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SHORT COMMUNICATIONS

Novel Derivatives of Adamantyl-substituted Quinolin-6-amines and Synthesis of Imidazo[4,5-*f*]quinolines Therefrom

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Abstract—*N*-(Adamantan-1-yl)alkyl-substituted 5-nitrosoquinolin-6-amines were synthesized for the first time by the amination of 5-nitrosoquinolin-6-ol with primary *N*-[(adamantan-1-yl)alkyl]amines. The resulting nitrosoquinolinamines were reduced with hydrazine hydrate over Pd/C to N^6-[(adamantan-1-yl)alkyl]quinoline-5,6-diamines. The latter were heated in formic acid to obtain previously unknown 3-[(adamantan-1-yl)alkyl]-3*H*-imidazo[4,5-*f*]quinolines.

Keywords: amination, adamantanylalkylamines, reduction, cyclization, 5-nitroso-6-quinolinamines, quinoline-5,6-diamines, 3*H*-imidazo[4,5-*f*]quinolines

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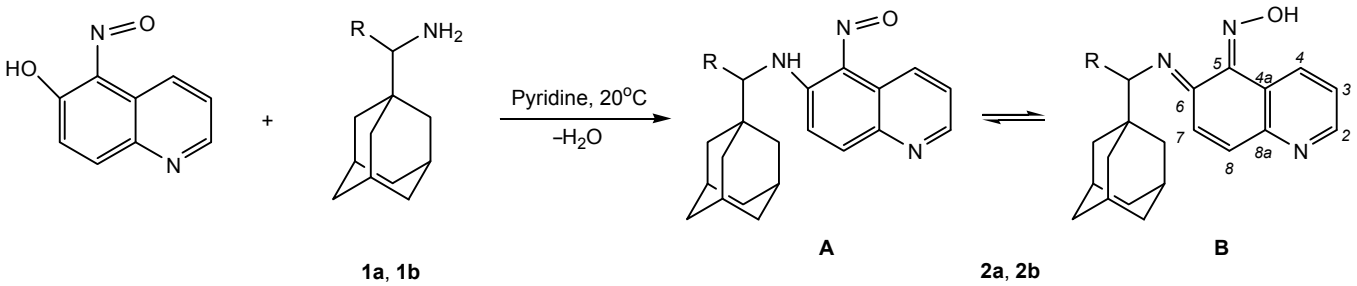
At present, 4- and 8-aminoquinoline derivatives have found practical application in antiprotozoal and antirheumatoid drugs, for example, Chloroquine and Chinocide. Some imidazo[4,5-*f*]quinolines were found to exhibit antibacterial and antifungal activities [1, 2]. The available evidence that adamantyl substitution can modify the pharmacological activity of a compound [3] stimulated studies on the synthesis of adamantane derivatives of quinolinamines [4]. However, adamantane derivatives of imidazo [4,5-*f*]quinolines are still unknown.

We previously found that the amination of 2-nitroso-1-naphthalen-1-ol and 5-nitrosoquinolin-8-ol with adamantyl-substituted amines form *N*-adamantylalkyl derivatives of 1-nitrosonaphthalen-2-amine and 5-nitrosoquinolin-8-amine, which readily reduced to the corresponding diamines [5, 6]. *N*-Adamantylalkyl-substituted naphthalene-1,2-diamines were used to synthesize naphtho[1,2-*d*]imidazoles containing an adamantyl fragment [7]. The amination of 5-nitrosoquinolin-6-ol with adamantyl-containing amines has never been studied, and *N*-adamantylalkyl-substituted 5-nitrosoquinolin-6-amines have never been synthesized, even though the presence of the easily modified nitroso group *ortho*- to the amino group opens up the way to previously unknown quinoline-5,6-diamines and imidazo[4,5-*f*]quinolines containing an *N*-adamantylalkyl fragment.

