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Synthetic Approaches to Physiologically Active Polycyclic Compounds: III.* Ritter Reaction with Ketones of the Adamantane and Oxahomoadamantane Series

N. V. Averina, G. S. Borisova, O. N. Zefirova, E. V. Selyunina, N. V. Zyk, and N. S. Zefirov

Faculty of Chemistry, Lomonosov Moscow State University, Leninskie gory, Moscow, 119992 Russia

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Abstract—Some previously unknown acetamino derivatives were synthesized by the Ritter reaction from ketones of the adamantane and oxahomoadamantane series. The presence of a hydroxy group as substituent in adamantan-2-one gives rise to formation of acetamino derivatives as products of replacement of the hydroxy group and transformation of the carbonyl group.

Computer simulation showed that some adamantane and bicyclo[3.3.1]nonane derivatives could bind to protein molecules which are targets for taxane antitumor agents. We have initiated studies on the development of synthetic methods for modification of functional groups in the above cage-like compounds with the goal of introducing thereto fragments of taxane derivatives, which are responsible for binding to proteins [1–4].

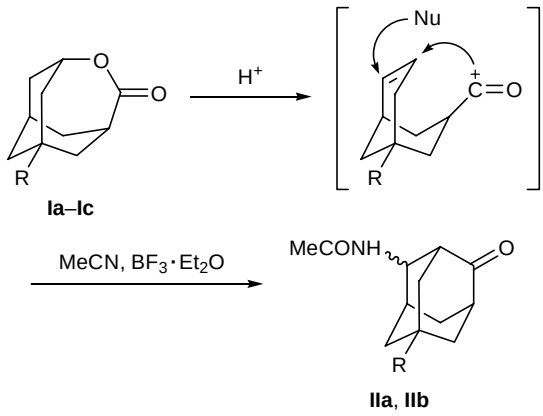
We previously [4] examined the possibility for synthesizing model compounds having substituents in positions *3*, *5*, and *7* of the bicyclo[3.3.1]nonane skeleton, one of which is 5-acetamino group. We proposed specific conditions for the Ritter reaction with 1-hydroxy-4-oxahomoadamantan-5-one (**Ia**) (heating with acetonitrile in trifluoroacetic acid in the presence of boron trifluoride–ether complex), which resulted in formation of compound **Ic** via replacement of the hydroxy group at the bridgehead position of the oxahomoadamantane system by acetamino group [4, 5]. Although oxahomoadamantanone (**Ib**) and its derivatives usually undergo cleavage–cyclization reactions (Scheme 1) leading to 2,4-disubstituted adamantanes [6, 7], we detected no compound **IIa** in the Ritter reaction with lactone **Ia** [4].

Insofar as the yield of 1-acetamino-5-oxahomoadamantan-4-one (**Ic**) was fairly low, the present study was aimed at synthesizing acetamino derivatives of adamantanone by the Ritter reaction. We examined the Ritter reaction with lactone **Ib**, adamantan-2-one, and 5-hydroxyadamantan-2-one (**III**).

The reaction of lactone **Ib** with acetonitrile in the system trifluoroacetic acid–$BF_3 \cdot Et_2O$ gave compound **IIb** as the only product (Scheme 1). In the mass spectrum of **IIb** we observed the molecular ion peak with *m*/*z* 207, and its elemental composition and the IR and ^1H and ^{13}C NMR spectra were consistent with the assumed structure. Gas chromatographic–mass spectrometric analysis of the reaction mixture showed the presence of a small amount (<5%) of an isomer differing by orientation of the acetamino group on C^4.

The reaction mixture obtained by the Ritter reaction with 5-hydroxyadamantan-2-one (**III**) in trifluoroacetic

Scheme 1.

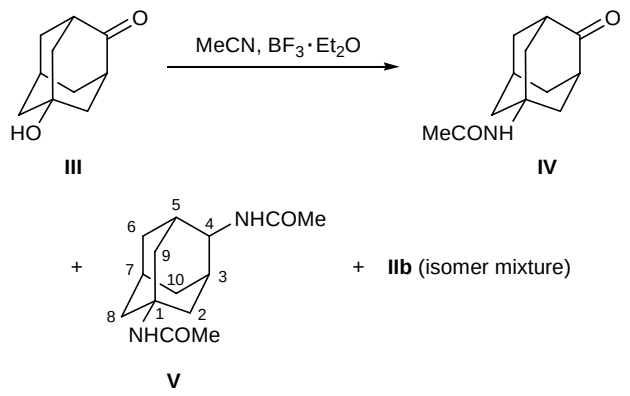


R = OH (**a**), H (**b**), NHCOMe (**c**).

