Russian Journal of Organic Chemistry, Vol. 41, No. 2, 2005, pp. 272–278. Translated from Zhurnal Organicheskoi Khimii, Vol. 41, No. 2, 2005, pp. 281–287.

Synthesis and Stereochemistry of 3-Hydroxy-1,2,3,6-tetrahydropyridines

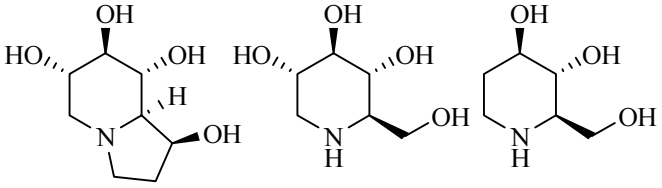
G.V. Grishina, A.A. Borisenko, I.S. Veselov, and A.M. Petrenko

Lomonosov Moscow State University, Moscow, 119992 Russia
e-mail: grishina@org.chem.msu.su

Received July 5, 2004

Abstract—A series of 1-benzyl-3-hydroxy-1,2,3,6-tetrahydropyridines, multipurpose synthons for fine organic synthesis and potential antiviral compounds, was prepared by the rearrangement of a number of 1-benzyl-3,4-epoxypiperidines under treatment with lithium amides. 3,4-Epoxypiperidines were obtained by oxidation of 1,2,5,6-tetrahydropyridines trifluoroacetates with a trifluoroperacetic acid. Convenient synthetic routes were found and developed. A conformation analysis of the series of stable 3,4-epoxypiperidines and 3-hydroxy-1,2,3,6-tetrahydropyridines was carried out.

In the last decade an interest grew to polyhydroxylated piperidine derivatives, synthetic substances related to alkaloids from the series of castanospermin (**I**) [nojiromycin (**II**), and fagomin (**III**)], which turned out to be strong glucosidase inhibitors and also exhibited antiviral, in particular, anti-HIV, activity [1].



I **II** **III**

We recently found that racemic and chiral N- and C-substituted *trans*-3,4-dihydroxypiperidines, substances a lot simpler structurally and stereochemically than castsnospermin alkaloids **I–III**, also exhibited to a different degree anti-HIV activity *in vitro* and were characterized by a low toxicity. Thus the fragment of "*trans*-3,4-dihy-droxypiperidine" may be regarded as anti-HIV pharmaco-phor [2, 3].

Looking for new hydroxylated piperidine derivatives with a potential anti-HIV activity, including also chiral nonracemic compounds, we used as synthons for further functionalization 3-hydroxy-1,2,3,6-tetrahydropyridines **IVa–IVe** that could be interesting on their own as potential antiviral agents.

The most conveniently the synthesis of piperidine series allyl alcohols **IVa–IVe** is performed using as precursors N- and C-substituted 3,4-epoxypiperidines **Va–Ve**.

The 3,4-epoxypiperidines with an N-amide group are commonly prepared by oxidation with peracids of the corresponding 1,2,5,6-tetrahydropyridines [4]. At the same time the data on the synthesis of *N*-alkyl-3,4-epoxypiperidines are scarce and ambiguous; the high lability of *N*-alkylepoxypiperidines is often indicated that significantly complicates their isolation and synthetic application. Besides the preliminary formation of N-oxide blocks the further oxidation of a double bond. Therefore in the synthesis of *N*-alkyl-3,4-epoxypiperidines arises a problem of nitrogen protection specific for each substrate. In some cases the nitrogen was successfully protected by a preliminary protonation [5–9] or by complexing with a Lewis acid, e.g., with a trifluoroboron etherate [10]. However this protection results in increased negative induction effect of the nitrogen thus requiring the use of more efficient oxidants (dimethyldioxirane, trifluoro-methylmethyldioxirane [5]) or the prolongation of the process.