In the present work we have studied amination of 5-nitrosoquinolin-6-ol with the aim to synthesize *N*-adamantylalkyl-substituted 5-nitrosoquinolin-6-amines and then use the latter to synthesize the corresponding quinoline-5,6-diamines and imidazo[4,5-*f*]quinolines.

N-Adamantylalkyl-substituted 5-nitrosoquinolin-6-amines **2a** and **2b** were synthesized by the amination of 5-nitrosoquinolin-6-ol with a double excess of respectively [(adamantan-1-yl)methyl]amine (**1a**) and [1-(adamantan-1-yl)ethyl]amine (**1b**) in pyridine at 20°C (Scheme 1).

Scheme 1.



1a, **2a**, R = H; **1b**, **2b**, R = Me (49%).

Compounds **2a** and **2b** were then reduced with hydrazine hydrate on Pd/C in dichloromethane to obtain adamantyl-containing quinoline-5,6-diamines **3a** and **3b** (Scheme 2). 3-[(Adamantan-1-yl)alkyl]-3*H*-imidazo[4,5-*f*]quinolines **4a** and **4b** were synthesized by refluxing quinoline-5,6-diamines **3a** and **3b** in formic acid (Scheme 2).

The compositions of compounds **2a**, **2b**, **3a**, **3b**, **4a**, and **4b** were established by elemental analysis. The ^{1}H and ^{13}C NMR data confirmed the structures of the synthesized compounds. The ^{1}H NMR spectra were assigned using 2D homonuclear (COSY) and heteronuclear techniques (HSQC).

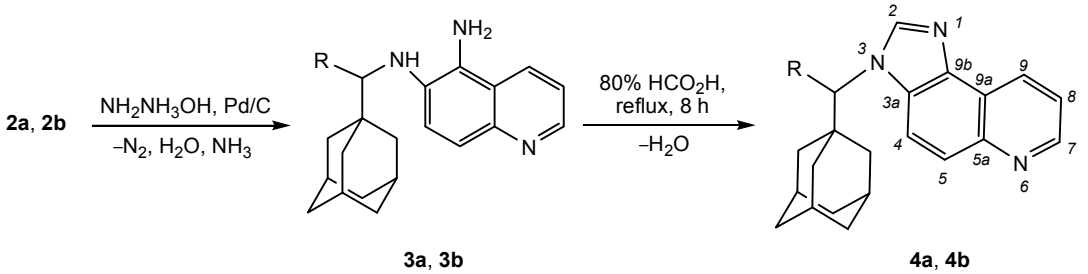
5-Nitrosoquinolin-6-amines **2a** and **2b** can exist in two tautomeric forms (Scheme 1).The ^{1}H NMR spectrum of compound **2a** in $CDCl_3$ displays two sets of signals at 6.81–14.71 ppm, one of which was assigned to the quinoline protons in hydroxyimine form **B**. The hydroxyimine OH proton signal appears at 14.75 ppm. The second set of signals can be assigned to the quinoline protons of nitroso form **A**. Evidence for the presence of the nitroso form is provided by the observation in the electronic absorption (EA) spectrum of compound **2a** in $CHCl_3$ of a band at 667 nm characteristic of the n,π^* transition of aromatic NO group. The fraction of nitroso form **A** in the $CDCl_3$ solution of compound **2a**, as estimated from the integral intensity ratio of the proton signals of the hydroxyimine and nitroso forms in the ^{1}H NMR spectrum, was 30%.

The ^{1}H NMR spectrum of compound **2b** in $CDCl_3$ shows signals of hydroxyimino form **B** only. The chemical shift 15.01 ppm is characteristic of hydroxyimine OH protons, and the EA spectrum of compound **2b** in $CHCl_3$ contains no absorption bands at 600–700 nm.

Amination of 5-nitrosoquinolin-6-ol (*general procedure*). A solution of 5.8 mmol of amine **1a** or **1b** in 20 mL of pyridine was added at 20°C to a solution of 0.5046 g (2.9 mmol) of 5-nitrosoquinolin-6-ol in 20 mL pyridine. In 96 h the mixture was poured into water with ice. The precipitate that formed was filtered off, washed with water, and dissolved in 50 mL of acetonitrile. The solution was filtered, the filtrate was evaporated in a vacuum, and the solid residue was washed with 10 mL of cold hexane and dried in a vacuum over NaOH.

