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# Synthesis of 1-Acetamido-2-acetyladamantane

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**Abstract**—The triple bond of 2-ethynyl-2-adamantanol virtually did not hydrolyze under Kucherov reaction conditions in aqueous ethanol and methanol. In aqueous acetic acid arose a mixture of 2-acetyl-2-adamantanol and its acetate. In good yield the 2-acetyl-2-adamantanol was obtained by Kucherov reaction in aqueous THF. This alcohol with acetonitrile under conditions of Ritter's reaction (catalysis with sulfuric acid) afforded a mixture of 1-acetamido-2-acetyl-, 1-acetamido-4-*cis*- and 1-acetamido-4-trans-acetyladamantanes in 8 : 1 : 1 ratio.

Adamantane derivatives are the most thoroughly investigated among the cage compounds. The interest of chemists to this compounds series was stimulated by special features of their chemical properties originating from the presence of a highly symmetrical tricyclic fragment in the molecule, and also by the presence of quite a number of biologically active substances among these compounds [1–4]. The transformations of adamantane derivatives under Ritter's reaction conditions were studied fairly extensively [5–9], because the amides resulting from this reaction are precursors of biologically active amines.

We formerly subjected [10] 2-ethynyl-2-adamantanol (**I**) to the conditions of the Ritter's reaction and obtained as products 2-acetamido-2-ethynyladamantane (**II**) and 1-acetamido-2-acetyladamantane (**III**) in ~20:1 ratio. The target of this study was development of a preparative procedure for uneasily accessible 1-acetamido-2-acetyladamantane (**III**).

We investigated the behavior of 2-ethynyl-2-adamantanol (**I**) in Kucherov reaction for the product of this reaction 2-acetyl-2-adamantanol (**IV**) was presumed to be the most convenient initial compound for the preparation of amidoketone **III** by Ritter's reaction.

It turned out that under conditions of Kucherov reaction in aqueous ethanol or methanol, the triple bond of 2-ethynyl-2-adamantanol virtually did not undergo hydrolysis. Even in 10 days, the content of target alcohol **IV** in the reaction mixture attained only few percent. This abnormally low reactivity of compound **I** under the above conditions was apparently caused by solvation effect: the association of the molecules of solvent alcohol with the hydroxy group of tertiary alcohol **I** which also contained a bulky adamantyl substituent resulted in almost complete spatial blocking of the ethynyl group and strongly hampered its hydration.

The attempt to hydrolyze 2-ethynyl-1-adamantanol by Kucherov reaction in aqueous acetic acid gave even more unexpected result: alongside the "normal" hydration product, 2-acetyl-2-adamantanol (**IV**), we obtained its acetate, and the latter prevailed in the reaction mixture (no less than 85%). Since esterification with acetic acid requires usually stringent conditions (boiling in the presence of concn. sulfuric acid as catalyst), this process hardly occurred in our experiment (at room temperature and 30% of water in the mixture). Acetate **V** formed presumably through addition of acetic acid to the triple bond of ethynyladamantanol **I**. The arising intermediate **VI** via cyclic transition state shown on the scheme transforms under the reaction conditions into acetate **V**. It is the predominant reaction product for the acetic acid is stronger nucleophile than water. Therefore in the presence of both nucleophiles the rate of formation of intermediate **VI** is higher, and thus the amount of compound **V** in the products is greater than that of hydration product **IV**.

The mixture of alcohol **IV** and its acetate **V** was separated by column chromatography on silica gel using as eluent ether–ethanol mixture in 10 : 1 ratio. The structure of compounds **IV** and **V** was derived from IR and $^1$H NMR spectra. In the IR spectrum of compound **IV** appear two characteristic absorption bands: a broad band at 3400 cm$^{-1}$ belonging to hydroxy group vibrations, and at 1720 cm$^{-1}$ corresponding to vibrations of ketone carbonyl group. In the $^1$H NMR spectrum alongside the multiplet of adamantane skeleton protons are observed signals from bound hydroxy group at 4.23 ppm, br.s, and a singlet

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from acetyl group methyl at 2.20 ppm with integral intensity corresponding to 3H. In the IR spectrum of 2-acetyl-2-acetoxyadamantane **V** the absorption band of hydroxy group is lacking, and two bands corresponding to vibrations of carbonyl groups at 1745 (ester) and 1720 $cm^{-1}$ (ketone) are present. In the $^1H$ NMR spectrum of this compound appear two singlet signals of integral intensity 3H each at 2.12 and 2.05 ppm belonging to keto and ester acetyl groups respectively.

