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Title **Process to Prepare 6(7)-R-1,5-dinitro-3-(2-hydroxyethyl)-3-azabicyclo[3.3.1]non-6-enes**
(560) Related Inventions **SU 1138022 A, Jan. 30, 1985; GB 1393253 A, May 7, 1975; FR 2555580 A, May 31, 1985; Zefirov, N.S. Conformational Analysis of Bicyclo[3.3.1]nonanes, Russian Chemical Reviews, 1975, vol.44, issue3, pages413-443.**

(711) Name of Applicant **Tulskii Government Pedagogical University in the name of L.N. Tolstoi**

(721) Name of Inventor **Atroshchenko, Yu.M.**

(721) name of Inventor **Nikiforova, E.G.**

(721) Name of Inventor **Shakheldian, I.V.**

(721) Name of Inventor **Gitis, S.S.**

(721) Name of Inventor **Valueva, T.N.**

(721) Name of Inventor **Subbotin, V.A.**

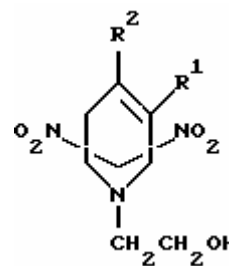
(721) Name of Inventor **Kaminskii, A.Ya.**

(731) Name of Patent Holder **Tulskii Government Pedagogical University in the name of L.N. Tolstoi**

(980) Address for Correspondence **300026, city ofTula, Lenin Prospect 125, TGPU in the name of L.N. Tolstoi, Atroshchenko, Yu.M.**

No. 2159766. Abstract

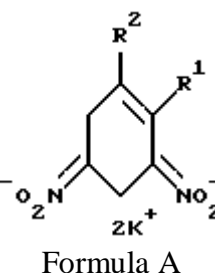
The invention is concerned with a novel process for preparing 6(7)-derivatized 3-(2-hydroxyethyl)-3-azabicyclo[3.3.1]non-6-enes. The process for preparing of 6(7)-R-1,5-dinitro-3-(2-hydroxyethyl)-3-azabicyclo[3.3.1]non-6-enes of the general formula I is described where $R^1 = CH_3$, $R^2 = H$; $R^1 = Cl$, $R^2 = H$; $R^1 = Br$, $R^2 = H$; $R^1 = OCH_3$, $R^2 = H$; $R^1 = OCH_2CH_2Cl$, $R^2 = H$; $R^1 = COOH$, $R^2 = H$; $R^1 = H$, $R^2 = COOH$; $R^1 = H$, $R^2 = CONH_2$; $R^1 = H$, $R^2 = CN$; $R^1 = H$, $R^2 = COOCH_3$; $R^1 = H$, $R^2 = OCH_3$, consisting of the parent 1- R^1 -2,4- and 1- R^1 -3,5-dinitrobenzenes being reduced with the aid of KBH_4 to the corresponding dipotassium salts 3,5-bis(aci-nitro)cyclohex-1-ene, which are then treated with a mixture of formaldehyde and 2-aminoethanol in a Mannich Reaction, with subsequent acidification of the reaction mixture with acetic acid to pH 6. The polyfunctional nature of the prepared compounds opens up the possibility of their broad chemical modification with substitutions and functionalized groups with the goal of improving their properties.