The stability of *N*-alkyl-3,4-epoxypiperidines depends to a large extent on the substrate structure. For instance, we failed to isolate the target epoxide from the reaction mixture obtained by treating 1-(1-phenyl-2-acetoxyethyl)-1,2,5,6-tetrahydropyridine with *m*-chloroperbenzoic acid. However already the introduction of an ethyl group into the position *3* of the piperidine ring favored the formation of a more stable 3,4-epoxy-1-(1-phenyl-2-acetoxyethyl)-3-ethyl-1,2,5,6-tetrahydropyridine. GC-MS analysis revealed in the epoxidation products of 1-(1-phenyl-2-oxyethyl)-1,2,5,6-tetrahydropyridine a complex mixture of compounds where we succeeded to identify a dimer

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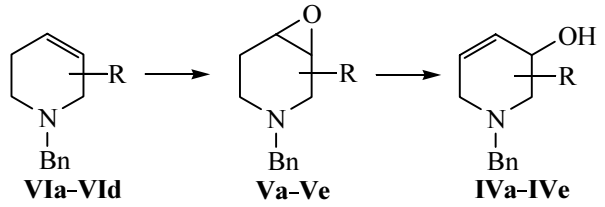
arising at the opening of the forming oxirane ring by the *N*-(1-phenyl-2-oxyethyl) group of the second molecule [6]. Although the GC-MS method detected the formation of 1-(1-phenylethyl)-3,4-epoxypiperidine, the latter compound was not sufficiently stable to be isolated by chromatography, and only a mixture of isomer alcohols was obtained [7].

All the mentioned data indicate the necessity of a cautious search for the synthesis conditions and for an appropriate oxidant in order to successfully prepare 1-benzyl-3,4-epoxypiperidines.

By careful adjustment of the process conditions and detailed chromatographic monitoring of the oxidation course we found that the optimum synthetic procedure for the target series of 1-benzyl-3,4-epoxypiperidines **Va–Vd** affording them in 60–72% yields was oxidation of tetrahydropyridines trifluoroacetates **VIa–VId** [7] with trifluoroperacetic acid at–5–0°C for 10–20 min. Even an insignificantly longer reaction period results in a drastic decrease in the yield of the target epoxides and leads not only to the opening of the oxirane ring but also to the other side products. GC-MS monitoring of the oxidation process of 1-benzyl-3-methyl-1,2,5,6-tetrahydropyridine (**VIb**) demonstarated that after 1.5 h the main reaction products were 1-benzyl-3-methyl-3,4-dihydroxypiperidine (58%, retention time 8.27 s, $[M]^+$ 221) and its monotrifluoroacetate (35%, retention time 7.38 s, $[M]^+$ 317). In the overall yield of 7% were obtained the target epoxide **Vb** (retention time 6.81 s) revealed in the mass spectrum by the characteristic fragment ion *m/z* 186 (hydroxide loss) and the tetrahydropyridine N-oxide (**VIb**) (retention time 7.03 s) with a fragment ion characteristic of N-oxides, *m/z* 187 (oxygen loss). The end of epoxidation we fixed by disappearance in the ^{1}H NMR spectrum of the reaction mixture of the vinyl protons signals at 5–6 ppm corresponding to the initial 1,2,5,6-tetrahydropyridines. Thus just the length of the epoxidation period is crucial: The careful monitoring in the course if oxidation provides a possibility to successfully obtain and isolate individual 3,4-epoxypiperidines **Va–Ve** (Scheme 1).

Scheme 1.



R = H (**a**), 3-Me (**b**), 4-Me (**c**), 6-Me (**d**, *cis*-), (**e**, *trans*-).

On completion of epoxidation the peracid excess was deactivated with sodium sulfite saturated solution, and the target epoxides were isolated as individual compounds by means of column chromatography on silica gel.

Although an extreme instability of N-alkyl-3,4-epoxypiperidines was described in the literature epoxides **Va–Ve** proved to be quite stable both during isolation and purification, and were stored without changes for a year at 5–10°C.

