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Short Note

(Z)-2′-((Adamantan-1-yl)thio)-1,1′-dimethyl-2′,3′-dihydro-[2,4′-biimidazolylidene]-4,5,5′(1*H*,1′*H*,3*H*)-trione

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Abstract: The title compound, (*Z*)-2′-((adamantan-1-yl)thio)-1,1′-dimethyl-2′,3′-dihydro-[2,4′-biimidazolylidene]-4,5,5′(1*H*,1′*H*,3*H*)-trione, was found to be a by-product of the reaction of 1,3-dehydroadamantane with 3-methyl-2-thioxoimidazolidin-4-one and characterized via single-crystal X-ray diffraction.

Keywords: adamantane; thiohydantoin; by-product; X-ray structure

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1. Introduction

2-Thioxoimidazolidin-4-one (2-thiohydantoin, Figure 1) is a very promising scaffold for the creation of biologically active compounds, with the possibility of independent functionalization in four directions [1–4]. Moreover, thiohydantoins substituted at all possible positions are available, albeit in low yields, through four-component one-pot domino-reactions [5]. However, most of the synthesized 2-thiohydantoin derivatives bear substituents in the position 3 [6,7] or 5 [8,9]. It is not surprising that many recent works have been published on the study of the biological activity of compounds derived from 2-thiohydantoin. 2-Thiohydantoin derivatives exhibit anticonvulsant [10], fungicidal [11–13], antiviral [14,15], antimutagenic [16,17], and immunomodulatory [18] bioactivities, and some of them are also considered in the hormone-independent treatment of prostate cancer [19–22].

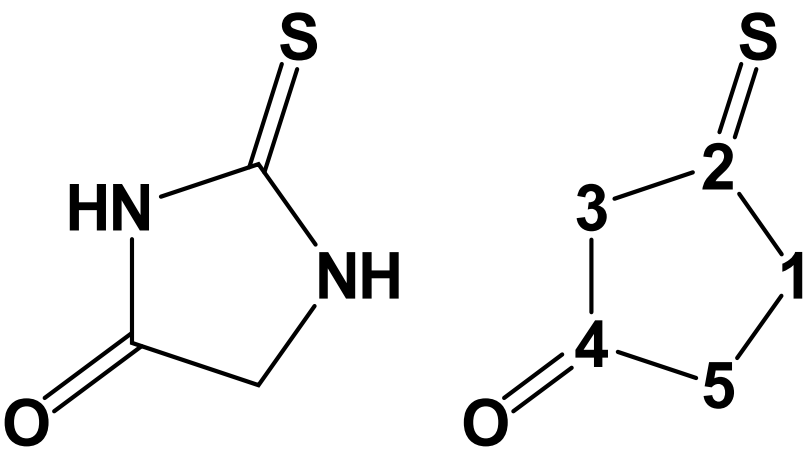
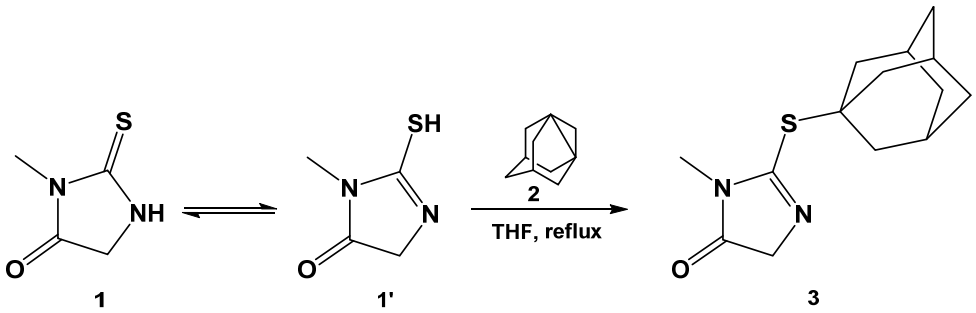


Figure 1. Structure of 2-thiohydantoin with numbered atoms.

The adamantyl fragment, due to its high lipophilicity, is part of many biologically active compounds [23]. 1,3-Dehydroadamantane (tetracyclo[3.3.1.1.^{3,7}.0.^{1,3}]decane, 1,3-

DHA, **2**, Scheme 1) is a convenient reagent for the direct introduction of the adamantyl moiety into the molecules of various organic compounds with activated C–H [24] as well as ordinary N–H bonds [25–28]. In this regard, we carried out the modification of 2-thiohydantoin and its 3-alkyl- and aryl- derivatives using 1,3-DHA. Herein, we report a very unusual side compound obtained from the reaction of 1,3-DHA with 3-methyl-2-thioxoimidazolidin-4-one (**1**).

