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ORGANIC SYNTHESIS AND INDUSTRIAL ORGANIC CHEMISTRY

Condensation of Adamantanone with Methylene-Active Compounds

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Abstract—A convenient method was developed for the preparation of potentially bioactive substances with 2-adamantyl radical and of intermediates for their synthesis. Condensation of adamantanone with methylene-active compounds was performed, and the reaction features were determined.

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Chemistry of polyhedrane compounds, especially of those containing adamantyl radical, attracts much researchers' attention. It is known that a wide series of adamantane derivatives exhibit various kinds of biological activity [1]; some of them are included in the catalog of the Ministry of Public Health of the Russian Federation and are produced under various trade names. In particular, nitrogen-containing adamantane derivatives exhibit biological activity and are used as antiviral drugs (Remantadine, Midantane, Adapromine, etc.). The adamantane derivatives bearing a substituent at the methylene carbon atom (2-position) are often more promising from the viewpoint of biological activity than the derivatives substituted at the methine atom (1-position) [2]. Thus, search for routes to 2-substituted adamantane derivatives is a topical problem.

The goal of this work was the development of convenient methods for preparing these compounds, based on condensation of adamantanone with various CH acids, and study of further transformations of the products obtained into amine.

To choose the structure of the target products and plan the routes of their synthesis, the probable biological activity of a series of 2-substituted adamantane derivatives was predicted. The development of procedures for preparing 2-(2-amino)ethyladamantane, which exhibits the properties of dopamine release stimulant and ligase inhibitor, was shown to be topical. 2-(Adamantylidenemethyl)quinoline can exhibit the same properties, acting, in particular, as taurine inhibitor. 4-Adamantylidene-3-methyl-1-phenylpyrazolidin-5-one may also be of considerable interest.

The anticipated practical significance of these compounds was confirmed by Zoidis et al. [3], who studied the synthesis and biological activity of 1- and 2-substituted amino derivatives of adamantane. They showed, in particular, that adamantane-containing derivatives of pyrrolidine, oxazolone, pyrazolone, pyrazolinethione, and cyclopentylamine exhibit antiviral activity toward influenza A viruses and kill parasitic microorganisms trypanosomes. Adamantane-substituted pyrrolidine exhibits 4 times higher antiviral activity than Amantadine and Remantadine do, and toward African blood trypanosomes the corresponding substituted oxazolone is 3 times more active than Remantadine and 50 times more active than Amantadine [3].

Therefore, it is topical to search for procedures for adamantane functionalization with the formation of a new C–C bond in the 2-position of the adamantyl group.

It is known that condensation of adamantanone with CH acids is a convenient method for introducing a side carbon into 2-position of the adamantyl group.

Data on reactions of adamantanone with malonic acid mononitrile derivatives $CNCH_2COX$ (X = OH, OMe, OEt, NH_2) with the formation of the corresponding adamantylidenemalonic acid derivatives are reported in [4]. Reactions of adamantanone with potassium or sodium cyanide and morpholine or ethyl 2-aminopropionate in DMSO yield 2-morpholino-2-cyanoadamantane and 2-cyano-2-(1-ethoxycarbonylethylamino)adamantane, respectively [5, 6]. 2-Benzylamino-2-cyanoadamantane can be prepared in 67% yield by the reaction of adamantanone with benzylamine and trimethylsilyl cyanide [7]. However, published data on condensation of adamantanone with ketones and carboxylic acid derivatives are virtually lacking.

This study deals with crotonic condensation of adamantanone with ketones and aliphatic carbonitriles in the presence of strong bases and acid catalysts, and also with condensation of adamantanone with some heterocyclic CH acids.

As shown previously [8], the reaction of adamantanone with acetonitrile in the presence of finely divided KOH and 18-crown-6 as catalyst yields the unsaturated nitrile, and the same reaction performed in the presence of NaH in dimethyl sulfoxide yields 2-hydroxyadamant-2-ylacetonitrile.