The structure of epoxides **Va–Ve** was confirmed by elemental and GC-MS analysis data. The presence of the epoxy ring is demonstrated by the signals of C^3 and C^4 atoms of the epoxy ring in the region 50–60 ppm in the ^{13}C NMR spectra and by characteristic multiplets of the protons attached to these carbons at 3 ppm in the ^{1}H NMR spectra. The oxidation of 1-benzyl-6-methyl-1,2,5,6-tetrahydropyridine (**VId**) gave rise to an inseparable mixture of epoxides **Vd, Ve** in 1:1 ratio and an overall yield 65%, as was established from the integral intensity values of resonances corresponding to protons attached to C^5. In the ^{1}H NMR spectrum of the isomer mixture of epoxides **Vd, Ve** only the following proton signals were assigned: from methylene protons attaced to C^5, from 6-methyl, and N-benzyl groups. Due to strong overlapping the precise attribution of the other signals to *cis*- or *trans*-isomer was too complicated. Inasmuch as the chromatographic mobility of *cis*- and *trans*-epoxides **Vd, Ve** proved to be identical we were obliged to use further the isomer mixture.

Target 1-benzyl-3-hydroxy-1,2,3,6-tetrahydropyridines **IVa–IVe** were obtained by a rearrangement of **Va**–**Ve** derivatives effected by lithium diisopropylamide (LDA) (sometimes lithium diethylamide was applied) in THF under argon atmosphere within 2 h at room temperature [7, 8]. The column chromatography on silica gel permitted isolation of the series of 1-benzyl-3-hydroxy-1,2,3,6-tetrahydropyridines **IVa–IVe** in a 61–80% yield. The rearrangement of the isomer mixture of 6-methyl-3,4-epoxypiperidines **Vd, Ve** gave rise to isomeric 1-benzyl-3-hydroxy-6-methyl-1,2,3,6-tetrahydropyridines **IVd, IVe** that were isolated by column chromatography as individual substances in a 63% yield in a 1:1 weight ratio. According to GC-MS data the chemical purity of the first isomer **IVd** (retention time 14.28 s) attained 99%, the purity of the second isomer **IVe** (retention time 14.62 s) was 98%. The decomposition of both isomers **IVd, IVe** in the mass spectrometer was of a similar character although the fragment ions $[M - \mathrm{Me}]^+$ formed in different amounts

The relative intensities (I_{rel}, %) of fragment ions in the mass spectra of isomers **IVd, IVe** are given below:

Ion	**IVd**	**IVe**
$[M]^+$	1	1
$[M - Me]^+$	10	20
$[M - C_5H_7O]^+$	50	45
$[C_7H_7]^+$	100	100

The presence of a hydroxyallyl system in compounds **IVa–IVe** is confirmed by the presence in their IR spectra of bands belonging to the stretching vibrations of the double bond at 1660 and of hydroxy group at 3410 cm^{-1}. Further proof of the structure of compounds **IVa–IVe** provides the presence in their ^{13}C NMR spectra of characteristic signals in the region 120–135 ppm corresponding to C^4 and C^5 atoms of the double bond and of signal from the C^3 atom linked to the hydroxy group at 64–68 ppm. The vinyl proton signals in the ^1H NMR spectra of compounds **IVa–IVe** appear in the region 5.4–5.9 ppm.

We planned to determine the spatial structure of isomers **IVd, IVe** from the coupling constants values of the protons attached to pairs of atoms C^2,C^3 and C^3,C^4 of the 1,2,3,6-tetrahydropyridine ring applying the double resonance technique. However the measured coupling constants given below proved to be very close, apparently due to a fast conformational equilibrium. Therefore we considered these coupling constants values as unsuitable for the exact assignment of reciprocal orientation of the methyl and the hydroxy groups in the isomers.

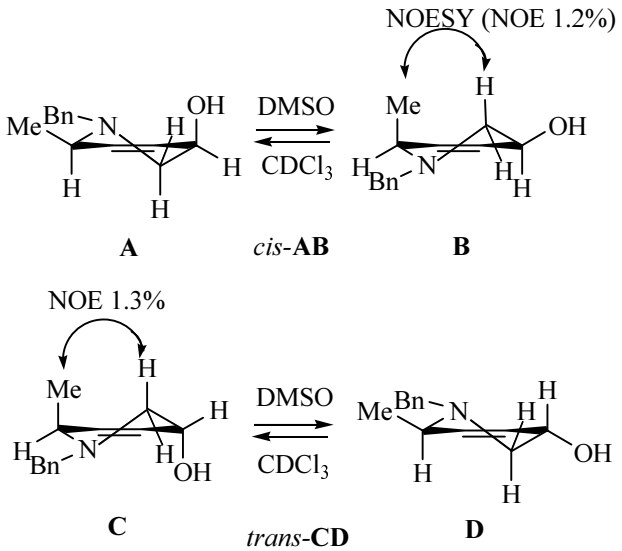
Coupling constant, Hz	**IVd**	**IVe**
$^3J(H^2H^3)$	2.6	5.1
$^3J(H^2H^3)$	3.0	4.0
$^3J(H^4H^3)$	5.0	3.5
$^3J(H^5H^6)$	2.0	3.4