***N*-[(Adamantan-1-yl)methyl]-5-nitrosoquinolin-6-amine (2a).** Yield 0.45 g (49%), yellow green crystals, mp 162–164°C. EA spectrum ($CHCl_3$), λ_{max}, nm (ε): 246 (34180), 317 (13320), 667 (45). **A**/**B** ratio 1 : 3.3. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: **A** + **B**:

Scheme 2.



2a, **3a**, **4a**, R = H; **2b**, **3b**, **4b**, R = Me (57–67%, 50–60%).

1.60–1.66 m (6H, β-CH_{2Ad}), 1.66–1.81 m (6H, δ-CH_{2Ad}), 2.03–2.10 m (3H, γ-CH_{Ad}), nitroso form **A**: 3.02 s (2H, CH_2), 6.50 br.s (1H, NH), 6.81 s (1H, H^8), 7.25 s (1H, H^7), 7.49 br.s (1H, H^3), 8.68 d (1H, H^4, *J* 8.7 Hz), 8.73 d (1H, H^2, *J* 3.4 Hz); hydroxyimine form **B**: 3.17 br.s (2H, NCH_2), 7.32 d (1H, H^7, *J* 9.8 Hz), 7.54 d.d (1H, H^3, *J* 8.0 Hz, 4.4 Hz), 8.01 d (1H, H^8, *J* 9.6 Hz), 8.79 d (1H, H^2, *J* 2.9 Hz), 9.39 d (1H, H^4, *J* 8.2 Hz), 14.71 br.s (1H, NOH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: hydroxyimine form **B**: 28.10 (γ-CH_{2Ad}), 36.55 (α-C_{Ad}), 36.62 (δ-CH_{2Ad}), 40.36 (β-CH_{2Ad}), 54.30 (NCH_2), 118.36 (C^7), 124.46 (C^3), 128.96 (C^4), 130.75 (C^{4a}), 138.51 (C^{8a}) 142.03 (C^6), 142.73 (C^8), 146.99 (C^5), 148.87 (C^2). Found, %: C 74.42; H 6.92; N 12.73. $C_{20}H_{23}N_3O$. Calculated, %: C 74.74; H 7.21; N 13.07.

***N*-[1-(Adamantan-1-yl)ethyl]-5-nitrosoquinolin-6-amine (2b).** Yield 0.48 g (49%), yellow green crystals, mp 143–145°C. EA spectrum ($CHCl_3$), λ_{max}, nm (ε): 247 (12774), 315 (6585), 439 (4745). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.25 d (3H, CH_3, *J* 6.9 Hz), 1.57–1.64 m (3H, β-CH_{2Ad}), 1.67 m (5H, δ-CH_{2Ad}), 1.70–1.77 m (4H, β- and δ-CH_{2Ad}), 2.02–2.08 m (3H, γ-CH_{Ad}), 3.61 br.q (3H, CH–Me, *J* 6.9 Hz), 7.34 d (1H, H^7, *J* 9.8 Hz), 7.54 d.d (1H, H^3, *J* 8.5 Hz, 4.4 Hz), 8.00 d (1H, H^8, *J* 9.8 Hz), 8.78 d (1H, H^2, *J* 4.4 Hz), 9.38 d (1H, H^4, *J* 8.2 Hz), 15.00 br.s (1H, NOH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.77 (CH_3), 28.18 (γ-CH_{2Ad}), 36.14 (α-C_{Ad}), 36.75 (δ-CH_{2Ad}), 38.47 (β-CH_{2Ad}), 57.56 (NCH), 118.46 (C^7), 124.44 (C^3), 128.95 (C^4), 130.89 (C^{4a}), 138.15 (C^{8a}), 142.00 (C^6), 142.74 (C^8), 146.71 (C^5), 148.82 (C^2). Found, %: C 74.91; H 7.20; N 12.34. $C_{21}H_{25}N_3O$. Calculated, %: C 75.19; H 7.51; N 12.53.

