-chair* conformation. This statement is in agreement with the observed values of the vicinal coupling constants of protons attached to the skeleton which contain important information on the geometry of molecules. In the spectra of 3-aza- and 3,7-diazabicyclo[3.3.1]nonanes existing in the *chair-chair* conformation the vicinal coupling constants between the protons attached to the ring (H^2, H^4, H^6, H^8) and nodal (H^1, H^5) carbons lie in the range from 2 to 4 Hz, whereas for the *chair-boat* conformation the ^3J value is commonly 10–12 Hz [10, 11]. In the ^1H NMR spectrum of compound **II** the narrow triplet at δ 2.22 ppm assigned to H^5 proton has a half-width $W_{1/2}$ 2.69 Hz. The downfield signal of proton H^7 at δ 5.945 ppm appears as a doublet of doublets due to the coupling with the neighboring protons H^8 (^3J 11.5 and 7.0 Hz, Table 1). One of the vicinal constants observed in the spectrum (11.5 Hz) has relatively large value characteristic of the *trans*-diaxial protons in the *chair*-like cyclohexane systems [12]; therefore, the proton H^7 takes an axial position. The stereochemistry of substituents attached to atom C^7 in compound **II** was unambiguously established from the one-dimensional difference NOE spectrum registered under presaturation of proton H^7. In the difference spectrum (Fig. 1) the responses are well seen on the protons H^2 and H^4 unambiguously indicating the equatorial position of the nitro group and axial orientation of the H^7 proton in the six-membered ring $C^1C^8C^7C^6C^5C^9$.

The structure of isomer **II** was also proved by X-ray diffraction analysis (Fig. 2). The piperidine ring in the molecule of compound **II** is present in the *chair* conformation. The deviations of atoms N^3 and C^9 from
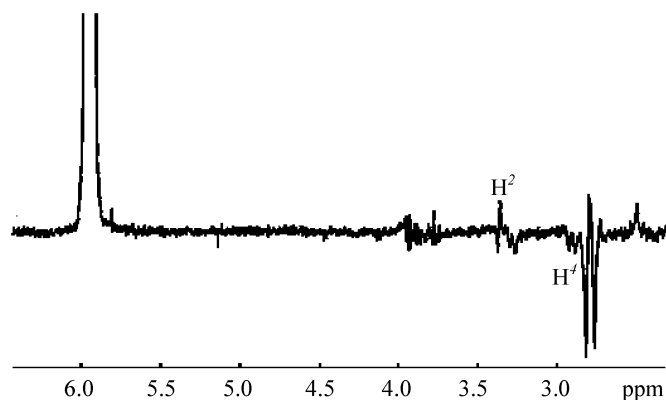

Fig. 1. Difference NOE spectrum under conditions of presaturation of proton H^7 for 3-methyl-6,6-ethylenedioxy-1,7-dinitro-3-azabicyclo[3.3.1]nonane (**II**).
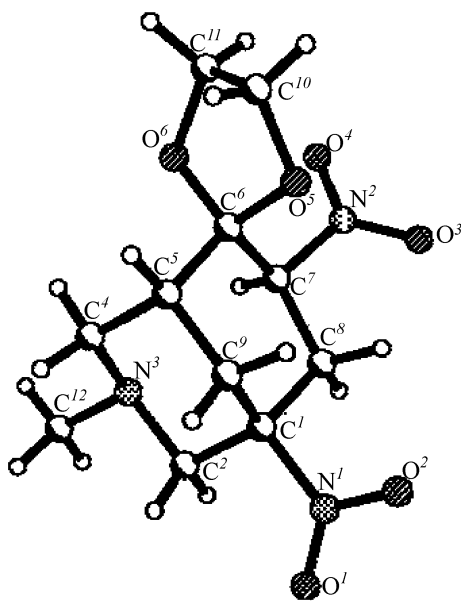
Fig. 2. Molecular structure of 3-methyl-6,6-ethylenedioxy-1,7-dinitro-3-azabicyclo[3.3.1]nonane (**II**).

the plane going through all the other atoms of the ring amount to 0.639 and −0.751 Å respectively. The cyclohexane ring $C^1C^8C^7C^6C^5C^9$ also has the *chair* conformation with deviation of atoms C^1 and C^6 from the plane of the other atoms of the ring equal to −0.733 and 0.653 Å respectively. The eight-membered ring $C^1\cdots C^8$ takes the *boat-boat* conformation and is characterized by the following Zefirov–Palyulin folding parameters [13]: S_2 1.389, S_3 0.066, S_4 −0.143, φ_2 0.68, φ_3 1.71. This conformation of the eight-membered ring results in appearance of a shortened intramolecular contact $N^3\cdots C^7$ 2.86(2) Å whereas the sum of van der Waals radii for C and N atoms is 3.21 Å [14]. The spiro-fused dioxolane ring exists in an *envelop* conformation. The C^{10} atom deviates from the root-mean-square plane of the other four atoms by 0.464 Å.