The comparative data on the changes in the ^{13}C NMR spectra taken in $CDCl_3$ and DMSO-d_6 were far more interesting and informative. Depending on the polarity of solvent the position of the signal from the methyl group attached to position *6* (δ, ppm) suffered significant changes occurring in the opposite direction for different isomers:

Solvent	**IVd**	**IVe**
$CDCl_3$	19.2	14.5
DMSO-d_6	15.4	19.0

Inasmuch as no studies on conformational analysis of such compounds were found in the literature the elucidation of the isomers structure required more thorough investigation.

Scheme 2.



Presumably the conformational equilibrium for *cis*- and *trans*-isomers **IVd, IVe** may be represented as conformer pairs *cis*-**AB** and *trans*-**CD** (Scheme 2).

In the spectrum of the first isomer **IVd** registered in the NOESY mode in DMSO-d_6 appeared a cross-peak for 6-Me and H^{2a} signals that should be expected for *cis*-isomer **IVd** in **B** conformation with a pseudoaxial orientation of the 6-Me group. Consequently, conformer **B** is predominant in DMSO. Similar results for isomer **IVd** were obtained in the NOE experiment carried out in DMSO-d_6: a considerable (1.2%) response of the proton at C^2 (2.48 ppm) was observed at irradiation of the 6-Me group evidencing the prevalence of conformer **B**.

In the nonpolar $CDCl_3$ in the NOE experiment with the first, presumably *cis*-isomer **IVd**, the irradiation of the 6-Me group caused but insignificant intensity increase (0.2%) in the peak of the proton at C^2 suggesting the prevailing presence of conformer **A**.

In the spectrum registered in the NOESY mode for the second isomer **IVe** in DMSO-d_6 no cross-peak between the 6-Me group and the axial proton at C^2 was observed suggesting that the 6-Me and 3-hydroxy groups were present in the diequatorial orientation, and thus conformer **D** of the *trans*-isomer **IVe** prevailed. The NOE experiment for *trans*-isomer **IVe** in DMSO-d_6 completely confirmed the results obtained by the NOESY method: In DMSO-d_6 the irradiation of the methyl did not cause a response of the protons at C^2 demonstrating

that in the equilibrium (**C** ⇆ **D**) of *trans*-isomer **IVe** conformer **D** was the dominant.

In $CDCl_3$ NOE experiment for *trans*-isomer **IVe** revealed a considerable (1.3%) increase in the integral intensity of the signal of proton linked to C^2 (2.35 ppm) at irradiation of the 6-Me group thus indicationg the prevalence of conformer **C**. According to the above data isomers **IVd, IVe** posess really *cis*- and *trans*-structure respectively.

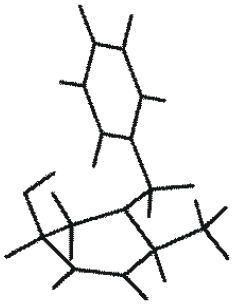
The effects observed evidence the strong influence of the solvent polarity on the conformational equilibrium of *cis*- and *trans*-isomers **IVd, IVe** that exist in a *semichair* conformation.

The conclusion on the *cis*- and *trans*-structure of isomers **IVd, IVe** was confirmed by semiempirical calculations using PM3 procedure for conformational simulation involving geometry and energy optimization of the preferential conformers of isomers **IVd, IVe** According to the results obtained the isomers *cis*- **IVd** and *trans*- **IVe** are involved into a fast, practically degenerate conformational equilibrium where the conformations **A** and **C** with a pseudoaxial orientation of the hydroxy group are preferable. The slightly greater stability of conformations **A** and **C** may be due to the possibility to form an intramolecular hydrogen bond between the hydroxy group and the lone electron pair of the nitrogen.

