DOI 10.1007/s10593-015-1792-4

Chemistry of Heterocyclic Compounds **2015**, *51*(10), 891–898

Synthesis of adamantyl-containing phenylpiperidines

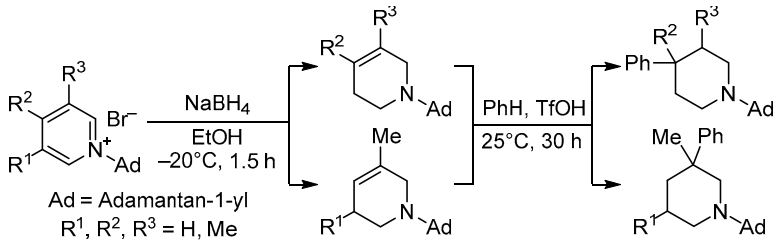
Vera A. Shadrikova[1]*, Evgeny V. Golovin[1], Vadim A. Shiryaev[1], Marat R. Baimuratov[1], Victor B. Rybakov[2], Yuri N. Klimochkin[1]

[1] *Samara State Technical University, 244 Molodogvardeiskaya St., Samara 443100, Russia; e-mail: shadricova@yandex.ru*

[2] *Lomonosov Moscow State University, 1, Build. 3 Leninskie Gory, Moscow 119991, Russia; e-mail: rybakov20021@yandex.ru*

Translated from Khimiya Geterotsiklicheskikh Soedinenii, 2015, *51*(10), 891–898

Submitted September 9, 2015
Accepted after revision November 5, 2015



The reduction of quaternary 1-(adamantan-1-yl)pyridinium salts with sodium borohydride in ethanol gave 1-(adamantan-1-yl)-1,2,3,6-tetrahydropyridines that reacted with benzene in trifluoromethanesulfonic acid medium, leading to the formation of 1-(adamantan-1-yl)-phenylpiperidines with various spatial orientation of the phenyl substituent. The structure of the obtained phenylpiperidines was confirmed by the spectral dataset. The thermodynamic stability calculations for the conformers of phenylpiperidines were performed with the B3LYP/6-311++(d,p) method.

Keywords: adamantane derivatives, phenylpiperidine, pyridinium salts, 1,2,3,6-tetrahydropyridine, conformer, DFT, hydroarylation, reduction.

Tetrahydropyridine and piperidine rings are important structural features in many drug molecules and other biologically active compounds.[1] Several examples of aryl-substituted piperidines are shown in Figure 1 (haloperidol (**A**), vesamicol (**B**), pethidine (**S**), trihexyphenidyl (**D**)), and 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (**E**). These compounds are used for the treatment of neurological and psychiatric disorders, such as Alzheimer's and Parkinson's diseases, schizophrenia, and other conditions.[2a–d] The tetrahydropyridine derivative MPTP (**E**) is used for modeling the symptoms of Parkinon's disease in order to study its etiology and pathogenesis, as well as for the development of new treatment methods.[2e,f]

Certain amines with cage type structures, such as aminoadamantane, have biologically active derivatives that exhibit a broad spectrum of effects.[3] Amantadine (**F**), memantine (**G**), and related drugs are used for combination therapy of Parkinson's and Alzheimer's diseases. The high pharmacological potential of piperidine and adamantane fragments attract interest with regard to the development of new molecules with such structural motifs, structural characterization, and the study of biological properties.

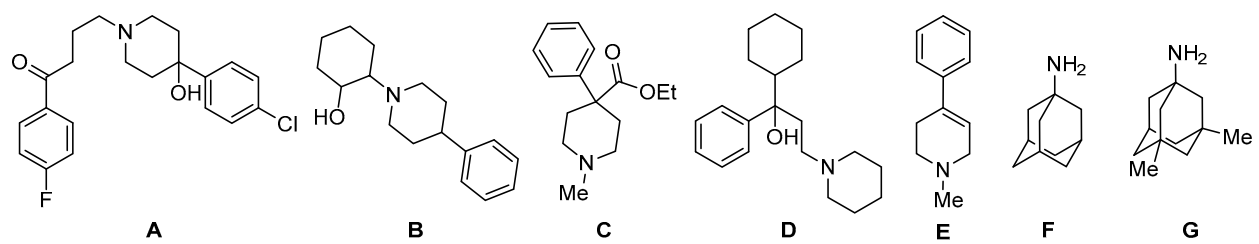
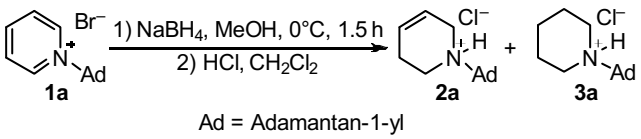


Figure 1. Some examples of biologically active piperidine and adamantane derivatives used in medicine.

N-Substituted arylpiperidines can be obtained by various methods,[4] including the Friedel–Crafts alkylation of arenes with 1,2,3,4-tetrahydropyridines.[5] While continuing our study of adamantyl derivatives of pyridine,[6] we converted adamantylpyridinium bromides to the corresponding tetrahydropyridines with the purpose of further transformation to previously unknown phenyl-substituted 1-(adamantan-1-yl)-piperidine systems. It can be proposed that the presence of a bulky cage type moiety in the structures may modify the reactivity of both pyridinium salts and adamantyl-containing tetrahydropyridines.

The most convenient and commonly used method for the preparation of 1-substituted 1,2,3,6-tetrahydropyridines is the reduction of quaternary pyridinium salts with sodium borohydride in a protic solvent medium.[7] The treatment of 1-(adamantan-1-yl)pyridinium bromide (**1a**) with sodium borohydride in methanol at 0°C leads to a 4:1 mixture of reduction products **2a** and **3a** according to GC-MS data (Scheme 1). The presence of 1-(adamantan-1-yl)piperidine (**3a**) as a side product significantly complicated the isolation and purification of the target tetrahydropyridine **2a**. Decreasing the reaction temperature to –20°C resulted in the same mixture of products **2a**:**3a** in a 9:1 ratio.

Scheme 1



When this reaction was performed in ethanol at –20°C, the formation of piperidine **3a** as a side product was not observed. Under these conditions the reduction of adamantylpyridinium bromides **1a**–**e** to 1-(adamantan-1-yl)-1,2,3,6-tetrahydropyridines **2a**–**e** was achieved in good yields (Scheme 2, Table 1).

Scheme 2

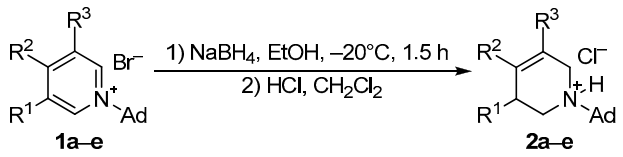
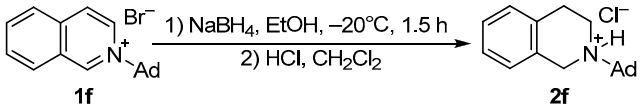


Table 1. Yields of 1,2,3,6-tetrahydropyridines **2a**–**e**

Product	R^1	R^2	R^3	Yield, %
2a	H	H	H	89
2b	H	Me	H	90
2c	H	H	Me	85
2d	H	Me	Me	89
2e	Me	H	Me	88

The reduction of 2-(adamantan-1-yl)isoquinolinium bromide (**1f**) gave 2-(adamantan-1-yl)-1,2,3,4-tetrahydro-isoquinoline **2f** in 90% yield (Scheme 3).

