ISSN 1070-4280, Russian Journal of Organic Chemistry, 2013, Vol. 49, No. 1, pp. 1–7. © Pleiades Publishing, Ltd., 2013.
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Dedicated to Full Member of the Russian Academy of Sciences G.A. Tolstikov on his 80th anniversary

Arylation of Adamantanamines: VI.* Palladium-Catalyzed Arylation of Amines and Diamines of the Adamantane Series with 3-Bromopyridine

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Received February 22, 2012

Abstract—Palladium-catalyzed amination of 3-bromopyridine with amines of the adamantane series in the presence of $Pd(dba)_2$/L [L = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl or 2-dimethylamino-2′-dicyclohexylphosphinobiphenyl] gave the desired *N*-(pyridin-3-yl)-substituted amines in 74–97% yields. Diamines of the adamantane series reacted with 2 equiv of 3-bromopyridine in a complicated fashion to produce mono- and triaryl-substituted derivatives as by-products, while the yields of *N*,*N*′-diarylation products were 18–56%.

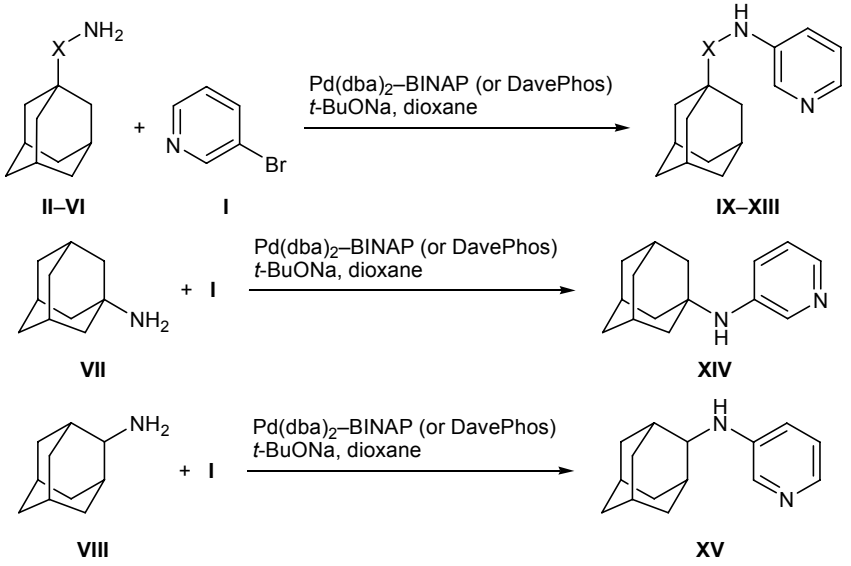
DOI: 10.1134/S1070428013010016

Until present, numerous adamantane derivatives, primarily adamantanamines, have been studied as physiologically active substances, and extensive studies in this field are now in progress. These compounds exhibit mainly psychotropic or antibacterial activity. An important place among adamantanamine derivatives is occupied by those containing heterocyclic substituents. Physiological action of *N*-pyridinyl-substituted adamantanamines has not been understood completely. It was found that some pyridin-3-yl derivatives of adamantan-2-amine produced two- or three-phase effect on spontaneous motor activity, which is typical of many adamantane derivatives; all these compounds were characterized by moderate to low acute daily toxicity [2]. Compounds possessing a high stimulating neuropsychotropic activity were revealed among adamantyl derivatives of 3-aminopyridine [3, 4], and search for low-toxic long-acting drugs enhancing working and mental capacities is possible in this series. Our studies are aimed at extending the series of adamantane amines modified with aromatic and heteroaromatic substituents. By palladium-catalyzed amination we synthesized a number of *N*-(halophenyl)- [5–8] and *N*-(pyridin-2-yl)adamantanamines [8], and two of the latter showed some nootropic activity. Taking the above stated into account, in the present work we studied the formation of isomeric *N*-(pyridin-3-yl)-substituted amines and diamines of the adamantane series in palladium-catalyzed amination reactions.

Palladium-catalyzed amination of 3-bromopyridine (**I**) with amines **II**–**VIII** of the adamantane series was carried out with equimolar amounts of the reactants in the presence of $Pd(dba)_2$/BINAP [4–4.5 mol %, BINAP = 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl] and sodium *tert*-butoxide as base by heating in boiling dioxane (c = 0.1 mol/l) for several hours (Scheme 1). In most cases, the yields of target *N*-(pyridin-3-yl)-substituted amines **IX**–**XII** and **XV** were 85–97% (see table, run nos. 1–4, 9; hereinafter, the yields refer to

* For communication V, see [1].

Scheme 1.



