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The Multigram-Scale Access to 2-Oxaadamantan-1-amine and 2-Oxaadamantan-1-ol *via* the Optimized Synthesis of Bicyclo[3.3.1]nonane-3,7-dione

Abstract

The practical tens-of-grams-scale access to 2-oxaadamantan-1-amine and 2-oxaadamantan-1-ol – two overlooked heteroadamantane building blocks of interest for medicinal chemistry – has been achieved through the optimization and scale-up of existing literature protocols. The key precursor – bicyclo[3.3.1]nonane-3,7-dione– and both target compounds can be obtained in good overall yields using straightforward procedures and standard reagents. It is noteworthy that 2-oxaadamantan-1-amine is an exceptionally stable *N*,*O*-acetal, in stark contrast to the high hydrolytic lability usually seen in this compound class.

Keywords: oxaadamantane; bicyclo[3.3.1]nonane-3,7-dione; *N*,*O*-acetal; hemiaminal; cage compounds; scale-up synthesis; heteroadamantane; building blocks

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Отримання 2-оксаадамантан-1-аміну та 2-оксаадамантан-1-олу в мультиграмових кількостях через оптимізований синтез біцикло[3.3.1]нонан-3,7-діону

Анотація

Завдяки оптимізації та масштабуванню вже відомих методик вдалося розробити практичний спосіб синтезу 2-оксаадамантан-1-аміну та 2-оксаадамантан-1-олу в кількостях, вимірюваних десятками грамів. Ці два структурні блоки, які раніше лишалися поза увагою дослідників, становлять особливий інтерес для медичної хімії. Ключовий прекурсор – біцикло-[3.3.1]нонан-3,7-діон – та обидві цільові сполуки можна отримати з високим загальним виходом, використовуючи нескладні процедури й стандартні реагенти. Показово, що 2-оксаадамантан-1-амін виявляє виняткову стабільність як *N*,*O*-ацеталь, що яскраво контрастує з високою гідролітичною лабільністю, зазвичай властивою сполукам цього класу.

Ключові слова: оксаадамантан; біцикло[3.3.1]нонан-3,7-діон; *N*,*O*-ацеталь; геміаміналь; каркасні сполуки; масштабований синтез; гетерадамантан; будівельні блоки

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■ Introduction

The 2-oxaadamantane motif appears in several biologically important natural products. Tetrodotoxin (TTX), a powerful neurotoxin from pufferfish, has a densely functionalized dioxaadamantane core that enables its highly selective blockage of voltage-gated Na^+ ion channels [1]. Other naturally occurring (poly)oxaadamantanes, including the trioxaadamantanes muamvatin and caloundrin B, the sedative daigremontianin, and bersaldegenin orthoacetate, further demonstrate the recurrence of this cage scaffold in nature [1]. In synthetic chemistry, despite the difficulties in constructing and functionalizing the heteroadamantane skeleton, several oxaadamantane-containing compounds show a significant biological activity across various targets, such as NMDA receptor antagonists and trypanocidal agents [2], heteroadamantyl cannabinoids with the nanomolar CB_1/CB_2 affinity [3], σ-receptor ligands [4], reversed-chloroquine antimalarial conjugates [5] (**Figure 1**), rigid acetylcholine-like pharmacophore models [6], and the highly efficient AZADO family of nitroxyl-radical oxidation catalysts [7]. Additionally, the constrained geometry of (oxa) adamantane systems has been used to explore the fundamental chemical reactivity, including the transition-state geometry in aldol condensations [8].

