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Novel 2,4-Methanoadamantane-Benzazepine by Domino Photochemistry of *N*-(1-adamantyl)phthalimide

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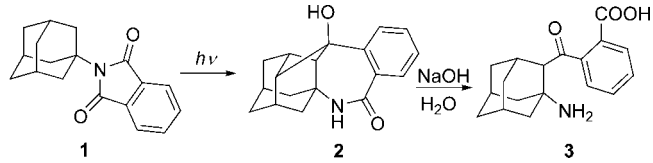
ABSTRACT



The photochemical reaction of *N*-(1-adamantyl)phthalimide (1) gives cleanly one product, the novel hexacyclic benzazepine derivative of 2,4-methanoadamantane 2. Its structure was characterized by spectroscopic methods and X-ray analysis and represent the first example of the 2-azahexacyclo[8.7.1.1^{1,4}.0^{4,9}.0^{11,16}.0^{12,18}]nonadeca-4,6,8-triene skeleton. The product is formed by a domino process of two consecutive excited-state intramolecular γ-hydrogen-transfer reactions. Base hydrolysis of the benzazepine 2 gives in high yield the keto derivative of the 1,2-substituted adamantane ε-amino acid 3.

The benzazepine skeleton is found in numerous biologically active compounds.[1] Synthetic methods for its preparation include the formation of the C−N bond by nucleophilic displacement of halogen by amines,[2] cyclization of the ε-amino hexanoic acid and its derivatives,[3] or Beckmann rearrangement of cyclohexanone oximes.[4] The other synthetic strategies to benzazepine derivatives are conducted via isomerization of azides,[5] ring expansion of arenes by electron-deficient nitrenes,[6] [2 + 2]-cycloaddition to aza five-membered heterocycles followed by ring enlargement,[7] ring expansion of quinolines,[8] or the formation of a C−C bond in a Bischler−Napieralski cyclization of *N*-acyl-γ-phenylpropylamines.[9]

In the context of the research in the Majerski group on the synthesis and chemistry of adamantane[10] and strained adamantane derivatives,[11] we became interested in adamantane phthalimides and the possibility of their photochemical transformation to biologically active compounds such as benzazepindiones. One of the pathways toward benzazepines is the photochemical homolytic H-activation[12] or electron transfer initiated decarboxylative cyclization of phthalim-

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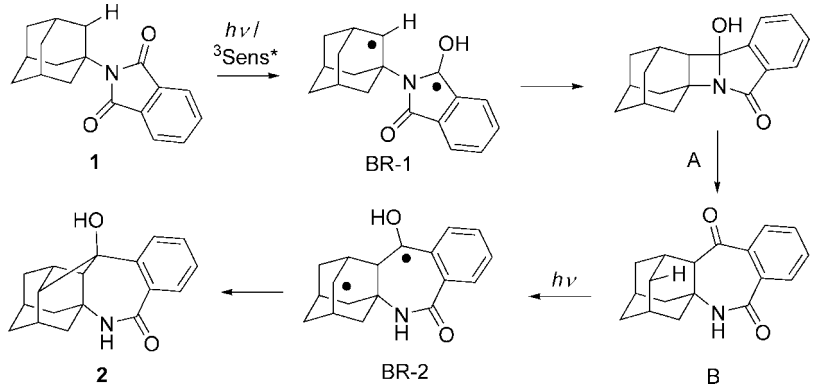
Scheme 1. Mechanism of the Photochemical Transformation of *N*-(1-Adamantyl)phthalimide (**1**)



ides,[13] which has been the subject of intensive research interest.[14] In this letter we report a highly selective photochemical CH activation of *N*-(1-adamantyl)phthalimide (**1**) giving a novel hexacyclic benzazepine and its hydrolysis to a derivative of the 1,2-substituted adamantane ε-amino acid. Preparation of cage amino acids is of high interest since it is known that several peptidomimetics with cage amino acids show anticancer activities.[15]

