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Reduction of Unsaturated Adamantane-Containing Nitriles

I. A. Novakov, B. S. Orlinson, N. N. Mamutova, E. N. Saveliev, and E. A. Potaenkova

Volgograd State Technical University, ul. Lenina 28, Volgograd, 400005 Russia
e-mail: phanchem@vstu.ru

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Abstract—The regularities of reduction of adamantane-containing unsaturated nitriles with Raney nickel were studied. It was shown that in the reaction conditions simultaneous reduction of both the double bond and the nitrile group occurs. The reduction of 2-(5-hydroxyadamant-2-ylidene)alkyl nitriles requires a longer time.

Keywords: adamantane, adamantanone, unsaturated nitriles, reduction, Raney nickel

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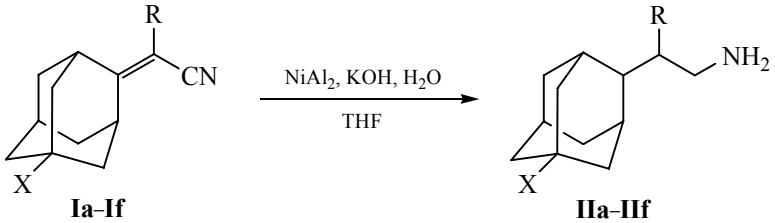
Adamantane amine derivatives exhibit various kinds of pharmacological activity [1], and may also be used as intermediates in the synthesis of polymers with high performance characteristics [2]. In [3–8] it was found that 2-substituted adamantanes exhibit a wider spectrum of biological activity compared to the 1-substituted derivatives. Thus, spiro[cyclopropane-1,2'-adamantane]-2-amines are active at micromolar concentrations against influenza A H2N2 strain in concentrations 125 times smaller than in the case of amantadine [3, 4].

Recent studies on the therapeutic drugs design showed that compounds containing bulky lipophilic groups like adamantyl-containing amides behave as substances that reduce the risk of developing type 2 diabetes, cardiovascular disease, apoplexy, and certain types of cancer [5, 6]. Thus, 2-adamantyl derivatives exhibit high inhibitory activity against 11β-hydroxyl-steroid dehydrogenase 11β-HSD1 [7]. It should also be noted that 4-({[2-(adamant-2-yl)ethyl]amino}methyl)-benzoic acid obtained on the basis of 2-(adamant-2-yl)-ethylamine exhibits high anticancer activity [8]. In this regard, developing effective methods for the preparation of 2-substituted amino derivatives of adamantane seems an urgent task.

In this work, reduction of adamantane-containing unsaturated nitriles with nickel-aluminum alloy was performed to obtain a number of adamant-2-yl substituted amines **IIa**–**IIf** in high yields The synthesis was carried out as follows.



Ia–**If** **IIa**–**IIf**

R = H, X = H (**a**); R = CH_3, X = H (**b**); R = C_2H_5, X = H (**c**); R = H, X = OH (**d**); R = CH_3, X = OH (**e**); R = C_2H_5, X = OH (**f**).

The reduction of unsaturated adamantane nitriles was carried out using active hydrogen obtained by reacting aluminum from Raney nickel-aluminum alloy (Al : Ni = 50 : 50) with potassium hydroxide. In this case potassium aluminate formed along with hydrogen that reduced both the conjugated double bond and the nitrile group.

The structure of the compounds obtained was confirmed by gas chromatography-mass spectrometry, IR and ^{1}H NMR spectroscopy.

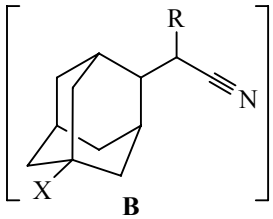
Several methods for the preparation of 2-(adamant-2-yl)ethylamine have been known. The starting compound was 2-adamantyleneacetonitrile. The reduction

has been performed with either hydrogen over palladium under pressure (50 at) to give adamantan-2-ylacetonitrile and reducing the latter with lithium aluminum hydride in tetrahydrofuran [9], or by lithium aluminum hydride in anhydrous tetrahydrofuran to give a mixture of 2-(adamant-2-yl)ethylamine and (2-adamantylidene)ethylamine in a weight ratio of 7 : 3, respectively [10].