The simplest way to synthesize 1-heteroatom-substituted 2-oxaadamantanes involves bicyclo-[3.3.1]nonane-3,7-dione, which acts as a common precursor for both the amine and the alcohol through the transannular cyclization. Several synthetic approaches to this diketone have been reported: the condensation of dicarboxylic acid derivatives [9], the fragmentation–ozonolysis of 1,3-dibromoadamantane [10], the double-condensation of dimethyl 3-oxoglutarate with malondialdehyde [11], routes *via* bicyclo[3.3.1]nonanone intermediates [12], and a three-step sequence from adamantan-2-one through a lactone and diol [13]. Of these, the latter route is arguably the most practical, employing inexpensive, commercially available adamantan-2-one and involving the Baeyer-Villiger oxidation, the $LiAlH_4$ reduction, and the chromium-based oxidation of the resulting diol – a versatile intermediate that has also been used in related skeletal transformations [14]. However, all reported procedures for the diketone have been developed and validated only on a small scale (typically ≤ 10 g), and reliable upscale methods have not been documented. This limitation has thus restricted practical access to the downstream target compounds – 2-oxaadamantan-1-amine and 2-oxaadamantan-1-ol – which remain underexplored as building blocks despite their potential. The amine itself has been prepared *via* reductive amination of the diketone [2, 10], but the reported protocols operate on a few-gram scale and require a high-pressure hydrogenation for the final deprotection step. Herein, we report modifications to existing protocols that enable a reliable, the tens-of-grams-scale access to the diketone in three steps with a good overall yield, thereby enabling the access to both the amine and the alcohol in multigram quantities – determining these compounds as practical building blocks for further research.

■ Results and discussion

Our approach follows the general strategy outlined by *Zalikowski et al.* [13], with modifications at each step to ensure reproducibility and enhanced yields during scale-up (**Scheme 1**). The Baeyer-Villiger oxidation of adamantan-2-one (**1**) with *m*CPBA in CH_2Cl_2 proceeded smoothly, delivering lactone **2** quantitatively on a 77 g scale –

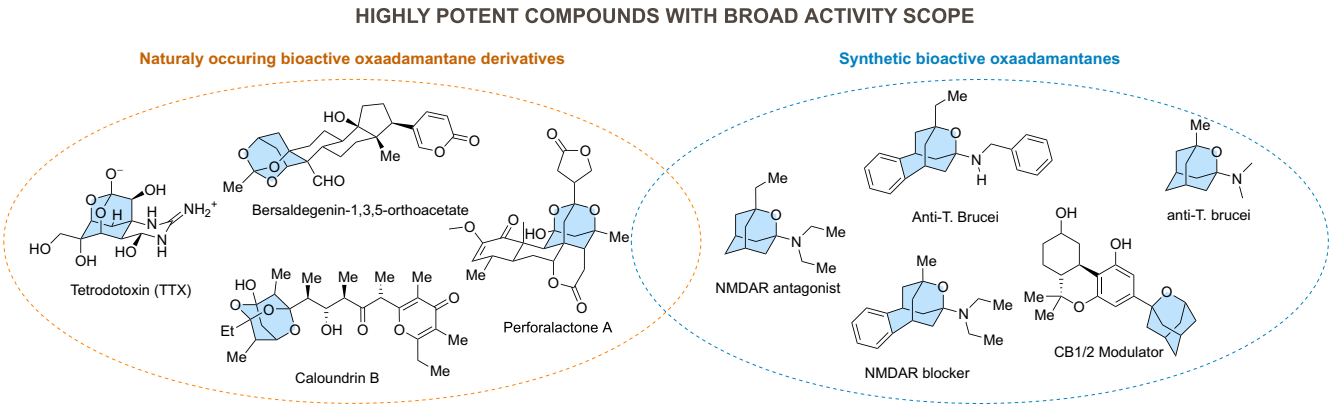
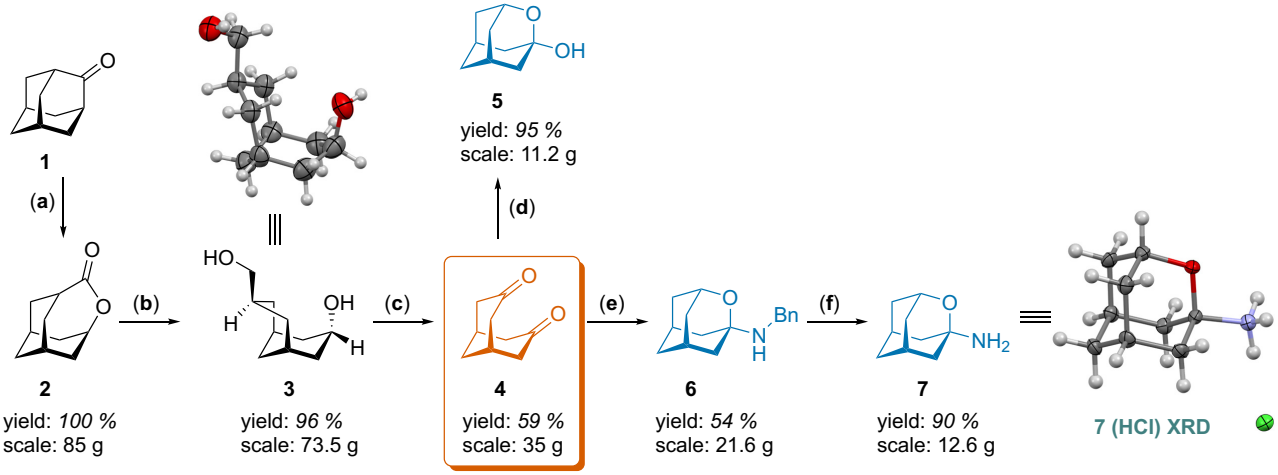