Nitro groups at the C^1 and C^7 atoms are located in equatorial positions [torsion angles $N^1C^1C^9C^5$ and $N^2C^7C^8C^1$ are equal to 179.3(2) and 169.3(2)° respectively]. The deviation of N^3 atom from the plane going through the three atoms attached thereto is 0.461 Å [where the sum of the corresponding bond angles equals to 331.9(4)°] indicating the trigonal-pyramidal configuration of this fragment.

The data obtained show that compound **II** in the crystalline state also exists in the *chair-chair* conformation, and the N-methyl group is equatorially oriented in agreement with the NMR data.

The interpretation of the structural data was also subjected to quantum-chemical calculations by PM3 method [15]) of possible conformations of molecule 3-methyl-6,6-ethylenedioxy-1,7-dinitro-3-azabicyclo-[3.3.1]nonane (**II**). As expected, the most stable (by ~2–10 kcal mol^{-1}) was the *double chair* conformation with the diequatorial positions of the NMe and 7-NO$_2$ groups, i.e., the stereoisomer of 1*S*,3*S*,5*R*,7*S*-configuration The value of the vicinal coupling constant for the dihedral angle between H^7 and H^{8a} atoms (φ −177.29°) in the optimized structure of the molecule of compound **II** calculated by the Karplus–Bothner-By formula [16] equals to 12.0 Hz in sufficiently good agreement with the experimental value of ^3J in the ^{1}H NMR spectrum (11.5 Hz). The distance between the N^3 and C^7 atoms was equal to 2.73 Å according to the calculations and 2.86 Å as measured by the X-ray diffraction analysis. Thus the quantum-chemical calculations support the conclusions on the structure of the molecule of compound **II** deduced previously from the experimental data.

The formation of isomeric 3-azabicyclo[3.3.1]nonanes **I** and **II** in the course of the reaction under study is presented in Scheme 2. At the treatment of 1-(2-hydroxy-ethoxy)-2,4-dinitrobenzene with sodium borohydride an anion forms due to deprotonation of the hydroxy group. The anion presumably may exist in solution in equilibrium with the cyclic form, spiroadduct **A** [17]. At excess NaBH$_4$ the hydride ion adds to the corresponding anions affording diadducts **B** and **C**. The latter undergo amino-methylation affording the isomeric 3-azabicyclo[3.3.1]-nonanes **I**–**III**. Although the existence of spiroadduct **A** in the reaction mixture is presumable we have not found in the reaction product spirocyclic bicyclononane **III**. The preparative yield of isomers **I** and **II** was 57 and 27% respectively. The optimization by the PM3 procedure of the anion of intermediate adduct **B** gave the following charge distribution values: −0.764 (C^2), −0.771 (C^4), and −0.391 (C^6). This result permits a suggestion of a charge control of the ratio of the reaction products.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer Specord 75IR from films prepared from acetonitrile solutions. ^{1}H and ^{13}C NMR spectra were registered on a spectrometer Bruker DRX-500 (500.13 and 125.13 MHz respectively) in DMSO-d_6 at 303 K (internal reference HMDS). Melting points of compounds were measured on a Koeffler heating block purchased from Boëtius at the heating rate 1 deg/min. Quantum-chemical calcula-

