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Synthetic Approaches to Physiologically Active Polycyclic Compounds: V.* Ritter Reaction of 4-Hydroxyadamantan-2-one

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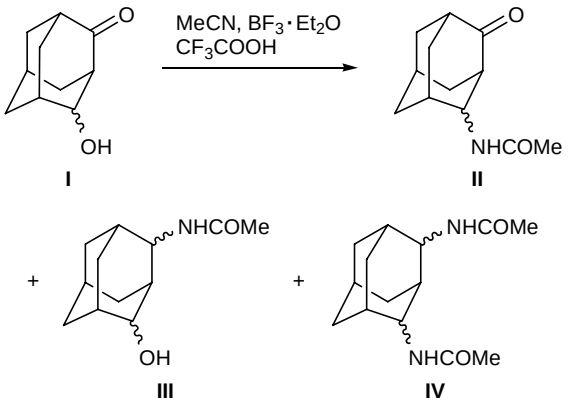
Abstract—The Ritter reaction of 4-hydroxyadamantan-2-one (with acetonitrile in the presence of boron trifluoride–ether complex and trifluoroacetic acid) takes an unusual path and yields diastereoisomeric 9-methyl-1-(4-oxo-2-adamantyloxy)-8-oxa-10-azatetracyclo[5.3.1^{12,6}.1^{4,11}]tridec-9-enes as the major products. Their structure was established by X-ray analysis.

While working in the field of the synthesis of potential ligands for tubulin [1–4], we examined the possibility for preparation of acetamino derivatives of adamantanone and oxahomoadamantanone via the Ritter reaction with acetonitrile in the presence of boron trifluoride–ether complex and trifluoroacetic acid [3, 4]. The goal of the present work was to study analogous reaction of 4-hydroxyadamantan-2-one (**I**).

Initial hydroxy ketone **I** was synthesized by reaction of oxahomoadamantanone with sulfuric acid [5] and was isolated as a mixture of two isomers (*endo* and *exo*) at a ratio of 4:1. These isomers behave differently in reactions accompanied by rearrangements or cleavage of the adamantane skeleton [6–8]. The Ritter reaction of ketone **I** with acetonitrile in the presence of boron trifluoride–ether complex and trifluoroacetic acid afforded a multicomponent mixture of products. Separation of this mixture by column chromatography on aluminum oxide (gradient elution with methylene chloride–ethyl acetate mixtures) gave five fractions: R_f 0.75 (A), 0.35 (B) (Alufol, CH_2Cl_2); R_f 0.56 (C), 0.29 (D), 0.15 (E) (Alufol, CH_2Cl_2–EtOAc, 10:1). In keeping with our previous data [3], we expected formation of compounds **II**–**IV** (Scheme 1). In fact, according to the GC–MS, NMR, and IR data, fractions D and E contained acetamino derivatives **II** and **III** (M^+ 207 and 209, respectively), as well as initial ketone **I** (M^+ 166) and its acetoxy derivative (M^+ 208). Each compound was a mixture of two isomers (2:1), and their yield was 20% of the overall amount of the products. No bis(acetamino) derivative **IV** was detected.

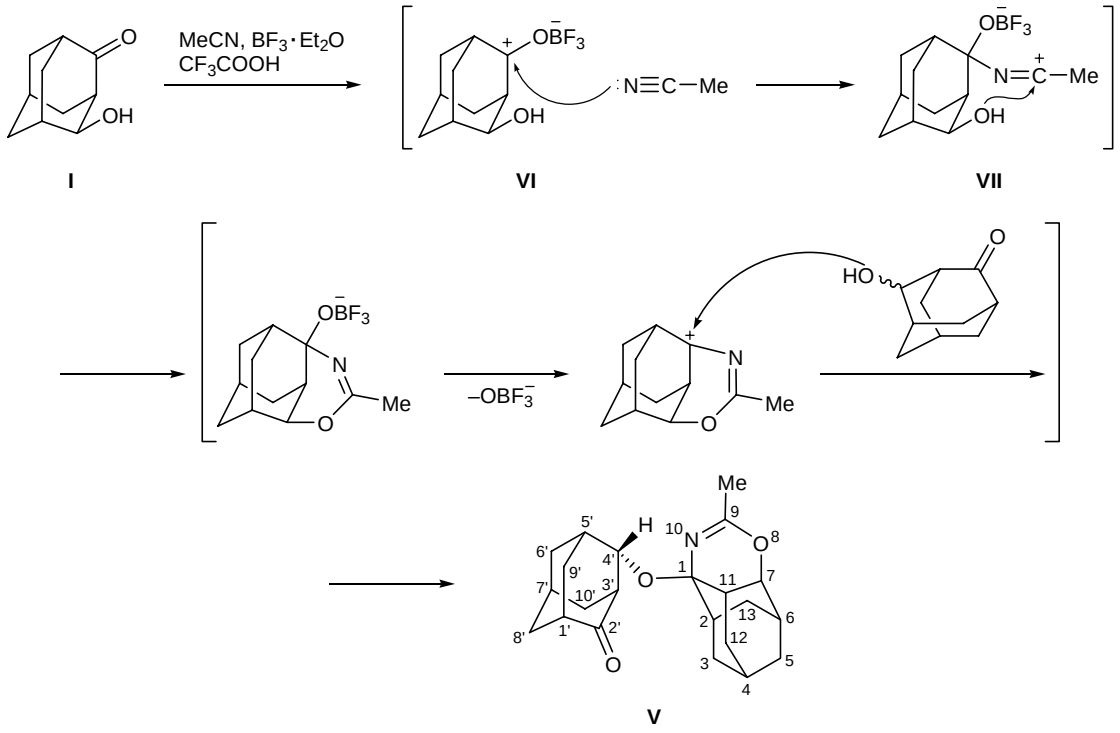
Scheme 1.



