Reduction of 3-(2-hydroxyethyl)-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene

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Reduction of the nitro groups in 3-(2-hydroxyethyl)-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene was studied. The structures of the reaction products were confirmed using ^1H and ^{13}C NMR spectroscopy.

Key words: reduction, heterogeneous catalysis, Raney nickel, carbon-activated palladium, molecular hydrogen, hydrazine, 3-(2-hydroxyethyl)-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene, 1,5-diamino-3-(2-hydroxyethyl)-3-azabicyclo[3.3.1]non-6-ene, 1,5-diamino-3-(2-hydroxyethyl)-3-azabicyclo[3.3.1]nonane.

In recent years, considerable attention has been given to the development of methods for the synthesis of heterocyclic compounds containing an aza- or diazabicyclo[3.3.1]nonane fragment.[1] First of all, this interest is due to the high biological activity of such compounds.[2] For example, cytisine, an alkaloid, which is a natural representative of these heterocyclic compounds, finds use in medical practice as a respiratory analeptic,[3] while methyllycaconitine is a selective antagonist of *n*AChR receptors.[4—6]

An interesting intermediate in the synthesis of azabicyclo[3.3.1]nonane derivatives is 1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene. It is known that functionalized nitroolefins can be selectively reduced to aminoolefins with certain difficulties associated, as a rule, with the choice of particular reaction conditions (which depend on the structure of the starting nitroolefin) and a reducing agent.[7,8] It should be noted that the reduction of tertiary dinitroolefins of the 3-azabicyclo[3.3.1]nonane structure has not been documented by the beginning of our study.

In the present work, we studied the reduction of nitro groups in 3-(2-hydroxyethyl)-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene (**1**) with various reducing agents to obtain new diaminoazabicyclononanes.

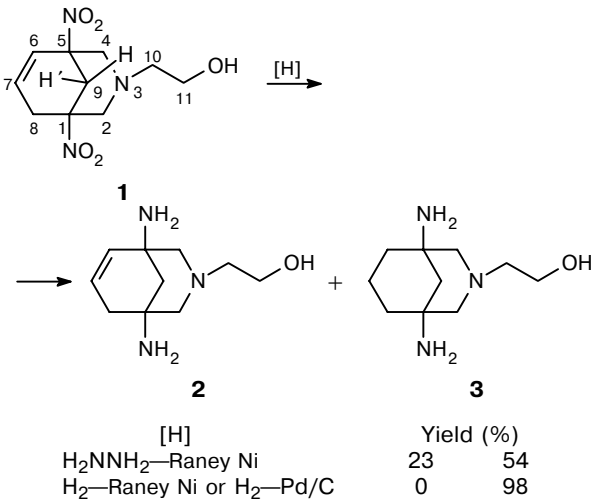
A known method for the synthesis of *N*-alkyl-1,5-dinitro-3-azabicyclo[3.3.1]non-6-enes includes the reduction of 1,3-dinitrobenzene with sodium borohydride to 1,3-dinitrocyclohex-5-ene, followed by the Mannich cyclization in the presence of formaldehyde and primary amines.[9,10] With monoethanolamine as a primary amine, dinitroolefin **1**, which had not been described in the papers cited above, was obtained in 56% yield.

It was also found that such reagents as iron filings in HCl,[11] KOH in ethylene glycol,[12] and $NaBH_4$ in the presence of $Cu(acac)_2$,[13] $CoCl_2$,[14] and $NiCl_2 \cdot 6H_2O$[15] cannot reduce the nitro group in compound **1**. This reaction occurs very smoothly when catalyzed by hydrazine or hydrogen in the presence of Raney nickel or carbon-activated palladium.

Thus, the reduction of compound **1** with a 50% aqueous solution of hydrazine in the presence of Raney nickel gives 3-(2-hydroxyethyl)-1,5-diamino-3-azabicyclo[3.3.1]non-6-ene (**2**) and 3-(2-hydroxyethyl)-1,5-diamino-3-azabicyclo[3.3.1]nonane (**3**) in 23 and 54% yields, respectively. Both products were isolated in the individual state by column chromatography using neutral Al_2O_3.