Formula I

No. 2159766. Claims

A process to prepare 6(7)-R-1,5-dinitro-3-(2-hydroxyethyl)-3-azabicyclo[3.3.1]non-6-enes of the general formula I where $R^1 = \text{CH}_3$, $R^2 = \text{H}$; $R^1 = \text{Cl}$, $R^2 = \text{H}$; $R^1 = \text{Br}$, $R^2 = \text{H}$; $R^1 = \text{OCH}_3$, $R^2 = \text{H}$; $R^1 = \text{OCH}_2\text{CH}_2\text{Cl}$, $R^2 = \text{H}$; $R^1 = \text{COOH}$, $R^2 = \text{H}$; $R^1 = \text{H}$, $R^2 = \text{COOH}$; $R^1 = \text{H}$, $R^2 = \text{CONH}_2$; $R^1 = \text{H}$, $R^2 = \text{CN}$; $R^1 = \text{H}$, $R^2 = \text{COOCH}_3$; $R^1 = \text{H}$, $R^2 = \text{OCH}_3$, which is characterized by the parent 1- R^1 -2,4- and 1- R^1 -3,5-dinitrobenzenes being reduced with the aid of KBH_4 to the corresponding dipotassium salts 3,5-bis(aci-nitro)cyclohex-1-ene of Formula A which are treated with a mixture of formaldehyde and 2-aminoethanol in a Mannich Reaction, with subsequent acidification of the reaction mixture with acetic acid to pH 6.

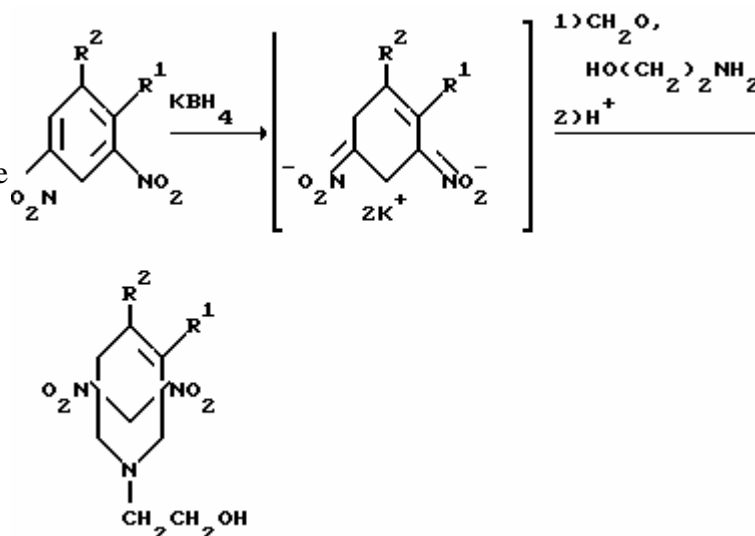


No. 2159766. Description

This invention concerns the area of organic chemistry, in particular with a process to prepare 2-aminoethanol derivatives, containing the 3-azabicyclo[3.3.1]nonane fragment.

These 2-aminoethanol derivatives have broad application as absorbents for the purification of gases, as cross-linking agents in the production of polyurethanes, and vulcanization accelerators (Purification of Technology Gases, edited by T.A. Semyonov and I.L. Leites, 2nd Ed., M.: 1977; Kirk-Othmer Encyclopedia, 3 ed., v. 1, N.Y.- [a.o.], 1978, p. 944-967). On the other hand, heteroanalogs of bicyclo[3.3.1]nonanes appear to be valuable intermediates in organic synthesis, serving as convenient models for conformational analysis, appearing in the structures of natural alkaloids and finding application as biologically active substances (Zefirov, N.C., Rogozina, S.V. // Russian Chemical Reviews, 1973, vol. 42, issue 3, pages 413-444; Zefirov, N.S., Palylin V.A. // Topics in Stereochemistry, Vol. 20 / Ed. E. L. Eliel, S.H. Wilen, 1991, p. 171-230).

The proposed process to prepare 2-aminoethanol derivatives, containing the bicyclononane fragment, includes the reduction of 1- R^1 -2,4- and 1- R^1 -3,5-dinitrobenzenes with potassium borohydride and subsequent Mannich condensation with formaldehyde and aminoethanol (Scheme) where $R^1 = \text{CH}_3$, $R^2 = \text{H}$; $R^1 = \text{Cl}$, $R^2 = \text{H}$; $R^1 = \text{Br}$, $R^2 = \text{H}$; $R^1 = \text{OCH}_3$, $R^2 = \text{H}$; $R^1 = \text{OCH}_2\text{CH}_2\text{Cl}$, $R^2 = \text{H}$; $R^1 = \text{COOH}$, $R^2 = \text{H}$; $R^1 = \text{H}$, $R^2 = \text{COOH}$; $R^1 = \text{H}$, $R^2 = \text{CONH}_2$; $R^1 = \text{H}$, $R^2 = \text{CN}$; $R^1 = \text{H}$, $R^2 = \text{COOCH}_3$; $R^1 = \text{H}$, $R^2 = \text{OCH}_3$.