However, implementation of this route to unsaturated nitriles of the adamantane series is restricted by high cost and relatively difficult availability of certain chemicals. An attempt was made to optimize the synthesis with the aim to simplify it and make preparation of the target product cheaper. In particular, dimethyl sulfoxide was used instead of 18-crown-6 as cosolvent for KOH. Despite the absence of the crown ether, almost quantitative yield of adamantylideneacetonitrile **IIIa** was attained in 4 h. An attempt to perform the reaction under heterogeneous conditions without DMSO was also successful, but the yield of **IIIa** in 6 h was lower, about 70% (the remainder was unchanged adamantanone).

Replacement of KOH by more readily available NaOH in the presence of DMSO showed that NaOH was also suitable, but quantitative yield of the desired nitrile was not attained. Finally, the worst result (no more than 30–40% yield of **IIIa**) was obtained when the condensation was performed in the presence of NaOH without dimethyl sulfoxide. It should be noted, however, that the low yield in this synthesis is not of crucial importance, because the unchanged adamantanone can be fully regenerated and the cost of the other chemicals is relatively low. The improved procedure appeared to be also suitable for preparing other adamantyl-containing unsaturated nitriles of similar structure. In particular, the products of the condensation of adamantanone **I** with propionitrile **IIb** and butyronitrile **IIc** (compounds **IIIb** and **IIIc**) were obtained in 65–70% yields:

IIIa–IIIc

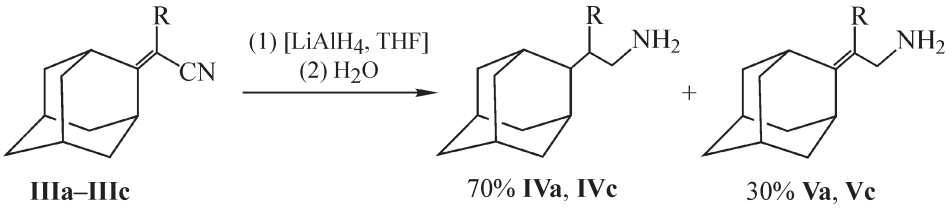
R = H (**a**), CH_3 (**b**), C_2H_5 (**c**).

Products **IIIb** and **IIIc** were purified by vacuum distillation. Despite the fact that these substances are structural analogs of readily polymerizing acrylonitrile, owing to the steric effect of the adamantyl group they are thermally stable and are distilled without polymerization or decomposition.

The compositions and structures of **IIIa–IIIc** were confirmed by ^1H NMR spectroscopy. In the spectra, there are characteristic singlets from two kinds of adamantane CH protons at 1.75 and 2.00 ppm and a singlet from the =CH–CN proton (in the case of adamantylideneacetonitrile) at 4.89 ppm.

Amines of the adamantane series are potential antiviral agents and antiparkinson drugs [1]. 2-(2-Aminoethyl) adamantane and its substituted homologs are used for treatment of neurodegenerative diseases; such compounds exhibit neuroprotective and positive symptomatic effect [9]. However, synthesis of aminoalkyladamantanes in which the alkyl group is bonded to the bridge carbon atom of adamantane has been developed relatively poorly. As a route of converting the product of condensation of **I** with **IIa** (compound **IIIa**) into 2-(2-aminoethyl)

adamantane **IV**, we chose reduction of **IIIa** with lithium aluminum hydride. It is known [8] that the reduction of adamantylideneacetonitrile **IIIa** in diethyl ether involves only the nitrile group, with the double bond remaining intact. Therefore, we used as solvent tetrahydrofuran and performed the reduction at its boiling point for 8 h. The reduction of adamantylidenebutyronitrile **IIIc** was performed similarly:



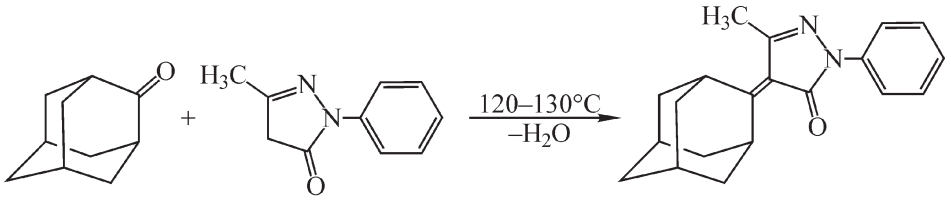
IIIa–IIIc 70% **IVa**, **IVc** 30% **Va**, **Vc**

R = H (**a**), C_2H_5 (**c**).