Raney nickel is used to reduce various compounds containing both unsaturated bonds (e.g., adamant-2-ylideneacetic acid [11]), and various functional groups (e.g. aliphatic-aromatic unsaturated nitriles) (yield of 17–36%). We investigated the simultaneous reduction of adamantane unsaturated nitriles with Raney nickel [12].

The reduction process was carried out in the temperature range of 25–65°C; the reaction time was 4–8 h. It was shown that by using **Ia**–**Ic** as a starting material the reaction proceeds with a satisfactory rate at room temperature: after 4 hours, the content of target compounds **IIa**–**IIc** was 48–62%. At the same time, in the case of **IId**–**IIf** the synthesis should be carried out at 65°C for 8 h.

We found that the reduction of unsaturated adamantane-containing nitriles with nickel-aluminum alloy occurred via initial hydrogenation of the double bond and subsequent reduction of the nitrile group. The reduction of compound **Ia** was studied as a model. According to gas chromatography-mass spectrometry data, an intermediate **B** was formed by the hydrogenation of the double bond, and the product of reducing the nitrile group with preserved unsaturation was not detected in the reaction mixture.



B

Depending on the structure of the starting nitrile, product **B** content in the reaction mixture ranges from 17 to 34%.

It should be noted that the introduction of the substituent into the α-position to the nitrile group (**Ib, Ic**) led to a prolongation of the synthesis. Thus, the reduction of 2-(5-hydroxyadamant-2-ylidene)alkyl nitriles **Id**–**If** proceeded longer. It has been found that the content of the target compounds **IId**–**IIf** did not exceed 3–5% when the reaction was carried out at 25°C for 8 h with the use of (4–5)-fold molar excess of hydrogen. The reduction of **Ia**–**Ic** under the same conditions afforded the target compounds in 97–99% yield. An increase in the temperature to 65°C resulted in a significant increase in the reaction rate. In addition, the yield of the target compounds increased sharply and amounted to 80–90%. At the same time, it should be noted that a temperature increase for all the hydroxy-containing nitriles led to a decrease in selectivity. For example, when reducing nitrile **Id** 2-(adamant-2-yl)ethylamine, 2-ethyladamantane, and 1,4-dioxyadamantane were detected in the reaction mixture as by-products. The formation of 2-(adamant-2-yl)ethylamine and 2-ethyladamante is due to successive hydrogenolysis of C–O and C–N bonds in the target compound; 1,4-dihydroxyadamantane is formed by hydrolysis of the starting **Id** at elevated temperature in the presence of alkali.

It should also be noted that a strong influence on the process selectivity and the reaction rate has an excess of a reducing reagent. Thus, a significant increase in the yield of the target amine **IIa**–**IIf** was observed when (4–5)-fold molar excess of hydrogen was used. It was also found that reducing compound **Ic** with 10-fold molar excess (compared with the theoretical) of hydrogen resulted in the formation of multicomponent mixture containing 11% of 2-methyladamantane. The formation of the latter is due to a subsequent fragmentation reaction by the action of the reducing agent.

In the mass spectra of compounds **IId**–**IIf** obtained peaks of molecular ions of isomeric compounds were observed. According to [13], it is presumable that 1,4-disubstituted adamantane derivatives are a mixture of *syn*- and *anti*-isomers in a ratio of 1 : 3 (**IId**), 1 : 1.2 (**IIe**), 1 : 1.15 (**IIf**). Mass spectra of the isomeric compounds were qualitatively the same, but have differences in intensity of certain peaks, such as *m*/*e* $[M - 18]^+$.

In summary, the introduction of a substituent into the α-position to the nitrile group led to an increase in the duration of the reduction of unsaturated adamantane nitriles. The reduction of 2-(5-hydroxyadamant-2-ylidene)alkyl nitrile is necessary to carry out at elevated temperatures.

EXPERIMENTAL

H^1 NMR spectra (CCl_4) were recorded on a Varian Mercury-300 BB spectrometer (300.73 MHz), internal

reference HMDS. Gas chromatography-mass spectrometry was performed on a Varian Saturn 2100 T/G C3900 instrumant. IR spectra were registered on a FTIR spectrometer Nicolet-6700 (Termo Electron Co.).

Nitriles **Ia**–**If** were prepared by the procedure described in [10].