Scheme

The composition and structures of the synthesized 6- R^1 -7- R^2 -3-(2-hydroxyethyl)3-azabicyclo[3.3.1]non-6-enes was confirmed on the basis of IR and $^1\text{H-NMR}$ spectroscopy, and also by the results of elemental analysis.

The distinctive features of the offered synthetic method present themselves in the introduction via the Mannich reaction of formaldehyde and 2-aminoethanol as acidic components into the bis(aci-nitro)cyclohexene, with the resulting selective reduction of the m-dinitrobenzenes by treatment with

KBH_4 . The polyfunctional nature of the prepared compounds opens up the possibility of their broad chemical modification with substitutions and functionalized groups with the goal of improving their properties.

The essence of the method consists of the following. To a solution of 1- R^1 -2,4- or 1- R^2 -3,5-dinitrobenzene together with THF- H_2O (1:1) with stirring and cooling over the course of 15 m was added a two-fold excess of solid KBH_4 and this was stirred for a further 15 m. The temperature of the reaction mixture was maintained at all times within the range of 5-15 °C. A chilled mixture of an aqueous solution of formaldehyde and 2-aminoethanol hydrochloride was poured into this, also taken in two-fold excess, after which the reaction mixture was acidified with glacial acetic acid to pH 6. The product was extracted with dichloroethane, the extract was washed with water and dried over calcium chloride, after which the solvent was distilled off under vacuum. The crude product was then purified, as explained in the examples.

Example 1. 3-(2-Hydroxyethyl)-6-methyl-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene

To a solution of 4 mmol (0.73 g) of 2,4-dinitrotoluene in 10 mL of a mixture of THF- H_2O (1: 1) with stirring and cooling over the course of 15 m was added 16 mmol (0.86 g) KBH_4 and this was stirred for another 15 m. The temperature of the reaction mixture was maintained within the range of 5-15 °C. After the reduction was finished a chilled solution of 16 mmol formaldehyde (1.5 mL of 30% formalin) and 8 mmol (0.78 g) of 2-aminoethanol hydrochloride in 20 mL of water was poured in, and this was acidified with glacial acetic acid to pH 6. Extraction was carried out with dichloroethane (3x15 mL), the extract was washed with water, dried over calcium chloride and concentrated under vacuum, and the residue was chromatographed on a column of silica gel (ASKG¹) (eluent - toluene), subsequently taken up in 15 mL of ethanol, treated with a small portion of activated charcoal and this was filtered over the course of a few minutes. The filtrate was evaporated under a stream of air, and the precipitated crystals were filtered off. m.p. 99-100 °C. Yield 16% Found, %: C 48.24, 48.34; H 6.09, 6.30; N 15.89, 16.33; $\text{C}_{11}\text{H}_{17}\text{N}_3\text{O}_5$. Calculated, %: C 48.70, H 6.32, N 15.49. IR spectrum, ν , cm^{-1} : 3456, 3090, 2980, 2890, 2825, 1635, 1558, 1484, 1432, 1350, 1115, 1052. PMR spectrum, δ , mult.: 4.71 t, 3.05 q, 2.50-2.90 m, 1.50-2.00 m, 1.13 br.s.