Scheme 3



There were characteristic absorption bands in IR spectra of compounds **2a**–**f**, corresponding to the stretching vibrations of C–H bonds in the adamantane fragment in the region of 2916–2897 cm^{-1} and at 2850 cm^{-1}. The double bond vibrations in 1,2,3,6-tetrahydropyridines **2a**–**e** were observed in the region of 1635–1617 cm^{-1}. The methine protons in compounds **2a**,**b**,**e** gave ^{1}H NMR signals in the range from 5.35 to 5.86 ppm. The presence of only one methine proton signal in ^{1}H NMR spectrum of tetrahydropyridine **2c** at 5.53 ppm and the absence of alkene proton signals in the spectrum of compound **2d** confirmed the formation of only one product with fully substituted double bond. The methyl group at the C-3 atom in tetrahydropyridine **2e** occupied a pseudoequatorial position. A doublet signal of three methyl group protons appeared in ^{1}H NMR spectrum of the alkene at 0.93 ppm (^3J = 6.7 Hz), which is characteristic of 3*e*-methyl-substituted 1,2,3,6-tetrahydropyridines.[8] The resonance signals of four aromatic protons in ^{1}H NMR spectrum of the tetrahydroisoquinoline **2f** were observed in the region of 7.17–7.22 ppm.

The method of arylpiperidine synthesis by reaction of 1,2,3,6-tetrahydropyridines with arenes in trifluoromethanesulfonic acid (TfOH) medium has been already described,[5a] but the configuration of substituents in the obtained products was not then established, and the effect of substituent orientation in the heterocycle on the reaction stereoselectivity was not determined.

The *N*-adamantylated 1,2,3,6-tetrahydropyridines **2a**–**e** were used in a Friedel–Crafts alkylation reaction of benzene. The bulky adamantane substituent, similarly to *tert*-butyl group,[9] increased the energy barrier to piperidine ring inversion, playing the role of a conformational anchor. Due to this effect, we were able to achieve stereoselective synthesis of phenyl-substituted 1-(adamantan-1-yl)piperidines **4a**–**e** in good yields (Scheme 4, Table 2). The reaction was performed in excess TfOH at room temperature for 30 h. We should note that elimination of adamantane fragment caused by the stability of 1-adamantanyl cation was not observed under these conditions, which is characteristic of adamantyl-containing tertiary amines and amides in acidic media.[10]

IR spectra of compounds **4a**–**e** contained characteristic C–H absorption bands of the adamantyl group in the regions of 2916–2897 and 2854–2846 cm^{-1}, and C–C bonds of the phenyl group in the region of 1600–1442 cm^{-1}. ^{1}H NMR spectra of compounds **4a**–**e** contained the signals of five aromatic protons of the phenyl ring in the region of 7.12–7.55 ppm. The assignment of ^{1}H and ^{13}C NMR

Scheme 4

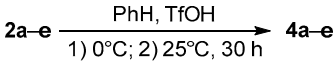
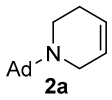
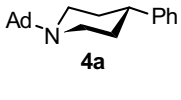
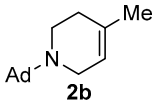
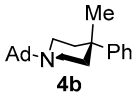
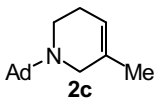
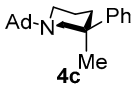
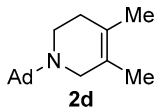
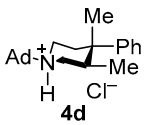
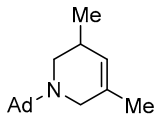
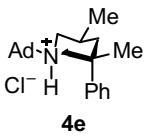


Table 2. Products and yields of Friedel–Crafts alkylation of benzene with 1,2,3,6-tetrahydropyridines **2a**–**e**

Starting tetrahydropyridine	Product	Yield, %
 **2a**	 **4a**	94
 **2b**	 **4b**	96
 **2c**	 **4c**	89
 **2d**	 **4d**	41*
 **2e**	 **4e**	90

* Isolated by fractional crystallization from an mixture with minor isomer.

signals for compounds **4a**–**e** was based on DEPT-135 ^{13}C NMR spectra, as well as on ^{1}H–^{13}C HMBC, ^{1}H–^{13}C HETCOR, and NOESY 2D NMR experiments.

When benzene was alkylated with tetrahydropyridines **2a** and **2b**, the 1-(adamantan-1-yl)-4-phenylpiperidines **4a** and **4b** were formed. The selective arylation at only C-4 position was confirmed by the presence of two ^{13}C NMR signals due to the piperidine ring methylene groups in DEPT correlation spectra of these compounds (34.4 and 45.1 ppm in the spectrum of compound **4a**; 37.9 and 40.8 ppm in the spectrum of compound **4b**). The adamantane moiety in piperidines **4a** and **4b** occupied a sterically more favorable equatorial position.[11] The equatorial orientation of the phenyl ring in piperidine **4a** was confirmed by ^{1}H NMR spectral data. The signal due to the proton at the C-4 atom appeared as a triple triplet at 2.46 ppm (^{3}J = 3.9, ^{3}J = 12.1 Hz); the difference in vicinal coupling constants between the 4-CH proton and the diastereotopic protons at C-3 and C-5 atoms indicated that it was axially oriented (Fig. 2).

The equatorial orientation of phenyl ring in piperidine **4b** was confirmed by 2D NOESY spectrum. The spectrum contained evidence of distant interaction of the phenyl ring *ortho* protons (7.34 ppm) with axial (1.76–1.82 ppm) and equatorial (2.11–2.17 ppm) protons at piperidine C-3 and C-5 atoms. The methyl group protons were close to the axial 2,6-CH_2 protons (2.70–2.75 ppm), which is possible only with

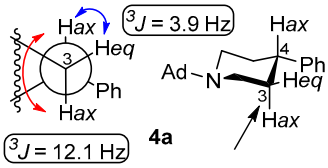


Figure 2. Newman projection of a part of phenylpiperidine **4a** molecule relative to the C(3)–C(4) bond.

equatorial position of the aromatic ring (Fig. 3*a*). Thus, the adamantane and phenyl substituents in piperidines **2a**,**b** were arranged in 1,4-*trans*-diequatorial configuration.

When benzene was alkylated with 5-methyltetrahydropyridine **2c**, only 3-methyl-3-phenylpiperidine **4c** was formed (Table 2). ^{13}C NMR spectrum of compound **4c** contained four signals of secondary carbon atoms and one signal of a quaternary carbon atom in the region of 23.7–55.7 ppm, belonging to 3,3-disubstituted piperidine ring. Based on 2D NOESY spectrum, it was established that the phenyl ring occupied an equatorial position, because its *ortho* protons (7.42 ppm) were coupled through space only with the diastereotopic protons at C-2 and C-4 atoms of the piperidine system (four cross peaks) and with the methyl group protons (1.25 ppm) (Fig. 3*b*). The adamantane and phenyl substituents in the piperidine **4c** were in a 1,3-*cis*-diequatorial configuration, which is characteristic of 1,3-disubstituted piperidines.[12]

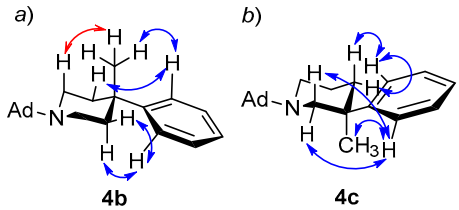


Figure 3. The spatial interactions of hydrogen atoms in 2D NOESY spectra of phenylpiperidines **4b** and **4c**.