Scheme 2.
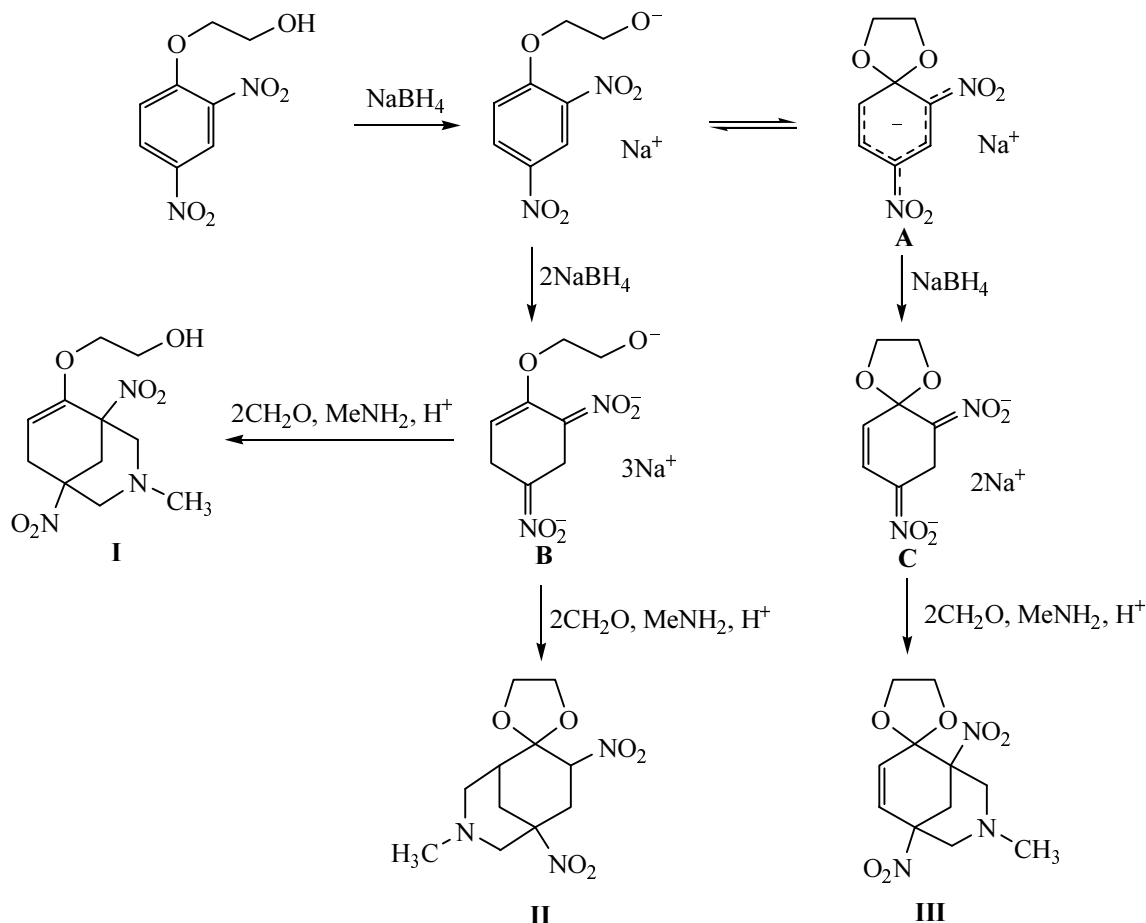
tions were carried out on PC (550 MHz) using HyperChem 6.02 software.

Dinitro derivatives of 3-azabicyclo[3.3.1]nonane I and II. To a solution of 0.912 g (0.004 mol) of nitro compound in 10 ml of a mixture THF–water, 1:1, was added at 0–5°C within 10 min a powder of 0.608 g (0.016 mol) of NaBH$_4$. The reaction mixture was stirred for 10 min maintaining the temperature in the range 10–20°C, then a solvent was added of 0.54 g (0.008 mol) of methylamine hydrochloride in 20 ml of water and 2.2 ml (0.024 mol) of 30% aqueous formaldehyde, and with the glacial AcOH the pH of the reaction mixture was adjusted at 6.0. The separated precipitate was filtered off, dissolved in toluene, and the filtrate was extracted with toluene. The combined toluene solutions were dried over anhydrous CaCl$_2$, and the solvent was distilled off in a vacuum. The separation of the isomers was performed by subjecting the residue to column chromato-graphy on silica gel (ASKG), eluent toluene–acetone, 10:1 for

compound **I**, 100:1 for compound **II**. The isolated products were recrystallized from ethanol.

6-(2-Hydroxyethoxy)-3-methyl-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene (I). Yield 57%, mp 105–106°C. IR spectrum, cm^{-1}: 3347 (OH), 2947, 2874, 2853, 2802, 2751 (CH$_{aliph}$), 1663 (C=C), 1528 [ν_{as}(NO$_2$)], 1374, 1342 [ν_s(NO$_2$)], 1459, 1445 [δ(CH$_{aliph}$)]. Found, %: C 45.30; H 5.26; N 14.52. C$_{11}$H$_{17}$N$_3$O$_6$. Calculated, %: C 45.96; H 5.96; N 14.62.