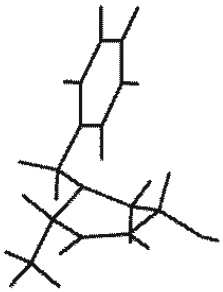
The results of the molecular simulation are well consistent with the experimental findings showing that in the nonpolar $CDCl_3$ the conformational equilibrium of *cis*- and *trans*-isomers **IVd** and **IVe** is displaced to conformers **A** and **C** respectively with a pseudoaxial orientation of the hydroxy group. The prevalence of conformers **A** and **C** in the nonpolar environment might actually originate from the stabilization provided by an intramolecular hydrogen bond between the hydroxy group and the lone electron pair of the nitrogen from the piperidine ring.

Consequently, according to the molecular simulation and conformational analysis isomers **IVd, IVe** are really *cis*- and *trans*-isomers, and the shift in their fast conformational equilibrium essentially depends on the solvent polarity.

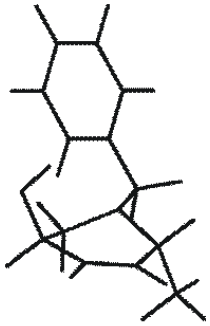
In this way we found and refined convenient synthetic procedures and carried out a conformational analysis for a series of stable 3,4-epoxypiperidines and 3-hydroxy-1,2,3,6-tetrahydropyridines, multipurpose synthons for the fine organic synthesis and for preparation of new biologically active substances.



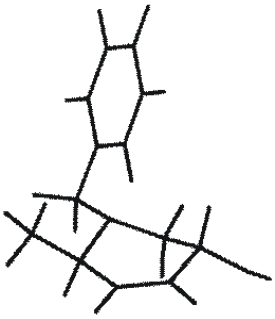
A (E = –12.17 kcal/mol)



B (E = –10.05 kcal/mol)



C (E = –12.25 kcal/mol)



D (E = –10.16 kcal/mol)

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer UR-20. NMR spectra were registered on spectrometers Varian VXR-400 and Brucker DRX-500 at operating frequencies 400 and 500 MHz respectively from solutions in $CDCl_3$ and DMSO-d_6 with TMS as internal reserence

GC-MS analyses were performed on spectrometers HP5989x-G and Finnigan SSQ7000, ionizing electrons energy 70 eV, column DB5 30 m.

The thin-layer chromatography was carried out on plates Silufol (Kavalier, Czechia) and Kodak (BRD). For column chromatography was used a column charged by wet procedure with silica gel of the grade Silica gel 60-40 (Merck, BRD).

1-Benzyl-3,4-epoxypiperidine (Va). To a mixture of 0.390 g (5.4 mmol) of 46.7% water solution of hydrogen peroxide and 15 ml of anhydrous methylene chloride was added at 0°C and vigorous stirring a solution of 2.52 g (12.0 mmol) of trifluoroacetic anhydride in 6 ml of anhydrous methylene chloride. The stirring at the same temperature was continued for 1.5 h. To thus obtained solution of trifluoroperacetic acid was added 1-benzyl-1,2,5,6-tetrahydropyridinium trifluoroacetate prepared from 0.390 g (2.3 mmol) of 1-benzyl-1,2,5,6-tetrahydropyridine (**VIa**) and 0.640 g (5.6 mmol) of