The following compounds were prepared in an analogous fashion: **3-(2-hydroxyethyl)-6-chloro-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene**. m.p. 85-86 °C. Yield 19%. Found, %: C 41.20, 40.36; H 4.82, 4.79; N 14.45, 14.64; Cl 12.08, 12.12. $\text{C}_{10}\text{H}_{14}\text{ClN}_3\text{O}_5$. Calculated, %: C 41.18, H 4.84, N 14.41, Cl 12.15. IR spectrum, ν , cm^{-1} : . PMR spectrum, δ , mult.: 5.06 t, 3.05 t, 2.50-3.00 m, 1.60-2.00 m, 1.90 t, 1.29 t.

3-(2-hydroxyethyl)-6-bromo-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene. m.p. 108-109 °C. Yield 21%. Found, %: C 35.59, 35.76; H 4.22, 4.00; N 12.66, 12.56; Br 23.61, 23.69. $\text{C}_{10}\text{H}_{14}\text{BrN}_3\text{O}_5$. Calculated, %: C 35.73, H 4.20, N 12.15, Br 23.77. IR spectrum, ν , cm^{-1} : 3468, 3072, 2972, 2912, 2862, 1636, 1570, 1482, 1445, 1350, 1118, 1041. PMR spectrum, δ , mult: 5.25 t, 3.10 t, 1.85 t, 2.50-3.00 m, 1.60...1.80 m, 1.10 br.s.

3-(2-hydroxyethyl)-6-methoxy-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene. m.p. 94-95 °C. Yield 9%. Found, %: C 46.08, 46.29; H 6.12, 6.16; N 15.15, 15.35; $\text{C}_{11}\text{H}_{17}\text{N}_3\text{O}_6$. Calculated, %: C 45.99, H 5.97, N 14.63. IR spectrum, ν , cm^{-1} : 3456, 3090, 3025, 2945, 2818, 2786, 1679, 1558, 1464, 1350, 1178, 1120, 1054. PMR spectrum, δ , mult: 3.87 t, 3.10 t, 2.60...3.00 m, 2.75 s, 2.10 t, 1.60-1.95 m.

3-(2-hydroxyethyl)-6-(2-chloroethoxy)-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene. m.p. 81-82 °C. Yield 13%. Found, %: C 43.24, 43.34; H 5.39, 5.30; N 12.89, 12.33, Cl 10.80, 10.99;

¹ ASKC corresponds to a grade of silica gel = АСКГ ~ Активированный Силикагель Крупнопористый Гранулированный, 'activated silica gel coarse-grained granulated.'

C₁₂H₁₈ClN₃O₆. Calculated, %: C 42.92, H 5.37, N 12.52, Cl 10.58. IR spectrum, ν , cm⁻¹: 3455, 2970, 2890, 2825, 1655, 1555, 1426, 1410, 1355. PMR spectrum, δ , mult.: 3.77 t, 2.60-3.20 m, 1.50-2.10 m.

3-(2-hydroxyethyl)-6-(carboxy)-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene. m.p. 183-184 °C (decomp.) Yield 12%. Found, %: C 43.79, 44.46; H 4.87, 5.27; N 14.36, 14.33; C₁₁H₁₅N₃O₇. Calculated, %: C 43.86, H 5.02, N 13.95. IR spectrum, ν , cm⁻¹: 3440, 2980, 2915, 2890, 2850, 2400-2700, 1714, 1695, 1568, 1558, 1452, 1445, 1382, 1262, 1042. PMR spectrum, δ , mult.: 6.95 t, 4.25 br.s., 3.45 t, 2.20-3.30 m.

Example 2. 3-(hydroxyethyl)-7-carboxamido-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene².