Figure 1. Selected natural products and synthetic bioactive compounds incorporating oxaadamantane and related (poly)oxaadamantane scaffolds

approximately fifteen-fold larger than the batch size reported in the previous work [13]. The single aqueous NaOH wash of the original protocol was replaced by sequential Na_2CO_3/$Na_2S_2O_3$ washes followed by the MTBE trituration; both were necessary to achieve complete removal of *m*CPBA and residual CH_2Cl_2 at this scale, which otherwise interfered with the subsequent reduction with $LiAlH_4$ in THF – substituted for the less practical diethyl ether used in the original protocol [13] – gave diol **3** in 96% yield (73.5 g). As previously noted [13], diol **3** is poorly soluble in common organic solvents; therefore, the inorganic residue from the $LiAlH_4$ quench must be washed repeatedly with a hot THF to ensure complete recovery of the product. The oxidation of diol **3** to diketone **4** was the main bottleneck in the sequence. While the literature protocol uses pyridinium dichromate (PDC) and reports a 75% yield on about 5 g [13], we could not replicate this result on larger scales. Testing alternatives, including PDC at higher temperatures and Dess-Martin periodinane, produced inferior or inconsistent results. Ultimately, 7 equiv. of pyridinium chlorochromate (PCC), on silica in CH_2Cl_2 at room temperature over three days delivered diketone **4** reproducibly in the yield of 59% (35 g from 66 g of **3**) – modestly below the 75% reported previously [13] on a ~5 g batch, but, crucially, reliably reproducible at the tens-of-grams scale, with lactone **2** (from over-oxidation) as the main by-product. The overall three-step yield of diketone from adamantan-2-one is 57%, and the entire sequence requires no chromatography, which is a key advantage for the routine preparation.

With a sustainable supply of diketone **4**, the target oxaadamantanes were synthesized *via* two different routes. 2-Oxaadamantan-1-ol (**5**) was obtained simply through the $NaBH_4$ reduction of **4** in methanol (95% yield, 11.2 g). The amine was synthesized through the two-step process adapted from *Duque et al.* [2] work: the one-pot condensation of **4** with benzylamine followed by the *in situ* $LiAlH_4$ reduction produced *N*-benzyl-2-oxaadamantan-1-amine (**6**) as its hydrochloride salt (54%, 21.6 g), and the subsequent hydrogenolysis over Pd/C at atmospheric pressure in methanol yielded the primary 2-oxaadamantan-1-amine as its hydrochloride **7** (90%, 12.6 g). Both the yield and operational simplicity of this debenzylation significantly improve upon the literature methods, which involve the high-pressure hydrogenation (40 atm, 100 °C), followed by the base extraction and sublimation, yielding only 70% on an around 1 g scale [2].

Compound **7** is a bridgehead hemiaminal: the amine nitrogen is directly attached to the carbon that also forms part of the oxaadamantane ether linkage, making it a cyclic *N*,*O*-acetal. This functional motif – a cyclic α-amino ether – belongs to a notoriously unstable compound class: most known representatives decompose upon the attempted isolation, and even the comparatively stabilized 1-aminoisochroman can only be handled *in situ* in solution and must be reacted immediately to avoid decomposition [15]. In contrast, **7** remains stable after the prolonged exposure to both acidic and basic aqueous conditions at high temperatures. This notable stability results from the geometric constraints of the Bredt's rule, which prevents the formation of