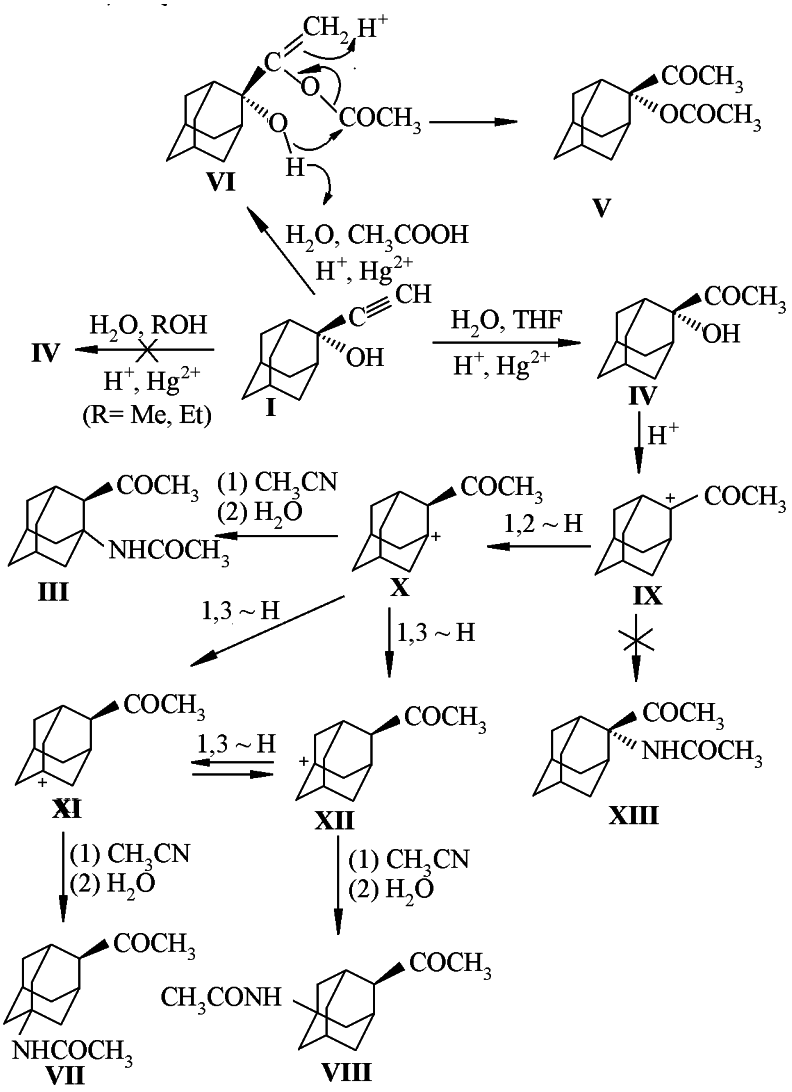
The conversion of 2-ethynyl-2-adamantanol (**I**) into 2-acetyl-2-adamantanol (**IV**) was carried out successfully in aqueous THF. The solvent is far less prone to association than alcohols and therefore does not hamper hydration. The $^1H$ NMR and IR spectra of compound **IV** obtained were identical to those described above. The relatively complete conversion of 2-ethynyl-2-adamantanol was attained within 6–7 days. The attempt to accelerate the reaction by heating to 60°C deteriorated its selectivity: in the chromatogram of the reaction mixture appeared a peak of a side product which grew with the time of heating. In the $^1H$ NMR spectrum of the arising products mixture were present two signals from acetyl groups and an additional unresolved multiplet at 2.44 ppm. Taking into account the analysis of $^1H$ NMR spectra of amides **III, VII, VIII** that will be given below the observed spectral pattern may be ascribed to isomerization of 2-acetyl-2-adamantanol into 2-acetyl-1-adamantanol with intermediate formation of carbocations **IX** and **X**.

It was previously presumed that the minor component resulting from Ritter's reaction of 2-ethynyl-2-adamantanol, namely 2-acetyl-1-acetamidoadamantane (**III**), originated from hydration of the triple bond proceeding slowly in the absence of mercury salts followed by a hydride shift in the initially generated acetyl cation [10]. The fact that in the reaction did not form a product with the geminal position of amide and acetyl groups we ascribed to the bulkyness of the latter preventing the nucleophile addition. In keeping with this scheme it was presumable that 2-acetyl-2-adamantanol **IV** under conditions of Ritter's reaction would yield exclusively amidoketone **III**.

