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SHORT COMMUNICATIONS

Synthesis of 3-R-1-Acetyladamantanes by Substitution in 3-Chloro- and 3-Hydroxy-1-acetyladamantanes

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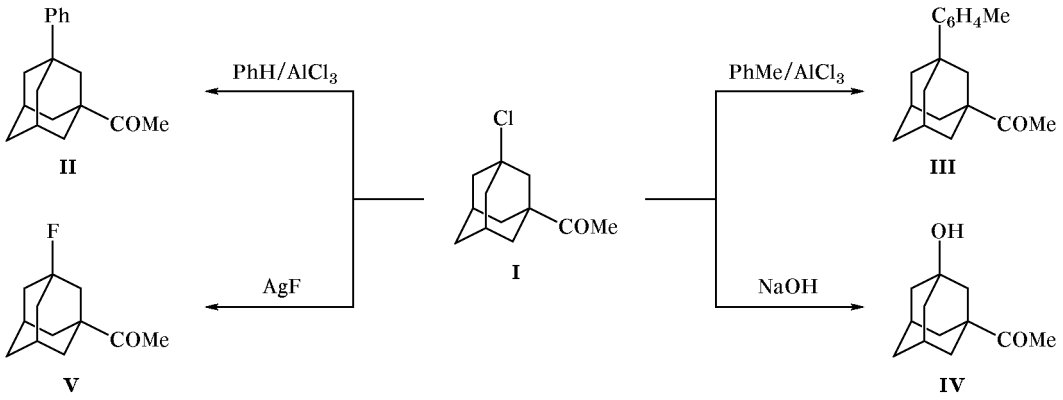
3-Substituted 1-acetyladamantanes possess three reaction centers, and they can be used as starting compounds in the synthesis of a large number of potential biologically active substances. In continuation of our studies on the synthesis of 3-substituted 1-acetyladamantanes [1, 2], we examined replacement of the chlorine and hydroxy group in 3-chloro- and 3-hydroxy-1-acetyladamantanes, respectively. Friedel–Crafts adamantylation of benzene with 1-acetyl-3-chloroadamantane (**I**) gave 1-acetyl-3-phenyladamantane (**II**). In the reaction of **I** with toluene, a mixture of 3-(*p*-tolyl)- and 3-(*o*-tolyl)-1-acetyladamantanes (**III**) at a ratio of 2 : 1 was obtained. By heating compound **I** in boiling aqueous NaOH we synthesized 1-acetyl-3-hydroxyadamantane (**IV**), and the reaction of **I** with AgF in cyclohexane gave 1-acetyl-3-fluoroadamantane (**V**) (Scheme 1).

We were the first to develop procedures for the preparation of keto acids of the adamantane series, starting from 1-acetyl-3-hydroxyadamantane (**IV**). The Koch–Haaf carboxylation of hydroxy ketone **IV** gave 3-acetyl-1-adamantanecarboxylic acid (**VI**). By reacting ketone **IV** with 1,1-dichloroethylene in sulfuric acid we obtained 70% of ketone **I** and 30% of 3-acetyl-1-adamantaneacetic acid (**VII**). The reaction of **IV** with 1,1,2-trichloroethylene afforded 3-acetyl-α-chloro-1-adamantaneacetic acid (**VIII**) (Scheme 2).

General procedure for the synthesis of ketones II and III by the Friedel–Crafts reaction. A solution of 2 g (9.4 mmol) of ketone **I** in 20 ml of dry benzene (or toluene) was added dropwise over a period of 30 min to a mixture of 1.51 g (11.3 mmol) of powdered $AlCl_3$ and 20 ml of dry benzene (or toluene) under stirring at 0–5°C. The mixture was stirred for 1 h at 5°C, warmed to 25°C, and left to stand for 12 h. It was then stirred for 2 h at 50–55°C, cooled, and poured onto 200 g of crushed ice. The organic phase was separated, washed with water until neutral reaction, and dried, and the solvent was distilled off. The residue was distilled in a vacuum.

Scheme 1.



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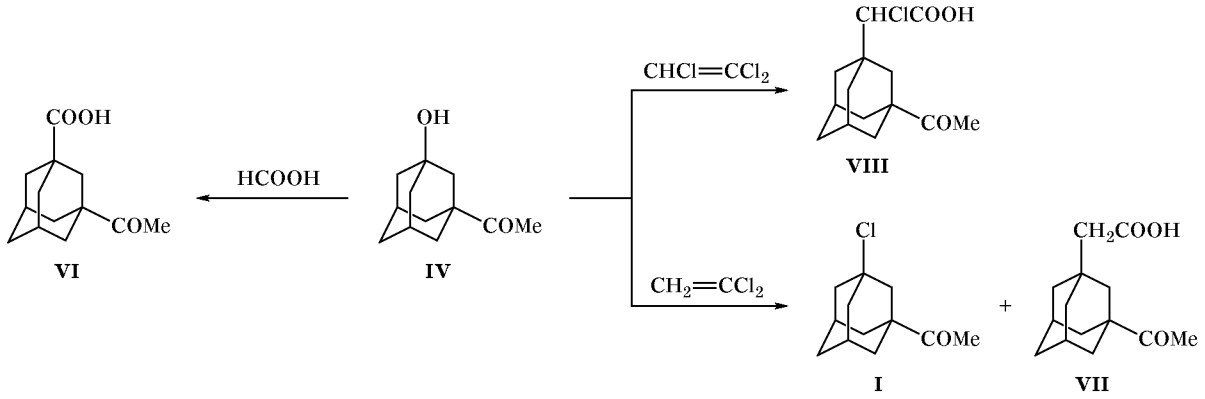
Scheme 2.