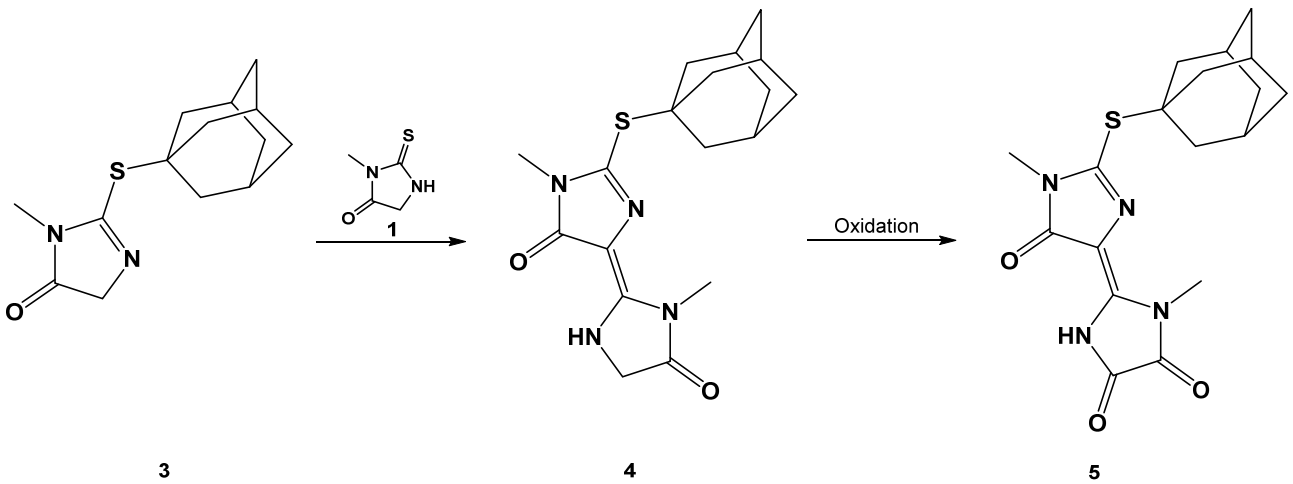


Scheme 1. Main route of the reaction of 1,3-dehydroadamantane (**2**) with 3-methyl-2-thioxoimidazolidin-4-one (**1**).

2. Results and Discussion

It is known that 2-thiohydanoin and its 3-substituted derivatives undergo a tautomeric transformation, as is shown in Scheme 1 [29]. Thus, our study intended to establish which form of 3-methyl-2-thiohydanoin reacts with 1,3-DHA (**2**). The reaction was carried out in THF under reflux for 8 h. We discovered that the main product of the reaction is 2-((adamantan-1-yl)thio)-3-methyl-3,5-dihydro-4*H*-imidazol-4-one (**3**), which corresponds to the involvement of the S–H bond of **1′**, instead of the N–H of **1**.

However, during the isolation of main reaction product **3**, we found a small amount (3%) of an unidentified by-product, which was insoluble in acetone. Separated by the filtration of the acetone solution, it was then dissolved in ethanol and left for slow crystallization. The resulting crystals were of good quality for a single-crystal X-ray diffraction study. The analysis (see supplementary) showed that the by-product was (*Z*)-2′-((adamantan-1-yl)thio)-1,1′-dimethyl-2′,3′-dihydro-[2,4′-biimidazolylidene]-4,5,5′(1*H*,1′*H*,3*H*)-trione (**5**, Scheme 2, Figure 2).



Scheme 2. Putative route of formation of the (*Z*)-2′-((adamantan-1-yl)thio)-1,1′-dimethyl-2′,3′-dihydro-[2,4′-biimidazolylidene]-4,5,5′(1*H*,1′*H*,3*H*)-trione (**5**).

