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SYNTHESIS AND REACTIONS OF POLYHEDRAL COMPOUNDS. 27*. DEVELOPMENT OF A SYNTHETIC ROUTE FOR 2- SPIRO-SUBSTITUTED 6-HYDROXY-5,7-DIMETHYL-1,3-DIAZAADAMANTANES.

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Alternative methods for the synthesis of 2-spiro-substituted 6-hydroxy-5,7-dimethyl-1,3-diazaadamantanes have been developed. These are the reduction of the ketone group to hydroxyl in the corresponding 6-oxo-1,3-diazaadamantanes and the condensation of 9-hydroxy-1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonane (obtained by different routes from 5,7-dimethyl-6-oxo-1,3-diazaadamantane) in reaction with cyclic ketones.

Keywords: 3,7-diazabicyclo[3.3.1]nonane, spiro-1,3-diazaadamantane, cyclic ketones, reduction, condensation.

We have previously developed the synthesis of various 2-spiro-substituted 5,7-dimethyl-6-oxo-1,3-diazaadamantanes (**1**) by the condensation of 1,5-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane with cyclic ketones [2, 3]. With the object of synthesizing 2-spiro-substituted 6-hydroxy-5,7-dimethyl-1,3-diazaadamantanes (**2**) and then studying their biological properties we have, in the present work, investigated several alternative routes for their preparation. These are the reduction of the ketone group in 2-spiro-substituted 5,7-dimethyl-6-oxo-1,3-diazaadamantanes **1a-c** and the condensation with cyclic ketones of 9-hydroxy-1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonane (**3**), which had been prepared by various routes described below.

The ketone group of the previously synthesized 6-oxo-1,3-diazaadamantanes **1a-c** were reduced using $LiAlH_4$ (**1a,b**) or $NaBH_4$ (**1c**) and this led to the corresponding 2-spiro-substituted 6-hydroxy-5,7-dimethyl-1,3-diazaadamantanes **2a-c**.

Reduction of the ketonic group of 1,5-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane (**4**) [4] using $LiAlH_4$ or $NaBH_4$ gave the corresponding alcohol **3**. Reduction of the ketone group of 3,7-diacetyl-1,5-dimethyl-9-oxo-3,7-diazabicyclo[3.3.1]nonane (**5**) [5] with the help of $NaBH_4$ gave the corresponding diacetyl-substituted alcohol **6**. Removal of the acetyl groups of the latter using hydrochloric acid also gave the alcohol **3**. The action of $LiAlH_4$ on the diacetyl derivative **5** caused the reduction of all three keto groups and led to the formation of 3,7-diethyl-9-hydroxy-1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonane (**7**).

* For Communication 26 see [1].

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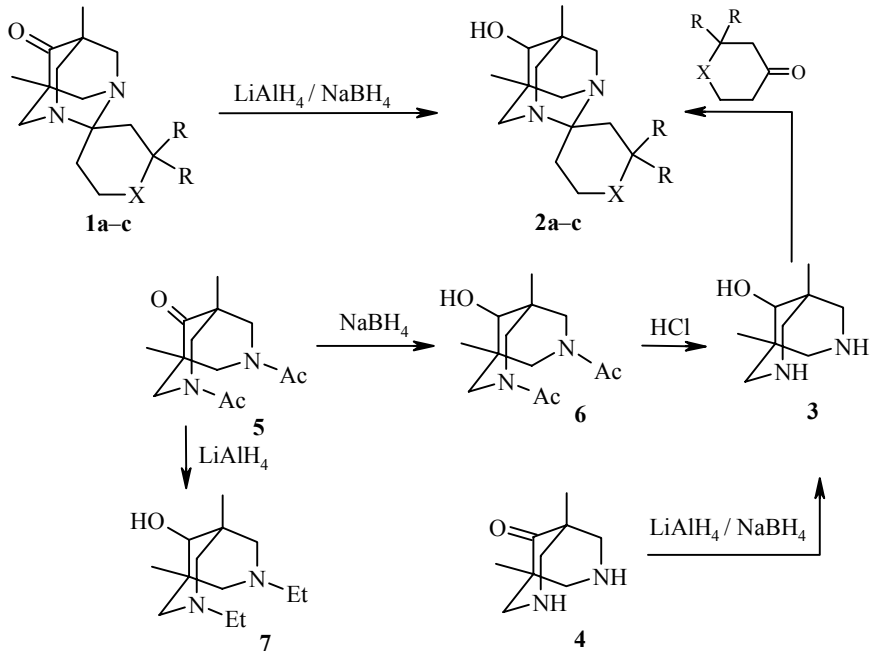