Experimental conditions: (**a**) *m*CPBA, DCM, 25 °C, 24 h; (**b**) LAH, THF, 0 °C → r.t., overnight; (**c**) PCC, SiO_2, DCM, r.t., 3 d; (**d**) $NaBH_4$, MeOH, 0 °C → r.t., 1 d; (**e**) $BnNH_2$, THF, 65 °C, 0.5 h; then LAH, THF, 0 °C → r.t., overnight; then HCl, MeAc; (**f**) H_2, Pd/C (10%), MeOH, r.t., 1 d

Scheme 1. The synthesis of 2-oxaadamantan-1-ol (**5**) and 2-oxaadamantan-1-amine (**7**) from adamantan-2-one (**1**). Thermal ellipsoid plots from the single-crystal X-ray diffraction of **7·(HCl)** and **5** are given with the 50% probability (*see* SI File)

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the bridgehead iminium ion needed for the hydrolytic cleavage – a stabilization first noted by Stetter for the related 1-hydroxy-2-oxaadamantane [9]. The structures of **5** and **7** (hydrochloride) were confirmed by the single-crystal X-ray diffraction (**Scheme 1**).

Since 2-oxaadamantane-derived 1-amines have already withstood the conditions of biological assays without the apparent breakdown of the *N*,*O*-acetal linkage (see Introduction), the question is whether this robustness extends to both amine **7** and alcohol **5** derivatives in more challenging environments, such as extended metabolic exposure and *in vivo* testing. With multigram quantities now available, we plan to undertake a systematic ADMET profiling as the next logical step.

■ Conclusions

We have shown that two previously overlooked heteroadamantane building blocks – 2-oxaadamantan-1-amine and 2-oxaadamantan-1-ol – can be reliably prepared on the tens-of-grams scale from commercially available adamantan-2-one by optimizing existing literature protocols. All steps use standard reagents, do not require chromatographic purification, and yield good overall results. The exceptional hydrolytic stability of 2-oxaadamantan-1-amine – a rare trait for an *N*,*O*-acetal – is a unique feature that, along with the increased practical accessibility of both compounds, may promote their wider study as rigid, heteroatom-containing scaffolds in medicinal chemistry and drug discovery.

■ Experimental part

General Information

The solvents were purified according to the standard procedures. All starting materials were obtained from Enamine Ltd. Melting points were measured on an automated melting point system. ^{1}H, and ^{13}C NMR spectra were recorded on a Bruker Avance 500 spectrometer (at 500 MHz for Protons and 126 MHz for Carbon-13) and a Varian Unity Plus 400 spectrometer (at 400 MHz for ^{1}H, 101 MHz for ^{13}C). Tetramethyl silane (^{1}H, ^{13}C) was used as a standard. HPLC analyses were done on an Agilent 1200 instrument. Mass spectra were recorded on an Agilent 1100 LCMSD SL instrument (chemical ionization (APCI)). The column chromatography was performed using silica gel (200–300 mesh). The high-resolution mass spectrometric analyses (HRMS) were conducted using an Agilent instrument, specifically a hybrid system comprising the 6200 Series Time-of-Flight (TOF) and the 6500 Series Quadrupole Time-of-Flight (Q-TOF). This system was operated with the software version B.08.00 (B8058.0). Elemental analyses were performed at the Laboratory of Organic Analysis, Institute of Organic Chemistry, National Academy of Sciences of Ukraine.

All crystallographic measurements for this publication were performed at 173K on a Bruker Smart Apex II diffractometer operating in the φ and w scans mode. The intensity data were collected using the Mo-K_a radiation (l = 0.71078 Å). The crystals were mounted on a glass fiber and mounted on the diffractometer. The structures were solved by direct methods and refined by the full-matrix least-squares technique using the Bruker SHELXTL program package [16].

Non-hydrogen atoms were refined anisotropically. All CH hydrogen atoms were placed at calculated positions and refined as 'riding' model, with U_{iso}(H)=1.2U_{eq}(CH_2) and U_{iso}(H)=1.5U_{eq}(CH_3).

The NH hydrogen atoms in structures **5** and **7 (HCl)** were found in difference Fourier syntheses and refined isotropically. The absolute configuration of **8** is not determined because no heavy atoms are present in the molecule. The X-ray crystallographic data for all compounds are listed in the SI File.