In the case when hydroarylation was performed with tetrahydropyridine **2d**, a 6.7:1 mixture of phenylpiperidines was obtained according to ^{1}H NMR spectral data. The proton signal of methyl group at the C-3 atom in the major isomer **4d** was found at higher field (0.54 ppm), compared to the 3-CH_3 signal of the minor isomer (0.73 ppm). Fractional recrystallization from EtOH allowed to isolate only phenylpiperidine **4d** as hydrochloride in 41% yield.

The structure of hydrochloride **4d** was unequivocally established by X-ray structural analysis (Fig. 4). The phenyl substituent and 3-CH_3 group occupied equatorial positions in the obtained product. Due to a *gauche* interaction between the 3*eq*-CH_3 and 4*ax*-CH_3 methyl groups, their ^{13}C NMR signals were shifted upfield and were located at 13.6 and 14.8 ppm, respectively. A similar shifting of ^{13}C NMR signals of the methyl groups is characteristic of 3*eq*,4*ax*-dimethyl-4-arylpiperidines.[13] There were three cross peaks in 2D NOESY spectrum of compound **4d**, corresponding to the coupling through space (Fig. 5*a*) of aromatic *ortho* protons (7.54 ppm) only with

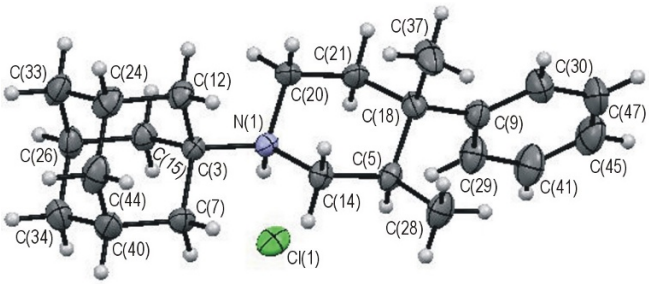


Figure 4. The molecular structure of compound **4d** with non-hydrogen atoms represented by thermal vibration ellipsoids of 50% probability.

the axial protons at C-3 and C-5 atoms of the piperidine ring (3.02–3.12 and 3.12–3.22 ppm, respectively) and with the 4-CH_3 protons (1.24 ppm).

Based on ^{1}H and ^{13}C NMR spectral data for the isomer mixture, it appears that the minor product was 1-(adamantan-1-yl)-3,4-dimethyl-3-phenylpiperidine – the result of an attack at the intermediate cationic center at the C-3 atom of the piperidine ring.

Alkylation of benzene with tetrahydropyridine **2e** gave compound **4e** as the sole product with axial orientation of the phenyl substituent, isolated as hydrochloride in 90% yield. The structure of piperidine **4e** was established from its 2D NMR dataset. NOESY cross peaks indicated a spatial coupling of the aromatic *ortho* protons (7.21–7.29 ppm) only with the equatorial proton at the C-2 atom (4.02 ppm) and the axial proton at the C-5 atom (a multiplet at 2.50–2.64 ppm) of the piperidine ring (Fig. 5*b*). The equatorial orientation of methyl group at the C-5 atom confirmed the pseudoequatorial orientation of the 3-CH_3 group in the starting alkene **2e**.

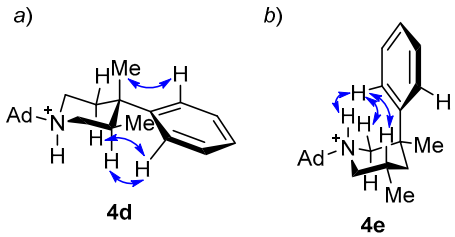


Figure 5. The spatial interactions of hydrogen atoms in 2D NOESY spectra of phenylpiperidines **4d** and **4e**.

The formation of the single isomer **4e** was apparently caused by the lack of steric hindrance against axial attack. An equatorial attack was problematic due to the 5-CH_3 group and pseudoaxial protons at the C-2 and C-4 atoms, which acted as steric obstacles to the approach of benzene molecule towards the cationic center.

Despite performing the synthesis of phenylpiperidines **4b**–**e** at room temperature, we could not exclude the possible formation of thermodynamically favored products, since it is known that such systems are capable of isomerization in acidic media.[14]

In order to thermodynamically evaluate the conformer stability of the obtained phenylpiperidines in hydrochloride form, we calculated the relative energy for isomers of compounds **4b**–**e**, which differed depending on the axial and equatorial orientation of the phenyl substituents. The calculations were performed in accordance with DFT theory, using the B3LYP method with 6-311++(d,p) basis set, taking into account solvation effects in chloroform with the IEFPCM polarizable continuum model and including the thermochemical effects at 298 K temperature (Table 3).

The calculations showed that in the case of piperidines **4c** and **4d** the thermodynamically favored conformer had an equatorial orientation of the phenyl substituent. The conformer with axially oriented phenyl substituent was thermodynamically favored in the case of piperidines **4b** and **4e**.

We calculated the geometry of monocationic (**I**) and dicationic (**II**) intermediates, which can arise from the tetrahydropyridine **2b** *via* a protonation step (Fig. 6). The calculations showed that the dication **II** was highly unstable. Destabilized intermediates of this type would participate in an alkylation reaction even with such deactivated arene as nitrobenzene.[15] Since it was demonstrated experimentally that no such reaction takes place,[5] the existence of dication **II** as a kinetically independent particle appears to be unlikely.

One of the most convenient parameters used for estimating the reactivity is the global electrophilicity index introduced by Parr.[16] Quantum-chemical calculations showed that the structure **I** did not correspond to an energy minimum, and its geometry optimization resulted in a transformation to open-chain product *via* cleavage of the bond between C-2 and C-3 atoms in the piperidine ring. The dication **II** was characterized with very high electrophilicity index (89.6 eV), significantly exceeding the electrophilicity of common cations.[17]

The cationic center at the C-4 atom in the dication **II** was practically planar, and for this reason, the 4-CH_3 group had no substantial influence on the direction of attack. An equatorial attack leading to 4*eq*-phenylpiperidine **4b** most probably is kinetically favored, since in this case the piperidine ring in transition state has a "chair" type conformation. An axial attack would have led to an

Table 3. The calculated free energy values for conformers **4b**–**e** with equatorial (G^0_{eq}) and axial (G^0_{ax}) orientation of phenyl group

Compound	G^0_{eq}, Hartree	G^0_{ax}, Hartree	ΔG^{298}, Hartree	ΔG^{298}, kJ/mol
4b	–911.567174	–911.567985	0.000811	2.13
4c	–911.566680	–911.566335	–0.000345	–0.91
4d	–951.294004	–951.290536	–0.003468	–9.11
4e	–951.298295	–951.301667	0.003372	8.85

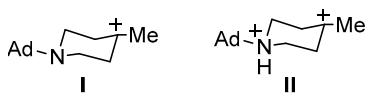


Figure 6. The structures of cationic intermediates involved in arylation of tetrahydropyridine **2b**.

intermediate twist conformation of piperidine ring. The dependence of reaction product structure on the direction of attack by the reagent on the cyclohexene or related system can be interpreted within the framework of Furst–Plattner effect.[18]

Thus, we have developed a method for selective reduction of 1-(adamantan-1-yl)pyridinium salts to adamantyl-containing 1,2,3,6-tetrahydropyridines. The hydroarylation of tetrahydropyridines in trifluoromethanesulfonic acid allowed to stereoselectively prepare 1-(adamantan-1-yl)-phenylpiperidines. It was established that hydroarylation resulted mainly in products with equatorial orientation of phenyl group, and stereoselective formation of phenylpiperidine with axial orientation of the phenyl substituent was observed only in the case of 1-(adamantan-1-yl)-3,5-dimethyl-1,2,3,6-tetrahydropyridine.