* For communications I and II, see [1, 2].

acid in the presence of boron trifluoride–ether complex (Scheme 2) contained three products with R_f 0.52, 0.41, and 0.1 (TLC on Alufol plates with chloroform as eluent). These products were separated by column chromatography on aluminum oxide using the same eluent. The fraction with R_f 0.52 was additionally purified by column chromatography on Al_2O_3 using CH_2Cl_2–acetone (4:1) as eluent. In the IR spectrum of the product with R_f 0.41 we observed absorption bands assignable to amide (1645 cm^{-1}), free C=O (1725 cm^{-1}), and NH groups (3290 cm^{-1}). The mass spectrum contained the molecular ion peak with *m*/*z* 207. These data allowed us to identify the product with R_f 0.41 as *N*-(4-oxoadamantan-1-yl)acetamide (**IV**). Its structure was also confirmed by the ^1H NMR spectrum and elemental analysis.

Scheme 2.

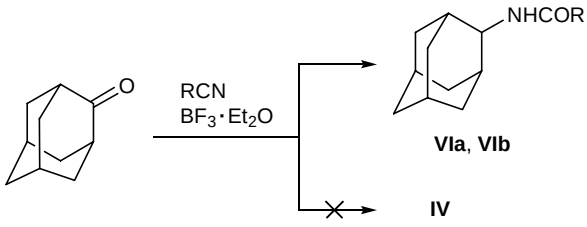


According to the analytical data, the product with R_f 0.52 (yield 10%) had the formula $C_{12}H_{17}NO_2$, but its melting point (119–120°C) and mass spectrum considerably differed from those found for compound **IV**. GC–MS analysis and NMR data showed that this product is most likely to be a mixture of stereo- and structural isomers of compound **IIb** with a molecular weight of 207.

The IR spectrum of the product with R_f 0.1 contained a broad absorption band from amide carbonyl (1650 cm^{-1}) and NH group (3300 cm^{-1}), while no ketone carbonyl absorption was observed. In the ^1H NMR spectrum of this compound, broadened singlets at δ 5.68 and 5.29 ppm were present. These signals were assigned to protons of two NH groups. Therefore, we presumed that the product has structure **V** having two acetamino groups. The signal at δ 4.05 ppm corresponds to the NCH proton in position *4*, and two narrow singlets at δ 1.93 and 2.01 ppm (which are partially obscured by multiplet signals from the adamantane ring protons) belong to two acetyl groups. In the ^{13}C NMR spectrum we observed signals from two carbon atoms attached to nitrogen. Using the APT pulse sequence, we found that the signals at δ_C 52.69 and 53.28 ppm (intensity ratio 4:1) belong to C^4 of two isomers and that the signal at δ_C 50.40 ppm arises from the C^1 carbon atom linked to nitrogen. These data, in combination with the proton signal intensities in the ^1H NMR spectrum, indicate that bis(acetamino) derivative **V** was obtained as a mixture of two stereoisomers. The mass spectrum of **V** contained the molecular ion peak, *m*/*z* 250, and fragment ion peaks with the following *m*/*z* values: 235 ($M^+ - CH_3$), 207 ($M^+ - CH_3CO$), 191 ($M^+ - NHCOCH_3$), 176 (191 – CH_3), 148 (191 – CH_3CO), 132 (191 – CH_3CONH_2). The fragmentation pattern is consistent with the presence in molecule **V** of two acetamino groups, one of which is attached to a tertiary carbon atom, and the other, to CH.