II, **IX**, X = OCH_2CH_2; **III**, **X**, X = CH_2; **IV**, **XI**, X = CHPh; **V**, **XII**, X = $CH_2CH(Me)$; **VI**, **XIII**, X = CH(Et).

the products isolated by column chromatography on silica gel). Some difficulties were encountered in the arylation of sterically hindered amines **VI** and **VII**. The yields of **XIII** and **XIV** in the presence of BINAP as ligand were as low as 37 and 20%, respectively (run nos. 5, 7); however, replacement of BINAP by a more efficient ligand, DavePhos [2-(dicyclohexylphosphino)-2′-dimethylaminobiphenyl] and increase of the amount of the catalyst to 8 mol % improved the yields to 70–74% (run nos. 6, 8).

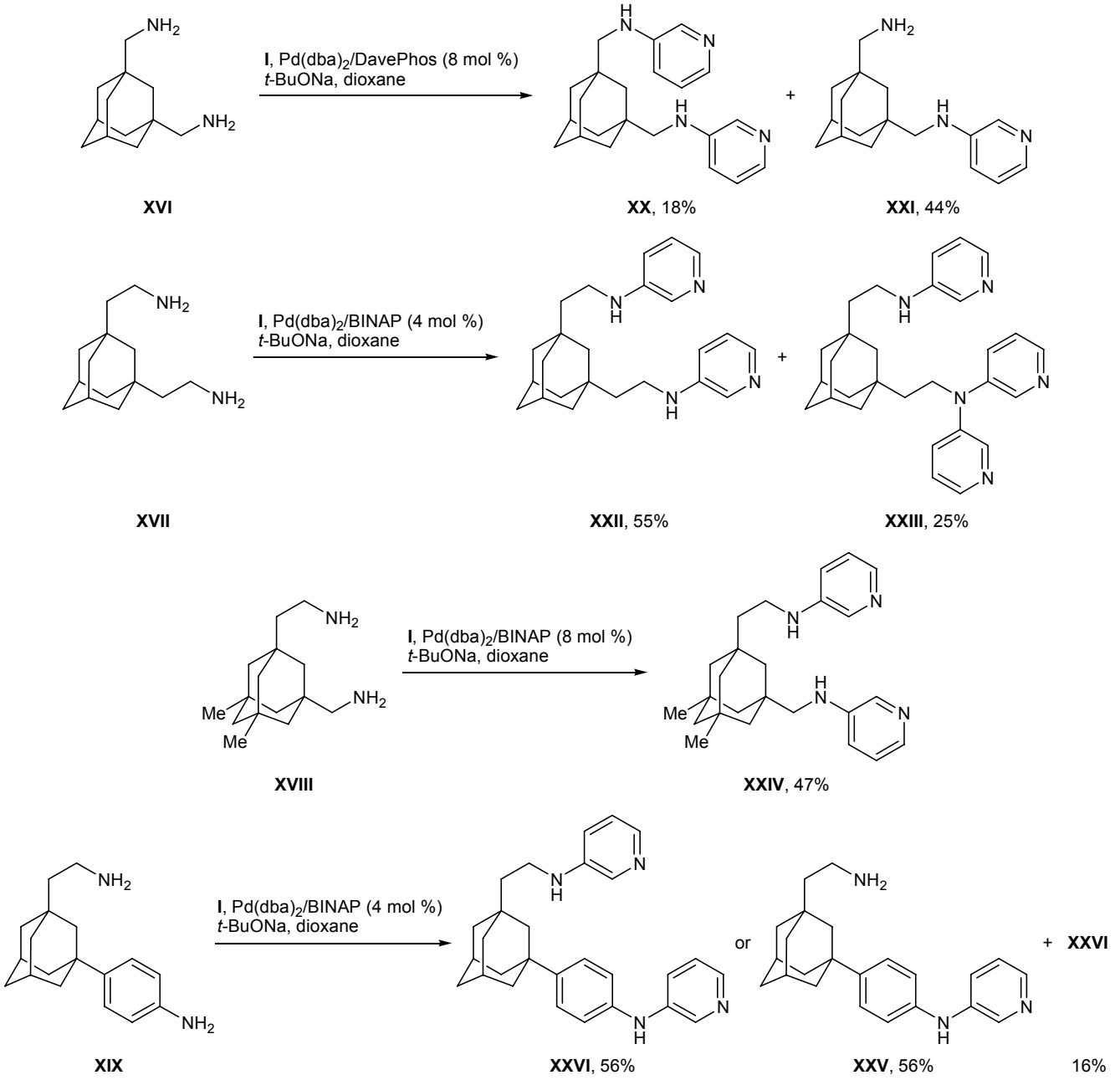
In no case even traces of *N*,*N*-diarylation product were detected, though the formation of tertiary amines was a serious competing process in reactions of amines **II**–**VI** with more reactive 2-bromopyridine [8]. Our attempts to obtain *N*,*N*-diarylation products by raising the amount of 3-bromopyridine to 4 equiv and using 8 mol % of the catalyst were unsuccessful even with least sterically hindered amine **II**; as a result, only compound **IX** was obtained.