Experimental

IR spectra were recorded on a Shimadzu IRAffinity-1 FT-IR spectrometer in KBr pellets. ^{1}H and ^{13}C NMR spectra (400 and 100 MHz, respectively), as well as DEPT and two-dimensional ^{1}H–^{13}C HMBC, ^{1}H–^{13}C HETCOR, and NOESY (mixing time 0.6 s) spectra were acquired on a JEOL JNM-ESCX 400 instrument in DMSO-d_6 (compounds **2a**–**f**, **3a**) and $CDCl_3$ (the rest of the compounds), the internal standard was TMS. Mass spectra were recorded on a Thermo Finnigan DSQ GC-MS instrument with a BPX5 capillary column (30 m×0.32 mm), EI ionization at 70 eV. Elemental analysis was performed on a Euro Vector EA-3000 automated CHNS-analyzer. Melting points were determined on a PTP-M apparatus (Russia) by the capillary method. Thin-layer chromatography was performed on Sorbfil plates, visualization with iodine vapor. The starting quaternary salts **1a**–**f** were obtained according to published procedures.[6,19] The thermodynamic stability of phenylpiperidine conformers was calculated with the GAUSSIAN g09a software.[20]

Reduction of 1-(adamantan-1-yl)pyridinium bromide (1a). Sodium borohydride (0.31 g, 7.5 mmol) was added portionwise over 30 min to a stirred solution of compound **1a** (1.47 g, 5 mmol) in methanol (10 ml) at 0°C. The cooling bath was then removed and the reaction mixture was stirred for another 1 h. The reaction mixture was diluted with water (50 ml), and the product was extracted with dichloromethane (3×15 ml). The combined organic extracts were washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, giving a mixture of products **2a** and **3a** (1.05 g). The mixture was dissolved in dichloromethane, saturated with HCl, (10 ml) then the solvent was evaporated under vacuum. The residue was purified by recrystallization from a 3:1 mixture of acetonitrile and THF, giving tetrahydropyridine hydrochloride **2a**. The piperidine hydrochloride **3a** was then isolated from the remaining mother liquors.

1-(Adamantan-1-yl)-1,2,3,6-tetrahydropyridine hydrochloride (2a). Yield 0.60 g (45%), white powder, mp 280–282°C. IR spectrum, ν, cm^{-1}: 3400, 2908 (C–H Ad), 2850 (C–H Ad), 2574, 2470, 1635, 1452, 1367, 1066, 912, 669. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.59 (6H, s, $3CH_2$ Ad); 1.90–1.98 (6H, m, $3CH_2$ Ad); 2.11 (3H, s, 3CH Ad); 2.46–2.54 (2H, m, 3-CH_2); 3.60–3.63 (4H, m, 2,6-CH_2); 5.66–5.67 (1H, m) and 5.85–5.86 (1H, m, 4,5-CH); 10.08 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 23.6 (CH_2); 29.3 (CH Ad); 35.6 (CH_2 Ad); 35.7 (CH_2 Ad); 42.2 (CH_2); 43.8 (CH_2); 63.6 (C Ad); 121.6 (CH=); 125.9 (CH=). Mass spectrum (free amine), *m*/*z* (I_{rel}, %): 217 [M]$^+$ (84), 160 (100), 135 [Ad]$^+$ (46), 79 (14). Found, %: C 71.07; H 9.50; N 5.41. $C_{15}H_{24}ClN$. Calculated, %: C 70.98; H 9.53; N 5.52.

1-(Adamantan-1-yl)piperidine hydrochloride (3a). Yield 0.14 g (10%), white powder, mp 309–311°C (mp 311–313°C)[21]. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.59 (6H, s, $3CH_2$ Ad); 1.79–1.86 (6H, m, $3CH_2$); 1.92 (6H, s, $3CH_2$ Ad); 2.10 (3H, s, 3CH Ad); 3.43–3.60 (4H, m, 2,6-CH_2); 10.06 (1H, br. s, NH). Mass spectrum (free amine), *m*/*z* (I_{rel}, %): 219 [M$^+$] (20), 162 (100). Found, %: C 70.33; H 10.18; N 5.53. $C_{15}H_{26}ClN$. Calculated, %: C 70.42; H 10.24; N 5.48.

Reduction of 1-(adamantan-1-yl)pyridinium bromides 1a–f (General method). Sodium borohydride (0.94 g, 22.5 mmol) was added portionwise with stirring over 30 min to a solution of salt **1a**–**f** (15 mmol) in ethanol (25 ml) cooled to –20°C. Then the cooling bath was removed, and the reaction mixture was stirred for another 1 h. The reaction mixture was diluted with water (100 ml), and the product was extracted with dichloromethane (3×25 ml). The combined organic extracts were washed with water and dried over anhydrous Na_2SO_4. The solvent was evaporated under vacuum, giving the corresponding tetrahydropyridine **2a**–**f**. The product was dissolved in dichloromethane, saturated with HCl, (15 ml) followed by evaporation of the solvent at reduced pressure. The residue was purified by recrystallization from chloroform, giving the respective hydrochloride.

1-(Adamantan-1-yl)-1,2,3,6-tetrahydropyridine hydrochloride (2a). Yield 3.40 g (89%), white powder. The melting point and spectra matched compound **2a** obtained by reduction of salt **1a** in MeOH at 0°C.

1-(Adamantan-1-yl)-4-methyl-1,2,3,6-tetrahydropyridine hydrochloride (2b). Yield 3.61 g (90%), white powder, mp 259–261°C. IR spectrum, ν, cm^{-1}: 3633, 3383, 2897 (C–H Ad), 2850 (C–H Ad), 2665, 2592, 2484, 1627, 1442, 1365, 1064, 906, 802, 779. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.62–1.73 (9H, m, $3CH_2$ Ad, 4-CH_3); 1.85–1.98 (6H, m, $3CH_2$ Ad); 2.05 (3H, s, 3CH Ad); 2.12–2.22 (1H, m), 2.42–2.55 (1H, m), 2.70–2.85 (1H, m) and 3.45–3.67 (3H, m, 2,3,6-CH_2); 5.35 (1H, s, 5-CH); 10.12 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 22.5 (CH_3); 28.1 (CH_2); 29.3 (CH Ad); 35.6 (CH_2 Ad); 35.7 (CH_2 Ad); 42.2 (CH_2); 43.5 (CH_2); 63.3 (C Ad); 115.4 (C-5); 133.5 (C-4). Mass spectrum (free amine), *m*/*z* (I_{rel}, %): 231 [M]$^+$ (50), 217 (84), 174 (100), 135 [Ad]$^+$ (69), 79 (34). Found, %: C 71.86; H 9.69; N 5.15. $C_{16}H_{26}ClN$. Calculated, %: C 71.75; H 9.78; N 5.23.