Crystallographic data for the structures in this paper were deposited at the Cambridge Crystallographic Data Centre as supplementary publication numbers CCDC 2543739 (compound **3**) and 2543738 (compound **7**). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB21EZ, UK, (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

4-Oxatricyclo[4.3.1.1^{3,8}]undecan-5-one (2)

The solution of adamantan-2-one (**1**; 77.2 g, 0.514 mol, 1.0 equiv.) in CH_2Cl_2 (2400 mL) was stirred at room temperature (25 °C) with a magnetic stirrer (400 rpm). *m*CPBA (177.4 g, 90% purity, 1.028 mol, 2.0 equiv.) was added portionwise over 5 min. The reaction mixture was stirred at room temperature for 24 h, then washed with a 10% aqueous Na_2CO_3 (2 × 1400 mL) and a 10% aqueous $Na_2S_2O_3$ (2 × 1400 mL), dried over Na_2SO_4, and filtered. The filtrate was concentrated under reduced pressure, MTBE (600 mL) was added, and the mixture was evaporated again to remove residual CH_2Cl_2. The product was obtained as white crystals.

Yield – 85 g (100%). M. p. 238–248 °C (dec.). Anal. Calcd for $C_{10}H_{14}O_2$, %: C 72.26, H 8.49. Found, %: C 72.38, H 8.28. ^{1}H NMR (500 MHz, Chloroform-*d*), δ, ppm: 1.73 (1H, s), 1.79–1.88 (2H, m), 1.89–1.98 (2H, m), 1.98–2.07 (3H, m), 2.10 (1H, br.s), 2.98–3.13 (4H, m), 4.47 (1H, s). ^{13}C NMR (126 MHz, Chloroform-*d*), δ, ppm: 26.0, 31.1, 33.9, 35.9, 41.4, 73.3, 179.0. ^{13}C NMR_APT (126 MHz, Chloroform-*d*), δ, ppm: 25.7, 30.9, 33.7, 35.7, 41.1, 73.0. GC-MS, *m/z* (EI): 166 $[M]^+$.

7-(Hydroxymethyl)bicyclo[3.3.1]nonan-3-ol (3)

To an ice-cooled dry THF (1100 mL), $LiAlH_4$ (20.55 g, 0.542 mol, 1.2 equiv.) was added portionwise. The suspension was stirred at 0 °C for 10 min, then lactone **2** (75.0 g, 0.451 mol, 1.0 equiv.) was added portionwise over 5 min at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the dropwise addition of water (75 mL) at 0 °C, followed by stirring at 0 °C for 15 min. Na_2SO_4 (150 g) was added, and the inorganic solids were collected by the filtration and washed thoroughly with a hot THF. The combined filtrates were concentrated under reduced pressure, and the residue was triturated with CH_2Cl_2 (300 mL).

Note: The product is insoluble in $CHCl_3$; NMR spectra were recorded in DMSO-d_6.

A white-yellow solid. Yield – 73.5 g (96%). M. p. 175 °C. Anal. Calcd for $C_{10}H_{18}O_2$, %: C 70.55, H 10.66. Found, %: C 70.67, H 10.54. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.04 (1H, d, J = 12.39 Hz), 1.48–1.84 (8H, m), 1.97 (2H, s), 2.54 (1H, s), 3.14 (2H, t, J = 5.51 Hz), 3.32 (2H, br.s), 3.93 (1H, s), 4.09–4.24 (1H, m). ^{13}C NMR (126 MHz, DMSO-d_6), δ, ppm: 23.7, 28.2, 29.6, 32.9, 65.3, 67.4. ^{13}C NMR_APT (126 MHz, DMSO-d_6), δ, ppm: 23.6, 28.1, 29.5, 32.7, 65.1, 67.2, 108.8, 109.2, 159.2. GC-MS, *m/z* (EI): 152 $[M\text{-}H_2O]^+$.

Bicyclo[3.3.1]nonane-3,7-dione (4)

To the solution of diol **3** (66.0 g, 0.388 mol, 1.0 equiv.) in CH_2Cl_2 (3000 mL), SiO_2 (600 g) and PCC (585 g, 2.71 mol, 7.0 equiv.) were added. The resulting mixture was stirred at room temperature for 3 days. EtOAc (600 mL) was added, and the mixture was filtered through a silica pad, which was washed with EtOAc (2000 mL), and the combined filtrates were concentrated under reduced pressure. The residue was dissolved in MTBE (2000 mL) and heated to reflux; the mixture was filtered while hot, and the filtrate was partially concentrated to approximately one-quarter of its original volume, cooled with ice, and the precipitate was collected by the filtration and air-dried for 1 h.