We also studied palladium-catalyzed *N*,*N*′-diarylation of diamines **XVI**–**XIX** under analogous conditions (Scheme 2). The reaction of 3-bromopyridine with adamantane-1,3-diyldimethanamine (**XVI**) was difficult to occur, BINAP as ligand turned out to be completely ineffective, and only the catalytic system $Pd(dba)_2$/DavePhos allowed us to obtain *N*,*N*′-diaryl derivative **XX** in 18% yield; the major product was monoarylation product **XXI** (yield 44%). The reaction of 2,2′-(adamantane-1,3-diyl)diethanamine (**XVII**) with 2 equiv of 3-bromopyridine gave 55% of *N*,*N*′-di-

Synthesis of *N*-(pyridin-3-yl)-substituted adamantane amines **IX**–**XV**

Run no.	Initial amine	Ligand	$Pd(dba)_2$/L, mol %	Product	Yield, %
1	**II**	BINAP	4:4.5	**IX**	85
2	**III**	BINAP	4:4.5	**X**	95
3	**IV**	BINAP	4:4.5	**XI**	97
4	**V**	BINAP	4:4.5	**XII**	88
5	**VI**	BINAP	4:4.5	**XIII**	37
6	**VI**	DavePhos	8:9	**XIII**	74
7	**VII**	BINAP	8:9	**XIV**	20
8	**VII**	DavePhos	8:9	**XIV**	70
9	**VIII**	BINAP	4:4.5	**XV**	95

Scheme 2.



arylation product **XXII** and 25% of *N*,*N*,*N*′-triaryl derivative **XXIII**. This reaction is the only example of diarylation of a primary amino group with 3-bromopyridine. Arylation of both amino groups in unsymmetrical diamine **XVIII** containing aminomethyl and 2-aminoethyl fragments was fairly successful in the presence of BINAP as ligand, and the yield of *N*,*N*′-diarylation product **XXIV** was 47%. As might be expected, unsymmetrical diamine **XIX** reacted with 1 equiv of 3-bromopyridine mainly at the aromatic amino group to produce 31% of compound **XXV** and 16% of diaryl derivative **XXVI**. The latter was isolated in 56% yield in the reaction of **XIX** with 2 equiv of 3-bromopyridine.

EXPERIMENTAL

The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance-400 spectrometer at 400 and 100.6 MHz, respectively, using $CDCl_3$ as solvent and reference (δ 7.25, δ_C 77.00 ppm). The mass spectra (MALDI-TOF, positive ion detection) were obtained

on a Bruker Daltonics Ultraflex instrument using 1,8,9-trihydroxyanthracene as matrix and poly(ethylene glycols) as internal references. Preparative column chromatography was performed on silica gel (40–60 μm; Merck). Commercially available 3-bromopyridine, sodium *tert*-butoxide, BINAP, and DavePhos were used without additional purification. Amines **II** [9] and **III**–**VIII** [8, 10–12] and diamines **XVI**–**XIX** [8, 10] were synthesized according to known methods; $Pd(dba)_2$ was prepared as described in [13] and was used without recrystallization. Dioxane was distilled first over alkali and then over metallic sodium; methylene chloride and methanol were distilled.

***N*-Pyridinyl-substituted amines IX–XV (*general procedure*).** A two-necked flask was charged under argon with 0.25 mmol (40 mg) of 3-bromopyridine, 4 mol % (6 mg) of $Pd(dba)_2$, and 4.5 mol % (7 mg) of BINAP, and 2.5 ml of anhydrous dioxane, 0.25 mmol of amine **II**–**VIII**, and 0.38 mmol (35 mg) of sodium *tert*-butoxide were added. The mixture was stirred for 7 h under reflux and cooled, the precipitate was filtered off, the filtrate was evaporated, the solid residue was dissolved in methylene chloride, the solution was washed with water, the organic phase was dried over sodium sulfate and evaporated under reduced pressure, and the residue was subjected to chromatographic separation on silica gel using a sequence of eluents: CH_2Cl_2, CH_2Cl_2–MeOH (200:1 to 3:1), CH_2Cl_2–MeOH–aq. NH_3. The products were isolated with CH_2Cl_2–MeOH (50:1) (unless otherwise stated) as colorless or light yellow oily substances.