1-(Adamantan-1-yl)-5-methyl-1,2,3,6-tetrahydropyridine hydrochloride (2c). Yield 3.41 g (85%), white powder, mp 252–254°C. IR spectrum, ν, cm^{-1}: 3413, 2912 (C–H Ad), 2850 (C–H Ad), 2653, 2572, 2476, 1620, 1454, 1365, 1064, 910, 659. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.58 (6H, s, $3CH_2$ Ad); 1.63 (3H, s, CH_3); 1.96 (6H, s, $3CH_2$ Ad);

2.09 (3H, s, 3CH Ad); 2.42–2.54 (1H, m), 2.62–2.72 (1H, m) and 3.36–3.55 (4H, m, 2,3,6-CH_2); 5.53 (1H, s, 4-CH); 10.36 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 20.6 (CH_3); 23.1 (CH_2); 29.4 (3CH Ad); 35.6 (3CH_2 Ad); 35.7 (3CH_2 Ad); 41.9 (CH_2); 46.7 (CH_2); 63.6 (C Ad); 120.0 (C-4); 128.6 (C-5). Mass spectrum (free amine), *m*/*z* (I_{rel}, %): 231 $[M]^+$ (65), 217 (32), 175 (70), 135 $[Ad]^+$ (100), 79 (15). Found, %: C 71.79; H 9.84; N 5.32. $C_{16}H_{26}ClN$. Calculated, %: C 71.75; H 9.78; N 5.23.

1-(Adamantan-1-yl)-4,5-dimethyl-1,2,3,6-tetrahydropyridine hydrochloride (2d). Yield 3.76 g (89%), white powder, mp 230–232°C. IR spectrum, ν, cm^{-1}: 3383, 2912 (C–H Ad), 2850 (C–H Ad), 2735, 2634, 2430, 1617, 1458, 1369, 1056, 898, 817, 540. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.50–1.70 (12H, m, 3CH_2 Ad, 4,5-CH_3); 1.86–2.05 (6H, m, 3CH_2 Ad); 2.11 (3H, s, 3CH Ad); 2.15–2.23 (2H, m) and 3.42–3.70 (4H, m, 2,3,6-CH_2); 9.83 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 16.4 (CH_3); 18.3 (CH_3); 29.1 (CH_2); 29.3 (CH Ad); 35.6 (CH_2 Ad); 35.8 (CH_2 Ad); 42.3 (CH_2); 47.2 (CH_2); 63.4 (C Ad); 120.3 (C-4(5)); 125.4 (C-5(4)). Mass spectrum (free amine), *m*/*z* (I_{rel}, %): 245 $[M]^+$ (63), 230 (100), 188 (62), 135 $[Ad]^+$ (76), 79 (16). Found, %: C 72.35; H 9.93; N 5.04. $C_{17}H_{28}ClN$. Calculated, %: C 72.44; H 10.01; N 4.97.

1-(Adamantan-1-yl)-3,5-dimethyl-1,2,3,6-tetrahydropyridine hydrochloride (2e). Yield 3.72 g (88%), white powder, mp 248–250°C. IR spectrum, ν, cm^{-1}: 3352, 2904 (C–H Ad), 2850 (C–H Ad), 2755, 2639, 2423, 1622, 1458, 1378, 1047, 977, 815. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.93 (3H, d, ^3J = 6.7, 3-CH_3); 1.52–1.62 (6H, s, 3CH_2 Ad); 1.64 (3H, s, 5-CH_3); 1.88–2.15 (10H, m), 2.24–2.34 (1H, m), 2.68 (1H, br. s) and 3.52–3.62 (2H, m, 3CH_2 Ad, 3CH Ad, 2,3,6-CH_2); 5.40 (1H, s, 4-CH); 10.25 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 18.3 (CH_3); 20.4 (CH_3); 28.6 (3-CH); 29.4 (CH Ad); 35.6 (CH_2 Ad); 35.7 (CH_2 Ad); 46.6 (CH_2); 48.0 (CH_2); 63.6 (C Ad); 126.7 (C-4); 127.8 (C-5). Mass spectrum (free amine), *m*/*z* (I_{rel}, %): 245 $[M]^+$ (98), 230 (45), 188 (100), 164 (10), 135 $[Ad]^+$ (99), 79 (43). Found, %: C 72.32; H 9.95; N 5.06. $C_{17}H_{28}ClN$. Calculated, %: C 72.44; H 10.01; N 4.97.

2-(Adamantan-1-yl)-1,2,3,4-tetrahydroisoquinoline hydrochloride (2f). Yield 4.10 g (90%), light-yellow powder, mp 235–238°C. IR spectrum, ν, cm^{-1}: 3413, 2916 (C–H Ad), 2850 (C–H Ad), 2472, 2408, 1454, 1365, 1110, 1056, 898, 750. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.62 (6H, s, 3CH_2 Ad); 2.03 (6H, s, 3CH_2 Ad); 2.15 (3H, s, 3CH Ad); 2.92–2.96 (1H, m), 3.00–3.09 (1H, m), 3.21–3.26 (1H, m), 3.80–3.82 (1H, m) and 4.35–4.37 (2H, m, 1,3,4-CH_2); 7.17–7.22 (4H, m, H-5,6,7,8); 10.41 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 26.5 (CH_2); 29.4 (CH Ad); 35.6 (CH_2 Ad); 35.8 (CH_2 Ad); 43.0 (CH_2); 46.0 (CH_2); 64.1 (C Ad); 127.0 (CH Ar); 127.4 (CH Ar); 127.8 (CH Ar); 128.6 (CH Ar); 130.0 (C Ar); 132.8 (C Ar). Mass spectrum (free amine), *m*/*z* (I_{rel}, %): 267 $[M]^+$ (40), 210 (100), 173 (18), 135 $[Ad]^+$ (29), 117 (27), 105 (53), 91 (24), 79 (34). Found, %: C 75.24; H 8.67; N 4.50. $C_{19}H_{26}ClN$. Calculated, %: C 75.10; H 8.62; N 4.61.

Alkylation of benzene with 1-(adamantan-1-yl)-1,2,3,6-tetrahydropyridines 2a–e (General method). Trifluoromethanesulfonic acid (10 ml, 11.3 mmol) was added portionwise with stirring to a solution of 1,2,3,6-tetrahydropyridine **2a**–**e** (5 mmol) in benzene (10 ml), while cooling the reaction mixture on an ice bath. After stirring for 30 h at 25°C, the reaction mixture was poured on ice, adjusted with 30% NaOH to pH 10–11, and extracted with dichloromethane (3×15 ml). The combined organic extracts were dried over anhydrous Na_2SO_4 and evaporated at reduced pressure. The products **4a**–**c** were purified by recrystallization from a 15:1 mixture of hexane and ethyl acetate.