Reduction of *N*-[(adamantan-1-yl)alkyl]-5-nitrosoquinolin-6-amines (2a, 2b) (*general procedure*). To a solution of 0.87 mmol of *N*-substituted 5-nitrosoquinolin-6-amine **2a** or **2b** and 0.25 g of 0.5% Pd/C in 30 mL of dichloromethane we added 0.3 mL (6 mmol) of 95% hydrazine hydrate. In 1 h, the catalyst was filtered off, and the solvent was removed in a vacuum to leave an oily residue.

***N*^{6}-[(Adamantan-1-yl)methyl]quinoline-5,6-diamine (3a).** The residue was washed with 10 mL of hexane. Yield 0.18 g (67%), orange crystals, mp 168–170°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.67–1.81 m (12H, β- and δ-CH_{2Ad}), 2.02–2.07 m (3H, γ-CH_{Ad}), 2.92 s (1H, NCH_2), 3.71 br.s (2H, NH_2), 4.78 s (1H, NH), 7.30 d.d (1H, H^3, *J* 8.6 Hz, 4.1 Hz), 7.37 d (1H, H^7, *J* 9.1 Hz), 7.66 d (1H, H^8, *J* 9.1 Hz), 8.09 d.d (1H, H^2, *J* 8.6 Hz, 0.7 Hz), 8.68 d.d (1H, H^4, *J* 4.0 Hz, 1.6 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 28.40 (γ-CH_{2Ad}), 33.92 (α-C_{Ad}), 37.12 (δ-CH_{2Ad}), 40.81 (β-CH_{2Ad}), 57.26 (NCH_2), 119.09 (C^7), 119.89 (C^3), 120.17 (C^{4a}), 121.82 (C^8), 125.73 (C^5), 127.91 (C^4), 134.99 (C^{8a}), 143.17 (C^6), 146.53 (C^2). Found, %: C 78.77; H 8.05; N 12.97. $C_{20}H_{25}N_3$. Calculated, %: C 78.14; H 8.20; N 13.67.

***N*^{6}-[1-(Adamantan-1-yl)ethyl]quinoline-5,6-diamine (3b).** The residue was washed with 10 mL of cold ethyl acetate. Yield 0.167 g (57%), yellow crystals, mp 163–165°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.11 d (3H, CH_3, *J* 6.4 Hz), 1.58–1.83 m (12H, β- and δ-CH_{2Ad}), 2.00–2.09 m (3H, γ CH_{Ad}), 3.16 q (1H, CHMe, *J* 6.4 Hz), 3.51 br.s (2H, NH_2), 3.69 br.s (1H, NH), 7.30 d.d (1H, H^3, *J* 8.5 Hz, 4.1 Hz), 7.34 d (1H, H^7, *J* 8.9 Hz), 7.65 d (1H, H^8, *J* 8.9 Hz), 8.08 d.d (1H, H^2, *J* 8.7 Hz), 8.68 d.d (1H, H^4, *J* 2.8 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.79 (CH_3), 28.57 (γ-CH_{2Ad}), 36.68 (α-C_{Ad}), 37.29 (δ-CH_{2Ad}), 38.89 (β-CH_{2Ad}), 58.32 (CH-Me), 119.93 (C^3), 120.40 (C^7), 120.79 (C^{4a}), 122.11 (C^8), 125.90 (C^5), 127.85 (C^4), 134.53 (C^{8a}), 143.38 (C^6), 146.52 (C^2). Found, %: C 78.95; H 8.86; N 12.87. $C_{21}H_{27}N_3$. Calculated, %: C 78.46; H 8.47; N 13.07.

