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Organic Chemistry

Synthesis of Derivatives of Acylaminoadamantane Carboxylic Acids and some Transformations

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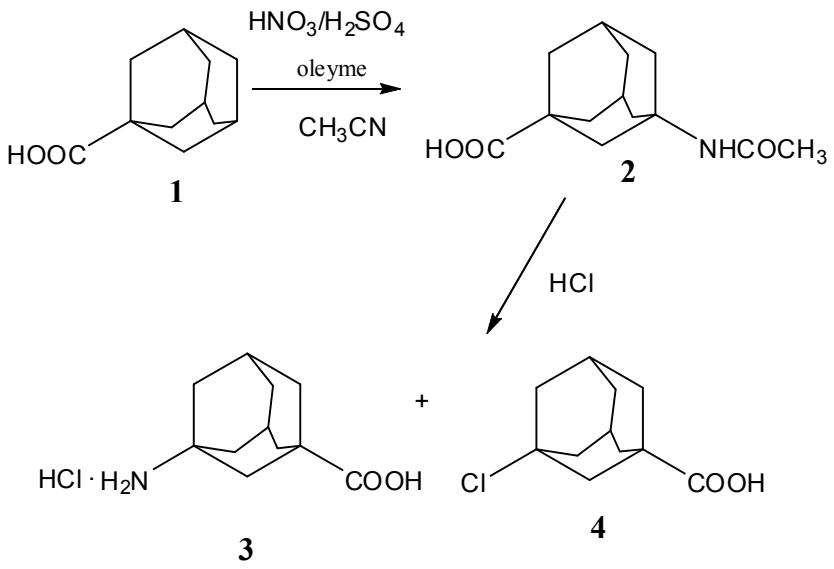
ABSTRACT. Amethodology for synthesis of 3-acetylamino-, 3-acetylaminophenyl- and 3-hydroxyadamantane-1-carboxylic acids. Certain amino acids are synthesized by acid hydrolysis of acyl derivatives. A supposed mechanism of the reaction 3-acetaminoadamantane-1-carboxylic acid is given. Found, that high-purity 3-acetylaminoadamantane-1-carboxylic acid is obtained by interaction of 3-hydroxyadamantane-1-carboxylic acid and acetonitrile in the sulfuric acid medium.Two products are obtained as a result of hydrolysis of 3-acetylaminoadamantane-1-carboxylic acid in aqueous solution of HCL boiling for 5-10 hrs. Those are main product 3-aminoadamantane-1-carboxylic acid hydrochloride and by-product 3-chloradamantane-1-carboxylic acid.Benzoylation of 3-aminoadamantane-1-carboxylic acid hydrochloride is conducted and 3-(N-benzoyl)aminoadamantane-1-carboxylic acid is obtained. Structure of synthesized compounds is confirmed by the data of IR, ^{1}H-NMR, ^{13}C-NMRspectra. *© 2017 Bull. Georg. Natl. Acad. Sci.*

Key words: adamantane, acylaminoacid, hydrolysis, acylation

Adamantane-containing amino acids and their derivatives such as salts of organic and inorganic acids and bases, esters and amides are characterized with antiviral, antimicrobial, antiprotozoin and other activities [1-5]. The goal of the work was conducting of synthesis of 3-acetaminoadamantane-1-carboxylic acid and 3-acetaminophenyladamantane-1-carboxylic acid via Ritter reaction in the electrophilic medium (nitric acid, sulfuric acid, oleum) and determination of the influence of ratio and temperature of the reactants on their yield; also the hydrolysis of the obtained compounds in the hydrochloric acid medium with the aim of the further application for the synthesis of peptides of the obtained compounds and benzimidazoles.

We conducted synthesis of 3-acetylamino-adamantane-1-carboxylic acid via Ritter reaction and its hydrolysis according to Scheme 1.

Adamantane carboxylic acid is cooled with ice and solved in mixture of HNO_3, H_2SO_4 and oleum.



Scheme 1. Synthesis of 3-acetaminoadamantane-1-carboxylic acid via Ritter reaction and its hydrolysis.