The reaction products were purified by vacuum distillation. They were colorless transparent liquids. A study by gas chromatography–mass spectrometry showed that the reactions yielded mixtures of saturated (**IVa**, **IVc**) and unsaturated (**Va**, **Vc**) amines, with the prevalence of saturated amines. The **IVa** : **Va** ratio was 7 : 3 (total yield 68%), and the **IVc** : **Vc** ratio was 1 : 1 (total yield 65%).

The presence of unsaturated amines can be attributed to the steric effect of the adamantyl group, preventing 1,4-addition of metal hydrides to α,β-unsaturated nitriles, despite the fact that exhaustive reduction of acrylonitrile homologs with lithium aluminum hydride has been reported [9]. Nevertheless, all the amines synthesized are of interest for further evaluation of their probable pharmacological activity.

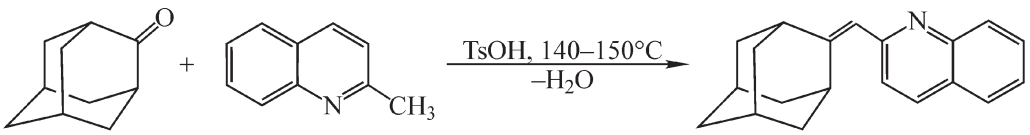
Along with derivatives of carboxylic acids and carbonyl compounds, there are a number of other compounds with labile CH protons. As one of such substances we took 3-methyl-N-phenylpyrazolidin-5-one **VI**. First, it was brought into condensation with adamantanone **I** in the presence of toluenesulfonic acid in toluene with azeotropic distillation of the released water. By this procedure, we obtained condensation product **VII** in 60% yield. However, we showed later that these compounds can react without solvent and catalyst at temperatures higher than 120°C, with the yield of **VII** increasing to 90%:



I **VI** **VII**

The structure of **VII** was proved by ^{1}H NMR spectroscopy. In particular, the signal from the CH_2 protons of the starting heterocycle **VI** was absent, and signals of the adamantyl and phenyl groups were observed.

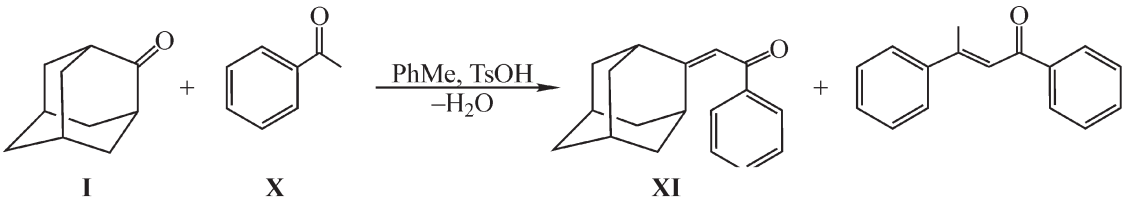
We also used 2-methylquinoline **VIII** as the starting methylene-active compound. The condensation of **VIII** occurred under relatively severe conditions in the presence of toluenesulfonic acid; the yield of product **IX** did not exceed 50%:



I **VIII** **IX**

2-Adamantylidenemethylquinoline **IX** was purified by vacuum distillation.