The adamantane phthalimide **1**[16] was synthesized from 1-aminoadamantane and phthalic anhydride using the procedure of Kidd and Sheehan.[17] Photolysis of **1** was performed in a Rayonet reactor at $\lambda = 300$ nm under N_2 in different solvents: CH_3CN, CH_3CN/H_2O (3:1), and acetone and acetone/H_2O (3:1). In all investigated solvents only one product was formed. For example, 24 h photolysis in acetone gave **2** in 82% yield. The pure product crystallized from the solution upon evaporation of the solvent after photolysis and no further purification was required. To our surprise, the isolated product was not the anticipated benzazepindione (B, Scheme 1), but a novel 2-aza-10-hydroxyhexacyclo-[8.7.1.1^{1,4}.0^{4,9}.0^{11,16}.0^{12,18}]nonadeca-4,6,8-triene-3-one (**2**), hitherto not reported. In addition, **2** is a derivative of 2,4-methanoadamantane (MAd), a strained compound involving a cyclobutane ring and a boat cyclohexane ring in a rigid tetracyclic system. There are only a few reports on the synthesis of this cage system. MAd can be prepared in two steps from ethanoadamantan-3-one[18] involving diazotization[19] and photolysis.[20] The other pathway to MAd involves formation of a [3.1.1]propellane[21] and its subsequent reduction with Li or by free radical reaction.[22]

The MAd derivative **2** was characterized by spectroscopic methods. In the IR spectrum of **2**, the characteristic bands corresponding to the amide NH and the alcohol OH vibrations were observed at 3336 and 3238 cm^{-1}, as well as the amide C═O valence at 1634 cm^{-1}. In the ^{1}H NMR spectrum of **2** (in $CDCl_3$) in the aliphatic region two singlets showed up at δ 6.16 and 2.04 ppm that were assigned to the protons of NH and OH groups, respectively, which disappeared on addition of D_2O. In the ^{13}C NMR spectrum (in DMSO-d_6) in the aliphatic region, four triplets, five doublets, and one singlet were observed which correspond to the hexacyclic structure. Furthermore, 2D homonuclear COSY and heteronuclear HSQC spectra were also in accordance with the assigned structure. The structure of product **2** was addition-

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ally proven by X-ray structural analysis (Figure 1).[23] To the best of our knowledge, this is the first example of the

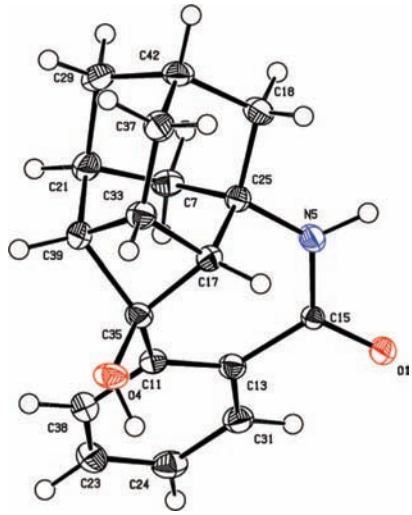

Figure 1. ORTEP drawing of **2**.[23]

2-azahexacyclo[8.7.1.1^{1,4}.0^{4,9}.0^{11,16}.0^{12,18}]nonadeca-4,6,8-triene skeleton.

Photochemical transformation of **1** into **2** does not take place in nonpolar solvents such as cyclohexane and occurs very inefficiently in CH_3CN ($\Phi \sim 10^{-4}$).[24] The reaction is 10 times more efficient in acetone, suggesting that it occurs via the triplet excited state. Interestingly, the addition of a protic solvent (H_2O) to CH_3CN or acetone increases the quantum yield of the product formation by a factor of 2−3. Low quantum yields of the reaction may be due to a $\pi\pi^*$ nature of the lowest excited-state of the phthalimide moiety which is not reactive in the H-abstraction reactions.[25]

According to the product **2**, we propose the reaction mechanism as shown in Scheme 1. The triplet excited state **1** is formed either by acetone sensitization (vide supra) or by direct excitation and ISC. In the most stable ground-state conformer, the distance between the closest H-atom at the adamantane skeleton (γ-H atom, position 2 of the adamantane) and the phthalimide carbonyl moiety is only 2.4 Å.[26] Thus, an intramolecular γ-H-transfer and formation of the 1,4-biradical (BR-1, Scheme 1) is feasible.[27] However, the influence of the solvent polarity and proticity on the quantum yield of the reaction suggest that BR-1 can also be formed via intramolecular photoinduced electron transfer giving the adamantane radical-cation[28] and the phthalimide radical-anion (BRI-1), followed by the intramolecular proton transfer, a process that should be preferred in polar protic solvents.