2-(Adamant-2-yl)ethylamine (IIa). To a solution of 8.9 g (0.052 mol) of 2-adamantylideneacetonitrile **Ia** in 110 mL of THF were added with stirring 7.48 g (0.13 mol) of KOH and 110 mL of water. Then 33.7 g (0.624 g-atom Al) of Raney Ni/Al-alloy (Ni : Al = 50 : 50) was added in portions within 4 h while maintaining moderate gas evolution. The reaction mixture was refluxed for 3 h. The precipitate was filtered off and washed with THF. The aqueous layer was extracted with toluene (3 × 100 mL), the organic phase was evaporated, and the residue was distilled in a vacuum. Yield 8.7 g (0.048 mol, 93%), bp 98–102°C (4 mmHg). IR spectrum, ν, cm^{-1}: 1013.6, 1042.4, 1065.1, 1099.3, 1214.8, 1309.5, 1353.5, 1452.2, 1469.4, 1605.4, 1652.9, 2745.7, 2805.4, 2848.4 (CH_{Ad}), 2893.7, 3348.2 (NH_2). ^{1}H NMR spectrum, δ, ppm: 0.77 s (2H, NH_2), 1.22 m (1H, CH_{Ad}), 1.42–1.80 m (17H, $C\underline{H}_2CH_2NH_2$, Ad), 2.57–2.64 m (2H, $CH_2C\underline{H}_2NH_2$). Mass spectrum (EI, 70 eV), *m*/*e* (I_{rel}, %): 180 (100) $[M]^+$, 179.3 (10) [*M*], 178.3 (5), 176.5 (1), 175.7 (1), 105.2 (1).

2-(Adamant-2-yl)propan-1-amine (IIb) was prepared similarly from 9.7 g (0.052 mol) of 2- (adamant-2-ylidene)propionitrile **Ib**, 33.7 g (0.624 g-atom Al) of Raney alloy and 7.48 g (0.13 mol) of KOH. Yield 9.6 g (0.050 mol, 96%), bp 115–118°C (4 mmHg). IR spectrum, ν, cm^{-1}: 932.8, 977.0, 94.8, 1043.3, 1061.4, 1099.0, 1314.6, 1354.3, 1452.2, 1469.4, 1605.4, 1653.0, 2329.5, 2840.8 (CH_{Ad}), 2898.7, 2960.1, 3346.2 (NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.70 s (2H, NH_2), 0.81–0.83 d (3H, CH_3, *J* 6.4), 1.27 d (1H, CH_{Ad}, *J* 10.7) 1.44 d (2H, CH_{Ad}, *J* 12.0), 1.617–1.815 m (14H, Ad), 2.35 d.d [1H, $CH(CH_3)C\underline{H}_2NH_2$, *J* 12.6, 7.1], 2.64 d.d [1H, $CH(CH_3)C\underline{H}_2NH_2$, *J* 12.4, 3.0]. Mass spectrum (EI, 70 eV), *m*/*e* (I_{rel}, %): 194.9 (6) $[M]^+$, 194 (41) [*M*], 177 (14), 177 (14) $[M - 17]^+$, 176 (100) [*M* – 17], 162 (8), 161.1 (12), 133.2 (9).

2-(Adamant-2-yl)butan-1-amine (IIc) was prepared similarly from 10.5 g (0.052 mol) of 2-(adamant-2-ylidene)butyronitrile **Ic**, 33.7 g (0.624 g-atom Al) of Raney alloy and 7.48 g (0.13 mol) of KOH. Yield 9.7 g (0.047 mol, 90%), bp 126–128°C (4 mmHg). IR spectrum, ν, cm^{-1}: 934.8, 1013.6, 1042.4, 1065.1, 1099.3, 1214.8, 1309.5, 1353.5, 1452.2, 1469.4, 1605.4, 1652.9, 2329.5, 2840.8 (CH_{Ad}), 2898.9, 2962.1, 3348.2 (NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.80 d.t (3H, CH_3, *J* 7.1, 0.2), 1.24–1.32 m [1H, $\underline{CH}(C_2H_5)CH_2NH_2$], 1.44–1.84 m [17H, NH_2, $CH(C\underline{H}_2CH_3)CH_2NH_2$], 2.75 d.d [2H, $CH(C_2H_5)C\underline{H}_2NH_2$, *J* 12.4]. Mass spectrum (EI, 70 eV), *m*/*e* (I_{rel}, %): 208 (100), 207 (10) [*M*], 192 (2), 178 (17), 177 (14), 176.5 (1), 162 (8), 161.1 (12), 135 (8).