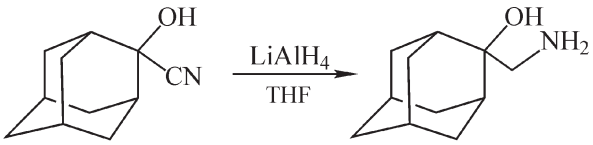
To evaluate the reactivity of adamantanone **I** in condensation with ketones, we studied its reaction with acetophenone **X**. The reaction was performed in toluene under acid catalysis at **I** : **X** molar ratio of 1 : 1 and temperature of approximately 110°C for 16–18 h. Along with the desired adamantylideneacetophenone **XI**, acetophenone self-condensation product was obtained (1 : 1 ratio under reaction conditions):



I **X** **XI**

We found that the reaction was slow and was accompanied by the release of an equimolar amount of water. Adamantanone was considerably inferior in reactivity to both aromatic aldehydes and aliphatic ketones. Similar results were obtained when the condensation was performed in ethanol with KOH as catalyst. The yield of the target product did not exceed 45–50%. The synthesized compound **XI** can be used for preparing amino and heterocyclic derivatives of adamantane.

As starting reagent for preparing 2-hydroxy-2-aminomethyladamantane **XIII** we used 2-hydroxy-2-cyanoadamantane **XII** synthesized as described in [10]. 2-Hydroxy-2-cyanoadamantane was reduced to 2-hydroxy-2-aminomethyladamantane with lithium aluminum hydride in absolute tetrahydrofuran; the reaction was performed for 6 h:



XII **XIII**

2-Hydroxy-2-aminomethyladamantane can be used as reagent in synthesis of spiro heterocycles of the adamantane series. It is also of interest from the viewpoint of testing for antiviral and antiparkinson activity.

EXPERIMENTAL

Adamantylideneacetonitrile IIIa. Example 1. A round-bottomed flask equipped with a magnetic stirrer was charged with 5 g (0.03 mol) of adamantanone **I**, 16 ml (0.45 mol) of acetonitrile **IIa**, and 5.04 g (0.09 mol) of granulated KOH in the presence of 10 ml of DMSO. The mixture was refluxed with stirring for 10 h. After the reaction completion, 50 ml of water was added, the mixture was cooled, the solid phase was filtered off, and product **IIIa** was dried and recrystallized from hexane. Yield of adamantylideneacetonitrile **IIIa** 5.14 g (0.03 mol, 100%), white crystalline substance with characteristic odor, mp 74–75°C.

^{1}H NMR spectrum, δ, ppm: 1.75–2.00 m (12H, 2,2-Ad); 2.52 s (1H, CH, Ad); 3.07 s (1H, CH, Ad); 4.89 s (1H, CHCN). Mass spectrum, *m*/*e* (I_{rel}, %): 174 [M^+] (100), 173 (56), 158 (12), 117 (10).

Example 2. Similarly to example 1, from 5 g (0.03 mol) of **I**, 16 ml (0.45 mol) of **IIa**, and 5.04 g (0.09 mol) of granulated KOH without DMSO, in the reaction performed for 10 h, we obtained 3.6 g (0.02 mol, 70%) of **IIIa**.

Example 3. Similarly to example 1, from 5 g (0.03 mol) of **I**, 16 ml (0.45 mol) of **IIa**, and 3.6 g (0.09 mol) of granulated NaOH in the presence of 10 ml of DMSO, we obtained 4.5 g (0.026 mol, 90%) of **IIIa**.

Example 4. Similarly to example 1, from 5 g (0.03 mol) of **I**, 16 ml (0.45 mol) of **IIa**, and 3.6 g (0.09 mol) of NaOH without DMSO, we obtained 1.54 g (0.0089 mol, 30%) of **IIIa**.

2-Adamantylidenepropionitrile IIIb. Similarly to example 1, from 3 g (0.02 mol) of **I**, 10 g (0.18 mol) of **IIb**, and 3 g (0.05 mol) of NaOH, we obtained 2.6 g (0.014 mol, 70%) of **IIIb**. ^{1}H NMR spectrum, δ, ppm: 1.54–1.72 m (12H, Ad); 1.83 s (3H, CH_3); 2.90 s (1H, Ad); 3.02 s (1H, Ad). Mass spectrum, *m*/*e* (I_{rel}, %): 187 [M^+] (100), 172 (28), 133 (14).