1,**2 a** $XCR_2 = CH_2$; **b** R = H, X = CH_2; **c** R = Me, X = O

Treatment of 6-hydroxy-1,5-dimethyl-1,3-diazaadamantane [6] with acetic anhydride in the conditions described in [5] gave an inseparable mixture of the diacetate **6** and its *o*-acetyl derivative (mass spectrometric data). Hydrochloric acid hydrolysis of the indicated mixture, carried out similarly to the preparation of compound **3** using method A (see Experimental), gave 9-hydroxydiazabicyclononane **3** in only 20% yield. Hence the latter route for the synthesis of alcohol **3** is the less favored.

Condensation of the 9-hydroxydiazabicyclononane **3**, which had been prepared by the routes described above, with cyclopentanone, cyclohexanone, and 2,2-dimethyltetrahydropyran-4-one led to the formation of the same spiroazaadamantanes **2a-c** as in the case of the reduction of the ketones **1a-c**. For the preparation of a series of materials preference should be given to the cyclic ketone reaction with the 9-hydroxydiazabicyclononane **3** (preparation of the latter *via* reduction of the 9-oxodiazabicyclononane **4** having a number of advantages) because of the absence of the need in each case to carry out the reduction of the ketonic group to hydroxyl as in the example of compounds **1a-c**.

The structure of the synthesized compounds was confirmed by elemental analytical, IR, ^{1}H NMR , and mass spectroscopic data. The purity of the compounds was monitored using TLC. Because of the disturbance to the molecular symmetry, the axial and equatorial protons of the four methylene groups of the diazaadamantane and diazabicyclononane fragments appear in the ^{1}H NMR spectra of the spirodiazaadamantanes **2a-c** and also the diazabicyclononanes **3** and **7** as four doublets (2 AB systems) in the region 2.43-3.57 ppm. In turn, the hindrance to rotation of the acetyl groups around the amide bond in the diacetyldiazabicyclononane molecule **6** leads to a further disruption of the equivalence of the eight methylene protons. As a result, the ^{1}H NMR spectrum shows eight doublets in the region 2.50-4.68 ppm

EXPERIMENTAL

IR spectra were taken using vaseline oil on a UR-20 spectrometer and ^{1}H NMR spectra on a Varian Mercury-300 instrument (300 MHz). Molecular weights were determined mass spectrometrically on an MX-1320 instrument with direct introduction of the sample into the ion source. The reaction yield and

compound purity were monitored using TLC on Silufol UV-254 plates in the systems: *n*-propanol–water 7:3 (a), *n*-butanol–saturated ammonia (b) and were visualized using iodine vapor.

3,7-Diacetyl-9-hydroxy-1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonane (6). $NaBH_4$ (0.54 g, 15 mmol) was added over 1 h at room temperature to a solution of the diazabicyclononane **5** (2.52 g, 10 mmol) in methanol (20 ml), the reaction mixture was stirred for 1 h, and then held at room temperature for 16 h. Solvent was distilled off, the dry residue was refluxed in benzene (3 × 20 ml), then the hot benzene was decanted and the precipitate formed on cooling was filtered off to give compound **6** (55.0%); mp 176-177°C (benzene), R_f 0.58 (a). IR spectrum (thin film), ν, cm^{-1}: 1630-1650 (C=O amide), 3320-3370 (O–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 4.68 (1H, dd, *J* = 13.2, *J* = 2.5, CH_e–N); 4.39 (1H, d, *J* = 12.9, CH_e–N); 3.75 (1H, dd, *J* = 13.5, *J* = 2.5, CH_e–N); 3.43 (1H, d, *J* = 13.5, CH_e–N); 3.30 (1H, d, *J* = 4.7, CH–OH); 3.01 (1H, dd, *J* = 13.5, *J* = 2.5, CH_a–N); 2.86 (1H, dd, *J* = 13.5, *J* = 2.5, CH_a–N); 2.84 (1H, dd, *J* = 12.9, *J* = 2.5, CH_a–N); 2.82 (1H, d, *J* = 4.7, OH); 2.50 (1H, dd, *J* = 13.2, *J* = 2.5, CH_a–N); 2.08 (6H, s, 2 CH_3). M^+ 254. Found, %: C 61.80; H 8.37; N 11.22. $C_{13}H_{22}N_2O_3$. Calculated, %: C 61.42; H 8.66; N 11.02.