1-(Adamantan-1-yl)-4*eq*-phenylpiperidine (4a). Yield 1.4 g (94%), colorless needles, mp 111–113°C. IR spectrum, ν, cm^{-1}: 3442, 2910 (C–H Ad), 2848 (C–H Ad), 1598, 1494, 1452, 1311, 1097, 1018, 950, 821, 750, 698. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.58–1.70 (6H, m, 3CH_2 Ad); 1.72–1.91 (10H, m, 3CH_2 Ad, 3,5-CH_2); 2.10 (3H, br. s, 3CH Ad); 2.22–2.32 (2H, t, ^3J = 11.4, 2,6-CH*ax*); 2.46 (1H, tt, ^3J = 3.9, ^3J = 12.1, 4-CH*ax*); 3.27 (2H, d, ^3J = 11.9, 2,6-CH*eq*); 7.15–7.19 (1H, m, H-4 Ph); 7.22–7.30 (4H, m, H-2,3,5,6 Ph). ^{13}C NMR spectrum, δ, ppm: 29.8 (CH Ad); 34.4 (3,5-CH_2); 37.0 (CH_2 Ad); 38.5 (CH_2 Ad); 43.4 (4-CH); 45.1 (2,6-CH_2); 54.6 (C Ad); 126.0 (C-4 Ph); 127.0 (C-2,6 Ph); 128.4 (C-3,5 Ph); 146.7 (C-1 Ph). Mass spectrum, *m*/*z* (I_{rel}, %): 295 $[M]^+$ (40), 238 (100), 201 (6), 135 $[Ad]^+$ (100), 91 (8). Found, %: C 85.29; H 9.95; N 4.81. $C_{21}H_{29}N$. Calculated, %: C 85.37; H 9.89; N 4.74.

1-(Adamantan-1-yl)-4*ax*-methyl-4*eq*-phenylpiperidine (4b). Yield 1.48 g (96%), colorless crystals, mp 98–100°C. IR spectrum, ν, cm^{-1}: 3394, 2912 (C–H Ad), 2846 (C–H Ad), 1600, 1496, 1446, 1315, 1122, 1076, 960, 821, 763, 702, 547. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.20 (3H, s, 4*ax*-CH_3); 1.54–1.66 (6H, m, 3CH_2 Ad); 1.70 (6H, s, 3CH_2 Ad); 1.76–1.82 (2H, m, 3,5-CH*ax*); 2.05 (3H, br. s, 3CH Ad); 2.11–2.17 (2H, m, 3,5-CH*eq*); 2.56–2.64 (2H, m, 2,6-CH*eq*); 2.70–2.75 (2H, m, 2,6-CH*ax*); 7.13–7.18 (1H, m, H-4 Ph); 7.27–7.36 (4H, m, H-2,3,5,6 Ph). ^{13}C NMR spectrum, δ, ppm: 29.7 (4*ax*-CH_3); 29.8 (CH Ad); 36.4 (C-4); 37.0 (CH_2 Ad); 37.9 (3,5-CH_2); 38.5 (CH_2 Ad); 40.8 (2,6-CH_2); 54.5 (C Ad); 125.5 (C-4 Ph); 125.9 (C-2,6 Ph); 128.3 (C-3,5 Ph); 149.4 (C-1 Ph). Mass spectrum, *m*/*z* (I_{rel}, %): 309 $[M]^+$ (100), 253 (84), 215 (12), 135 $[Ad]^+$ (42), 79 (14). Found, %: C 85.46; H 10.04; N 4.59. $C_{22}H_{31}N$. Calculated, %: C 85.38; H 10.10; N 4.53.

1-(Adamantan-1-yl)-3*ax*-methyl-3*eq*-phenylpiperidine (4c). Yield 1.37 g (89%), colorless crystals, mp 50–51°C. IR spectrum, ν, cm^{-1}: 3375, 2904 (C–H Ad), 2850 (C–H Ad), 1600, 1492, 1446, 1311, 1114, 1099, 987, 821, 756, 694, 540. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.25 (3H, s, 3*ax*-CH_3); 1.44–1.66 (9H, m, 3CH_2 Ad, 5-CH_2, 4-CH*ax*); 1.71 (6H, s, 3CH_2 Ad); 1.83–1.87 (1H, m, 4-CH*eq*); 2.07 (3H, br. s, 3CH Ad); 2.42–2.52 (1H, m, 6-CH*ax*); 2.61–2.65 (1H, m, 2-CH*ax*); 2.68–2.82 (2H, m, 2,6-CH*eq*); 7.17 (1H, dd, ^3J = 7.0, ^3J = 8.0, H-4 Ph); 7.31 (2H, t, ^3J = 8.0, H-3,5 Ph); 7.42 (2H, dd, ^3J = 7.0, ^3J = 8.0, H-2,6 Ph). ^{13}C NMR spectrum, δ, ppm: 23.7 (5-CH_2); 27.7 (CH_3); 29.9 (CH Ad); 37.1 (CH_2 Ad); 37.4 (4-CH_2); 38.2 (C-3); 38.8 (CH_2 Ad); 45.3 (6-CH_2); 53.9 (C Ad); 55.7 (2-CH_2); 125.5 (C-4 Ph); 126.2 (C-2,6 Ph); 128.0 (C-3,5 Ph); 149.8

(C-1 Ph). Mass spectrum, *m*/*z* (I_{rel}, %): 309 $[M]^+$ (26), 252 (62), 178 (77), 135 $[Ad]^+$ (100). Found, %: C 85.49; H 10.02; N 4.61. $C_{22}H_{31}N$. Calculated, %: C 85.38; H 10.10; N 4.53.

1-(Adamantan-1-yl)-3*eq*,4*ax*-dimethyl-4*eq*-phenylpiperidine hydrochloride (4d). The obtained mixture of isomers (1.50 g, 83%) was dissolved in dichloromethane, saturated with HCl, (5 ml); the solvent was evaporated, and the hydrochloride **4d** was isolated by fractional recrystallization from EtOH. Yield 0.75 g (41%), colorless crystals, mp 267–270°C. IR spectrum, ν, cm^{-1}: 3425, 2912 (C–H Ad), 2850 (C–H Ad), 2499, 2453, 1600, 1473, 1442, 1369, 1056, 1033, 894, 756, 698. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 0.54 (3H, d, ^3J = 6.9, 3*eq*-CH_3); 1.24 (3H, s, 4*ax*-CH_3); 1.58 (1H, d, ^3J = 14.7, 5-CH*eq*); 1.67 (6H, s, 3CH_2 Ad); 2.13 (6H, s, 3CH_2 Ad); 2.21 (3H, br. s, 3CH Ad); 2.59 (1H, q, *J* = 11.9, 2-CH*ax*); 2.80–2.92 (1H, m, 6-CH*ax*); 3.02–3.12 (1H, m, 5-CH*ax*); 3.12–3.22 (1H, m, 3-CH*ax*); 3.35 (1H, d, ^3J = 11.9, 2-CH*eq*); 3.54 (1H, d, ^3J = 10.6, 6-CH*eq*); 7.12–7.16 (1H, m, H-4 Ph); 7.25–7.30 (2H, m, H-3,5 Ph); 7.52–7.55 (2H, m, H-2,6 Ph); 9.69 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 13.6 (3*eq*-CH_3); 14.8 (4*ax*-CH_3); 29.6 (CH Ad); 35.7 (CH_2 Ad); 36.3 (3-CH); 36.4 (CH_2 Ad); 37.2 (5-CH_2); 38.7 (C-4); 41.6 (6-CH_2); 46.9 (2-CH_2); 64.2 (C Ad); 126.3 (C-2,6 Ph); 126.5 (C-4 Ph); 128.5 (C-3,5 Ph); 146.3 (C-1 Ph). Mass spectrum (free amine), *m*/*z* (I_{rel}, %): 323 $[M]^+$ (76), 266 (100), 136 (19), 135 $[Ad]^+$ (16), 79 (14). Found, %: C 76.65; H 9.58; N 3.98. $C_{23}H_{34}ClN$. Calculated, %: C 76.74; H 9.52; N 3.89.

The residue from mother liquors (0.6 g) contained an intractable mixture of hydrochlorides **4d** and the minor isomer.