2-Adamantylidenebutyronitrile IIIc. Similarly to example 1, from 3 g (0.02 mol) of **I**, 10 g (0.15 mol) of **IIc**, and 3 g (0.05 mol) of NaOH, after vacuum distillation

we obtained 2.6 g (0.013 mol, 65%) of **IIIc**. ^{1}H NMR spectrum, δ, ppm: 1.05 t (3H, CH_3); 1.64–1.74 m (12H, Ad); 2.03 q (2H, CH_2); 2.87 s (1H, Ad); 3.03 s (1H, Ad).

2-(2-Aminoethyl)adamantane IVa and 2-(2-aminoethylidene)adamantane Va. A round-bottomed flask equipped with a magnetic stirrer was charged with 4 g (0.105 mol) of lithium aluminum hydride, 30 ml of absolute tetrahydrofuran, and 5 g (0.03 mol) of adamantylideneacetonitrile **IIIa**. The mixture was refluxed with stirring for 8 h. After the reaction completion, 6 ml of water was added, the precipitate was filtered off, tetrahydrofuran was distilled off from the filtrate, and the residue was vacuum-distilled. The mixture of **IVa** and **Va** is a colorless transparent liquid with characteristic amine odor, bp140–150°C (20 mm Hg).

Mass spectrum of 2-(2-aminoethyl)adamantane IVa, *m*/*e* (I_{rel}, %): 179 [M^+] (1), 175 (76), 148 (13), 135 [$C_{10}H_{15}^+$] (100), 80 (29); 2-(2-aminoethylidene) adamantane Va: 177 [M^+] (27), 162 (100), 133 (17).

1-Amino-2-(2-adamantyl)butane IVc and 1-amino-2-adamantylidenebutane Vc. A flat-bottomed flask equipped with a magnetic stirrer was charged with 2 g (0.53 mol) of lithium aluminum hydride, 30 ml of absolute tetrahydrofuran, and 4 g (0.02 mol) of 2-adamantylidenebutyronitrile **IIIc**. The mixture was refluxed with stirring for 8 h. After the reaction completion, 4 ml of water was added, the precipitate was filtered off, tetrahydrofuran was distilled off from the filtrate, and the residue was vacuum-distilled. The mixture of **IVc** and **Vc** is a colorless transparent liquid with characteristic amine odor, bp 150–155°C (20 mm Hg).

Mass spectrum of 1-amino-2-(2-adamantyl)butane IVc, *m*/*e* (I_{rel}, %): 208 [M^+] (100), 191 (9), 161 (8); 1-amino-2-adamantylidenebutane **Vc**: 205 [M^+] (21), 189 (32), 176 (100).

4-Adamantylidene-3-methyl-1-phenylpyrazolidin-5-one VII. Example 1. A flask was charged with 3 g (0.02 mol) of I and 3.3 g (0.02 mol) of 3-methyl-N-phenylpyrazolidin-5-one **VI**. The mixture was refluxed for 4 h at 120–130°C. After recrystallization from *n*-hexane, 5.3 g (0.02 mol, 90%) of **VII** was obtained; yellow crystals, mp 121–123°C.

^{1}H NMR spectrum, δ, ppm: 1.19–2.07 m (14H, Ad); 2.26 s (3H, CH_3); 7.01–7.88 m (5H, Ph).

Mass spectrum, *m*/*e* (I_{rel}, %): 306 [M^+] (90.6), 265 [M – MeCN] (25.8), 229 [M – C_6H_5] (6.6), 77 [C_6H_5] (100).

IR spectrum, ν, cm^{-1}: 1820 (C=O), 3358 (NH).

Example 2. A flask was charged with 3 g (0.02 mol) of I, 3.3 g (0.02 mol) of **VI**, and 0.1 g of toluenesulfonic acid. The mixture was refluxed in toluene with azeotropic distillation of the released water. After the catalyst neutralization, solvent removal by distillation, and recrystallization from hexane, we obtained 3.9 g (0.015 mol, 60%) of **VII**.