Cyclization (*general procedure*). To 0.8 mmol of quinoline-5,6-diamine **3a**, **3b** we added 10 mL of 80% formic acid. The reaction mixture was heated under reflux for 8 h, cooled down, poured into water with ice, and 5% NaOH was added to pH ≈ 8. The precipitate that formed was filtered off, washed with 20 mL of water, and recrystallized from 40% ethanol with activated charcoal.

3-[(Adamantan-1-yl)methyl]-3*H*-imidazo[4,5-*f*]-quinoline (4a). Yield 0.127 g (50%), light beige crystals, mp 129–131°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.60 m (6H, β-CH_{2Ad}), 1.71–1.58 m (6H, δ-CH_{2Ad}), 1.98–2.05 m (3H, γ-CH_{Ad}), 3.97 s (2H, NCH_2), 7.55 d.d (1H, H^8, *J* 8.2 Hz, 4.1 Hz), 7.78 d (1H, H^4, *J* 9.2 Hz), 7.95 s (1H, H^2), 7.99 d (1H, H^5, *J* 9.1 Hz), 8.92 d.d (1H, H^7, *J* 4.2 Hz, 1.7 Hz), 8.96 d.d.d (1H, H^9, *J* 8.2 Hz, 1.7 Hz, 0.8 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 28.06 (γ-CH_{2Ad}), 35.25 (α-C_{Ad}), 36.48 (δ-CH_{2Ad}), 40.73 (β-CH_{2Ad}), 57.45 (NCH_2), 114.30 (C^4), 121.36 (C^8), 122.43 (C^{9a}), 125.00 (C^5), 130.05 (C^9), 131.30 (C^{5a}), 142.94 (C^2), 142.94 (C^{3a}), 145.79 (C^{9b}), 148.48 (C^7). Found, %: C 79.97; H 7.05; N 12.98. $C_{21}H_{23}N_3$. Calculated, %: C 79.46; H 7.30; N 13.24.

3-[(Adamantan-1-yl)ethyl]-3*H*-imidazo[4,5-*f*]-quinoline (4b). Yield 0.16 g (60%), light beige crystals, mp 144–146°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.53 d (3H, CH_3, *J* 9.9 Hz), 1.55–1.73 m (12H, β- and δ-CH_{2Ad}), 2.00 br.s (3H, γ-CH_{Ad}), 4.26 br.s (1H, CH-Me), 7.55 d.d (1H, H^8, *J* 8.2 Hz, 4.3 Hz), 7.79 d (1H, H^4, *J* 7.9 Hz), 7.98 d (1H, H^5, *J* 8.7 Hz), 8.08 br.s (1H, H^2), 8.92 d.d (1H, H^7, *J* 4.2 Hz, 1.4 Hz), 8.96 d.d (H, H^9, *J* 8.2 Hz, 0.9 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 15.00 (CH_3), 28.17 (γ-CH_{2Ad}), 36.62 (δ-CH_{2Ad}), 37.53 (α-C_{Ad}), 39.06 (β-CH_{2Ad}), 60.71 (CH-Me), 114.34 (C^4), 121.31 (C^8), 122.46 (C^{9a}), 124.80 (C^5), 130.02 (C^9), 131.39 (C^{5a}), 140.13 (C^{3a}), 140.13 (C^2), 145.88 (C^{9b}), 148.48 (C^7). Found, %: C 80.06; H 7.15; N 12.14. $C_{22}H_{25}N_3$. Calculated, %: C 79.72; H 7.60; N 12.68.

The EA spectra were measured on a Helios Omega instrument in the range 200–500 nm for concentrations of 5×10^{-5} M and 500–800 nm for concentrations of 1×10^{-2} M. The ^{1}H, ^{13}C, COSY, and HSQC NMR spectra were registered on a Bruker Avance III 600 spectrometer, Krasnoyarsk Regional Center for Research Equipment, Krasnoyarsk Research Center, Siberian Branch, Russian Academy of Sciences. The ^{1}H and ^{13}C NMR spectra in $CDCl_3$ were referenced relative to the residual proton signals and the carbon signals of the solvent (δ_H 7.24, δ_C 77.2 ppm).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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