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# Synthesis of Aminoalcohols of the Adamantane Series

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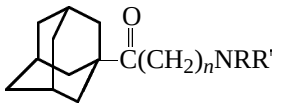
**Abstract** — The reduction of α- and β-aminoketones and enaminoketones of the adamantane series with sodium borohydride in methanol at room temperature gives the corresponding adamantylaminoalkanols.

Aminoalkanols are widely used as drugs [1]. They have also found application as starting materials in synthesis of heterocycles, such as aziridines [2, 3], oxazines [4], 2-thiazolines [5], 2-thiazolidinethiones [6], 2-oxo-1,2,3-oxathiazolidines [7], tetrahydroquinolines [8], and isoquinolines [9]. As to aminoalcohols of the adamantane series, only a few their representatives have been described in the literature. Thus, Lauria *et al.* [10] reported the synthesis of a γ-aminoalcohol by reduction with $LiAlH_4$ of 3-(1-adamantyl)-1-morpholylpropan-3-one prepared from 1-adamantyl methyl ketone, Paraform, and morpholine hydrochloride. β-Aminoalcohols were prepared in 33–86% yield by reduction with $NaBH_4$ of α-aminoketones of the general formula *p*-$RC_6H_4C(=O)CH_2NHAd$ (R = F, Br, I, Me, MeO, OH, Ph) in 2-propanol [11]. The information on reduction of β-aminovinyl ketones is scarce. Thus, Maruoka *et al.* [12] reported the reduction of β-aminovinyl ketones on Pt/C to γ-aminoalcohols. The same result was obtained by the reduction with $NaBH_4$ in the presence of $FeCl_3$ [13]. However, the reaction in other conditions gave β-aminoketones and enamines [14].

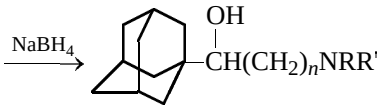
Directed synthesis of β- and γ-aminoalcohols of the adamantane series has not yet been performed. Aiming at preparing the new class of aminoalcohols of the adamantane series and proceeding with studies on the chemical properties of adamantyl-containing α- and β-aminoketones and β-aminovinyl ketones [15–17], we turned to reduction of these compounds with sodium borohydride in methanol at room temperature.

It is known that reduction of 1-adamantyl aryl ketones with lithium aluminum hydride [18] or sodium borohydride [19] may result not only in alcohol formation, but also in exhaustive hydrogenation of the carbonyl group to methylene.

By the reduction of *N*,*N*-disubstituted 2-(1-adamantyl)-1-aminoethan-2-ones **I** and 3-(1-adamantyl)-1-aminopropan-3-ones **II** with sodium borohydride in methanol at room temperature we obtained *N*,*N*-disubstituted 2-(1-adamantyl)-1-aminoethan-2-ols **III** and 3-(1-adamantyl)-1-aminopropan-3-ols **IV**.



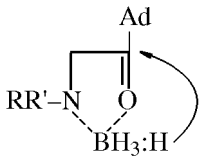
**Ia–Id, IIa–IIc**



**IIIa–IIId, IVa–IVc**

**I, III**, $n$ = 1, R = R' = $CH_2CH_2OH$ (**a**); R = $CH_3$, R' = 1-adamantyl (**b**); R = R' = $CH_2C_6H_5$ (**c**), NRR' = piperidyl (**d**). **II, IV**, $n$ = 2, R = R' = $CH_3$ (**a**); R = $CH_3$, R' = 1-adamantyl (**b**), NRR' = piperidyl (**c**).

The facility of reduction of the keto group is a function of its steric accessibility. Presumably, with α-aminoketones **I**, the following intermediate state takes place.



The structure of aminoalcohols **III** and **IV** was proved by $^1H$ NMR and IR spectroscopy. The IR spectra contain an OH absorption band at 3200–3420 $cm^{-1}$, and the $^1H$ NMR spectra show OH and CH proton signals (see Table 1).