After complete solving acetonitrile is added drop by drop at low temperature (5-7°C). The reaction mixture is stirred for 2.5 hr, decomposed by pouring in the ice water. The formed sediment is filtered, washed with water until neutral reaction and dried. Two products are obtained as a result of hydrolysis of 3-acetylaminoadamantane-1-carboxylic acid (2) in aqueous solution of HCL boiling for 5-10 hrs. Those are main product 3-aminoadamantane-1-carboxylic acid hydrochloride (3) and by-product 3-chloradamantane-1-carboxylic acid (4). Pure hydrochloride 3 is obtained after processing of mixture with acetone.

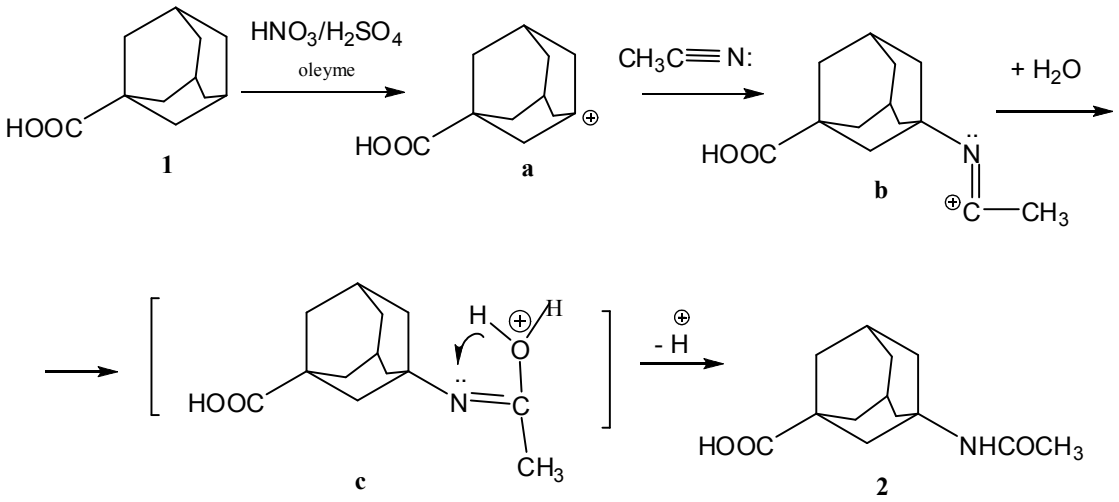
A supposed mechanism of the reaction is given (Scheme 2). Solving adamantane-1-carboxylic acid (1) in the electrophilic medium (mix of sulfuric acid+oleum+nitric acid) carbocation of adamantane-1-carboxylic acid (a) in the third position is formed, which is affected by acetonitrile as nucleophile and supposedly a structure (b) and after water attack a structure (c) are formed. Then as a result of deprotonation of (c) and hydrogen ion migration onto a nitrogen atom 3-acetylaminoadamantane-1-carboxylic acid (2) is obtained.

We found that high-purity 3-acetylaminoadamantane-1-carboxylic acid (2) is obtained by interaction of 3-hydroxyadamantane-1-carboxylic acid (5) and acetonitrile in the sulfuric acid medium.

Benzoylation of 3-aminoadamantane-1-carboxylic acid hydrochloride (3) is conducted and 3-(N-benzoyl)aminoadamantane-1-carboxylic acid (6) is obtained.