A white-yellow solid. Yield – 35.0 g (59%). M. p. 214–223 °C. Anal. Calcd for $C_9H_{12}O_2$, %: C 71.03, H 7.95. Found, %: C 70.89, H 8.05. ^{1}H NMR (500 MHz, Chloroform-*d*), δ, ppm: 2.20 (2H, s), 2.41 (4H, d, J = 15.42 Hz), 2.58 (4H, dd, J = 15.46, 5.41 Hz), 2.86 (2H, br.s). ^{13}C NMR (126 MHz, Chloroform-*d*), δ, ppm: 31.7, 32.8, 48.0, 208.4. ^{13}C NMR_APT (126 MHz, Chloroform-*d*), δ, ppm: 31.7, 32.8, 48.0. GC-MS, *m/z* (EI): 152 $[M]^+$.

2-Oxaadamantan-1-ol (5)

To an ice-cooled solution of diketone **4** (11.69 g, 76.8 mmol, 1.0 equiv.) in a dry MeOH (210 mL), $NaBH_4$ (3.49 g, 92.2 mmol, 1.2 equiv.) was added portionwise. The reaction mixture was stirred at room temperature for 24 h, then concentrated under reduced pressure. The residue was quenched with a saturated aqueous Na_2CO_3 (350 mL) and stirred for 10 min. The aqueous layer was extracted with $CHCl_3$/MeOH (6:1, 3 × 400 mL). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated under reduced pressure.

A white solid. Yield – 11.2 g (95%). M. p. 195–238 (dec.). Anal. Calcd for $C_9H_{14}O_2$, %: C 70.10, H 9.15. Found, %: C 70.26, H 9.03. ^{1}H NMR (500 MHz, Chloroform-*d*), δ, ppm: 1.55 (2H, d, J = 12.35 Hz), 1.72 (1H, d, J = 11.90 Hz), 1.76–1.87 (5H, m), 1.92 (2H, d, J = 11.59 Hz), 2.30 (2H, s), 2.96 (1H, br. s, H-bond), 4.28 (1H, s). ^{13}C NMR (101 MHz, Chloroform-*d*), δ, ppm: 29.3, 34.7, 42.0, 72.2, 93.8. ^{13}C NMR_APT (101 MHz, Chloroform-*d*), δ, ppm: 29.3, 34.7 42.0, 72.2, 93.8. EIMS, *m/z* (EI): 154 $[M]^+$.

***N*-Benzyl-2-oxaadamantan-1-amine hydrochloride (6)**

To the solution of diketone **4** (22.0 g, 0.144 mol, 1.0 equiv.) in a dry THF (800 mL), benzylamine (17.6 mL, 0.159 mol, 1.1 equiv.) was added. The mixture was stirred at 65 °C for 30 min, then cooled to room temperature to form the solution of the corresponding imine. Separately, to an ice-cooled dry THF (280 mL), $LiAlH_4$ (10.8 g, 0.289 mol, 2.0 equiv.) was added portionwise and stirred at 0 °C for 10 min. The solution of the imine was then added dropwise to the $LiAlH_4$ suspension at 0 °C. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction was quenched by the dropwise addition of the solution of NaOH (5.6 g, 0.144 mol, 1.0 equiv.) in H_2O (40 mL) at 0 °C, stirred for 15 min, and Na_2SO_4 (400 g) was added. The inorganic solids

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were removed by the filtration and washed with EtOAc. The combined filtrates were concentrated under reduced pressure. The residue was taken up in methyl acetate (440 mL), treated with 10 M HCl (22 mL), and stirred at 0 °C for 10 min. The precipitate was collected by the filtration and air-dried.