***N*-[2-(Adamantan-1-yloxy)ethyl]pyridin-3-amine (IX)** was synthesized from 0.25 mmol (49 mg) of amine **II**. Yield 58 mg (85%). ^{1}H NMR spectrum, δ, ppm: 1.55–1.64 m (6H), 1.70–1.72 m (6H), 2.13 br.s (3H), 3.22 q (2H, ^3J = 5.2 Hz), 3.60 t (2H, ^3J = 5.2 Hz), 4.12 br.s (1H), 6.87 d.d.d (1H, ^3J = 8.2, ^4J = 2.8, 1.3 Hz), 7.04 d.d (1H, ^3J = 8.2, 4.7 Hz), 7.92 d.d (1H, ^3J = 4.7, ^4J = 1.3 Hz), 8.03 d (1H, ^4J = 2.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 30.4 (3C), 36.3 (3C), 41.5 (3C), 43.9 (1C), 58.0 (1C), 72.4 (1C), 118.9 (1C), 123.6 (1C), 136.4 (1C), 138.8 (1C), 144.3 (1C). Mass spectrum: *m*/*z* 273.193 $[M + H]^+$. $C_{17}H_{25}N_2O$. Calculated: (*M* + H) 273.197.

***N*-(Adamantan-1-ylmethyl)pyridin-3-amine (X)** was synthesized from 0.25 mmol (41 mg) of amine **III**. Yield 58 mg (95%). ^{1}H NMR spectrum, δ, ppm: 1.53–1.55 m (6H), 1.60–1.73 m (6H), 1.97 br.s (3H), 2.76 d (2H, ^3J = 6.1 Hz), 3.79 br.s (1H), 6.84 d.d.d (1H, ^3J = 8.2, ^4J = 2.8, 1.3 Hz), 7.00 d.d (1H, ^3J = 8.2, 4.5 Hz), 7.87 d.d (1H, ^3J = 4.5, ^4J = 1.3 Hz), 8.01 d (1H, ^4J = 2.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 28.2 (3C), 33.9 (1C), 36.9 (3C), 40.5 (3C), 55.6 (1C), 117.9 (1C), 123.5 (1C), 135.9 (1C), 137.9 (1C), 145.1 (1C). Mass spectrum: *m*/*z* 243.190 $[M + H]^+$. $C_{16}H_{23}N_2$. Calculated (*M* + H) 243.186.

***N*-[Adamantan-1-yl(phenyl)methyl]pyridin-3-amine (XI)** was synthesized from 0.25 mmol (60 mg) of amine **IV**; eluent CH_2Cl_2–MeOH (50:1 to 35:1). Yield 77 mg (97%). ^{1}H NMR spectrum, δ, ppm: 1.46–1.52 m (3H), 1.55–1.61 m (3H), 1.65–1.74 m (6H), 1.99 br.s (3H), 3.85 d (1H, ^3J = 6.3 Hz), 4.42 d (1H, ^3J = 6.3 Hz), 6.65 d.d.d (1H, ^3J = 8.3, ^4J = 2.7, 1.1 Hz), 6.89 d.d (1H, ^3J = 8.2, 4.7 Hz), 7.19–7.29 m (5H), 7.81 d (1H, ^3J = 4.7 Hz), 7.98 d (1H, ^4J = 2.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 28.4 (3C), 36.5 (1C), 36.9 (3C), 39.3 (3C), 67.7 (1C), 118.7 (1C), 123.5 (1C), 127.1 (1C), 127.8 (2C), 128.7 (2C), 136.7 (1C), 138.2 (1C), 139.3 (1C), 143.8 (1C). Mass spectrum: *m*/*z* 319.214 $[M + H]^+$. $C_{22}H_{27}N_2$. Calculated: (*M* + H) 319.217.

***N*-[1-(Adamantan-1-yl)propan-2-yl]pyridin-3-amine (XII)** was synthesized from 0.25 mmol (48 mg) of amine **V**. Yield 59 mg (88%). ^{1}H NMR spectrum, δ, ppm: 1.14 d (3H, ^3J = 6.2 Hz), 1.24 d.d (1H, ^2J = 14.5, ^3J = 4.3 Hz), 1.29 d.d (1H, ^2J = 14.5, ^3J = 7.0 Hz), 1.50–1.52 m (6H), 1.55–1.69 m (6H), 1.91 br.s (3H), 3.44 br.s (1H), 3.57 br.s (1H), 6.80 d.d.d (1H, ^3J = 8.3, ^4J = 2.9, 1.3 Hz), 7.03 d.d (1H, ^3J = 8.3, 4.7 Hz), 7.87 d.d (1H, ^3J = 4.7, ^4J = 1.3 Hz), 7.94 d (1H, ^4J = 2.9 Hz). ^{13}C NMR spectrum, δ_C, ppm: 23.0 (1C), 28.5 (3C), 32.4 (1C), 36.9 (3C), 43.0 (3C), 43.9 (1C), 52.7 (1C), 118.3 (1C), 123.7 (1C), 136.1 (1C), 137.8 (1C), 143.2 (1C). Mass spectrum: *m*/*z* 271.224 $[M + H]^+$. $C_{18}H_{27}N_2$. Calculated: (*M* + H) 271.217.