The reduction of *N*,*N*-disubstituted 3-(1-adamantyl)-1-aminoprop-1-en-3-ones **V** and 4-(1-adamantyl)-1-aminobut-1-en-3-ones **VI** in methanol at 20–25°C with $NaBH_4$ gave *N*,*N*-disubstituted 3-(1-adamantyl)-

**Table 1.** Adamantane derivatives **III, IV, VII**, and **VIII**

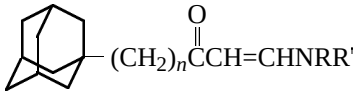
| Comp. no. | Yield, % | mp, °C (solvent for crystallization) | $R_f$ | IR spectrum, $\nu$, $cm^{-1}$ | $^1H$ NMR spectrum, δ, ppm |
|---|---|---|---|---|---|
| **IIIa** | 67 | 30–31 (alcohol) | 0.71[a] | 2870, 2920 (adamantane $CH_2$), 3450 (OH) | 1.60–1.75 d (12N, adamantane $CH_2$), 2.00 s (3H, adamantane CH), 2.65 t (4H, 2 $HOCH_2CH_2N$), 2.85 d (2H, $CH_2N$), 3.05 d (1H, OH), 3.55 q (4H, $2CH_2OH$), 3.70 t (1H, CH) |
| **IIIb** | 80 | 45–47 (alcohol) | 0.67[a] | 2850, 2900 (adamantane $CH_2$), 3350 (OH) | – |
| **IIIc** | 30 | 98–100 (alcohol) | 0.13[a] | 2850, 2900 (adamantane $CH_2$), 3200 (OH) | 1.65–1.75 d (12H, adamantane $CH_2$), 1.95 s (3H, adamantane CH), 2.90 d (2H, $CH_2N$), 3.85 q (1H, CH), 4.20 d (1H, OH), 4.60 m (4H, $2CH_2C_6H_5$), 7.00–8.10 m (10H, $2C_6H_5$) |
| **IIId** | 83 | 103–105 (methanol) | 0.28[a] | 2840, 2890 (adamantane $CH_2$), 3250 (OH) | – |
| **IVa** | 34 | 63–65 (alcohol) | 0.28[b] | 2850, 2900 (adamantane $CH_2$), 3400 (OH) | 1.65–1.75 d (12H, adamantane $CH_2$), 1.95 s (3H, adamantane CH), 2.50 q (2H, $CH_2CH$), 2.65 m [6H, $N(CH_3)_2$], 2.75 t (2H, $CH_2N$), 3.85 d (1H, OH), 4.85 q (1H, CH) |
| **IVb** | 82 | 50–52 (alcohol) | 0.27[a] | 2850, 2900 (adamantane $CH_2$), 3300 (OH) | – |
| **IVc** | 85 | 141–142 (ether) | 0.30[a] | 2850, 2900 (adamantane $CH_2$), 3250 (OH) | 1.25 m (2H, piperidine $C^4H_2$), 1.5 m (4H, piperidine $C^3H_2$), 1.60–1.75 d (12H, adamantane $CH_2$), 1.95 s (3H, adamantane CH), 2.50 m (4H, piperidine $C^2H_2$), 2.70 q (2H, $CH_2CH$), 3.30 t (2H, $CH_2N$), 4.88 q (1H, CH), 6.28 d (1H, OH) |
| **VIIa** | 78 | 77–79 (hexane) | 0.64[c] | 2850, 2900 (adamantane $CH_2$), 3410 (NH, OH) | 1.60–1.75 d (12H, adamantane $CH_2$), 1.95 s (3H, adamantane CH), 2.50 d (3H, $NHCH_3$), 2.76 d (1H, OH), 3.00 q (2H, $CH_2CH$), 4.20 q (2H, $CH_2NH$), 5.12 q (1H, CH), 6.25 br.s (1H, NH) |
| **VIIb** | 50 | 184–185 (chloroform) | 0.77[a] | 2850, 2900 (adamantane $CH_2$), 3350 (NH, OH) | 1.65–1.75 d (24H, adamantane $CH_2$), 1.90 s (6H, adamantane CH), 2.50 q (2H, $CH_2CH$), 3.40 q (2H, $CH_2NH$), 5.40 q (1H, CH), 8.05 d (1H, OH), 11.90 br.s (1H, NH) |
| **VIIIa** | 75 | 131–132 (alcohol) | 0.76[a] | 2870, 2920 (adamantane $CH_2$), 3420 (NH, OH) | – |
| **VIIIb** | 52 | 160–161 (alcohol) | 0.54[a] | 2860, 2910 (adamantane $CH_2$), 3380 (OH) | 1.25 m (2H, piperidine $C^4H_2$), 1.5 m (4H, piperidine $C^3H_2$), 1.60–1.75 d (12H, adamantane $CH_2$), 1.95 s (3H, adamantane CH), 2.12 d (2H, $CH_2Ad$), 2.50 m (4H, piperidine $C^2H_2$), 2.70 d (1H, OH), 2.80 q (2H, $CH_2CH$), 3.30 t (2H, $CH_2N$), 4.05 m (1H, CH) |