9-Hydroxy-1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonane (3). A. A mixture of the diacetate **6** (1.0 g, 4 mmol) and 5N HCl (10 ml) was refluxed for 5 h. Two thirds of the solvent was distilled from the reaction mixture and the cooled residue was treated dropwise with a concentrated NaOH solution to an alkaline reaction. The mixture was cooled and the precipitate was filtered off, dried, and recrystallized from benzene to give compound **3** (0.4 g, 58.8%); mp 192-194°C (benzene), R_f 0.24 (b). IR spectrum (thin film): 3300-3350 (O–H). ^{1}H NMR spectrum (acetone-d_6), δ, ppm (*J*, Hz): 3.35 (2H, d, *J* = 13.0, 2 CH_e–N); 3.15 (1H, s, C<u>H</u>–OH); 3.05 (2H, d, *J* = 13.5, 2 CH_e–N); 3.00 (2H, s, 2 NH); 2.97 (2H, d, *J* = 13.5, 2 CH_a–N); 2.85 (1H, br. s, OH); 2.50 (2H, d, *J* = 13.0, 2 CH_a–N); 0.68 (6H, s, 2 CH_3). Found, %: C 63.42; H 10.81; N 16.37. $C_9H_{18}N_2O$. Calculated, %: C 63.53; H 10.59; N 16.47.

B. A solution of the diazabicyclononane **4** (3.4 g, 20 mmol) [4] in ether (30 ml) was added dropwise over 1 h to a refluxing mixture of ether (50 ml), methanol (10 ml), and $NaBH_4$ (0.8 g, 20 mmol). The reaction mixture was refluxed for a further 2 h, the solvent distilled off to dryness, and the residue extracted with refluxing benzene (3 × 50 ml). After cooling the filtrate the precipitate was filtered off to give the product **3** (2.2 g 64.7%); mp 192-194°C (benzene), R_f 0.24 (b).

C. A solution of the diazabicyclononane **4** (7.5 g, 45 mmol) in absolute ether (50 ml) was added dropwise with stirring to a solution of $LiAlH_4$ (4.5 g, 135 mmol) in absolute ether (100 ml), the mixture was refluxed for 15 h, then cooled, and water (30 ml) was added to it dropwise. The solvent was decanted, the residue was washed several times with ether, and the combined ether extract was dried over $MgSO_4$. After distillation of the ether the residue was refluxed in benzene similarly to method B to give the product **3** (4.3 g, 55.7%); mp 192-194°C (benzene) R_f 0.24 (b).

6-Hydroxy-5,7-dimethylspiro(1,3-diazaadamantane-2-cyclopentane) (2a). A. A solution of the diazabicyclononane **3** (0.85 g, 5 mmol) and cyclopentanone (0.6 g, 7 mmol) in ethanol (20 ml) was refluxed for 5 h. The solvent was removed to dryness and the residue was recrystallized from ethyl acetate to give compound **2a** (0.85 g, 72.0%); mp 150-151°C (ethyl acetate), R_f 0.50 (b). IR spectrum (thin film), ν, cm^{-1}: 3300 (O–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.30 (2H, d, *J* = 12.5, 2 CH_e–N); 3.28 (1H, s, C<u>H</u>–OH); 3.12 (2H, d, *J* = 13.0, 2 CH_e–N); 3.00 (2H, d, *J* = 13.0, 2 CH_a–N); 2.65 (2H, d, *J* = 12.5, 2 CH_a–N); 1.88-2.03 (8H, m, 4 CH_2); 0.72 (6H, s, 2 CH_3). M^+ 236. Found, %: C 71.03; H 10.51; N 12.02. $C_{14}H_{24}N_2O$. Calculated, %: C 71.19; H 10.17; N 11.86.

B. Prepared similarly to compound **3** (method B) from $LiAlH_4$ (1.2 g, 30 mmol) and the spirodiazaadamantane **1a** (1.8 g, 8 mmol) [2] in absolute ether (250 ml). After distillation of ether the remaining oil was crystallized from ether and recrystallized from benzene to give compound **2a** (0.8 g, 45.2%); mp 150-151°C (benzene), R_f 0.50 (b), identical to the sample obtained by method A (TLC, absence of melting point depression for a mixed sample).