***N*-[1-(Adamantan-1-yl)propyl]pyridin-3-amine (XIII).** *a*. Compound **XIII** was synthesized from 0.25 mmol (48 mg) of amine **VI** using $Pd(dba)_2$/BINAP (4/4.5 mol %, 6/7 mg) as catalytic system. Yield 25 mg (37%).

b. The reaction was carried out with the same amounts of the reactants using $Pd(dba)_2$/DavePhos (8/9 mol %, 12/9 mg) as catalytic system. Eluent CH_2Cl_2–MeOH (100:1). Yield 50 mg (74%). ^{1}H NMR spectrum, δ, ppm: 0.87 t (3H, ^3J = 7.3 Hz), 1.16 d.d.q (1H, ^2J = 14.6, ^3J = 10.8, 7.3 Hz), 1.47–1.72 m (12H), 1.79 d.q.d (1H, ^2J = 14.6, ^3J = 7.3, 2.9 Hz), 1.95 br.s (3H), 2.78 t.d (1H, ^3J = 10.5, 2.9 Hz), 3.42 d (1H, ^3J = 10.0 Hz), 6.83 d.d.d (1H, ^3J = 8.4, ^4J = 2.6, 0.9 Hz), 6.98 d.d (1H, ^3J = 8.4, 4.6 Hz), 7.81 d (1H, ^3J = 4.6 Hz), 8.01 br.s (1H). ^{13}C NMR spectrum, δ_C, ppm: 11.9 (1C), 22.9 (1C), 28.4 (3C), 37.1 (3C), 37.8 (1C),

39.0 (3C), 64.3 (1C), 117.6 (1C), 123.6 (1C), 135.8 (1C), 137.2 (1C), 146.3 (1C). Mass spectrum: *m*/*z* 271.211 $[M + H]^+$. $C_{18}H_{27}N_2$. Calculated: (*M* + H) 271.217.

***N*-(Adamantan-1-yl)pyridine-3-amine (XIV).** *a*. Compound **XIV** was synthesized from 0.25 mmol (38 mg) of amine **VII** using $Pd(dba)_2$/BINAP (8/9 mol %, 12/14 mg) as catalytic system. Yield 12 mg (20%).

b. The reaction was carried out with the same amounts of the reactants in the presence of $Pd(dba)_2$/DavePhos (8/9 mol %, 12/9 mg). Yield 40 mg (70%). ^{1}H NMR spectrum, δ, ppm: 1.61–1.70 m (6H), 1.84–1.86 m (6H), 2.10 br.s (3H), 3.35 br.s (1H), 7.02 d.d (1H, ^3J = 8.1, 4.4 Hz), 7.07 d.d.d (1H, ^3J = 8.1, ^4J = 2.7, 1.5 Hz), 7.98 d (1H, ^3J = 4.4 Hz), 8.10 d (1H, ^4J = 2.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 29.6 (3C), 36.3 (3C), 43.2 (3C), 52.3 (1C), 123.2 (1C), 124.3 (1C), 139.9 (1C), 140.7 (1C), 142.3 (1C). Mass spectrum: *m*/*z* 229.173 $[M + H]^+$. $C_{15}H_{21}N_2$. Calculated: (*M* + H) 229.171.

***N*-(Adamantan-2-yl)pyridin-3-amine (XV)** was synthesized from 0.25 mmol (38 mg) of amine **VIII**; eluent CH_2Cl_2–MeOH (100:1 to 50:1). Yield 54 mg (95%). ^{1}H NMR spectrum, δ, ppm: 1.60 d (2H, *J* = 12.6 Hz), 1.74 br.s (2H), 1.76–1.92 m (8H), 1.99 br.s (3H), 3.51 br.s (1H), 3.99 br.s (1H), 6.82 d.d.d (1H, ^3J = 8.3, ^4J = 2.8, 1.3 Hz), 7.03 d.d (1H, ^3J = 8.3, 4.7 Hz), 7.88 d.d (1H, ^3J = 4.7, ^4J = 1.3 Hz), 8.00 d (1H, ^4J = 2.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 27.2 (1C), 27.3 (1C), 31.3 (2C), 31.4 (2C), 37.2 (2C), 37.5 (1C), 56.5 (1C), 118.5 (1C), 123.6 (1C), 136.4 (1C), 138.0 (1C), 143.3 (1C). Mass spectrum: *m*/*z* 229.163 $[M + H]^+$. $C_{15}H_{21}N_2$. Calculated: (*M* + H) 229.171.