**Table 1.** (Contd.)

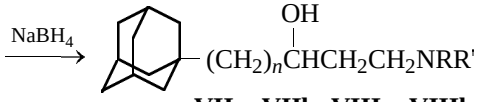
| Comp. no. | Found, % | | | Formula | Calculated, % | | |
|---|---|---|---|---|---|---|---|
| | C | H | N | | C | H | N |
| **IIIa** | 87.80 | 10.45 | 5.00 | $C_{16}H_{29}NO_3$ | 67.81 | 10.31 | 4.94 |
| **IIIb** | 80.47 | 10.80 | 4.00 | $C_{23}H_{37}NO$ | 80.41 | 10.86 | 4.08 |
| **IIIc** | 83.15 | 8.93 | 3.77 | $C_{26}H_{33}NO$ | 83.15 | 8.86 | 3.73 |
| **IIId** | 78.50 | 10.49 | 5.00 | $C_{18}H_{29}NO$ | 78.49 | 10.61 | 5.09 |
| **IVa** | 75.90 | 11.58 | 6.00 | $C_{15}H_{27}NO$ | 75.89 | 11.46 | 5.90 |
| **IVb** | 80.65 | 11.00 | 3.90 | $C_{24}H_{39}NO$ | 80.62 | 10.99 | 3.92 |
| **IVc** | 77.95 | 11.20 | 5.00 | $C_{18}H_{31}NO$ | 77.92 | 11.26 | 5.05 |
| **VIIa** | 75.30 | 11.32 | 6.29 | $C_{14}H_{25}NO$ | 75.28 | 11.28 | 6.27 |
| **VIIb** | 80.45 | 10.90 | 4.00 | $C_{23}H_{37}NO$ | 80.41 | 10.86 | 4.08 |
| **VIIIa** | 80.20 | 9.75 | 4.70 | $C_{20}H_{29}NO$ | 80.22 | 9.76 | 4.68 |
| **VIIIb** | 78.30 | 11.50 | 4.85 | $C_{19}H_{33}NO$ | 78.29 | 11.41 | 4.81 |

Eluent: [a] acetone, [b] acetone–$CCl_4$, 1:12, and [c] hexane–chloroform, 1:4.

1-aminopropan-3-ols **VII** and 4-(1-adamantyl)-1-aminobutan-3-ols **VIII**.



**Va, Vb, VIa, VIb**

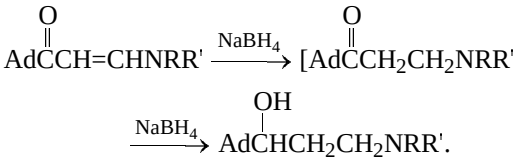


**VIIa, VIIb, VIIIa, VIIIb**

**V, VII,** $n$ = 0, R = H, R' = $CH_3$ (**a**); R = H, R' = 1-adamantyl (**b**). **VI, VIII**, $n$ = 1, R = H, R' = $C_6H_5$ (**a**); NRR' = piperidyl (**b**).

The structure of aminoalcohols **VII** and **VIII** was proved by $^1$H NMR spectroscopy (see Table 1).

As known [14], reduction of β-aminovinyl ketones sometimes results in isolation of intermediate β-aminoketones. This implies that, most probably, the first stage of the reaction of enaminoketones with reductants involves saturation of the double bond and the second, reduction of the keto group to hydroxyl. Thus, the formation of γ-aminoalcohols from β-aminovinyl ketones can be represented by the following scheme.



To conclude, reduction of α- and β-aminoketones of the adamantanes series gives rise to the corresponding aminoalcohols.

## EXPERIMENTAL

The IR spectra were obtained on a Specord M-80 instrument in KBr pellets. The $^1$H NMR spectra were measured on a Bruker AC-300 instrument (300.13 MHz) in DMSO, internal reference HMDS. The purity of the compounds was controlled by TLC on Silufol UV-254 plates. The physicochemical characteristics of the compounds are given in the table.

The synthesis of 3-(1-adamantyl)-1-(1-piperidyl)-propan-3-one hydrochloride (**IIc**) [16], 3-(1-adamantyl)-1-(methylamino)prop-1-en-3-one (**Va**) [17], 3-(1-adamantyl)-1-(1-adamantyl)aminoprop-1-en-3-one (**Vb**) [17], 4-(1-adamantyl)-1-(phenylamino)but-1-en-3-one (**VIa**) [21], and 4-(1-adamantyl)-1-(1-piperidyl)but-1-en-3-one (**VIb**) was described previously [21].