6-Hydroxy-5,7-dimethylspiro(1,3-diazaadamantane-2-cyclohexane) (2b). A. Prepared similarly to compound **2a** (method A) from the diazabicyclononane **3** (0.7 g, 4 mmol) and cyclohexanone (0.6 g, 6 mmol) in ethanol (20 ml) to give 0.67 g (67.0%); mp 175-176°C (hexane), R_f 0.63 (b). IR spectrum (thin film), ν, cm^{-1}: 3080-3100 (O–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 3.42 (2H, d, *J* = 13.0, 2 CH_e–N); 3.25 (1H, s, C<u>H</u>–OH); 3.15 (2H, d, *J* = 12.5, 2 CH_e–N); 3.05 (2H, d, *J* = 12.5, 2 CH_a–N); 2.55 (2H, d, *J* = 13.0, 2 CH_a–N); 1.40-2.00 (10H, m, 5 CH_2); 0.73 (6H, s, 2 CH_3). Found, %: C 72.38; H 10.32; N 11.05. $C_{15}H_{26}N_2O$. Calculated, %: C 72.0; H 10.40; N 11.20.

B. Prepared similarly to compound **2a** (method B) from the spirodiazaadamantane **1b** (2.8 g, 11 mmol) [2] in absolute diethyl ether (200 ml) and $LiAlH_4$ (1.5 g, 40 mmol) in absolute ether (300 ml) to give 2.3 g (82.2%); mp 175-176°C (benzene–octane, 1:1), R_f 0.63 (b). A mixed sample of the compound **2b** prepared by the methods A and B did not show a depression of melting point.

6-Hydroxy-2'2'5,7-tetramethylspiro(1,3-diazaadamantane-2,4'-tetrahydropyran) (2c). A. Prepared similarly to compound **2a** (method A) from the diazabicyclononane **3** (0.85 g, 5 mmol) and 2,2-dimethyltetrahydropyran-4-one (0.7 g, 5.5 mmol) in ethanol (20 ml). After distillation of solvent the residue was recrystallized from benzene to give 1.1 g (78.5%); mp 197-199°C (benzene), R_f 0.33 (b). IR spectrum (thin film), ν, cm^{-1}: 1090 (C–O–C), 3100-3170 (O–H). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm (*J*, Hz): 3.57 (2H, d, *J* = 12.5, 2 CH_e–N); 3.25 (2H, d, *J* = 13.2, 2 CH_e–N); 3.00 (2H, d, *J* = 13.2, 2 CH_a–N); 2.87 (3H, m CH–OH, CH_2–O); 2.50 (1H, s, OH); 2.43 (2H, d, *J* =12.5, 2 CH_a–N); 1.82-1.90 (4H, m, 2 CH_2); 1.20 (6H, s, 2 CH_3); 0.65 (6H, d, 2 CH_3). M^+ 280. Found, %: C 68.72; H 9.91; N 10.08. $C_{16}H_{28}N_2O_2$. Calculated, %: C 68.57; H 10.0; N 10.0.

Prepared similarly to compound **3** (method B) from $NaBH_4$ (0.18 g, 5 mmol) and the spirodiazaadamantane **1c** (1.0 g, 3.5 mmol) [3] in ether (50 ml) and methanol (10 ml). Yield 0.5 g (51.0%); mp 197-199°C (benzene), R_f 0.33 (b).

A mixed sample of the compound **2c** prepared by methods A and B did not show a depression of melting point.

3,7-Diethyl-9-hydroxy-1,5-dimethyl-3,7-diazabicyclo[3.3.1]nonane (7) was prepared similarly to compound **3** (method B) from $LiAlH_4$ (0.6 g, 16 mmol) in absolute ether (30 ml) and the diazabicyclononane **5** (0.6 g, 2.4 mmol) [5] in absolute THF (50 ml). After distillation of solvent the residue was recrystallized twice from hexane. Yield 0.35 g (64.5%); mp 58-60°C (hexane), R_f 0.25 (b). IR spectrum (thin film), ν, cm^{-1}: 3340 (O–H). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm (*J*, Hz): 2.70 (2H, br. s, CH–OH); 2.58 (2H, d, *J* = 12.0, 2 CH_e–N); 2.36 (2H, d, *J* = 12.5, 2 CH_e–N); 2.15 (2H, d, *J* = 12.5, 2 CH_a–N); 1.65 (2H, d, *J* = 12.0, 2 CH_a–N); 1.10 (6H, s, 2 CH_3); 0.85-1.10 (10H, m, 2 CH_2CH_3). Found, %: C 69.16; H 11.80; N 12.17. $C_{13}H_{26}N_2O$. Calculated, %: C 69.03; H 11.50; N 12.38.

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