3-Methyl-6,6-ethylenedioxy-1,7-dinitro-3-azabicyclo[3.3.1]nonane (II). Yield 27%, mp 98–99°C. IR spectrum, cm^{-1}: 2950, 2899, 2852, 2789 (CH$_{aliph}$), 1544 [ν_{as}(NO$_2$)], 1393, 1358 [ν_s(NO$_2$)], 1486, 1461 [δ(CH$_{aliph}$)]. Found, %: C 46.30; H 5.28; N 14.12. C$_{11}$H$_{17}$N$_3$O$_6$. Calculated, %: C 45.96; H 5.96; N 14.62.

X-ray diffraction study of compound (II). C$_{11}$H$_{17}$N$_3$O$_6$. Crystals at 110(2) K rhombic, *a* 7.7162(6), *b* 11.0922(8), *c* 14.6767(12) Å, *V* 1256.2(2) Å^3, crystal size 0.5×0.4×0.3 mm, space group $P2_12_12_1$, *Z* 4,

Table 3. Bond lengths (d, Å) and bond angles (ω, deg) in the molecule of 3-methyl-6,6-ethylenedioxy-1,7-dinitro-3-azabicyclo[3.3.1]-nonane (**II**)

Bond	d	Bond	d
O^1–N^1	1.216(2)	N^3–C^4	1.468(2)
O^2–N^1	1.221(2)	N^3–C^2	1.470(2)
O^3–N^2	1.223(2)	C^1–C^2	1.521(2)
O^4–N^2	1.222(2)	C^1–C^9	1.524(2)
O^6–C^6	1.4260(18)	C^1–C^8	1.535(2)
O^6–C^{11}	1.443(2)	C^4–C^5	1.533(2)
O^5–C^6	1.4197(18)	C^5–C^9	1.530(2)
O^5–C^{10}	1.436(2)	C^5–C^6	1.540(2)
N^1–C^1	1.534(2)	C^6–C^7	1.547(2)
N^2–C^7	1.5197(18)	C^7–C^8	1.522(2)
N^3–C^{12}	1.461(2)	C^{10}–C^{11}	1.510(3)
Angle	ω	Angle	ω
$C^6O^6C^{11}$	107.83(12)	$N^3C^4C^5$	111.60(13)
$C^6O^5C^{10}$	105.94(12)	$C^9C^5C^4$	109.60(13)
$O^1N^1O^2$	123.18(16)	$C^9C^5C^6$	109.62(12)
$O^1N^1C^1$	118.97(15)	$C^4C^5C^6$	114.00(13)
$O^2N^1C^1$	117.82(15)	$O^5C^6O^6$	107.10(12)
$O^4N^2O^3$	123.22(14)	$O^5C^6C^5$	110.61(12)
$O^4N^2C^7$	117.79(13)	$O^1C^6C^5$	109.02(12)
$O^3N^2C^7$	118.98(13)	$O^5C^6C^7$	107.91(11)
$C^{12}N^3C^4$	110.17(13)	$O^6C^6C^7$	111.43(12)
$C^{12}N^3C^2$	109.39(13)	$C^5C^6C^7$	110.71(12)
$C^4N^3C^2$	112.30(13)	$N^2C^7C^8$	108.03(12)
$C^2C^1C^9$	110.63(13)	$N^2C^7C^6$	109.48(11)
$C^2C^1N^1$	108.37(12)	$C^8C^7C^6$	112.78(13)
$C^9C^1N^1$	108.07(13)	$C^7C^8C^1$	112.40(12)
$C^2C^1C^8$	115.17(13)	$C^1C^9C^5$	106.20(13)
$C^9C^1C^8$	109.29(12)	$O^5C^{10}C^{11}$	101.71(13)
$N^1C^1C^8$	104.95(13)	$O^6C^{11}C^{10}$	102.60(14)
$N^3C^2C^1$	109.10(12)		

d_{calc} 1.519 g/cm^3, F(000) 608, μ 0.124 mm^{-1}. The intensity of 4849 reflections (3302 independent, R_{int} 0.024) were measured on an automatic diffractometer Bruker 1K SMART CCD (graphite monochromator, MoK_α radiation, φ and ω scanning, $2\theta_{max}$ 60°). The processing of the diffraction data was performed using SAINT program [18]. The structure was solved by the direct method applying SHELXTL-97 software [19]. The hydrogen atoms position was revealed from the difference synthesis of the electron density. The refining by F^2 in anisotropic approximation (isotropic for hydrogen atoms) in full-matrix least-squares procedure (249 parameters) for 3302 reflections was carried out till R$_1$ 0.058 [for reflections with F > 4σ(F)], wR$_2$ 0.159, S 1.04. Bond lengths and bond angles are given in Table 3. Zefirov–Palyulin folding parameters were calculated by RICON program [20].