When heated in methanol (50 °C, 5 h) in a steel autoclave (70 atm of H_2) in the presence of Raney Ni or Pd/C, nitro alcohol **1** is quantitatively reduced to amino alcohol **3**. Note that fully hydrogenated product **3** is not formed when the reaction is carried out at ~20 °C and an atmospheric pressure of hydrogen.

The structure of compound **1** was proved by ^1H and ^{13}C NMR data with the use of the $^1H—^1H$ COSY and



[H]	Yield (%)	
H_2NNH_2—Raney Ni	23	54
H_2—Raney Ni or H_2—Pd/C	0	98

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CHCORR procedures. The ^{13}C NMR spectrum of compound **1** contains two doublets from the C(7) (δ 125.86) and C(6) atoms (δ 130.00), which confirm that they are doubly bonded. Signals from the quaternary C atoms bound to the nitro group appear at δ 86.83 (C(5)) and 84.32 (C(1)), while a triplet from the allylic C(8) atom lies at δ 37.68. A CHCORR spectrum was used to assign triplets from the methylene groups at δ 57.8—62.0 and refine the chemical shifts of protons. In the ^1H NMR spectrum, the lowest-field signal (δ 3.65) from these protons corresponds to the $H_2C(11)$ protons bound to the hydroxy group, while a ^{13}C signal at δ 58.23 was assigned to the C(11) atom. The $^1H—^1H$ COSY spectrum and spin-spin coupling constants were used to determine the chemical shifts of $H_2C(10)$ protons (δ 2.85) and the C(10) atom (δ 57.85). In the ^{13}C NMR spectrum, a signal at δ 57.87 corresponds to the C(2) atom, which gives two signals in the CHCORR spectrum for two diastereotopic protons. Accordingly, the C(4) atom manifests itself by a signal at δ 61.99. In the ^1H NMR spectrum, the diastereotopic $H_2C(2)$, $H_2C(4)$, and $H_2C(9)$ protons have geminal constants of the order of 11 Hz. The equatorial $H_2C(2)$ and $H_2C(4)$ protons are shifted downfield relative to the axial ones and give a doublet with a geminal spin-spin coupling constant and a triplet distorted by a long-range interaction with H′(9).

The hydrogenation of the double bond is confirmed by the absence of signals from the olefinic protons in the ^1H NMR spectrum of compound **3** and the absence of ^{13}C signals at δ 125—130. An upfield shift of C(1) and C(5) atoms in the ^{13}C NMR spectrum to δ 50.88 indicates that the nitro group is reduced to NH_2. Clearly distinguished signals from the hydroxyethyl protons $\delta_{H(11)}$ 3.62 and $\delta_{H(10)}$ 2.40 in the ^1H NMR spectrum made it possible to distinguish between C(10) and C(11) (δ 61.47 and 60.55, respectively) using the data on CHCORR. The protons at the C(2) and C(4) atoms are diastereotopic (^2J = 10.4 Hz), with a retained long-range coupling constant for the H′C(9) proton (^4J = 1.8 Hz).

Experimental

^1H and ^{13}C NMR spectra were recorded on a Bruker AM-300 spectrometer (300.13 and 75.47 MHz, respectively) in $CDCl_3$ or CD_3OD with Me_4Si as the internal standard. IR spectra were recorded on a Specord M-80 instrument (thin film or Vaseline oil). Mass spectra were obtained with the use of an MX-1300 spectrometer (bleeding-in temperature 100 °C, ionizing voltage 12 and 70 eV). GLC analysis was performed on a Chrom-5 chromatograph (flame ionization detector, stainless steel column 1200×5 mm, 5% SE-30 on Inerton N-AW DMCS (0.125—0.160), helium as the carrier gas). TLC analysis was carried out on Alufol chromatographic plates (neutral Al_2O_3).