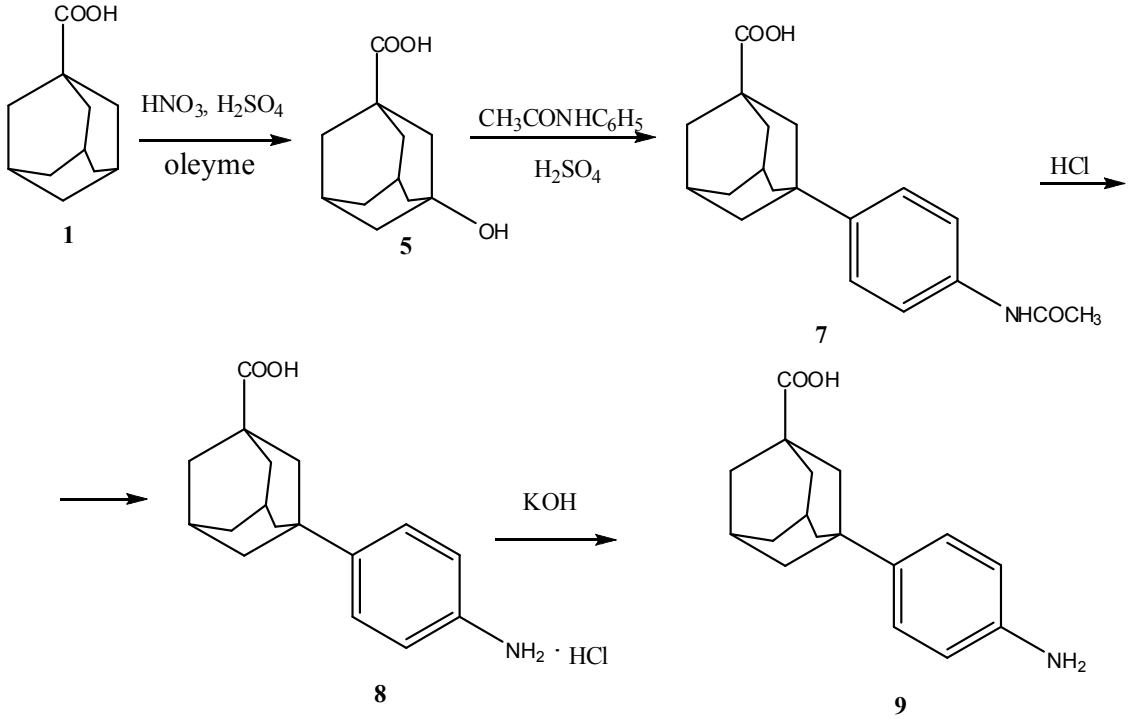
Synthesis of 3-(*p*-aminophenyl)adamantane-1-carboxylic acid is fulfilled in 6 stages: 1) reacting on adamantane by bromine, 1-bromo-adamantane is obtained; 2) interaction of 1-bromo-adamantane and benzene at the presence of catalyst $FeCl_3$ gives 1-phenyladamantane; 3) by nitration of the latter compound (mixture of nitric acid and sulfuric acid is used) 4-nitrophenyladamantane is obtained; 4) further bromination gives 1-bromo-4-nitro phenyl-adamantane; 5) reacting on 1-bromo-4-nitrophenyl-adamantane with formic acid in sulfuric acid medium one obtaines 4-nitrophenyladamantane-1-carboxylic acid; 6) reduction of the latter with molecular hydrogen using catalyst Raney nickel we obtain 3-aminophenyladamantane-1-carboxylic acid.

We developed a simplified scheme to obtain the mentioned product. The scheme excludes using bromine and increases the yield of end product (Scheme 3). Adamantane-1-carboxylic acid is processed with a mix of sulfuric acid, nitric acid and oleum at 5-10°C for 2.5 hours, decomposed by pouring on the ice,



A supposed mechanism of the reaction

Scheme 3



Scheme 2. Synthesis of 3-(*p*-acetaminophenyl) adamantane-1-carboxylic acid and its hydrolysis.

boiled for 2 hrs; The sediment is filtered and 3-hydroxyadamantane-1-carboxylic acid (5) is obtained. As a result of the influence of acetanilide on the compound 5 in the sulfuric medium 3-(*p*-acetaminophenyl) adamantane-1-carboxylic acid (7) is obtained. Hydrolyzing compound (7) in hydrochloric acid medium 3-(*p*-aminophenyl)-adamantane-1-carboxylic acid hydrochloride (8) is isolated. After processing potassium or sodium alkali 3-*(p*-aminophenyl) adamantane-1-carboxylic acid (9) is obtained.

Experimental part

IR spectra were registered on a Thermo Nikolet Avatar 370 (USA) spectrometer in petroleum jelly or hexachlorobutadiene. ^1H and ^{13}C NMR spectra were acquired on a Bruker AM-400 (400 and 100 MHz, respectively) spectrometer in DMSO-d_6, $CDCl_3$ with TMS as internal standard. Melting points were determined on a Boetius heating bench with a PHMKO5 visual device. Monitoring of the reaction progress and assessment of the purity of synthesized compounds were done by TLC on Silicagel on TLC PET-foils, visualization in an iodine chamber.

Synthesis of 3-acetaminoadamantane-1-carboxylic acid (2):

Method A. 20 g (0.11 mol) of adamantane-1-carboxylic acid is added in small portions to the mixture of 35 ml 54% HNO_3, 60 ml 98% H_2SO_4 and 80 ml 20%-oleum, which is intensively stirred and cooled to (2–5)°C. The reaction mixture is stirred at (10-15) °C for 2.5 hrs and then 80 ml acetonitrile is added. After stirring for 2.5 hrs the reaction mixture is poured in ice water. The isolated sediment is filtered, washed with water until neutral reaction and dried. 20.66g(78.7%) of technical product is got. $T_{melt.}$ – 242-246 °C.