REFERENCES

1. Jeuaraman, R. and Avila, S., *Chem. Rev.,* 1981, vol. 81, p. 149.
2. Kogel, B., Christoph, T., Friderichs, E., Hennies, H.-H., Mathie-sen, T., Schneider, J., and Holzgrabe, U., *CNS Drug Rev.,* 1998, vol. 4, p. 54.
3. Yunusov, M.S., *Khimiya v interesakh ustoichivogo razvitiya* (Chemistry Aiding Stable Developmetn), 1997, vol. 5, p. 47.
4. Atroshchenko, Yu.M., Nikiforova, E.G., Gitis, S.S., Grudtsyn, Yu.D., Shishkin, O.V., Andrianov, V.F., and Shakhkel'dyan, I.V., *Zh. Org. Khim.,* 1999, vol. 35, p. 1339.
5. Atroshchenko, Yu.M., Nikiforova, E.G., Shakhkel'dyan, I.V., Grudtsyn, Yu.D., Akhmedov, N.G., Alifanova, E.N., Borbulevich, O.Ya., Shishkin, O.V., Gitis, S.S., and Kaminskii, A.Ya., *Zh. Org. Khim.,* 2000, vol. 36, p. 771.
6. Shakhkel'dyan, I.V., Nikiforova, E.G., Grudtsyn, Yu.D., Atroshchenko, Yu.M., Borbulevich, O.Ya., Efremov, Yu.A., Gitis, S.S., Moiseev, D.N., Alifanova, E.N., Chudakov, P.V., and Kovalevskii, A.Yu., *Zh. Org. Khim.,* 2001, vol. 37, p. 617.
7. Shakhkel'dyan, I.V., Melekhina, E.K., Atroshchenko, Yu.M., Efremov, Yu.A., Alifanova, E.N., Kopyshev, M.V., Troitskii, N.A., Subbotin, V.A., and Nikishina, M.B., *Zh. Org. Khim.,* 2003, vol. 39, p. 625.
8. Shishkin, O.V., Atroshchenko, Yu.M., Gitis, S.S., Shakheldyan, I.V., and Alifanova, E.N., *Acta, Cryst. (C),* 1998, vol. 54, p. 271.
9. Zefirov, N.S. and Palyulin, V.A., *Topics Stereochemistry,* 1991, vol. 20, p. 171.
10. Garrison, G.L., Berlin, K.D., Scherlag, J.B., Lazzara, R., Patterson, E., Fazekag, T., Sangiak, S., Chun-Lin, Chen, Schubot, F.D., and van der Helm, D., *J. Med. Chem.,* 1996, vol. 39, p. 2559.
11. Klepikova, S.G., Solomin, V.A., Iskakova, T.K., Yu, V.K.,

Praliev, K.D., Zhumanova, N.A., and Berlin, K.D., *Khim. Geterotsikl. Soed*., 2003, p. 586.

12. *Ustanovlenie struktury organicheskikh soedinenii fizicheskimi i khimicheskimi metodami* (Structure Determination of Organic Comounds by Physical and Chemical Methods), Moscow: Khimiya, 1967, vol. 1, 532 p.

13. Zefirov, N.S., Palyulin, V.A., and Dashevskaya, E.E., *J. Phys. Org. Chem.,* 1990, vol. 3, p. 147.

14. Zefirov, Yu.V. and Zorkii, P.M., *Usp. Khim.*, 1989, vol. 58, p. 713.

15. Stewart, J.J.P., *J. Comput. Chem.,* 1989, vol. 10, p. 209.

16. Aliev, A.E. and Sinitsina, A.A., *Izv. Akad. Nauk, Ser. Khim.,* 1992, p. 1483.

17. Shakhkel'dyan, I.V., Gitis, S.S., and Glaz, A.I., *Zh. Obshch. Khim.*, 1988, vol. 58, p. 2316.

18. SMART, V5.051 and SAINT V5.00, *Area Detector Control and Integration Software*, 1998, Bruker AXS Inc., Madison WI-53719.

19. Sheldrick, G.M., SHELXTL-97 V5.10, 1997, Bruker AXS Inc., Madison WI-53719.

20. Zotov, A.Yu., Palyulin, V.A., and Zefirov, N.S., *J. Chem. Inf. Comput. Sci.*, 1997, vol. 37, p. 766.