Fractions A–C contained compounds with a molecular weight of M^+ 355; their elemental compositions corresponded to the general formula $C_{22}H_{29}NO_3$. According to the GC–MS data, fraction A was a mixture of isomers at a ratio of 2:1, fraction B contained less than 5% of the second isomer, and fraction C was an individual compound. The IR spectra of all compounds with M^+ 355 were identical: they showed in the spectra carbonyl absorption at 1730 cm^{-1} and a band at

* For communications I–IV, see [1–4].

Scheme 2.



1625 cm^{-1}, which was assigned to C=N stretching vibrations. No OH or NH absorption was present.

The ^1H NMR spectrum of the product in fraction C lacked NH signal but contained two signals with equal intensities (1H each) at δ 4.48 (q) and 4.33 ppm (t); these signals may be attributed to OCH protons. In addition, two broadened singlets were observed at δ 2.72 (1H) and 2.50 ppm (2H), and a narrow singlet at δ 1.97 ppm (3H, CH_3) was located in the region corresponding to resonance of protons of the adamantane skeleton (δ 1.46–2.22 ppm, 21H). In the ^{13}C NMR spectrum of this compound we observed signals from carbonyl carbon atom (δ_C 216 ppm) and two ether carbon atoms (δ_C 79.2 and 76.45 ppm).

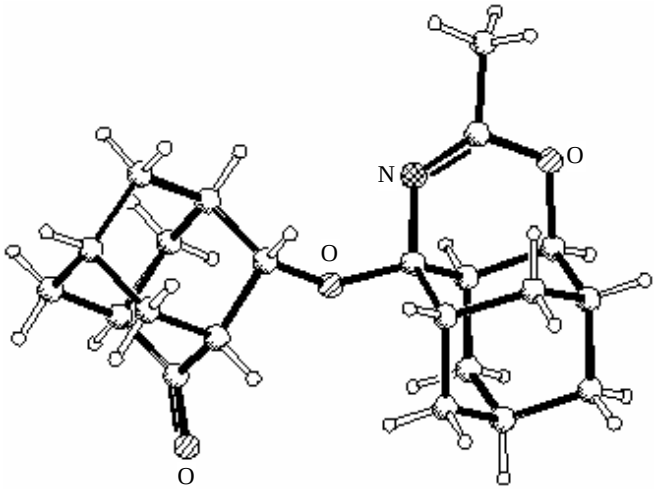


Fig. 1. Structure of the molecule of 9-methyl-1-(4-oxo-2-adamantyloxy)-8-oxa-10-azatetracyclo[5.3.1.1^{2,6}.1^{4,11}]tridec-9-ene (**V**).

The above data indicated that the reaction gave isomeric compounds possessing two adamantane fragments. Their structure was established by X-ray analysis. For this purpose, fractions B and C were subjected to additional chromatographic purification on aluminum oxide using chloroform–ethyl acetate (5:1) as eluent, and crystals suitable for X-ray analysis were grown from the purified fractions. The results showed that the product isolated from fraction C has the structure of 9-methyl-1-(4-oxo-2-adamantyloxy)-8-oxa-10-azatetracyclo[5.3.1.1^{2,6}.1^{4,11}]tridec-9-ene (**V**) (Fig. 1).

A probable mechanism of this unusual Ritter reaction is shown in Scheme 2. Addition of BF_3 at the carbonyl group of 4-hyroxyadamantan-2-one (**I**) yields carbocationic intermediate **VI** which takes up acetonitrile molecule to afford intermediate **VII** possessing an –N=C$^+$–CH_3 fragment. Intramolecular nucleophilic attack by the *exo*-4-hydroxy group in **VII** leads to closure of 1,3-oxazine ring (intermediate **VIII**). The oxazine structure of **VIII** should favor formation of a carbocationic center (intermediate **IX**) via elimina-

tion of the $^{-}OBF_3$ group. The reaction is completed by nucleophilic attack by the second molecule of **I** on intermediate **IX**.