***N*,*N*′-[Adamantane-1,3-diylbismethylene]dipyridin-3-amine (XX)** was synthesized from 0.25 mmol (49 mg) of diamine **XVI** and 0.55 mmol (87 mg) of 3-bromopyridine in the presence of 8 mol % (12 mg) of $Pd(dba)_2$, 9 mol % (9 mg) of DavePhos, and 0.73 mmol (70 mg) of sodium *tert*-butoxide in 2.5 ml of dioxane. The product was isolated by chromatography using CH_2Cl_2–MeOH (10:1) as eluent. Yield 16 mg (18%). ^{1}H NMR spectrum, δ, ppm: 1.38 br.s (2H), 1.46–1.59 m (8H), 1.64 br.s (2H), 2.12 br.s (2H), 2.83 s (4H), 3.78 br.s (2H), 6.85 d (2H, ^3J = 8.1 Hz), 7.03 d.d (2H, ^3J = 8.1, 4.5 Hz), 7.89 d (2H, ^3J = 4.5 Hz), 8.02 br.s (2H). ^{13}C NMR spectrum, δ_C, ppm: 28.3 (2C), 34.8 (2C), 36.3 (1C), 40.0 (4C), 43.5 (1C), 55.4 (2C), 118.1 (2C), 123.6 (2C), 136.0 (2C), 138.2 (2C), 145.0 (2C). Mass spectrum: *m*/*z* 349.245 $[M + H]^+$. $C_{22}H_{29}N_4$. Calculated: (*M* + H) 349.239.

***N*-{[3-(Aminomethyl)adamantan-1-yl]methyl}-pyridin-3-amine (XXI)** was the major product of the reaction of diamine **XVI** with 3-bromopyridine. It was isolated by chromatography using CH_2Cl_2–MeOH–aq. NH_3 (100:20:1) as eluent. Yield 30 mg (44%). ^{1}H NMR spectrum, δ, ppm: 1.33 br.s (2H), 1.38–1.55 m (8H), 1.60 br.s (2H), 2.07 br.s (2H), 2.41 s (2H), 2.80 s (2H), 2.83 br.s (2H), 3.93 s (1H), 6.85 d.d (1H, ^3J = 8.1, ^4J = 2.5 Hz), 7.02 d.d (1H, ^3J = 8.1, 4.6 Hz), 7.85 d (1H, ^3J = 4.6 Hz), 8.03 d (1H, ^4J = 2.5 Hz). ^{13}C NMR spectrum, δ_C, ppm: 28.3 (2C), 34.2 (1C), 34.6 (1C), 36.4 (1C), 39.4 (2C), 40.1 (2C), 42.7 (1C), 53.7 (1C), 55.4 (1C), 118.1 (1C), 123.7 (1C), 135.8 (1C), 137.8 (1C), 145.2 (1C). Mass spectrum: *m*/*z* 272.210 $[M + H]^+$. $C_{17}H_{26}N_3$. Calculated: (*M* + H) 272.213.

***N*,*N*′-[Adamantane-1,3-diylbis(ethane-2,1-diyl)]-dipyridin-3-amine (XXII).** *a*. Compound **XXII** was synthesized from 0.25 mmol (56 mg) of diamine **XVII** and 0.55 mmol (87 mg) of 3-bromopyridine in the presence of 8 mol % (12 mg) of $Pd(dba)_2$, 9 mol % (14 mg) of BINAP, and 0.73 mmol (70 mg) of sodium *tert*-butoxide in 2.5 ml of dioxane. The product was isolated by chromatography using CH_2Cl_2–MeOH (20:1 to 10:1) as eluent. Yield 51 mg (54%).