A white-yellow solid (HCl salt). Yield – 21.6 g (54%). M. p. 218–227 °C (dec.). Anal. Calcd for $C_{16}H_{21}NO$, %: C 78.97, H 8.70, N 5.76. Found, %: C 78.81, H 8.55, N 5.66. ^{1}H NMR (500 MHz, Chloroform-*d*), δ, ppm: 1.55 (2H, d, J = 12.84 Hz), 1.74 (3H, s), 1.83–2.04 (5H, m,), 2.11–2.24 (2H, m), 4.06 (1H, t, J = 5.44 Hz), 4.19–4.37 (1H, m), 7.20–7.34 (3H, m), 7.61 (2H, d, J = 7.47 Hz), 9.83 (2H, s). ^{13}C NMR (126 MHz, Chloroform-*d*), δ, ppm: 28.0, 34.0, 34.4, 37.0, 44.1, 72.0, 85.7, 128.8, 131.5. ^{13}C NMR_APT (126 MHz, Chloroform-*d*), δ, ppm: 27.7, 33.9, 36.7, 43.9, 71.7, 85.5, 128.5, 131.3, 159.8. LC-MS, *m*/*z* (CI): 244.2 $[M+H]^+$.

2-Oxaadamantan-1-amine Hydrochloride (7)

To the solution of **6** (21.0 g, 74.9 mmol, 1.0 equiv.) in MeOH (630 mL), 10% Pd/C (7.0 g) was added. The flask was evacuated and backfilled with hydrogen five times, then stirred under the hydrogen atmosphere (1 atm, balloon) at room temperature for 24 h. The reaction mixture was filtered through a thin pad of SiO_2, and the filtrate was concentrated under reduced pressure. The residue was triturated with a dry MeCN (350 mL) and concentrated under reduced pressure.

A beige powder (HCl salt). Yield – 12.6 g (90%). M. p. >200 °C (gradual dec.). Anal. Calcd for $C_9H_{15}NO$, %: C 70.55, H 9.87, N 9.14. Found, %: C 70.39, H 9.97, N 9.25. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.63 (2H, d, J = 12.47 Hz), 1.71 (1H, d, J = 12.42 Hz), 1.75–1.99 (8H, m), 2.24 (2H, s), 4.21 (1H, s), 8.60 (2H, s). ^{13}C NMR_APT (126 MHz, DMSO-d_6), δ, ppm: 27.1, 33.5, 38.3, 39.9, 70.3, 80.6. GC-MS, *m*/*z* (EI): 153 $[M]^+$.