As follows from Scheme 2, the N=C(CH_3)O bridge at the adamantane skeleton can be formed only from the *exo*-4-OH isomer. The resulting six-membered ring $C^{11}C^7O^8C^9N^{10}C^1$ in molecule **V** in crystal adopts a slightly distorted *envelope* conformation with a flap including the C^{11} atom; this follows from the puckering coordinates calculated according to Zefirov–Palyulin [9]: $S = 0.770$, $\theta = 38.0°$, $\psi_2 = 3.4°$, $\sigma = 1.57$.

Compound **V** can be formed as several stereoisomers due to asymmetry intrinsic to the oxazine ring and asymmetric structure of hydroxy ketone **I**, which arises from mutual arrangement of the carbonyl and hydroxy groups. In molecule **V** shown in Scheme 2, the initial hydroxy ketone fragment is characterized by *exo* orientation of the hydroxy group with respect to carbonyl (as indicated above, such configuration is necessary for formation of oxazine ring). Permutation of the carbonyl group from position *2′* to *9′* (provided that the atom numbering remains unchanged) does not alter the *exo* orientation of the hydroxy group but leads to a different diastereoisomeric structure. Permutation of the carbonyl group to position *6′* or *10′* implies that the *endo* isomer of **I** would react in the final step, giving rise to two more diastereoisomers. In order to distinguish possible diastereoisomers of **V**, it is sufficient to define configurations of three chiral centers, e.g.: *1*, *4′*, and *5′*. Successive carbonyl permutation from position *2′* to *6′*, *9′*, and *10′* is equivalent to transformation of stereoisomer **A** (1*S*,4′*S*, 5′*R*) (Fig. 1) into **B** (1*S*,4′*R*,5′*R*), **C** (1*S*,4′*R*,5′*S*), and **D** (1*S*,4′*S*,5′*S*), respectively. For each stereoisomer **A–D**, variation of the configuration at C^1 (migration of the C^7–O^8 bond in molecule **V** to form the C^{13}–O^8 bond) leads to appearance of four new structures: **E** (1*R*,4′*S*,5′*R*), **F** (1*R*,4′*R*,5′*R*), **G** (1*R*,4′*R*,5′*S*), and **H** (1*R*,4′*S*,5′*S*), which are enantiomeric to the above stereoisomers (i.e., the following enantiomer pairs are obtained: **A**/**G**, **B**/**H**, **C**/**E,** and **D**/**F)**. Thus compound **V** may be formed as a mixture of eight stereoisomers, i.e., four pairs of D,L-diastereoisomers.

According to the X-ray diffraction data, crystals of **V** isolated from fraction B included all the above stereoisomers. The asymmetric part of a unit cell contain one "mixed" molecule of **V** (Fig. 2) in which the oxygen atoms of both carbonyl group and N=C–O bridge are disordered, respectively, by three or two positions. The presence of such a "mixed" molecule is explained by the fact that the asymmetric part of a unit cell is statistically (with different probabilities) occupied by four possible diastereoisomers of **V**. The fraction of each diastereoisomer was calculated from the populations found for the positions of disordered oxygen atoms (Fig. 2):

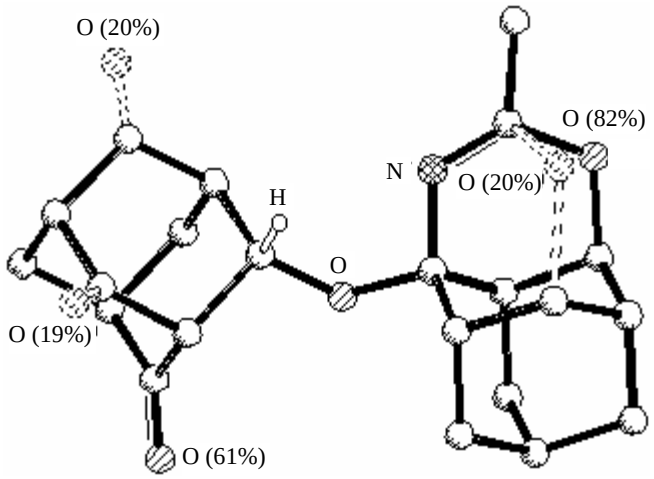


Fig. 2. Structure of "mixed" molecule **V** in crystal; positions of most hydrogen atoms and low-populated positions of disordered carbon atoms are not shown; populations of the positions of disordered oxygen atoms are given in parentheses.