3-(2-Hydroxyethyl)-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene (1). $NaBH_4$ (4.2 g, 111 mmol) was added in small portions at 0—10 °C over 0.5 h to a stirred solution of 1,3-dinitrobenzene (6 g, 29 mmol) in 18 mL of THF, formamide (12 mL), and EtOH (36 mL). The reaction mixture was diluted with ice water (100 mL), and a mixture of 33% formalin (32 mL) and ethanolamine (26 mL) was added. Then, glacial AcOH (32 mL) was added, and the organic material was extracted with chloroform (3×100 mL). The extract was washed with water (3×40 mL), dried over Na_2SO_4, and concentrated *in vacuo*. The residue was successively recrystallized from MeOH and EtOH to give compound **1** (5.2 g, 56%) as white crystals (Alufol, R_f 0.8, $CHCl_3$—MeOH, 2 : 3), m.p. 106—107 °C. Found (%): C, 46.75; H, 5.85; N, 16.37. $C_{10}H_{15}N_3O_5$. Calculated (%): C, 46.69; H, 5.83; N, 16.34. MS: m/z 257 $[M]^+$. IR, ν/cm^{-1}: 3600 (OH); 1560 (NO_2); 1365 (NO); 1075 (C—O); 730 (CH=CH). ^1H NMR ($CDCl_3$), δ: 2.21 (t, 1 H, OH, J = 5.5 Hz); 2.65 (d, 1 H, $H_a(2)$, J = 10.6 Hz); 2.68—2.80 (m, 6 H, $H_2C(8)$, H(9), $H_a(4)$, $H_2C(10)$); 2.9 (dt, 1 H, H(9′), ^2J = 11.4 Hz, ^4J = 2.1 Hz; 2.1); 3.17 (dt, 1 H, $H_e(2)$, ^2J = 10.6 Hz, ^4J = 1.8 Hz; 2.1); 3.38 (dt, 1 H, $H_e(4)$, ^2J = 15.6 Hz, ^4J = 1.8 Hz; 2.1); 3.65 (m, 2 H, $H_2C(11)$); 6.04 (m, 2 H, each 1 H, H(6), H(7)). ^{13}C NMR, δ: 35.58 (t, C(9)); 37.68 (t, C(8)); 57.85 (t, C(10)); 57.87 (t, C(2)); 58.23 (t, C(11)); 61.99 (t, C(4)); 84.32 (s, C(1)); 86.83 (s, C(5)); 125.86 (d, C(7)); 130.07 (d, C(6)).

Reduction of compound 1 with hydrazine. A 50% aqueous hydrazine (9.00 g, 180 mmol) was added dropwise at 55 °C for 6 h to a solution of compound **1** (0.40 g, 1.6 mmol) and freshly prepared Raney nickel (0.20 g, 3.2 mmol) in 20 mL of Pr^iOH, new portions of Raney nickel (0.05 g, 0.8 mmol) being added every hour. The reaction mixture was filtered, the mother liquor was concentrated, and the residue was chromatographed on neutral Al_2O_3 in $CHCl_3$—MeOH (3 : 1) to give compounds **2** (0.07 g, 23%) and **3** (0.17 g, 54%).

3-(2-Hydroxyethyl)-1,5-diamino-3-azabicyclo[3.3.1]non-6-ene (2). Oil. Found (%): C, 60.80; H, 9.65; N, 21.10. $C_{10}H_{19}N_3O$. Calculated (%): C, 60.91; H, 9.64; N, 21.32. MS: m/z 197 $[M]^+$. IR, ν/cm^{-1}: 3360 (OH), 3336 (NH_2), 3272 (NH_2), 1592 (NH_2), 1056 (C—O), 752 (NH_2), 664 (CH=CH). ^1H NMR (CD_3OD), δ: 1.45 (d, 1 H, $H_a(8)$, ^2J = 10.8 Hz); 1.78 (d, 1 H, $H_e(8)$, ^2J = 10.8 Hz); 1.96 (d, 1 H, $H_a(2)$, J = 10.4 Hz); 2.07—2.21 (m, 3 H, each 1 H, $H_a(4)$, H(9′), $H_e(2)$); 2.57 (m, 3 H, $H_2C(10)$, H(9)); 2.77 (d, 1 H, $H_e(4)$, J = 10.6 Hz); 3.60 (t, 2 H, H(11), J = 6.0 Hz); 5.49 (dd, 1 H, H(6), ^2J = 9.8 Hz, J = 1.5 Hz); 5.80 (dt, 1 H, H(7), ^2J = 9.8 Hz, ^3J = 3.4 Hz). ^{13}C NMR, δ: 40.76 (t, C(9)); 47.50 (t, C(8)); 51.16 (t, C(2)); 53.50 (s, C(1)); 60.03 (t, C(10)); 60.13 (s, C(5)); 63.46 (t, C(11)); 67.54 (t, C(4)); 129.58 (d, C(7)); 133.67 (d, C(6)).