When we performed photolysis of **1** (16 h, 100 mg in 200 mL of CH_3CN/H_2O 3:1) at pH 2 and 7, only product **2** was obtained in 20% yield. On the other hand, at pH 10, the conversion of **1** was lower (9%) and in addition to **2** smaller amounts of side products were formed, but no attempt was made to characterize them. These results suggest that photoinduced intramolecular H-abstraction and intramolecular electron transfer (followed by the proton transfer) might be competing processes but yet no unambiguous conclusion can be made since under highly acidic and basic conditions since ring opening of the phthalimide moiety takes place.

After cyclization, BR-1 gives azetidinol **A** which is unstable and rapidly undergoes ring enlargement to azepindione **B**.[29] Subsequently, azepindione **B** undergoes a second photochemical reaction which is more efficient than the first transformation of **1**. Namely, in the most stable conformer of the azepindione, the distance between the H-atom at the position 4 of the adamantane skeleton and the carbonyl oxygen is only 2.3 Å.[30] Therefore, efficient intramolecular H-abstraction is anticipated giving biradical BR-2. The cyclization of BR-2 furnishes the final product **2**.

To obtain the ε-amino acid derivative, MAd benzazepine **2** was submitted to base hydrolysis. The hydrolysis performed in refluxing 10% NaOH H_2O/EtOH furnished **3** in high yield (>80%). The structure of **3** was characterized by spectroscopic methods. Comparison of ^{1}H NMR spectra (DMSO-d_6) of **2** and **3** indicated the disappearance of the signals corresponding to the amide-NH and OH. Moreover, the pattern of the aliphatic region of the spectrum after hydrolysis was significantly simplified. The most important structural information was obtained from the ^{13}C NMR spectrum. Two characteristic singlets were observed in the low field region that were assigned to ketone C═O and carboxylic acid C═O

(23) X-ray data of compound **2**: $C_{18}H_{19}NO_2$ (281.34), T = 100 K, monoclinic, $P2_1/c$, a = 11.8433(7) Å, b = 8.0475(6) Å, c = 14.4207(7) Å, $\alpha = \gamma = 90°$, β = 96.435(3)°, V = 1365.75(15) Å^3, crystal size: 0.3 × 0.3 × 0.15 mm, θ range: 1.73−27.0°, reflections, collected 6486, reflections, unique 2976, reflections, observed with $I > 2\sigma(I)$: 2233, final R ($I > 2\sigma(I)$): R_1 = 0.0432, wR_2 = 0.1076.

(24) The quantum yield for the formation of **2** was estimated using the valerophenone actinometer.

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(26) The same value of 2.4 Å has been found by X-ray analysis (see: Orzeszko, A.; Maurin, J. K.; Melonksyta, D. *Z. Naturforsch.* **2001**, *55b*, 1035) and has been calculated by us for the gas phase by AM1 semiempirical calculation implemented in the Gausian 98 software.

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(28) The adamantane radical cation has been produced under photochemical electron transfer conditions: Mella, M.; Freccero, M.; Albini, A. *Tetrahedron* **1996**, *52*, 5533.

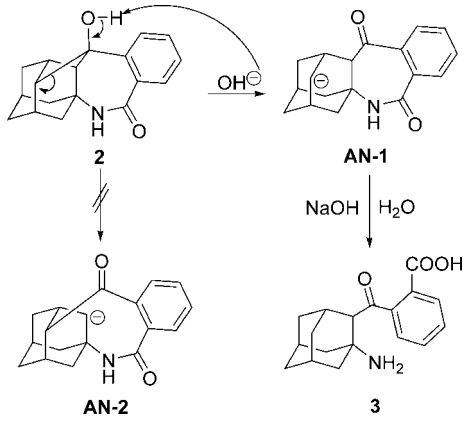
(29) We could not detect the presence of azepindione B even at low conversion (<5%) photolysis of **1** by ^{1}H NMR. In the UV spectra, an increase in the bathochromic reagion appeared at low conversion and clear non-isosbestic behavior was observed indicating an intermediate light-absorbing species.