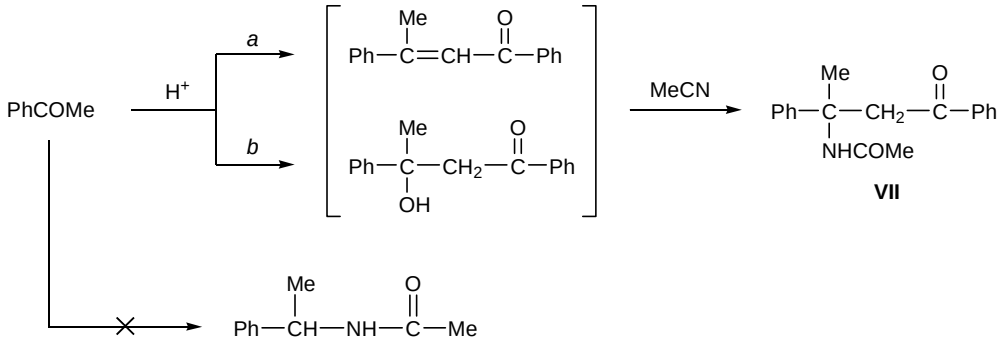
The observed transformation of carbonyl group into acetamino was surprising, for there are no published data on such reactions. Taking into account that no analogous acetamino derivatives were formed from 5-hydroxyadamantan-2-one and adamantan-2-one under standard conditions of the Ritter reaction [4], we examined the reaction of unsubstituted adamantanone with acetonitrile in trifluoroacetic acid in the presence of boron trifluoride–ether complex, which was expected to afford compound **IV**. However, the IR spectrum of the product contained a broad absorption band only from amide carbonyl group (1645 cm^{-1}) and NH group (3300 cm^{-1}). In the ^1H NMR spectrum, apart from the NH proton signal and those belonging to the adamantane ring, a multiplet at δ 4.05 ppm was present, which was identical to the NCH signal in the spectrum of **V**. The ^{13}C NMR spectrum, where only the amide carbonyl carbon signal was observed, completely coincided with the spectrum of compound **VIa** [8]. The above data indicate that the Ritter reaction with adamantan-2-one gives compound **VIa**, in which

Scheme 3.



R = Me (**a**), Ph (**b**).

Scheme 4.



the acetamino group occupies position *2* of the adamantane skeleton (Scheme 3).

The transformation of carbonyl group into acetamino in the system trifluoroacetic acid–$BF_3 \cdot Et_2O$ was also observed in the reaction of adamantan-2-one with benzonitrile. The major product was compound **VIb**, and benzamide was also formed as by-product. Presumably, the reaction involves intermediate formation of trifluoroacetoxy derivatives which are capable of readily eliminating trifluoroacetyl group thus favoring generation of adamantyl cation with the positive charge centered at position *2* [9–11].

It should be emphasized that the formation of acylamino derivatives **V**, **VIa**, and **VIb** is not the result of somewhat unusual Ritter reaction conditions. For example, acetophenone reacts with acetonitrile under standard conditions (with H_2SO_4 as catalyst) to afford *N*-(1-methyl-4-oxo-2,4-diphenylbutyl)acetamide (**VII**) (the reaction follows pathway *a* or *b* [12] in Scheme 4). The same product was obtained by us from acetophenone and acetonitrile in trifluoroacetic acid in the presence of boron trifluoride–ether complex. Although the melting point of our product **VII** slightly differed from that reported in [12], its elemental composition and spectral parameters were consistent with the assumed structure.

Our results showed that acetamino-substituted adamantanones can be prepared by the Ritter reaction in trifluoroacetic acid, catalyzed by boron trifluoride–ether complex, from both unsubstituted oxahomoadamantanone and adamantanone having a hydroxy group in the bridgehead position. However, in the latter case, replacement of the hydroxy group by acetylamino is accompanied by reductive substitution at the ketone carbonyl. Analogous products, 2-aminoadamantanes, can readily be obtained under similar conditions from unsubstituted adamantan-2-one. Acetamino derivatives **II** and **IV** can be used in the synthesis of trisubstituted bicyclo[3.3.1]nonanes which are potential antitumor agents.

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-400 instrument (400 MHz for ^1H) using tetramethylsilane as internal reference. The IR spectra were recorded on a UR-20 spectrometer from samples dispersed in mineral oil. The progress of reactions was monitored by thin-layer chromatography on Silufol UV-254 and Alufol plates. Silicagel L 40/100 μm and Al_2O_3 (Brockman activity grade II) were used for column chromatography.