1-(Adamantan-1-yl)-3*eq*,5*eq*-dimethyl-3*ax*-phenylpiperidine hydrochloride (4e). The obtained piperidine was dissolved in dichloromethane (5 ml) saturated with HCl, then the solvent was evaporated, and the residue was recrystallized from acetonitrile. Yield 1.62 g (90%), colorless crystals, mp 185–187°C. IR spectrum, ν, cm^{-1}: 3394, 2916 (C–H Ad), 2854 (C–H Ad), 2198, 1496, 1446, 1303, 1107, 925, 759, 729, 698. ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 1.00 (3H, d, ^3J = 6.4, 5-CH_3); 1.12–1.20 (1H, m, 4-CH*ax*); 1.24 (3H, s, 3-CH_3); 1.67 (6H, br. s, 3CH_2 Ad); 2.05–2.30 (10H, m, 3CH Ad, 3CH_2 Ad, 6-CH*ax*); 2.50–2.64 (3H, m, 2,5-CH*ax*, 4-CH*eq*); 3.59 (1H, d, ^2J = 11.0; 6-CH*eq*); 4.02 (1H, d, ^2J = 11.0, 2-CH*eq*); 7.21–7.29 (3H, m, H-2,4,6 Ph); 7.35–7.42 (2H, m, H-3,5 Ph); 9.60 (1H, br. s, NH). ^{13}C NMR spectrum, δ, ppm: 19.2 (5-CH_3); 25.7 (CH-5); 29.7 (CH Ad); 33.3 (3-CH_3); 35.6 (CH_2 Ad); 36.2 (CH_2 Ad); 38.8 (C-3); 42.5 (4-CH_2); 52.0 (6-CH_2); 54.2 (2-CH_2); 66.2 (C Ad); 125.6 (C-2,6 Ph); 127.4 (C-4 Ph); 129.5 (C-3,5 Ph); 141.5 (C-1 Ph). Mass spectrum (free amine), *m*/*z* (I_{rel}, %): 323 $[M]^+$ (40), 266 (100), 178 (62), 164 (18), 135 $[Ad]^+$ (58), 79 (28). Found, %: C 76.82; H 9.60; N 3.95. $C_{23}H_{33}N$. $C_{23}H_{34}ClN$. Calculated, %: C 76.74; H 9.52; N 3.89.

X-ray structural study of compound 4d. Crystals suitable for X-ray structural analysis were grown from a 1:1 mixture of $CHCl_3$ and *i*-PrOH by slow evaporation at room temperature. Monocrystal X-ray structural study of compound **4d** was performed on an Enraf-Nonius CAD-4 diffractometer (CuKα radiation). The structure was solved by direct method and refined by full matrix method of least squares in anisotropic approximation for non-hydrogen atoms. All calculations were performed with the SHELX-97 software suite.[22] The molecule was visualized with the Mercury software, version 3.5.1.[23] The structural parameters of compound **4d** were deposited at the Cambridge Crystallographic Data Center (deposit CCDC 1416385).

The Supplementary information file containing the data of ^{1}H and ^{13}C NMR spectra, ^{1}H–^{13}C HMBC, ^{1}H–^{13}C HETCOR, and NOESY two-dimensional NMR experiments for compounds **2a–f**, **4a–e**, as well as the log files for calculating the energy of conformers **4b–e** is available online at http://link.springer.com/journal/10593.

This work was supported by a grant from the Russian Scientific Fund (project No. 15-13-0084).

References

1. (a) Buffat, M. G. P. *Tetrahedron* **2004**, *60*, 1701. (b) Matveeva, N. N.; Winfield, L. L.; Redda, K. K. *Curr. Med. Chem.* **2005**, *12*, 551. (c) Fries, D. S.; de Vries, J.; Hazelhoff, B.; Horn, A. S. *J. Med. Chem.* **1986**, *29*, 424. (d) Källström, S.; Leino, R. *Bioorg. Med. Chem.* **2008**, *16*, 601. (e) Bourin, M.; Chue, P.; Guillon, Y. *CNS Drug Rev.* **2001**, *7*, 25. (f) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *5*, 435. (g) Pinard, E.; Alberati, D.; Alvarez-Sanchez, R.; Brom, V.; Burner, S.; Fischer, H.; Hauser, N.; Kolczewski, S.; Lengyel, J.; Mory, R.; Saladin, C.; Schulz-Gasch, T.; Stalder, H. *ACS Med. Chem. Lett.* **2014**, *5*, 428.
2. (a) Lee, J.-H.; Seo, S. H.; Lim, E. J.; Cho, N.-C.; Nam, G.; Kang, S. B.; Pae, A. N.; Jeong, N.; Keum, G. *Eur. J. Med. Chem.* **2014**, *74*, 246. (b) Russell, M. G. N.; Baker, R.; Billington, D. C.; Knight, A. K.; Middlemiss, D. N.; Noble, A. J. *J. Med. Chem.* **1992**, *35*, 2025. (c) Rogers, G. A.; Parsons, S. M.; Anderson, D. C.; Nilsson, L. M.; Bahr, B. A.; Kornreich, W. D.; Kaufman, R.; Jacobs, R. S.; Kirtman, B. *J. Med. Chem.* **1989**, *32*, 1217. (d) Gu, X.; Izenwasser, S.; Wade, D.; Housman, A.; Gulasey, G.; Rhoden, J. B.; Savoie, C. D.; Mobley, D. L.; Lomenzo, S. A.; Trudell, M. L. *Bioorg. Med. Chem.* **2010**, *18*, 8356. (e) Araki, T.; Mikami, T.; Tanji, H.; Matsubara, M.; Imai, Y.; Mizugaki, M.; Itoyama, Y. *Eur. J. Pharm. Sci.* **2001**, *12*, 231. (f) Di Monte, D. A.; Jewell, M. A. In *Encyclopedia of the Neurological Science*; 2nd ed.; Daroff, R. B., Aminoff, M. J., Eds.; Academic Press: Oxford, 2014, p. 131.
3. (a) Joubert, J.; Geldenhuys, W. J.; Van der Schyf, C. J.; Oliver, D. W.; Kruger, H. G.; Govender, T.; Malan, S. F. *ChemMedChem* **2012**, *7*, 375. (b) Lipton, S. A. *Nat. Rev. Drug Discovery* **2006**, *5*, 160. (c) Wanka, L.; Iqbal, K.; Schreiner, P. R. *Chem. Rev.* **2013**, *113*, 3516.
4. (a) Schmidle, C. J.; Mansfield, R. C. *J. Med. Chem. Soc.* **1955**, *77*, 5698. (b) Prostakov, N. S.; Varlamov, A. V.; Vasil'ev, G. A. *Chem. Heterocycl. Compd.* **1977**, *13*, 639. [*Khim. Geterotsikl. Soedin.* **1977**, 787.] (c) Thompson, D.; Reeves, P. C. *J. Heterocycl. Chem.* **1983**, *20*, 771. (d) Conway, R. J.; Valant, C.; Christopoulos, A.; Robertson, A. D.; Capuano B.; Crosby, I. T. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 2560. (e) Chen, H.; Liang, X.; Xu, B.; He, X.; Huang, B.; Yuan, M. *Molecules* **2014**, *19*, 12048. (f) Anxionnat, B.; Robert, B.; George, P.; Ricci, G.; Perrin, M.-A.; Pardo, D. G.; Cossy, J. *J. Org. Chem.* **2012**, *77*, 6087. (e) Sargsyan, M. S.; Hayotsyan, S. S.; Khachatryan, A. Kh.;