1-Acetyl-3-phenyladamantane (II). Yield 71%, bp 112–113°C (2 mm), n_D^{20} = 1.5615. The IR and ^{1}H NMR spectra of the product were identical to those of a sample described in [2].

3-(*p*-Tolyl)- and 3-(*o*-tolyl)-1-acetyladamantanes (III) (isomer mixture). Yield 68%, bp 118–120°C (2 mm), n_D^{20} = 1.5565. IR spectrum, ν, cm^{-1}: 2900 (C–H); 1720 (C=O); 1620, 1530, 1240, 840, 800 (arom.); ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.65–1.80 m (12H, CH_2, Ad), 2.15 s (2H, CH, Ad), 2.08 s (3H, $COCH_3$), 2.25 s (3H, *p*-CH_3), 2.30 s (3H, *o*-CH_3), 6.98–7.22 m (4H, C_6H_4).

Hydrolysis of ketone I in an aqueous solution of sodium hydroxide. A mixture of 5 g (23.5 mmol) of ketone **I** and 500 ml of a 0.1 N solution of NaOH was heated at the boiling point until it became homogeneous. The solution was cooled and extracted with chloroform, the extract was washed with water, and the solvent was distilled off. The residue was recrystallized from hexane. Yield of ketone **IV** 4.2 g (92%), mp 89–91°C; published data [1]: mp 87–89°C.

1-Acetyl-3-fluoroadamantane (V). A mixture of 2 g (9.4 mmol) of ketone **I** and 2.4 g (18.8 mmol) of powdered silver fluoride in 50 ml of cyclohexane was heated for 75 h under reflux. The mixture was cooled, the precipitate of silver salt was filtered off, and the filtrate was evaporated. The residue was recrystallized from hexane at low temperature. Yield 1.5 g (81%), mp 60–61°C; published data [3]: mp 60.5–61.5°C. Mass spectrum: *m*/*z* 196 $[M]^+$.

3-Acetyl-1-adamantanecarboxylic acid (VI). To a solution of 2 g (0.01 mol) of ketone **IV** in 40 ml of 95% sulfuric acid at 20°C we added dropwise over a period of 2 h 20 ml of 99% (or 84%) formic acid. The mixture was stirred for 1 h and poured onto ice. The precipitate was filtered off, washed with water, reprecipitated from an aqueous alkali solution, and recrystallized from hexane. Yield 1.85 g (80.5%; in the reaction with 99% formic acid) or 1.55 g (68%; in the reaction with 84% formic acid). mp 124–125°C. IR spectrum, ν, cm^{-1}: 2940, 2860 (Ad); 2660 (OH); 1710 (CO). ^{1}H NMR spectrum, δ, ppm: 1.65–1.75 m (12H, CH_2, Ad), 2.10 s (5H: 2H, CH, Ad; 3H, CH_3), 12.05 s (1H, COOH). Mass spectrum: *m*/*z* 222 $[M]^+$.

3-Acetyl-1-adamantaneacetic acid (VII). To a solution of 1 g (5 mmol) of ketone **IV** in 40 ml of 95% sulfuric acid at 0°C we added dropwise over a period of 1 h 10 ml of freshly distilled 1,1-dichloroethylene. The mixture was stirred for 2 h at 10°C and poured onto ice. The precipitate was filtered off, washed with water, and dried. We thus isolated 0.7 g of ketone **I**, mp 53–55°C. The acid filtrate was extracted with chloroform to isolate 0.35 g of keto acid **VII**, which was recrystallized from hexane. Yield 0.3 g (25%), mp 99–101°C. IR spectrum, ν, cm^{-1}: 2920, 2860 (Ad); 2670 (OH); 1710, 1640 (C=O, acid and ketone). ^{1}H NMR spectrum, δ, ppm: 1.55–1.75 m (12H, CH_2, Ad), 2.15 s (3H, CH_3), 2.19 s (2H, CH, Ad), 2.22 s (2H, CH_2), 11.9 s (1H, COOH). Mass spectrum: *m*/*z* 236 $[M]^+$.

3-Acetyl-α-chloro-1-adamantaneacetic acid (VIII). A mixture of 1 g (5 mmol) of ketone **IV**, 5 ml of 1,1,2-trichloroethylene, and 15 ml of 90% sulfuric acid was stirred for 6 h at 90°C. The mixture was cooled and poured onto ice. The crystals were filtered off, washed with water, reprecipitated, dried, and recrystallized from cyclohexane. Yield 0.7 g (50.4%), mp 113.5–115°C. IR spectrum, ν, cm^{-1}: 2920, 2860 (Ad); 2670 (OH); 1750, 1680 (C=O, acid and ketone). ^{1}H NMR spectrum, δ, ppm: 1.55–1.95 m (12H, CH_2, Ad), 2.22 s (2H, CH, Ad), 2.15 s (3H,

CH_3), 4.05 s (1H, CH), 10.05 s (1H, COOH). Mass spectrum: *m*/*z* 270 $[M]^+$.

The IR spectra were recorded on IKS-22 and Specord M-80 spectrometers. The ^1H NMR spectra were measured on a Bruker AM-300 instrument at 300 MHz using DMSO-d_6 and $CDCl_3$ as solvents and HMDS as internal reference. The mass spectra were obtained on Finnigan MAT Incos 50 and Varian MAT CH-6 spectrometers (electron impact, 70 eV).

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