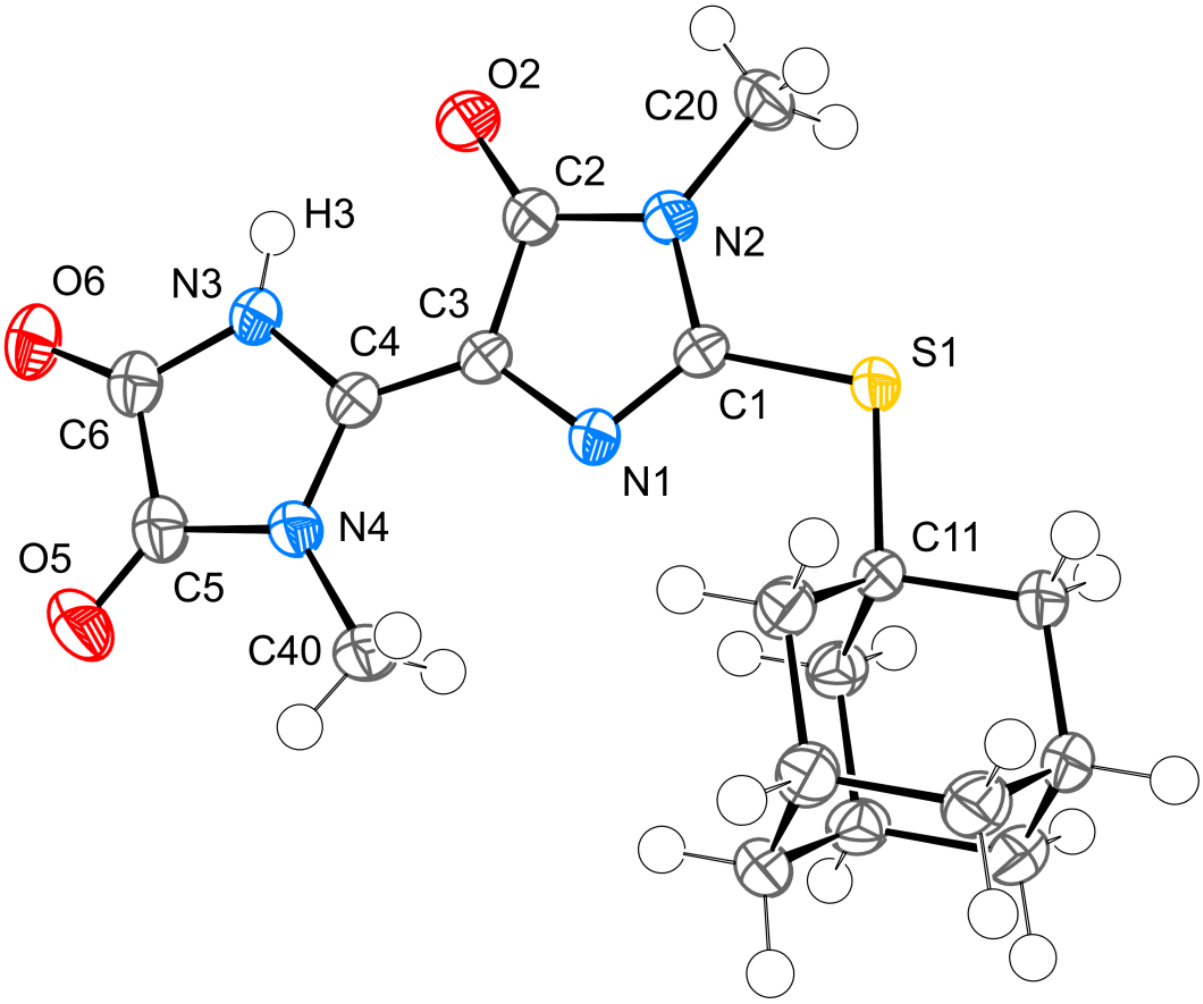
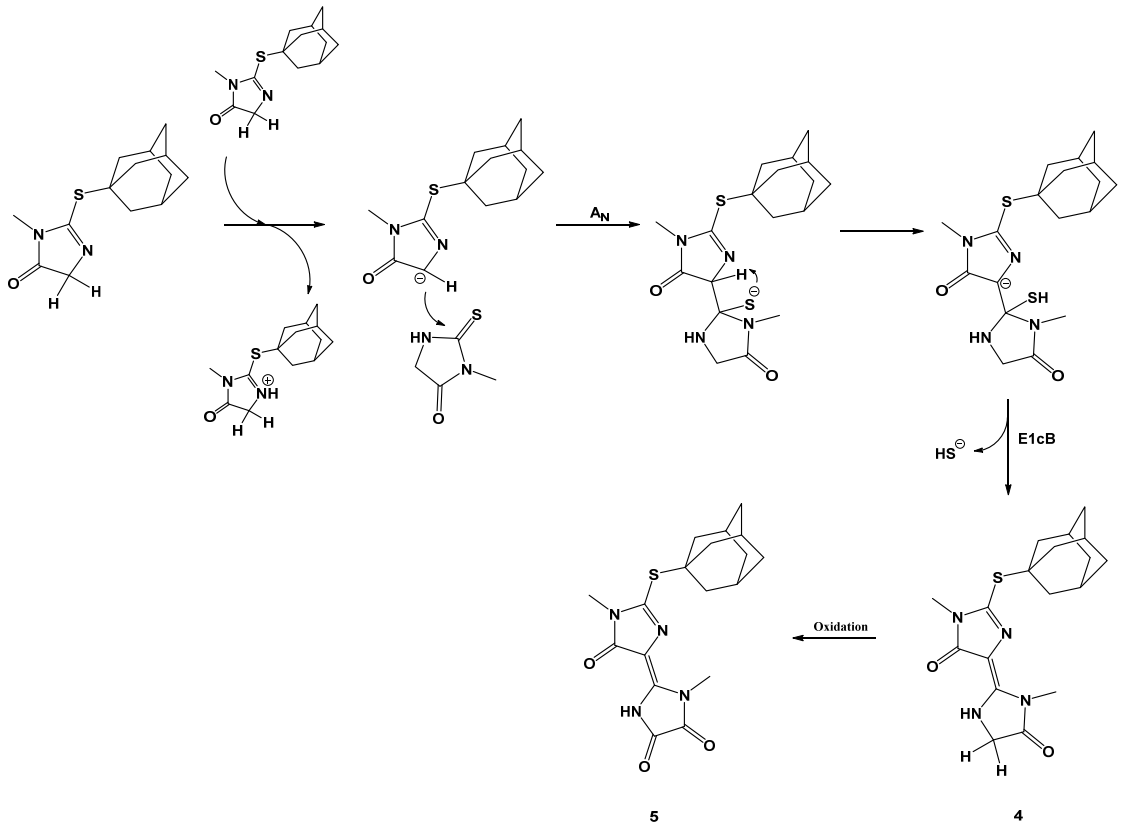