Method B. Suspension of10g(5.1 mmol) of 3-hydroxyadamantane-1-carboxylic acid (5) and 30 ml of acetonitrile is heated up to 50 ^{0}C and added little by little to 10 ml of concentrated H_2SO_4 during 30 min. The reaction mixture is stirred at 50-60 ^{0}C for 5 hrs, cooled and a viscous mass is poured on the ice permanently stirring. The formed sediment is filtered, washed with water until a neutral reaction and dried. 10.5g (82.7%) of white crystals are got. $T_{melt.}$=252-254°C (ethanol)(Lit.257-258°C [5]). IR spectrum, ν, cm^{-1}: 3371 (NH); 2908, 2854 (C-H, Ad,CH_3); 1689 (C=O). ^1HNMR (DMSO, 400 MHz), δ, ppm: 12.09 (1H, s, OH); 7.40(1H,s,NH); 2.08 (3H, s, Ad), 1.98-1.69 (11H, m, Ad), 1.55 (3H, s, CH_3). ^{13}C NMR ($CDCl_3$, 100 MHz): 177.62, 168.61, 42.06, 41.35, 37.59, 34.95, 28.43, 23.63.

Hydrochloride of 3-aminoadamantane-1-carboxylic acid (3). 40ml water and 50 ml concentrated hydrochloric acid are added to 5g (2.1 mmol) 3-acetaminoadamantane-1-carboxylic acid (T_{melt}=242-246 ^{0}C). The mixture is boiled during 6 hrs. After the reaction is finished the reaction mixture is evaporated up to obtaining dry residue, processed with acetone, as a result of which 4.3 g (88%) of product is obtained (decomposed). $T_{melt.}$ >300 °C. IR spectrum, ν, cm^{-1}: 3371, 3139.7, 3098.98 (NH); 2923, 2861.99 (C-H, Ad); 1697 (C=O). ^1H NMR (DMSO, 400 MHz), δ, ppm: 12.31 (1H, s, OH); 8.08(NH_3+); 2.08 (3H, s, Ad), 1.86-1.52 (11H, m, Ad). ^{13}C NMR (DMSO, 100 MHz): 193.73, 176.81, 41.26, 37.58,36.86, 33.98, 28.42, 27.99.

Synthesis of 3-hydroxyadamantane-1-carboxylic acid (5). Mixture of 35 ml HNO_3 (54%), 60 ml H_2SO_4 (98-100%) and 80 ml oleum (20%) is added in small portions to 20g (0.11 mol) of adamantine-1-carboxylic acid intensively stirring and cooling to (2–5)°C. The reaction mixture is stirred in the range of 10-15 °C for 2.5 hrs. Then it is decomposed pouring in ice water and obtained suspension is boiled for 1 hour, kept for night. The obtained sediment is filtered, washed with water until a neutral reaction and dried. 18g (82.5%) of white needle-shaped crystals are got. $T_{melt.}$ = 202-204°C (according literature data 203-205 °C [6,7]).IR spectrum, ν, cm^{-1}: 3440 (OH); 3200-2500(OH, COOH); 2946, 2908, 2862, 2808 (C-H, Ad); 1712 (CO).

3-(N-benzoyl)aminoadamantane-1-carboxylic acid (6). 10 ml of water, 1g of $NaHCO_3$ and 2.5 ml of benzoylchloride is added to 1g (4.3 mmol) of 3-aminoadamantane-1-carboxylic acid hydrochloride. The mixture is intensively stirred for 1 hrs at the room temperature, then for 30 min at 30-35 °C. The reaction mixture is filtered, the filtrate is oxidized by 2%-HCL up to pH-3. The formed sediment is filtered, washed with water and crystallized from CCl_4. 0.9 g (69.8%) white crystals are obtained. $T_{melt.}$=178-180 °C. IR spectrum, ν, cm^{-1}: 3340, 3131(OH,NH); 3062 (C-H arom.), 2916, 2862 (C-HAd), 1705, 1635(C=O). ^1HNMR ($CDCl_3$, 400 MHz), δ, ppm: 10.54(1H, s, OH); 7.72-7.70(2H, m, C-H arom); 7.50-7.39(3H, m, C-H arom.), 5.85(1H, s, NH), 2.29-2.28(4H, m,C-HAd); 2.17-2.13(4H, m,C-

HAd); 2.09-1.92(4H, m,C-HAd); 1.76-1.66(2H, m,C-HAd). ^{13}C NMR (DMSO, 100 MHz): 181.31, 166.82, 135.66, 131.66, 131.22, 128.51, 126.70, 42.36, 42.27, 40.56, 37.67, 35.18, 29.03.