To a solution of 4 mmol (0.84 g) of 3,5-dinitrobenzamide in a mixture of 10 mL of THF-H₂O (1:1) with stirring and chilling over the course of 15 m was added 16 mmol (0.86 g) of KBH₄ and stirring was continued for another 15 m. The temperature of the reaction mixture was maintained in the range of 5-15 °C. After the reduction was finished a chilled solution of 16 mmol formaldehyde (1.5 mL of 30% formalin) and 8 mmol (0.78 g) of 2-aminoethanol hydrochloride in 20 mL of water was poured in, and this was acidified with glacial acetic acid to pH 6. Extraction was carried out with dichloroethane (3x15 mL), the extract was washed with water, dried over calcium chloride and concentrated under vacuum. The residue was crystallized from a mixture of acetone and dichloroethane. m.p. 109-110°C. Yield 31%. Found, %: C 43.62, 43.58; H 5.36, 5.15; N 19.56, 19.20; C₁₁H₁₆N₃O₄. Calculated, %: C 44.00, H 5.37, N 18.66. IR spectrum, ν , cm⁻¹: 3428, 3350, 3212, 3070, 2969, 2912, 2830, 1652, 1623, 1552, 1478, 1465, 1455, 1350, 1130, 1078, 1062. PMR spectrum, δ , mult.: 6.65 br.s., 3.35 t, 2.25 br.s., 2.10-3.20 m.

The following compounds were prepared in an analogous fashion: **3-(hydroxyethyl)-7-(carboxy)-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene**. m.p. 151-152°C. Yield 32%. Found, %: C 43.85, 43.63; H 5.14, 5.08; N 14.14, 14.25; C₁₁H₁₅N₃O₇. Calculated, %: C 43.86, H 5.02, N 13.95. IR spectrum, ν , cm⁻¹: 3450, 2958, 2898, 2870, 2825, 2400-2700, 1712, 1660, 1558, 1464, 1418, 1372, 1282, 1062. PMR spectrum, δ , mult.: 7.15 br.s., 3.30 t, 3.25 br.s., 2.10-3.20 m.

3-(hydroxyethyl)-7-(cyano)-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene. oil, Yield 30%. Found, %: C 46.62, 46.58; H 5.36, 5.15; N 19.55, 19.21; C₁₁H₁₄N₄O₅. Calculated, %: C 46.81, H 5.00, N 19.85. IR spectrum, ν , cm⁻¹: 3427, 3065, 2950, 2891, 2833, 2230, 1649, 1543, 1477, 1457, 1430, 1373, 1133, 1064, 1038. PMR spectrum, δ , mult.: 6.40 br.s., 3.25 t, 2.00...3.00 m.

3-(hydroxyethyl)-7-(methoxycarbonyl)-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene. oil, Yield 24%. Found, %: C 45.62, 45.58; H 5.37, 5.16; N 13.56, 13.20; C₁₂H₁₇N₃O₇. Calculated, %: C 45.71, H 5.44, N 13.33. IR spectrum, ν , cm⁻¹: 3423, 3085, 2956, 2899, 2850, 1667, 1659, 1544, 1443, 1377, 1286, 1132, 1098, 1073. PMR spectrum, δ , mult.: 6.95 br.s., 3.33 s, 3.17 t, 1.95-3.05 m.

3-(hydroxyethyl)-7-methoxy-1,5-dinitro-3-azabicyclo[3.3.1]non-6-ene. m.p. 80-81°C. Yield 10%. Found, %: C 45.64, 45.51; H 5.36, 6.15; N 14.56, 14.22; C₁₁H₁₇N₃O₆. Calculated, %: C 45.99, H 5.97, N 14.63. IR spectrum, ν , cm⁻¹: 3320, 3110, 2988, 2960, 2910, 2850, 1668, 1555, 1468, 1452, 1435, 1370, 1242, 1152, 1124, 1048.

Thus, the offered method for the synthesis of bicyclic compounds beginning with derivatives of m-dinitrobenzene discloses a new process for the preparation of 3-(2-hydroxyethyl)-3-azabicyclo[3.3.1]nonanes.

*Technical Translation by
Matthew F. Schlecht, PhD.
Word Alchemy*

² The '7-карбамоил' substituent mentioned in the name of this compound corresponds to '7-carbamoyl' substituent in English, but the name has been corrected to '7-carboxamido' on the basis of the chemistry described.