Figure 2. Structure of compound **5** in the crystal with thermal ellipsoids at the 80% probability level for nonhydrogen atoms according to single-crystal X-ray diffraction. Selected interatomic distances [Å]: S1–C1 1.7274(13), S1–C11 1.8432(13), O2–C2 1.2309(17), O5–C5 1.2087(18), O6–C6 1.2051(17), N1–C1 1.3038(17), N1–C3 1.3975(16), N2–C1 1.4032(16), N2–C2 1.3843(17), N2–C20 1.4628(17), N3–C4 1.3844(16), N3–C6 1.3734(17), N3–H3 0.86(2), N4–C4 1.3804(16), N4–C5 1.3810(17), N4–C40 1.4603(17), C2–C3 1.4660(18), C3–C4 1.3563(18), C5–C6 1.531(2).

We assume that, under the reaction conditions, main product **3** was involved in the interaction with starting compound **1** to produce a small amount of by-product **4** (Scheme 2). The reaction of 2-thiohydantoins at position 5 with carbonyl-containing compounds is well known [8,9] and the carbon atom at the position 5 of **3** could act as a potential nucleophile with respect to the thiocarbonyl group of **1**, which is present in the reaction mixture. By-product **4** could then be oxidized into **5** (Scheme 3). This fact reveals the possibility of the oligomerization of 2-thiohydanoins and should be noted in further studies as one of the yield-decreasing factors.



Scheme 3. Plausible mechanism for formation of compounds **4** and **5**.

3. Materials and Methods

Preparation of compound 5. A solution of 1,3-dehydroadamantane (**2**, 670 mg, 5 mmol) in 10 mL of DCM was added to the solution of 3-methyl-2-thioxoimidazolidin-4-one (**1**, 975 mg, 7.5 mmol) in 10 mL of DCM. The reaction mass was refluxed for 2 h and the solvent was removed *in vacuo*. Crude product was dissolved in acetone and filtered. Residue from the filter (35 mg) was dissolved in ethanol (2 mL) and left in a Schlenk flask for the process of slow crystallization to obtain crystals of compound **5**.