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References

1. (a) Dembitsky, V. M.; Gloriozova, T. A.; Poroikov, V. V. Pharmacological Profile of Natural and Synthetic Compounds with Rigid Adamantane-Based Scaffolds as Potential Agents for the Treatment of Neurodegenerative Diseases. *Biochem. Biophys. Res. Commun.* **2020**, *529* (4), 1225–1241. https://doi.org/10.1016/j.bbrc.2020.06.123. (b) Wanka, L.; Iqbal, K.; Schreiner, P. R. The Lipophilic Bullet Hits the Targets: Medicinal Chemistry of Adamantane Derivatives. *Chem. Rev.* **2013**, *113* (5), 3516–3604. https://doi.org/10.1021/cr100264t.
2. Duque, M. D.; Camps, P.; Profire, L.; Montaner, S.; Vázquez, S.; Sureda, F. X.; Mallol, J.; López-Querol, M.; Naesens, L.; Clercq, E. D.; Radhika Prathalingam, S.; Kelly, J. M. Synthesis and Pharmacological Evaluation of (2-Oxaadamant-1-Yl)Amines. *Bioorg. Med. Chem.* **2009**, *17* (8), 3198–3206. https://doi.org/10.1016/j.bmc.2009.02.007.
3. Dixon, D. D.; Sethumadhavan, D.; Benneche, T.; Banaag, A. R.; Tius, M. A.; Thakur, G. A.; Bowman, A.; Wood, J. T.; Makriyannis, A. Heteroadamantyl Cannabinoids. *J. Med. Chem.* **2010**, *53* (15), 5656–5666. https://doi.org/10.1021/jm100390h.
4. Banister, S. D.; Yoo, D. T.; Chua, S. W.; Cui, J.; Mach, R. H.; Kassiou, M. N-Arylalkyl-2-Azaadamantanes as Cage-Expanded Polycarbocyclic Sigma (σ) Receptor Ligands. *Bioorg. Med. Chem. Lett.* **2011**, *21* (18), 5289–5292. https://doi.org/10.1016/j.bmcl.2011.07.028.
5. Yvette, O. M.; Malan, S. F.; Taylor, D.; Kapp, E.; Joubert, J. Adamantane Amine-Linked Chloroquinoline Derivatives as Chloroquine Resistance Modulating Agents in Plasmodium Falciparum. *Bioorg. Med. Chem. Lett.* **2018**, *28* (8), 1287–1291. https://doi.org/10.1016/j.bmcl.2018.03.026.
6. Camps, P.; Muñoz-Torrero, D.; Muñoz-Torrero, V. Unusual Oxidation of Bridgehead Polycyclic 1,2-Diamines and 2-Aminoalcohols with Dimethyldioxirane: Formation of Dioximes and Monooximes by Cleavage of the Central Carbon-Carbon Bond. *Tetrahedron Lett.* **1995**, *36* (11), 1917–1920. https://doi.org/10.1016/0040-4039(95)00156-7.
7. Shibuya, M.; Sasano, Y.; Tomizawa, M.; Hamada, T.; Kozawa, M.; Nagahama, N.; Iwabuchi, Y. Practical Preparation Methods for Highly Active Azaadamantane-Nitroxyl-Radical-Type Oxidation Catalysts. *Synthesis* **2011**, *2011* (21), 3418–3425. https://doi.org/10.1055/s-0030-1260257.
8. Denmark, S. E.; Henke, B. R. Investigations on Transition-State Geometry in the Aldol Condensation. *J. Am. Chem. Soc.* **1991**, *113* (6), 2177–2194. https://doi.org/10.1021/ja00006a042.
9. Stetter, H.; Tacke, P.; Gärtner, J. Über Verbindungen Mit Urotropin-Struktur, XXX. Ringschlußreaktionen Ausgehend von Bicyclo [3.3.1]-Nonandion-(3.7). *Chem. Ber.* **1964**, *97* (12), 3480–3487. https://doi.org/10.1002/cber.19640971232.
10. Gagneux, A. R.; Meier, R. 1-Substituted 2-Heteroadamantanes. *Tetrahedron Lett.* **1969**, *10* (17), 1365–1368. https://doi.org/10.1016/S0040-4039(01)87887-4.
11. Bertz, S. H. Series on Chemistry under Physiological Conditions. Part 7. Tetramethyl 3,7-Dihydroxybicyclo[3.3.1]Nona-2,6-Diene-2,4,6,8-Tetracarboxylate: A Useful Companion to Meerwein's Ester. Topological Analysis of Bicyclo[3.3.1]Nonane Synthesis. *J. Org. Chem.* **1985**, *50* (19), 3585–3592. https://doi.org/10.1021/jo00219a027.
12. Momose, T.; Muraoka, O. Bicyclo[3.3.1]Nonanes as Synthetic Intermediates. I. Improved Synthetic Methods for Bicyclo[3.3.1]Nonan-3-One. *Chem. Pharm. Bull.* **1978**, *26* (1), 288–295. https://doi.org/10.1248/cpb.26.288.
13. Zalikowski, J. A.; Gilbert, K. E.; Borden, W. T. Oxidation of 7-(Hydroxymethyl)Bicyclo[3.3.1]Nonan-3-Ol. Convenient Synthesis of Bicyclo[3.3.1]Nonane-3,7-Dione. *J. Org. Chem.* **1980**, *45* (2), 346–347. https://doi.org/10.1021/jo01290a029.

14. Renzoni, G. E.; Borden, W. T. Synthesis of 7-Carboxytricyclo[3.3.1.03,7]Nonan-3-Ol. *J. Org. Chem.* **1983**, *48* (26), 5231–5236. https://doi.org/10.1021/jo00174a015.
15. Böhme, H.; Ziegler, F. Untersuchungen in Der Isochroman- Und Isothiochroman-Reihe, XVII[1)] Gewinnung, Umsetzungen Und Derivate von 1-Aminoisochroman Und 1-Aminoisothiochroman. *Justus Liebigs Ann. Chem.* **1974**, *1974* (9), 1474–1485. https://doi.org/10.1002/jlac.197419740911.
16. Sheldrick, G. M. Crystal Structure Refinement with *SHELXL*. *Acta Crystallogr., Sect. C:Struct. Chem.* **2015**, *71* (1), 3–8. https://doi.org/10.1107/S2053229614024218.

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