(30) Calculated for the gas phase by AM1 semiempirical calculations: *Gaussian 98*: Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Zakrzewski, V. G.; Montgomery, J. A., Jr.; Stratmann, R. E.; Burant, J. C.; Dapprich, S.; Millam, J. M.; Daniels, A. D.; Kudin, K. N.; Strain, M. C.; Farkas, O.; Tomasi, J.; Barone, V.; Cossi, M.; Cammi, R.; Mennucci, B.; Pomelli, C.; Adamo, C.; Clifford, S.; Ochterski, J.; Petersson, G. A.; Ayala, P. Y.; Cui, Q.; Morokuma, K.; Salvador, P.; Dannenberg, J. J.; Malick, D. K.; Rabuck, A. D.; Raghavachari, K.; Foresman, J. B.; Cioslowski, J.; Ortiz, J. V.; Baboul, A. G.; Stefanov, B. B.; Liu, G.; Liashenko, A.; Piskorz, P.; Komaromi, I.; Gomperts, R.; Martin, R. L.; Fox, D. J.; Keith, T.; Al-Laham, M. A.; Peng, C. Y.; Nanayakkara, A.; Challacombe, M.; Gill, P. M. W.; Johnson, B.; Chen, W.; Wong, M. W.; Andres, J. L.; Gonzalez, C.; Head-Gordon, M.; Replogle, E. S.; Pople, J. A. Gaussian, Inc., Pittsburgh, PA, 2001.

at δ 207.7 and 168.7 ppm, respectively. Furthermore, in the aliphatic region of the spectrum the low-field shifted doublet at 58.9 ppm for the C_α to carbonyl clearly indicates the 1,2-aminocarbonyl relation. Isomeric 1,4-disubstituted structures show 10 ppm upfield shifted carbon resonances.

The reaction mechanism for the formation of **3** can be explained by two parallel processes, the hydrolysis of the amide moiety and the cyclobutanol ring opening (Scheme 2). Although

Scheme 2. Mechanism of the Hydrolysis of **2**



MAd **2** is strained, heating in DMSO-d_6 for 24 h at 100 °C without base did not result in the opening of the cyclobutane ring, indicating that it is not a homolytic cleavage. On the other hand, the base-catalyzed cyclobutanol ring opening is known to give ketone derivatives.[31] In case of **2**, this ring opening is highly regioselective giving AN-1, which can be rationalized by formation of the more stabile 7-membered ring vs 9-membered ring in AN-2.

In order to demonstrate the synthetic scope of this new domino reaction, we have performed a 10 g photolysis (in 950 mL of acetone/water 3:1) in a falling-film reactor using a 3 kW XeCl excimer (λ_{em} = 308 nm) radiation source.[32] The precipitated solid (4.9 g analytically pure compound **2**) was collected. An additional 3.8 g was isolated from the crude by column chromatography resulting in a total yield of 83% of the domino product **2**.

In summary, we discovered a new domino photochemical reaction sequence desymmetrizing the adamantane skeleton by phthalimide activation. This domino reaction yields cleanly a derivative of 2,4-methanoadamantanebenzazepine system, the novel 2-aza-10-hydroxyhexacyclo-[8.7.1.1^{1,4}.0^{4,9}.0^{11,16}.0^{12,18}]nonadeca-4,6,8-triene-3-one (**2**), hitherto not reported. Base hydrolysis of MAd **2** gives in high yield the keto-substituted 1,2-adamantane derivative of ε-amino acid **3**, which is a valuable substrate for the synthesis of various peptidomimetics.

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Supporting Information Available: Physical characterization of compounds **2** and **3**, ^{1}H NMR spectra in $CDCl_3$ and d_6-DMSO and ^{13}C NMR spectrum in DMSO-d_6 of **2**, ^{1}H NMR and ^{13}C NMR (DMSO-d_6) of **3**, crystallographic data for **2**, and UV conversion data.This material is available free of charge via the Internet at http://pubs.acs.org.

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