***N*-(4-Oxoadamantan-2-yl)acetamide (IIb).** Oxahomoadamantanone **Ib**, 0.7 g (3.7 mmol), was dissolved in 5 ml of acetonitrile, 2 ml of boron trifluoride–ether complex in 5 ml of trifluoroacetic acid was added, and the mixture was stirred for 3 h on heating (after 1 h, the mixture turned dark red). The mixture was evaporated by half, treated with a saturated solution of $NaHCO_3$, and extracted with chloroform, and the extract was dried over Na_2SO_4. The extract contained intial lactone (R_f 0.7) and a product with R_f 0.38 (Silufol, benzene–ethyl acetate, 2 : 1). The products were separated by column chromatography on silica gel to isolate 0.13 g of initial lactone **Ib** and 0.44 g of compound **IIb** as colorless crystals. Yield of **IIb** 60%, mp 165–170°C. IR spectrum, ν, cm^{-1}: 3310 (NH), 1725 (C=O), 1645 (C=O, amide). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 5.92 br.s (1H, NH), 4.48 m (1H, NCH), 2.56 d (1H, 3-H), 1.8–2.25 m (14H, adamantane), 1.90 s (CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 217.7, 169.8 (C=O); 58.5 (CN); 52.3 (2C); 47.0, 39.5, 39.3, 36.0, 34.0 (adamantane); 24.3 (CH_3). Mass spectrum: 207 $[M]^+$, 179, 164, 148, 137. Found, %: C 69.97; H 8.69; N 6.61. $C_{12}H_{17}NO_2$. Calculated, %: C 69.54; H 8.27; N 6.76.

Ritter reaction with 5-hydroxyadamantan-2-one (III). Compound **III**, 0.6 g (3.6 mmol), was dissolved in 1.2 ml of acetonitrile, and 1.2 ml of boron trifluoride–ether complex was added. Trifluoroacetic acid, 2 ml, was then added dropwise under stirring, and the mixture was heated for 3 h and was left overnight at room temperature. The mixture was evaporated to dryness, the dark oily residue was treated with a saturated solution of $NaHCO_3$, the products were extracted into chloroform, and the extract was dried over Na_2SO_4, filtered through a layer of silica gel, and evaporated on a rotary evaporator. The residue was subjected to column chromatography on Al_2O_3 using chloroform as eluent to isolate 0.24 g of compound **IV** (R_f 0.41), 0.12 g of **V** (colorless crystals, R_f 0.1), and a product with R_f 0.52 (see above).

Compound IV. Yield 32%, mp 135–142°C. ^{1}H NMR spectrum (CCl_4), δ, ppm: 6.0 s (1H, NH), 3.85 s (1H, adamantane), 1.8–2.7 m (15H, adamantane), 1.93 s (CH_3). Mass spectrum: *m*/*z* 207 $[M]^+$. Found, %: C 69.25; H 8.36; N 6.42. $C_{12}H_{17}NO_2$. Calculated, %: C 69.54; H 8.27; N 6.76.

Compound V. Yield 13%, mp 216–218°C (decomp.). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.9 br.s and 5.68 br.s (1H, NH at C^4), 5.29 br.s (1H, NH at C^1), 3.05 m (1H, NCH), 1.6–2.2 m (19H, adamantane), 2.01 s and 1.93 s (CH_3). ^{13}C NMR spectrum (APT, DMSO-d_6), δ_C, ppm: 169.76 and 169.66 (C=O), 53.28 and 52.69 (1:4, C^4), 50.40 (C^1), 41.25 (CH_2), 40.79 ($2CH_2$), 32.59 (2CH), 30.25 ($2CH_2$), 28.9 (CH), 23.95 (CH_3), 22.95 (CH_3). Mass spectrum, *m*/*z*: 250 $[M]^+$, 235, 207, 191, 176, 148, 132. Found, %: C 66.91; H 9.27; N 10.92. $C_{14}H_{22}N_2O_2$. Calculated, %: C 67.17; H 8.85; N 11.18.