**2-(1-Adamantyl)-1-[*N*,*N*-bis(hydroxyethyl)-amino]ethan-2-one (Ia)** was obtained by the procedure in [15], yield 78%, mp 97–99°S. $R_f$ 0.16 ($CCl_4$). IR spectrum, ν, $cm^{-1}$: 1705 (C=O), 2850 and 2900 (adamantane $CH_2$), 3400 (OH). $^1$H NMR spectrum, δ, ppm: 1.60–1.75 d (12H, adamantane $CH_2$), 2.00 s (3H, adamantane CH), 2.90 s (2H, C$H_2$N), 3.10 m (2H, 2OH), 3.65 m (4H, 2C$H_2$OH). Found, %: C 68.30; H 6.75; N 5.00. $C_{16}H_{27}NO_3$. Calculated, %: C 68.29; H 9.67; N 4.98.

**2-(1-Adamantyl)-1-[*N*-(1-adamantyl)-*N*-methyl-amino]ethan-2-one (Ib)** was obtained by the procedure in [15], yield 96%, mp 150–152°C. $R_f$ 0.65 (alcohol). IR spectrum, ν, $cm^{-1}$: 1680 (C=O), 2860 and 2910 (adamantane $CH_2$). $^1$H NMR spectrum, δ, ppm: 1.65–1.75 d (24H, adamantane $CH_2$), 1.90 s (6H, adamantane CH), 2.50 s (3H, NC$H_3$), 2.90 s (2H,

C$H_2$NH). Found, %: C 80.95; H 10.25; N 4.10. $C_{23}H_{35}NO$. Calculated, %: C 80.89; H 10.33; N 4.10.

**2-(1-Adamantyl)-1-[*N,N*-dibenzylamino]ethan-2-one (Ic)** was obtained by the procedure in [15], yield 80%, mp 60–62°C. $R_f$ 0.34 (hexane–chloroform, 1 : 4). IR spectrum, ν, $cm^{-1}$: 1680 (C=O), 2850 and 2900 (adamantane $CH_2$). Found, %: C 83.69; H 8.41; N 3.74. $C_{26}H_{31}NO$. Calculated, %: C 83.60; H 8.37; N 3.75.

**2-(1-Adamantyl)-1-(1-piperidyl)ethan-2-one (Id)** was obtained by the procedure in [15], yield 93%, mp 55–57°C. $R_f$ 0.46 (acetone–$CCl_4$, 1 : 4). IR spectrum, ν, $cm^{-1}$: 1705 (C=O), 2850 and 2900 (adamantane $CH_2$). $^1$H NMR spectrum, δ, ppm: 1.40 m (2H, piperidine $C^4H_2$), 1.55 m (4H, piperidine $C^3H_2$), 1.70–1.80 d (12H, adamantane $CH_2$), 2.00 s (3H, adamantane CH), 2.45 m (4H, piperidine $C^2H_2$), 3.35 s (2H, C$H_2$N). Found, %: C 77.50; H 11.10; N 5.35. $C_{17}H_{27}NO$. Calculated, %: C 77.50; H 11.10; N 5.32.

**3-(1-Adamantyl)-1-(1-dimethylamino)propan-3-one hydrochloride (IIa)** was obtained by the procedure in [20], yield 67%, mp 178–180°C.

**3-(1-Adamantyl)-1-[*N*-(1-adamantyl)-*N*-methylamino]propan-3-one (IIb)** was obtained by the procedure in [16], yield 48%, mp 138–140°C. $R_f$ 0.16 (alcohol). IR spectrum, ν, $cm^{-1}$: 1690 (C=O), 2850 and 2900 (adamantane $CH_2$). Found, %: C 81.00; H 10.50; N 4.00. $C_{24}H_{37}NO$. Calculated, %: C 81.07; H 10.49; N 3.94.

**Reduction of α- and β-aminoketones I, II and β-aminovinyl ketones V, VI** *(general procedure).* To a solution of 2.3 mmol of aminoketone in 10 ml of methanol we added in small portions 0.17 g of $NaBH_4$. The reaction mixture was left to stand for 3 h and treated with 10% HCl to pH 5–6. The precipitate was filtered off, washed with water, and recrystallized.

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