Compound **5** crystallized in the $P2_1/m$ monoclinic space group with half of the molecule in the asymmetric cell. The molecule was located on the crystallographic mirror plane. It is interesting to note that a C2–C3 bond length of 1.4660(18) Å was expected for the C(sp^2)–C(sp^2) single bond (ca. 1.47 Å), while the C5–C6 bond was noticeably longer (1.531(2) Å). The C3–C4 bond length of 1.3563(18) Å meant that it was double the expected length (ca. 1.34 Å was expected). The bond lengths of the carbonyl groups (ca. 1.21 Å was expected) were in the range from 1.2051(17) to 1.2309(17) Å. The compound was characterized by the intramolecular hydrogen bond N3–H3···O2 with the following parameters: N3–H3 0.86(2) Å, H3···O2 2.23(2) Å, N3···O2 2.8299(15) Å, and ∠N3–H3···O2 126.6(17)°. Basically, due to nonclassical hydrogen bonds C–H···O, the molecules were combined into a layer parallel to the 0*ac* plane. Then, the layers were joined together along the shortest axis 0*b* of the unit cell due to π···π interactions. The nature of nonclassical hydrogen bonds and π···π interactions in crystals was previously considered in detail [30].

The deposition number CCDC 2,234,948 contains the supplementary crystallographic data for this paper. These data are provided free of charge by the joint Cambridge Crystallographic Data Centre and Fachinformationszentrum Karlsruhe Access Structures service www.ccdc.cam.ac.uk/structures.

Single-crystal X-ray diffraction. Suitable monocrystals of **5** were prepared by slow crystallization from an ethanol solution. The data set for a single crystal **5** was collected on a Bruker D8 QUEST diffractometer with a PHOTON III area detector and an IμS

DIAMOND microfocus X-ray tube using Mo $K\alpha$ (0.71073 Å) radiation at 100(2) K. The data reduction package *APEX*4 was used for data processing. Data were corrected for systematic errors and absorption: Numerical absorption correction based on integration over a multifaceted crystal model and empirical absorption correction based on spherical harmonics according to the point group symmetry $2/m$ using equivalent reflections. The structure was solved using the intrinsic phasing approach and *SHELXT*-2018/2 [31] and refined using full-matrix least-squares on F^2 using *SHELXL*-2018/3 [32]. Non-hydrogen atoms were refined anisotropically. The hydrogen atoms were found by difference Fourier maps and refined isotropically.

Crystallographic data for **5**. $C_{18}H_{22}N_4O_3S$, yellow prism (0.345 × 0.245 × 0.223 mm^3), formula weight 374.45 g mol^{-1}; monoclinic, $P2_1/m$ (No. 11), a = 11.4315(3) Å, b = 6.6765(2) Å, c = 11.5969(3) Å, β = 107.8509(5)°, V = 842.49(4) $Å^3$, Z = 2, Z' = 0.5, T = 100(2) K, d_{calc} = 1.476 g cm^{-3}, μ(Mo $K\alpha$) = 0.220 mm^{-1}, F(000) = 396; $T_{max/min}$ = 0.9583/0.8697; 66,553 reflections were collected (1.845° ≤ θ ≤ 28.304°, index ranges: –15 ≤ h ≤ 15, –8 ≤ k ≤ 8, and –15 ≤ l ≤ 15), 2268 of which were unique, R_{int} = 0.0334, R_σ = 0.0098; completeness to θ of 28.304° was 100.0%. The refinement of 198 parameters with 42 restraints converged to $R1$ = 0.0284 and $wR2$ = 0.0791 for 2195 reflections with $I > 2\sigma(I)$ and $R1$ = 0.0292 and $wR2$ = 0.0800 for all data with a goodness-of-fit of S = 1.045 and residual electron density $\rho_{max/min}$ = 0.407 and –0.215 e $Å^{-3}$, rms 0.045; max shift/e.s.d. in the last cycle 0.000.

4. Conclusions

In this work, we presented the previously unknown compound, (*Z*)-2′-((adamantan-1-yl)thio)-1,1′-dimethyl-2′,3′-dihydro-[2,4′-biimidazolylidene]-4,5,5′(1*H*,1′*H*,3*H*)-trione, which was isolated from a reaction mass and characterized by single-crystal X-ray diffraction.

Supplementary Materials: The following supporting information can be downloaded. Single-crystal X-ray diffraction data (cif).

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