However it turned out that although compound **III** was the main but not a single product. Basing on $^1H$ NMR and IR spectra we ascribed to the minor components of the reaction mixture the structures of 1-acetamido-4-cis- and 1-acetamido-4-trans-acetyladamantanes (**VII**) and (**VIII**).

Compound **III** was separated from the reaction mixture by column chromatography on silica gel. Its structure was confirmed by $^1H$ NMR, IR, and mass spectroscopy. In the spectrum of 1-acetamido-2-acetyladamantane (**III**) appear absorption bands of two carbonyl groups at 1725 (keto) and 1660 $cm^{-1}$ (amide), and also of amide NH group at 3360 and 1560 $cm^{-1}$. In the mass spectrum of the compound is present the peak of molecular ion $M^+$ 235 of integral intensity 17% relative to the peak of maximum intensity. In the $^1H$ NMR spectrum of compound **III** appear two singlets with integral intensity 3H each corresponding to acetyl (2.16 ppm) and acetamide (2.00 ppm) groups, and a broadened singlet of the proton attached to nitrogen at 5.62 ppm. The presence in the spectrum of a downfield signal at 2.32 ppm corresponding to a proton in the α-position with respect to a carbonyl group, and also of the broadened singlet at 2.06 ppm (1H) from the nodal proton $H^3$ neighboring to $COCH_3$ group supports the assumed structure of compound **III**. The positions of the other signals from the protons of adamantane skeleton also are well consistent with the assumed structure (see EXPERIMENTAL).

We failed to separate the minor components **VII** and **VIII** because of their virtually identical chromatographic mobility. The IR spectrum of the mixture of amidoketones **VII** and **VIII** is similar to the spectrum of compound **III**. The structure of 4-acetyl-substituted acetamidoadamantanes was assigned to the minor products proceeding from their $^1H$ NMR spectra. In the spectrum of isomer mixture are no signals with chemical shift ~4 ppm characteristic of protons in the α-position with respect to amido group. This fact indicates the bridgehead position of the acetamido groups in both isomers. On the contrary, the presence in the spectrum of the mixture of two broadened singlets of the same integral intensity at 2.36 and 2.28 ppm corresponding to protons in the α-position with respect to carbonyl groups shows that the acetyl groups of both compounds same as in the principal reaction product are attached to the bridging carbon atom. The acetyl group of the initial alcohol **IV** does not move in the course of reaction, and the various reaction products arise from successive hydride shifts. A 1,2-hydride shift in the initially formed carbocation **IX** affords ion **X** that via addition of an acetonitrile molecule followed by hydration yields the main reaction product, amidoketone **III**. The formation of two other compounds with a bridgehead position of the acetamide group is possible through transformation of cation **X** into ions **XI** and **XII** with sub-




sequent addition of the nucleophile thereto. Yet the problem of the pathways of isomerization of ion **X** into the other two tertiary cations remains unclear. Since due to the structure of the adamantane skeleton the 1,3-hydride shifts therein are hardly probable, might either successive 1,2-hydride shifts occur with no products with acetamide group at the bridging carbon because of too short lifetime of secondary ions compared to that of tertiary ones, or two 1,2-hydride shifts go on synchronously. From different directions of the hydride shifts in conversion of cation **X** into **XI** and **XII** originates formation of compounds with dissimilar spatial orientation of the acetyl group (syn or anti) with respect to the amide substituent. A minimal difference in the structure of compounds **VII** and **VIII** results in similar physico-chemical characteristics hampering their separation.

Same as in reaction of 2-ethynyl-2-adamantanol compound **IV** did not afford any product **XIII** with geminal position of the acetyl and amide groups.

## EXPERIMENTAL

$^1$H NMR spectra were registered on spectrometer Tesla BS-567 (100 MHz) in $CDCl_3$. IR spectra were recorded on spectrophotometer Specord 75IR. Mass spectra were measured on Chrommass GC/MS Hewlett Packard 5890/5972 instrument, column HP-5MS (70 eV). The reaction progress was monitored and the purity of compounds obtained was checked by GLC on chromatograph Chrom-5 equipped with a glass column (2000×2 mm) packed with Chromaton N-AW-DMCS (0.16–0.20), stationary phase Apiezon L.