b. The reaction was carried out with the same amounts of the reactants using 4 mol % (6 mg) of $Pd(dba)_2$ and 4.5 mol % (7 mg) of BINAP; eluent CH_2Cl_2–MeOH (35:1 to 10:1). Yield 53 mg (55%). ^{1}H NMR spectrum, δ, ppm: 1.31 br.s (2H), 1.39–1.48 m (8H), 1.51–1.57 m (4H), 1.61 br.s (2H), 2.05 br.s (2H), 3.07–3.13 m (4H), 3.58 br.s (2H), 6.83 d.d (2H, ^3J = 8.2, ^4J = 2.4 Hz), 7.05 d.d (2H, ^3J = 8.2, 4.7 Hz), 7.92 d (2H, ^3J = 4.7 Hz), 7.98 d (2H, ^4J = 2.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 28.8 (2C), 32.7 (2C), 36.3 (1C), 38.2 (2C), 41.9 (4C), 43.4 (2C), 47.7 (1C), 118.3 (2C), 123.7 (2C), 135.9 (2C), 138.4 (2C), 144.3 (2C). Mass spectrum: *m*/*z* 377.268 $[M + H]^+$. $C_{17}H_{26}N_3$. Calculated: (*M* + H) 377.271.

***N*-[2-(3-{2-[Di(pyridin-3-yl)amino]ethyl}adamantan-1-yl)ethyl]pyridin-3-amine (XXIII)** was isolated as the second product in the reaction of diamine **XVII** with 3-bromopyridine. Yield 32 mg (37%) (*a*; eluent CH_2Cl_2–MeOH, 10:1); 21 mg (25%) (*b*; CH_2Cl_2–MeOH, 20:10 to 10:1). ^{1}H NMR spectrum, δ, ppm: 1.28 br.s (2H), 1.38–1.48 (8H), 1.49–1.56 m (4H), 1.60 br.s (2H), 2.04 br.s (2H), 3.06–3.12 m (2H), 3.61 br.s (1H), 3.71–3.77 m (2H), 6.82 d (1H, ^3J = 8.2 Hz), 7.04 d.d (1H, ^3J = 8.2, 4.8 Hz), 7.17 d.d (2H, ^3J = 8.1, 4.5 Hz), 7.25 d (2H, ^3J =

8.1 Hz), 7.90 d (1H, ^3J = 4.8 Hz), 7.97 br.s (1H), 8.21 d (2H, ^3J = 4.5 Hz), 8.31 d (2H, ^4J = 2.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 28.8 (2C), 32.6 (2C), 36.3 (1C), 38.2 (1C), 40.1 (1C), 41.5 (2C), 41.8 (2C), 43.4 (1C), 46.9 (1C), 47.4 (1C), 118.3 (1C), 123.6 (1C), 123.8 (2C), 127.4 (2C), 135.8 (1C), 138.4 (1C), 142.7 (2C), 142.9 (2C), 143.2 (2C), 144.3 (1C). Mass spectrum: *m*/*z* 454.302 $[M + H]^+$. $C_{29}H_{36}N_5$. Calculated: (*M* + H) 454.297.

***N*-({3,5-Dimethyl-7-[2-(pyridin-3-ylamino)ethyl]-adamantan-1-yl}methyl)pyridin-3-amine (XXIV)** was synthesized from 0.25 mmol (59 mg) of diamine **XVIII** and 0.55 mmol (87 mg) of 3-bromopyridine in the presence of 4 mol % (6 mg) of $Pd(dba)_2$, 4.5 mol % (7 mg) of DavePhos, and 0.73 mmol (70 mg) of sodium *tert*-butoxide in 2.5 ml of dioxane. The product was isolated by chromatography using CH_2Cl_2–MeOH (20:1 to 10:1) as eluent. Yield 46 mg (47%). ^{1}H NMR spectrum, δ, ppm: 0.86 s (6H), 1.12–1.22 m (12H), 1.45–1.49 m (2H), 2.86 d (2H, ^3J = 5.8 Hz), 3.09–3.12 m (2H), 3.54 br.s (1H), 3.72 br.s (1H), 6.82 d.d.d (1H, ^3J = 8.3, ^4J = 2.9, 1.3 Hz), 6.85 d.d.d (1H, ^3J = 8.3, ^4J = 2.9, 1.3 Hz), 7.02–7.07 m (2H), 7.90 d.d (1H, ^3J = 4.6, ^4J = 2.9 Hz), 7.93 d.d (1H, ^3J = 4.7, ^4J = 2.9 Hz), 7.98 d (1H, ^4J = 1.3 Hz), 8.02 d (1H, ^4J = 1.3 Hz). ^{13}C NMR spectrum, δ_C, ppm: 30.1 (2C), 31.7 (2C), 34.2 (1C), 36.5 (1C), 38.4 (1C), 42.7 (1C), 44.4 (1C), 46.4 (2C), 48.3 (2C), 50.6 (1C), 54.9 (1C), 118.1 (1C), 118.3 (1C), 123.6 (2C), 135.9 (1C), 136.0 (1C), 138.3 (1C), 138.5 (1C), 144.3 (1C), 145.0 (1C). Mass spectrum: *m*/*z* 391.288 $[M + H]^+$. $C_{25}H_{35}N_4$. Calculated: (*M* + H) 391.286.