Badasyan, A. E.; Panosyan, G. A.; Kon'kova, S. G. *Chem. Heterocycl. Compd.* **2013**, *48*, 1805. [*Khim. Geterotsikl. Soedin.* **2012**, 1928.]
5. (a) Klumpp, D. A.; Beauchamp, P. S.; Sanchez, G. V., Jr.; Aguirre, S.; de Leon, S. *Tetrahedron Lett.* **2001**, *42*, 5821. (b) Olah, G. A., Klumpp D. A. *Superelectrophiles and their Chemistry*; Wiley-Intersciense: Hoboken, 2008, p. 250.
6. Shadrikova, V. A.; Golovin, E. V.; Klimochkin, Y. N. *Chem. Heterocycl. Compd.* **2015**, *50*, 1586. [*Khim. Geterotsikl. Soedin.* **2014**, 1725.]
7. (a) Grierson, D. S.; Harris, M.; Husson, H. *J. Am. Chem. Soc.* **1980**, *102*, 1064. (b) Wichitnithad, W.; O'Callaghan, J. P.; Miller, D. B.; Train, B. C.; Callery, P. S. *Bioorg. Med. Chem.* **2011**, *19*, 7482. (c) Rouchaud, A.; Kem, W. R. *J. Heterocycl. Chem.* **2010**, *47*, 569. (d) Terentiev, P. B.; Zilberstein, T. M.; Borisenko, A. A.; Shmorgunov, V. A.; Piskunkova, N. F.; Grishina, G. V. *Chem. Heterocycl. Compd.* **2003**, *39*, 885. [*Khim. Geterotsikl. Soedin.* **2003**, 1027.] (e) Keay, J. G. In *Comprehensive Organic Synthesis*; Trost, B. M.; Fleming, I., Eds.; Pergamon Press: Oxford, 1991, vol. 8, chap. 3.6; p. 579.
8. (a) Ischay, M. A.; Takase, M. K.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2013**, *135*, 2478. (b) Teichert, J. F.; Zhang, S.; van Zijl, A. W.; Slaa, J. W.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2010**, *12*, 4658.
9. (a) Eliel, E. L.; Wilen, S. H.; Doyle, M. P. *Basic Organic Stereochemistry;* Wiley-Interscience; New York, 2001, p. 448. (b) Salamone, M.; Martella, R.; Bietti, M. *J. Org. Chem.* **2012**, *77*, 8556.
10. (a) Klimochkin, Y. N.; Leonova, M. V.; Korzhev, I. R.; Moiseev, I. K.; Vladyko, G. V.; Korobchenko, L. V.; Boreko, E. I.; Nikolaeva, S. N. *Pharm. Chem. J.* **1992**, *26*, 616. [*Khim.-Farm. Zh.*, **1992**, *26*, 58.] (b) Kevill, D. N.; Upadhyay, V. *J. Phys. Org. Chem.* **1997**, *10*, 600.
11. (a) Alkorta, I.; Elguero, J. *Magn. Reson. Chem.* **2004**, *42*, 955. (b) Basso, E. A.; Gauze, G. F.; Abraham, R. J. *Magn. Reson. Chem.* **2007**, *45*, 749. (c) Rodríguez-Franco, M. I.; Fernández-Bachiller, M. I. *Magn. Reson. Chem.* **2002**, 40, 549. (d) Casy, A. F.; Dewar, G. H.; Al Deeb, O. A. A. *Chirality* **1989**, *1*, 202. (e) Casy, A. F.; Ogungbamila, F. O. *Org. Magn. Reson*. **1982**, *18*, 171.
12. (a) Cheng, A.; Uyeno, E.; Polgar, W.; Toll, L.; Lawson, J. A.; DeGraw, J. I.; Loew, G.; Camerman, A.; Camerman, N. *J. Med. Chem.* **1986**, *29*, 531. (b) Li, R.-L.; Liu, G.-Q.; Li, W.; Wang, Y.-M.; Li, L.; Duan, L.; Li, Y.-M. *Tetrahedron* **2013**, *69*, 5867. (c) Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 6042.
13. Casy, A. F.; Dewar, G. H.; Al-Deeb, O. A. A. *Magn. Reson. Chem.* **1989**, *27*, 964.
14. (a) Parker, W.; Riddell. F. G. In *Aliphatic, Alicyclic, and Saturated Heterocyclic Chemistry, Vol. 1, pt. III: Five- and Six-Membered Rings; Medium Sized Rings; Bridged and Caged Systems (Carbocyclic and Saturated Heterocyclic)*; Parker, W., Ed.; The Chemical Society: London, 1973, p. 41. (b) Pines, H. *Chemistry of Catalytic Hydrocarbon Conversions*; Academic Press: New York, 1981, p. 18.
15. (a) Kevill, D. N.; Weitl, F. l. *J. Am. Chem. Soc.* **1968**, *90*, 6416. (b) Prakash, G. K. S.; Paknia, F.; Mathew, T.; Mloston, G.; Joschek, J. P.; Olah, G. A. *Org. Lett.* **2011**, *13*, 4128. (c) Beak, P.; Trancik, R. J. *J. Am. Chem. Soc.* **1968**, *90*, 2714.
16. Parr, R. G.; Szentpály, L.; Liu, S. *J. Am. Chem. Soc.* **1999**, *121*, 1922.
17. Peìrez, P.; Toro-Labbeì, A.; Aizman, A.; Contreras, R. *J. Org. Chem.* **2002**, *67*, 4747.
18. Fürst, A.; Plattner, P. A. *Helv. Chim. Acta* **1949**, *32*, 275.
19. Krumkalns, E. V.; Pfeifer, W. *J. Med. Chem.* **1968**, *11*, 1103.
20. Frisch, M. J.; Trucks, G. W.; Schlegel, H. B.; Scuseria, G. E.; Robb, M. A.; Cheeseman, J. R.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, G. A.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, H. P.; Izmaylov, A. F.; Bloino, J.; Zheng, G.; Sonnenberg, J. L.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, J. A., Jr.; Peralta, J. E.; Ogliaro, F.; Bearpark, M.; Heyd, J. J.; Brothers, E.; Kudin, K. N.; Staroverov, V. N.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, J. C.; Iyengar, S. S.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, J. M.; Klene, M.; Knox, J. E.; Cross, J. B.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, R. E.; Yazyev, O.; Austin, A. J.; Cammi, R.; Pomelli, C.; Ochterski, J. W.; Martin, R. L.; Morokuma, K.; Zakrzewski, V. G.; Voth, G. A.; Salvador, P.; Dannenberg, J. J.; Dapprich, S.; Daniels, A. D.; Farkas, Ö.; Foresman, J. B.; Ortiz, J. V.; Cioslowski, J.; Fox, D. J. *Gaussian 09*, *Revision A.02*; Gaussian, Inc.: Wallingford, 2009.
21. Butov, G. M.; Mokhov, V. M. *Russ. J. Org. Chem.* **2014**, *50*, 447. [*Zh. Org. Khim.* **2014**, *50*, 455.]
22. Sheldrick, G. M. *Acta Crystallogr.*, *Sect. A: Found. Crystallogr*. **2008**, *A64*, 112.
23. http://www.ccdc.cam.ac.uk/mercury/henyl group.