The product with R_f 0.52 was subjected to additional chromatographic purification on Al_2O_3 using CH_2Cl_2–acetone (4:1) as eluent. Yield 0.04 g (10%). Found, %: C 69.37; H 8.43; N 6.85. $C_{12}H_{17}NO_2$. Calculated, %: C 69.54; H 8.27; N 6.76.

***N*-(2-Adamantyl)acetamide (VIa).** The procedure for the Ritter reaction was the same as described above for compound **III**. An analytical sample of **VIa** was obtained by vacuum sublimation at 170–180°C (10 mm). Yield 78%, mp 190°C (in a sealed capillary). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 5.93 s (1H, NH), 4.05 m (1H, NCH), 1.99 s (3H, CH_3), 1.6–1.95 m (14H, adamantane). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 168.6 (C=O), 53.2 (CN), 37.6 (C^6), 37.2 (C^8 and C^{10}), 32.0 (C^1, C^3, C^4, C^9), 27.5 (C^5, C^7), 23.5 (CH_3). Mass spectrum, *m*/*z*: 193 $[M]^+$, 178, 150, 134. Found, %: C 74.67; H 10.05; N 7.35. $C_{12}H_{19}NO$. Calculated, %: C 74.57; H 9.91; N 7.24.

***N*-(2-Adamantyl)benzamide (VIb).** A mixture of 1 g (6.7 mmol) of adamantan-2-one, 2 ml of benzonitrile, 2 ml of boron trifluoride–ether complex, and 3.2 ml of trifluoroacetic acid was stirred for 3 h on heating. Excess $BF_3 \cdot Et_2O$ and CF_3COOH was distilled off under reduced pressure, a saturated solution of sodium hydrogen carbonate and methylene chloride were added to the residue, and the mixture was extracted with methylene chloride. The combined extracts were dried over $MgSO_4$ and filtered through a layer of silica gel to remove tarry impurities. The resulting dark solution contained two compounds with R_f 0.95 and 0.5 (silica gel, CH_2Cl_2–ethyl acetate, 1:1). The products were separated by column chromatography on silica gel using chloroform as eluent to isolate benzamide (which was identified by the melting point, ^{1}H NMR spectrum, and elemental analysis) and compound **VIb** (R_f 0.27, chloroform). Compound **VIb** was additionally purified by recrystallization from toluene. Yield 1 g (59%), colorless crystals, mp 167–168°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.45–7.90 m (5H, Ph), 6.50 br.s (1H, NH), 4.27 m (1H, NCH), 2.08 br.s (2H, adamantane), 1.95–1.7 m (12H, adamantane) 1.92 s (CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 167.0 (C=O); 135.5, 131.5, 128.9, 127.1 (C_{arom}); 54.5 (CN); 37.9, 37.75, 31.15, 31.0 (adamantane); 27.6 (CH_3). Mass spectrum, *m*/*z*: 255 $[M]^+$, 254, 238, 212, 198, 150, 134. Found, %: C 80.16; H 8.57; N 5.51. $C_{17}H_{21}NO$. Calculated, %: C 79.96; H 8.29; N 5.48.

***N*-(1-Methyl-4-oxo-2,4-diphenylbutyl)acetamide (VII).** The procedure for the Ritter reaction was the same as decribed above for compound **III**. Yield 56%, mp 105–106°C; published data [12]: mp 93–94°C. IR spectrum, ν, cm^{-1}: 3300 (NH), 1700 (C=O), 1660 (C=O, amide). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 7.85–7.25 m (10H, H_{arom}), 6.99 br.s (1H, NH), 3.81 d (1H, *J* = 17 Hz) and 3.50 d (1H, *J* = 17 Hz) (diastereotopic CH_2 protons), 1.95 s (3H, CH_3), 1.85 s (3H, CH_3). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 199.0 (C=O); 169.0 (C=O, amide); 136.0, 133.4, 128.4, 128.0, 126.5, 124.6 (C_{arom}); 57.0 (CN); 47.5 (CH_2); 24.8 (CH_3); 25.5 (CH_3). Found, %: C 76.84; H 6.92; N 5.34. $C_{18}H_{19}NO_2$. Calculated, %: C 76.86; H 6.81; N 4.97.

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