***N*-{4-[3-(2-Aminomethyl)adamantan-1-yl]-phenyl}pyridin-3-amine (XXV)** was synthesized from 0.37 mmol (102 mg) of diamine **XIX** and 0.37 mmol (60 mg) of 3-bromopyridine in the presence of 4 mol % (9 mg) of $Pd(dba)_2$, 4.5 mol % (10 mg) of BINAP, and 0.56 mmol (54 mg) of sodium *tert*-butoxide in 3.5 ml of dioxane. The product was isolated by chromatography using CH_2Cl_2–MeOH–aq. NH_3 (100:20:1) as eluent. Yield 40 mg (31%). ^{1}H NMR spectrum, δ, ppm: 1.30–1.34 m (2H), 1.45–1.69 m (10H), 1.76–1.86 m (4H), 2.13 br.s (2H), 2.70–2.74 m (2H), 5.95 br.s (1H), 7.03 d (2H, ^3J = 8.7 Hz), 7.12 d.d (1H, ^3J = 8.3, 4.7 Hz), 7.26 d (2H, ^3J = 8.7 Hz), 7.35 d.d.d (1H, ^3J = 8.3, ^4J = 2.8, 1.5 Hz), 8.10 d.d (1H, ^3J = 4.7, ^4J = 1.5 Hz), 8.33 d (1H, ^4J = 2.8 Hz). ^{13}C NMR spectrum, δ_C, ppm: 29.2 (2C), 33.0 (1C), 36.1 (1C), 36.4 (1C), 36.5 (1C), 41.6 (2C), 42.6 (2C), 48.3 (1C), 48.6 (1C), 118.5 (2C), 122.6 (1C), 123.6 (1C), 125.8 (2C), 139.3 (1C), 139.5 (1C), 140.3 (1C), 141.2 (1C), 144.9 (1C). Mass spectrum: *m*/*z* 348.235 $[M + H]^+$. $C_{23}H_{30}N_3$. Calculated: (*M* + H) 348.244.

***N*-(4-{3-[2-(Pyridin-3-ylamino)ethyl]adamantan-1-yl}phenyl)pyridin-3-amine (XXVI)** was synthesized from 0.25 mmol (68 mg) of diamine **XIX** and 0.5 mmol (79 mg) of 3-bromopyridine in the presence of 4 mol % (6 mg) of $Pd(dba)_2$, 4.5 mol % (7 mg) of BINAP, and 0.75 mmol (73 mg) of sodium *tert*-butoxide in 2.5 ml of dioxane. The product was isolated by chromatography using CH_2Cl_2–MeOH (20:1) as eluent. Yield 60 mg (56%). ^{1}H NMR spectrum, δ, ppm: 1.45–1.49 m (2H), 1.51–1.71 m (8H), 1.84 br.s (4H), 2.17 br.s (2H), 3.11–3.15 m (2H), 3.62 br.s (1H), 6.07 br.s (1H), 6.82 d.d.d (1H, ^3J = 8.2, ^4J = 2.8, 1.4 Hz), 7.02–7.07 m (3H), 7.11 d.d (1H, ^3J = 8.2, 4.7 Hz), 7.26 d (2H, ^3J = 8.5 Hz), 7.34 d.d.d (1H, ^3J = 8.3, ^4J = 2.7, 1.5 Hz), 7.92 d (1H, ^3J = 4.7 Hz), 7.99 d (1H, ^4J = 2.8 Hz), 8.10 d (1H, ^3J = 4.7 Hz), 8.33 d (1H, ^4J = 2.7 Hz). ^{13}C NMR spectrum, δ_C, ppm: 29.2 (2C), 33.0 (1C), 36.0 (1C), 36.4 (1C), 38.2 (1C), 41.6 (2C), 42.5 (2C), 43.5 (1C), 48.5 (1C), 118.3 (1C), 118.5 (2C), 122.7 (1C), 123.6 (1C), 123.7 (1C), 125.8 (2C), 135.9 (1C), 138.4 (1C), 139.5 (1C), 139.6 (1C), 140.3 (1C), 141.3 (1C), 144.4 (1C), 144.6 (1C). Mass spectrum: *m*/*z* 425.266 $[M + H]^+$. $C_{28}H_{33}N_4$. Calculated: (*M* + H) 425.271.

This study was performed under financial support by the Russian Academy of Sciences (program no. P-8, "Development of the Methodology of Organic Synthesis and Design of Compounds with Valuable Practical Properties") and by the Russian Foundation for Basic Research (project no 10-03-01108).

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