3-(p-acetaminophenyl)adamantane-1-carboxylic acid (7). 60 ml of concentrated sulfuric acid is placed in the three-neck flask with a mechanical mixer, thermometer and air refrigerator; 16g of acetanilide and then 10g (51mmol)of 3-hydroxyadamantane-1-carboxylic acid are added in small portions. The reaction mixture is mixed in the range of 50-60 °C for about 6 hrs. The reaction mixture is poured on ice; the formed sediment is filtered. As a result 12.2g (76.4%) white powder of technical product is obtained. $T_{melt.}$=231-234 °C. IR spectrum, ν, cm^{-1}: 3324,84 (NH); 3124, 3030 (C-H arom); 2915.99, 2854.27 (C-H, Ad, CH_3); 1689.42, 1643.13 (C=O). ^{1}H NMR (DMSO, 400 MHz), δ, ppm: 12.08 (1H, s, OH); 9.85 (NH); 7.48 (2H, d, J=8.8, C-H arom); 7.26 (2H, d, J=8.8 C-H arom.), 2.14-1.67 (12H, C-HAd); 2.01 (3H, CH_3). ^{13}C NMR (DMSO, 100 MHz): 178.13, 167.93, 144.57, 136.89, 124.76, 118.77, 41.55, 40.60, 37.63, 37,58, 35.58, 35.54, 35.02, 28,42, 28.09, 23.82, 23,63.

3-(p-aminophenyl)adamantane-1-carboxylic acid (9). 400 ml concentrated hydrochloric acid and 400 ml distilled water were added to 17.5g (56 mmol) 3-(p-acetaminophenyl)adamantane-1-carboxylic acid (7), boiled during 10 hrs, dehydrated and dry residue is washed with acetone. Obtained hydrochloride is neutralized with soda water up to pH 6.8-7.0. The formed sediment is filtered. 11.5 g (75.9%)White powder is got. $T_{melt.}$=190-191.5°C. IR spectrum, ν, cm^{-1}: 3400, 3378, 3309(NH_2); 3048(C-H Arom); 2723, 2969, 2592(COOH); 2916, 2885, 2854(C-H, Ad); 1720(C=O).

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დამუშავებულია 3-აცეტილამინო-, 3-აცეტილამინოფენილ- და 3-ჰიდროქსიადამანტან-1-კარბონმჟავების სინთეზის მეთოდიკა. აცილნაწარმების მჟავა ჰიდროლიზით სინთეზირებულია შესაბამისი ამინომჟავები. მოწოდებულია 3-აცეტამინოადამანტან-1-კარბონმჟავას სინთეზის რეაქციის სავარაუდო მექანიზმი. დადგენილ იქნა, რომ მაღალი სისუფთავის 3-აცეტილამინოადამანტან-1-კარბონმჟავა მიიღება 3-ჰიდროქსიადამანტან-1-კარბონმჟავას ურთიერთქმედებით აცეტონიტრილთან გოგირდმჟავას არეში. 3-აცეტილამინოადამანტან-1-კარბონმჟავას ჰიდროლიზით მარილმჟავას წყალხსნარში დუღილის პირობებში (5-10სთ) წარმოიქმნება ორი პროდუქტი: ძირითადი 3-ამინოადამანტან-1-კარბონჟავას ჰიდროქლორიდი და მეორე თანაური პროდუქტი 3-ქლორადამანტან-1-კარბონმჟავა. ჩატარებულია 3-ამინოადამანტან-1-კარბონმჟავას ბენზოილირება ბენზოილქლორიდით და მიღებულია 3-(N-ბენზოილ)ამინოადამანტან-1-კარბონმჟავა. სინთეზირებული ნაერთების სტრუქტურა დადასტურებულია იწ, ბმრ-^{1}H, ბმრ-^{13}C სპექტრების მონაცემებით.

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