4-(2-Amino)ethyladamant-1-ol (IId) was prepared similarly from 10.7 g (0.052 mol) of (5-hydroxyadamant-2-ylidene)acetonitrile **Id**, 33.7 g (0.624 g-atom Al) of Raney alloy and 7.48 g (0.13 mol) of KOH. Yield 9.1 g (0.047 mol, 90%). IR spectrum, ν, cm^{-1}: 922.3, 1013.8, 1042.1, 1068.3, 1218.1, 1309.5, 1353.5, 1452.2, 1469.4, 1607.4, 1652.1, 2329.5, 2648.7, 2701.5, 2745.7, 2805.4 (CH_{Ad}), 2912.0, 3348.2 (NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.89–0.94 m (3H, NH_2, CH_{Ad}), 1.15–1.16 m (2H, $C\underline{H}_2CH_2NH_2$), 1.33–1.53 m (16H, Ad), 2.02 s (1H, OH), 2.25–2.31 d.t (2H, $CH_2C\underline{H}_2NH_2$, *J* 7.1, 0.9). Mass spectrum (EI, 70 eV), *m*/*e* (I_{rel}, %): 196.3 (6) $[M]^+$, 195.3 (41) [*M*], 177 (14), 176 (100) $[M - 17]^+$, 162 (8), 161.1 (12), 133.2 (9).

4-(1-Aminopropan-2-yl)adamantan-1-ol (IIe) was prepared similarly from 10.7 g (0.052 mol) of 2-(5-hydroxyadamant-2-ylidene)propanenitrile **Ie**, 33.7 g (0.624 g-atom Al) of Raney alloy and 7.48 g (0.13 mol) of KOH. Yield 9.9 g (0.047 mol, 91%). IR spectrum, ν, cm^{-1}: 810.0, 922.3, 965.3, 1054.6, 1091.7, 1151.7, 1303.3, 1339.8, 1451.1, 1596.7, 1665.7, 2912.0 (CH_{Ad}), 3507.8 (NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.83–0.84 d (3H, CH_3, *J* 6.6), 0.85–2.08 m [19H, NH_2, CH_{Ad}, OH, $C\underline{H}(CH_3)CH_2NH_2$], 2.36–2.44 d.d [1H, $CH(CH_3)C\underline{H}_2NH_2$, *J* 12.6, 7.1] 2.69–2.77 d.d [1H, $CH(CH_3)C\underline{H}_2NH_2$, *J* 12.4, 3.0]. Mass spectrum (EI, 70 eV), *m*/*e* (I_{rel}, %): 210.2 (100) $[M]^+$, 209.3 (9) [*M*], 192.3 (11), 191.3 (7), 190.4 (5).

4-(1-Aminobut-2-yl)adamantan-1-ol (IIf) was prepared similarly from 11.3 g (0.052 mol) of 2-(5-hydroxyadamant-2-ylidene)butanenitrile **Ie**, 33.7 g of (0.624 g-atom Al) of Raney alloy and 7.48 g (0.13 mol) of KOH. Yield 10.7 g (0.048 mol, 93%). IR spectrum, ν, cm^{-1}: 961.3, 1054.6, 1091.7, 1154.7, 1303.3, 1339.8, 1451.1, 1596.7, 1665.7, 2912.0 (CH_{Ad}), 3515.8 (NH_2). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.81–0.84 d.t (3H, CH_3, *J* 7.1), 1.24–1.32 m [1H, $\underline{CH}(C_2H_5)\cdot CH_2NH_2$], 1.44–1.84 m [17H, NH_2, $CH(C\underline{H}_2CH_3)\cdot CH_2NH_2$], 2.1 s (1H, OH), 2.60–2.80 d.d [2H, $CH(C_2H_5)\cdot C\underline{H}_2NH_2$, *J* 12.4, 3.0]. Mass spectrum (EI, 70 eV), *m*/*e* (I_{rel}, %): 224.1 (15) $[M]^+$, 223.2 (100), 206.8 (3), 206.2

(1), 194.2 (6), 193.2 (4), 192.3 (12), 188.5 (2), 187.1 (2), 178 (3), 177 (18), 134 (6), 133.2 (11).

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