3-(2-Hydroxyethyl)-1,5-diamino-3-azabicyclo[3.3.1]nonane (3). Oil. Found (%): C, 60.60; H, 10.55; N, 21.15. $C_{10}H_{21}N_3O$. Calculated (%): C, 60.30; H, 10.55; N, 21.11. MS: m/z 199 $[M]^+$. IR, ν/cm^{-1}: 3600 (OH), 3336 (NH_2), 1648 (NH_2), 1056 (C—O), 752 (NH_2). ^1H NMR (CD_3OD), δ: 1.33—1.46 (m, 3 H, each 1 H, $H_a(6)$, $H_a(8)$, H(9)); 1.46—1.58 (m, 3 H, each 1 H, $H_e(6)$, $H_e(8)$, H(9)); 1.60—1.81 (m, 2 H, H(7)); 1.94 (dd, 2 H, each 1 H, $H_a(2)$, $H_a(4)$, ^2J = 10.4 Hz, ^4J = 1.8 Hz); 2.40 (t, 2 H, H(10), J = 6.2 Hz); 2.81 (d, 2 H, each 1 H, $H_e(2)$, $H_e(4)$, ^2J = 10.4 Hz); 3.62 (t, 2 H, H(11), J = 6.2 Hz). ^{13}C NMR, δ: 22.40 (t, C(7)); 39.15 (t, C(9)); 50.00 (s, C(1), C(5)); 51.35 (t, C(6), C(8)); 60.33 (t, C(11)); 61.18 (t, C(10)); 66.74 (t, C(2), C(4)).

Reduction of compound 1 with molecular hydrogen. Compound **1** (0.50 g, 1.9 mmol), MeOH (50 mL), and freshly prepared Raney nickel (0.1 g) or 5% carbon-activated palladium (0.1 g) were placed in a steel autoclave (V = 100 cm^3).

Hydrogenation was carried out under a pressure of H_2 (70 atm) at 50 °C for 5 h. Then the reaction mixture was filtered and concentrated to give amine **3** (0.38 g, 98%).

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References

1. M. S. Yunusov, *Khimiya v interesakh ustoichivogo razvitiya* [*Chemistry for Steady Development*], 1997, **5**, 41 (in Russian).
2. M. S. Yunusov, *Diterpenoid Alkaloids. Natural Product Reports*, 1993, **10**, 471.
3. M. D. Mashkovskii, *Lekarstvennye sredstva* [*Medicaments*], Meditsina, Moscow, 1998, **1**, 127 (in Russian).
4. R. Jennings, *Experientia*, 1986, **42**, 611.
5. S. Wonnacott, *Methods in Neurosci.*, 1993, **12**, 263.
6. D. J. Hardick, *Tetrahedron Lett.*, 1994, **35**, 3367.
7. S. L. Ioffe and V. A. Tartakovsky, *Usp. Khim.*, 1966, **35**, 43 [*Russ Chem. Rev.*, 1966, **35** (Engl. Transl.)].
8. M. Laso Nieves, B. Guiclet-Sire, and Z. Zard Samir, *Tetrahedron Lett.*, 1996, **37**, 1605.
9. T. Severin, M. Schmitz, and R. Adam, *Chem. Ber.*, 1963, **96**, 3076.
10. R. T. Wall, *Tetrahedron*, 1970, **26**, 2107.
11. V. O. Lukashevich, *Usp. Khim.*, 1948, **17**, 692 [*Russ. Chem. Rev.*, 1948, **17** (Engl. Transl.)].
12. W. Tadros, M. S. Ishak, and E. Bassili, *J. Chem. Soc.*, 1959, 627.
13. K. Hanaya, H. Kudo, and T. Muramatsu, *J. Chem. Soc., Perkin Trans. 1*, 1979, 2409.
14. T. Satoh, S. Suzuki, Y. Miyaji, and Z. Imai, *Tetrahedron Lett.*, 1969, 4555.
15. J. Osby and B. Ganem, *Tetrahedron Lett.*, 1985, **26**, 52.

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