A/**G** = 0.61×0.82 + 0×0.18 = 50%;
B/**H** = 0.20×0.82 + 0.19×0.18 = 20%;
C/**E** = 0×0.82 + 0.61×0.18 = 11%;
D/**F** = 0.19×0.82 + 0.20×0.18 = 19%.

Each of the above pair includes equal fractions of the D- and L-enantiomers since the crystals are centrosymmetrical.

Thus our results showed that the Ritter reaction of 4-hydroxyadamantan-2-one (**I**) with acetonitrile in the presence of boron trifluoride–ether complex and trifluoroacetic acid yields acetamino derivatives **II** and **III** only as minor products while the main reaction path leads to formation of an unusual compound containing two adamantane fragments and fused 1,3-oxazine ring. According to the X-ray diffraction data, the major stereoisomers of **V** are (1*S*,4′*S*,5′*R*) and (1*R*,4′*R*,5′*S*).

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-400 spectrometer (400 MHz for ^1H) using tetramethylsilane as internal reference. The IR spectra were obtained on a UR-20 instrument from

samples dispersed in mineral oil. Gas chromatographic–mass spectrometric analysis was performed on a Finnigan SSQ-7000 instrument. The progress of reactions was monitored by thin-layer chromatography on Silufol UV-254 and Alufol plates. The products were separated by column chromatography on Silicagel L (40–100 μm) or aluminum oxide (Brockmann activity grade II).

Ritter reaction of 4-hydroxyadamantan-2-one (I). Hydroxy ketone **I**, 0.6 g (3.36 mmol), was dissolved in 3 ml of acetonitrile, 1.25 ml of boron trifluoride–ether complex was added, 2 ml of trifluoroacetic acid was then added dropwise under stirring, and the mixture was heated for 4 h, left overnight at room temperature, and evaporated to dryness. The dark oily residue was treated with a saturated solution of sodium hydrogen carbonate, the products were extracted into chloroform, and the extract was dried over sodium sulfate, filtered through a layer of silica gel, and evaporated on a rotary evaporator. The residue, 0.55 g, was a mixture of substances (for R_f values, see above). Chromatographic separation gave 0.08 g of isomers of **V** from fraction A (Found, %: C 74.33; H 8.48; N 3.49. $C_{22}H_{29}NO_3$. Calculated, %: C 74.33; H 8.22; N 3.94); 0.158 g from B (Found, %: C 74.27; H 9.09; N 3.52.); and 0.054 g from C [mp 128–130°C (in a sealed capillary); found, %: C 74.37; H 8.65; N 3.87].

X-Ray analysis. Colorless transparent crystals of **V** were grown by slow evaporation of the eluates obtained by additional chromatographic purification of fractions B and C. The unit cell parameters and reflection intensities (three-dimensional sets) were measured on a Kuma Diffraction KM-4 automatic diffractometer (MoK_α radiation, graphite monochromator). Crystals of **V** from fraction C: triclinic system: a = 6.767(3), b = 13.397(5), c = 20.851(6) Å; α = 83.05(3), β = 89.76(3), γ = 79.31(3)°; V = 1843(1) Å^3; Z = 4; d_{calc} = 1.281 g/cm^3; μ(MoK_α) = 0.84 cm^{-1}; space group $P\bar{1}$. Crystals from fraction B: monoclinic system: a = 13.740(5), b = 11.330(4), c = 12.310(5) Å; β = 107.56(4)°; V = 1827(1) Å^3; Z = 4; d_{calc} = 1.292 g/cm^3; μ(MoK_α) = 0.85 cm^{-1}; space group $P2_1/c$. The structures were solved by the direct method using SHELXS-97 program [10] and were refined with respect to F^2 by the full-matrix least-squares procedure using SHELXL-97 program [10] in anisotropic approximation for thermal vibrations of non-hydrogen atoms (except for disordered positions with very small populations, which were refined in isotropic approximation). In the final full-matrix refinement steps, the absolute shifts of all 384 (fraction B) and 613 varied parameters (fraction C) were less than 0.001σ. The final divergence factors were: fraction B: R_1 = 0.030 and ωR_2 = 0.078 from 1600 reflections with $I \geq 2\sigma(I)$; R_1 = 0.117 and ωR_2 = 0.142 from 3263 independent reflections; S = 0.92 [10]; fraction C: R_1 = 0.034 and ωR_2 = 0.083 from 2900 reflections with $I \geq 2\sigma(I)$; R_1 = 0.147 and ωR_2 = 0.121 from 6462 independent reflections; S = 0.88. The bond lengths and bond angles in molecules **V** in crystals from fractions B and C had almost standard values although most molecules are disordered.

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