**Kucherov reaction with 2-ethynyl-2-adamantanol.** To a solution containing 20 ml of organic

solvent, 7 ml of water, 4 ml of 70% $H_2SO_4$, and 9 g (3 mmol) of $HgSO_4$ was added 4.2 g (23 mmlol) of ethynyladamantanol (**I**). The reaction mixture was stirred at room temperature. The reaction progress was monitored by GLC. On completion of the reaction the mixture was diluted with water, neutralized with aqueous ammonia, and reaction products were extracted into ether. The extracts were dried with $CaCl_2$.

(a) The reaction carried out in aqueous acetic acid afforded a mixture of 2-acetyl-2-adamantanol (**IV**) and its acetate **V** in ~85 : 15 ratio, overall yield 76%. The compounds were not separated by distillation for they formed an azeotrope. The compounds were separated as individual substances by column chromatography on silica gel (Chemapol L 40/100), eluent ether–alcohol, 10 : 1. Thus isolated 2-acetyl-2-adamantanol (**IV**) on removing the solvents gradually crystallized, mp 77–78°C. IR spectrum, $cm^{-1}$: 3400 (OH), 2930, 2870 (C–H), 1720 (C=O). $^1H$ NMR spectrum ($CDCl_3$), δ, ppm: 4.23 br.s (1H, OH), 2.20 s (3H, $COCH_3$), 2.10–1.45 m (14H, adamantane skeleton).

**2-Acetyl-2-adamantyl acetate V** on removing the solvents was obtained as thick oily colorless substance, $n_D^{15}$ 1.4812. IR spectrum, $cm^{-1}$: 2920, 2860 (C–H), 1745 (C=O, ester), 1720 (C=O, ketone). $^1H$ NMR spectrum ($CDCl_3$), δ, ppm: 2.12 s (3H, $COCH_3$), 2.05 s (3H, $OCOCH_3$), 2.03–1.60 m (14H, adamantane skeleton).

(b) The reaction carried out in THF furnished an identical 2-acetyl-2-adamantanol in 80% yield. The relatively complete conversion of 2-ethynyl-2-adamantanol occurred within 6–7 days.

**Ritter's reaction with 2-acetyl-2-adamantanol** was carried out along the common procedure [10]. The overall yield of amides **III**, **VII**, and **VIII** was 79%. The main reaction product, 1-acetamido-2-acetyladamantane (**III**), was isolated from the mixture by column chromatography on silica gel (Chemapol L 40/100), eluent ether–alcohol, 10 : 1, column 40 × 3.6 cm. mp 132–133°C. IR spectrum, $cm^{-1}$: 3260 (NH), 2950, 2920, 2875 (C–H), 1725 (C=O ketone), 1660 (C=O amide I), 1560 (NH, amide II). Mass spectrum, *m/z*, ($I_{rel}$, %): 235 (17) $[M]^+$, 220 $[M–CH_3]^+$, 192 $[M–COCH_3]^+$, 177 $[M–COCH_3–CH_3]3^+$, 149 $[M–2COCH_3]^+$, 135 $[M–COCH_3–NCOCH_3]^+$, 122, 107, 93, 91, 77, 65, 43 (100). $^1H$ NMR spectrum ($CDCl_3$), δ, ppm: 5.62 br.s (1H, NH), 2.32 br.s (1H, $CH_3COCH$), 2.16 s (3H, $COCH_3$), 2.06 br.s (1H, 3H), 2.00 s (3H, $NCOCH_3$), 1.94 br.s [4H, $ACNHC(CH_2)_2$], 1.88 br.s (2H), 1.77 br.s (4H), 1.66 br.s (2H).

**The minor products, 1-acetamido-4-cis-acetyladamantane (VII) and 1-acetamido-4-trans-acetyladamantane (VIII)** were isolated as a thick oily 1 : 1 mixture that we were not able to separate by crystallization. Also failed an attempt to separate the isomers by chromatography even using a column of a double length and as eluent the least polar among the available solvents (hexane). IR spectrum of these compounds is similar to that of amidoketone **III**, $cm^{-1}$: 3260 (NH), 2960, 2930, 2880 (C–H), 1720 (C=O ketone), 1660 (C=O amide I), 1560 (NH amide **II**). $^1H$ NMR spectrum ($CDCl_3$), δ, ppm: 5.60 2 superimposed br.s (0.5H each, 2NH), 2.36 and 2.28, 2 br.s (0.5H each, $2CH_3COCH$), 2.14 and 2.12, 2 s (1.5H each, $2COCH_3$), 1.98 and 1.96, 2 s ($2NCOCH_3$, the signals appear superimposed on the multiplet of adamantane skeleton), 2.00–1.56 m (adamantane skeleton).

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