2-(Adamantylidenemethyl)quinoline IX. A flask was charged with 2 g (0.013 mol) of I, 3 g (0.02 mol) of 2-methylquinoline **VIII**, and catalytic amount of toluenesulfonic acid. The mixture was heated at 150°C for 7–10 h. The reaction is accompanied by the release of 0.24 g (0.013 mol) of water. After the reaction completion, excess 2-methylquinoline **VIII** was distilled off under reduced pressure. The product was vacuum-distilled, and 1.8 g (0.0065 mol, 50%) of 2-(adamantylidenemethyl) quinoline **IX** was obtained, bp 265°C (20 mm Hg), mp 67–70°C.

^{1}H NMR spectrum, δ, ppm: 0.81–2.37 m (12H, Ad); 2.44 s (1H, CH); 4.09 s (1H, CH); 6.2 s (1H, –CH=); 6.13–7.97 m (6H, C_7H_6N).

2-Adamantylideneacetophenone XI. To 11.3 g (0.075 mol) of I, 9.1 g (0.076 mol) of acetophenone X, 70 ml of toluene, and 0.5 g of toluenesulfonic acid were added. The mixture was refluxed for 7–8 h until the equivalent amount of water was released. Then the mixture was neutralized with a 10% sodium carbonate solution. The aqueous layer was separated, and toluene was distilled off from the organic layer. After fractional distillation of the residue, we obtained 9.05 g of 2-adamantylideneacetophenone **XI**, bp 253–256°C (25 mm Hg), yield 45%. ^{1}H NMR spectrum, δ, ppm: 1.50–2.42 m (14 H, Ad); 6.47 s (1H, CO–CH=); 7.30–7.82 m (5H, C_6H_5). Mass spectrum, *m*/*e* (I_{rel}, %): 252 [M^+] (48), 251 [M – 1] (100), 105 [$C_6H_5C(O)$] (6).

2-Hydroxy-2-aminomethyladamantane XIII. A solution of 5 g (0.033 mol) of adamantanone cyanohydrin **XII** in 30 ml of diethyl ether was added to a suspension of 2 g (0.053 mol) of lithium aluminum hydride in 20 ml of absolute tetrahydrofuran. The mixture was refluxed with stirring for 6 h, after which it was cooled, and the reduced complex was decomposed with water (5 ml) and 3 ml of 20% alkali to coagulate the precipitate. Then the mixture was separated from the inorganic precipitate on a Schott filter, the solvent mixture was distilled off, and the residue was recrystallized from ether–hexane. Yield of **XIII** 2.5 g (0.014 mol, 49%), mp 178–180°C.

^{1}H NMR spectrum, δ, ppm: 1.35–2.12 m (16H, Ad, NH_2); 2.30 d (2H, $–CH_2N$); 3.72 s (1H, –OH).

IR spectrum, ν, cm^{-1}: 3052, 3220 (NH, OH).

The compounds obtained were identified by IR and ^{1}H NMR spectroscopy and by gas chromatography–mass spectrometry (GC–MS). The ^{1}H NMR spectra were recorded with a Varian Mercury 300BB device operating at 300 MHz, with hexamethyldisiloxane as internal reference and CCl_4, $CDCl_3$, and $(CD_3)_2SO$ as solvents.

The GC–MS analysis was performed with a Varian Saturn 2100 T/GC 3900 spectrometer (electron impact, 70 eV).

The IR spectra were recorded with a UR-20 spectrophotometer (NaCl and KBr prisms). Liquid substances were taken as thin films, and crystalline substances, as mulls in mineral oil.

CONCLUSION

Condensation of adamantanone with methylene-active compounds was studied. Convenient procedures were developed for the preparation of potentially bioactive substances with the 2-adamantyl radical and of intermediates for their synthesis. The influence of the reaction conditions on the product yields was determined.

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