trifluoroacetic acid in 7 ml of anhydrous methylene chloride at 0°C. The epoxidation was monitored by TLC till complete consumption of the initial tetrahydropyridine. In 20 min the excess oxidant was decomposed by addition of 20 ml of aqueous sodium sulfite while vigorous stirring at 0–5°C. The organic layer was separated, washed with 20 ml of saturated water solution of sodium hydrogen carbonate, with water (3×10 ml), and dried on sodium sulfate. The solvent was removed on a rotary evaporator, 0.4 g of the crude product was applied to a column packed with silica gel (6 g) with hexane. Elution was performed with a mixture hexane–ethyl acetate, 3:1. Chromatographically uniform fractions were combined, the solvent was removed in a vacuum. We obtained 0.310 g (72%) of 1-benzyl-3,4-epoxypiperidine (**Va**). Colorless oily substance, R_f 0.7 (Silufol, hexane–acetone, 5:1). IR spectrum (thin film), ν, cm^{-1}: 905, 3010 (epoxide). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.99 m [1H, H^{5a}, ^2J(H^{5a}H^{5e}) 14.6, ^3J(H^{5a}H^{6a}) 9.4, ^3J(H^{5a}H^{6e}) 5.5, ^3J(H^{5a}H^4) 2.6 Hz], 2.03 d.d.t [1H, H^{5e}, ^2J(H^{5e}H^{5a}) 14.6, ^3J(H^{5e}H^{6a}) 4.4, ^3J(H^{5e}H^{6e}) 4.4, ^3J(H^{5e}H^4) 1.5 Hz], 2.19 d.d.d [1H, H^{6a}, ^2J(H^{6a}H^{6e}) 11.8, ^3J(H^{6a}H^{5a}) 9.2, ^3J(H^{6a}H^{5e}) 4.4 Hz], 2.32 m [1H, H^{6e}, ^2J(H^{6e},H^{6a}) 11.8, ^3J(H^{6e}H^{5a}) 5.8, ^3J(H^{6e}H^{5e}) 4.2, ^4J(H^{6e}H^{2e}) 1.2 Hz], 2.67 d [1H, H^{2a}), ^2J(H^{2a}H^{2e}) 13.5 Hz], 3.01 d.d.d [1H, H^{2e}, ^2J(H^{2e}H^{2a}) 13.5, ^3J(H^{2e}H^3) 4.1, ^4J(H^{2e}H^{6e}) 1.5 Hz], 3.18–3.23 m (2H, H^3, H^4), 3.44 s (2H, PhC$\underline{H}_2$), 7.21–7.32 m (5H, ArH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 25.51 (C^5), 45.71, 50.54, 51.19, 52.25, 62.24 (C^2, C^3, C^4, C^6, Ph$\underline{C}H_2$), 127.00, 128.14 (2C), 128.92 (2C), 137.88 (ArC). Picrate, mp 155–157°C (EtOH). Mass spectrum, *m/z* (I_{rel}, %): 189 (17) [*M*]$^+$, 188 (5), 172 (4), 160 (2), 146 (2), 133 (19), 132 (10), 118 (3), 112 (4), 104 (3), 98 (15), 92 (13), 91 (100). Found, %: C 52.04; H 4.26; N 13.52. $C_{18}H_{18}N_4O_8$. Calculated, %: C 51.68; H 4.34; N 13.39.

1-Benzyl-3,4-epoxy-3-methylpiperidine (Vb) was prepared similarly to compound **Va** from 0.410 g (2.2 mmol) of 1-benzyl-3-methyl-1,2,5,6-tetrahydropyridine (**VIb**). Yield 0.250 g (61%). Light-yellow oily substance, R_f 0.8 (Silufol, hexane–acetone, 4:1). IR spectrum (thin film), ν, cm^{-1}: 905, 1240 (epoxide). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.30 s (3H, CH_3), 1.93 m [1H, H^{5a}, ^2J(H^{5a}H^{5e}) 14.7, ^3J(H^{5a}H^{6a}) 7.8, ^3J(H^{5a}H^{6e}) 6.3, ^3J(H^{5a}H^4) 2.9 Hz], 2.00 m [1H, H^{5e}, ^2J(H^{5e}H^{5a}) 14.7, ^3J(H^{5e}H^{6a}) 5.0, ^3J(H^{5e}H^{6e}) 5.0, ^3J(H^{5e}H^4) 1.7 Hz], 2.22–2.26 m (2H, 6-CH_2), 2.66 d [1H, H^2, ^2J(H^{2}H^2) 12.9 Hz], 2.74 d [1H, H^2, ^2J(H^{2}H^2) 12.9 Hz], 3.04 m (1H, H^4), 3.44 d (1H, PhC$\underline{H}_2$N, ^2J 12.9 Hz), 3.46 d (1H, PhC$\underline{H}_2$N, ^2J 13.2 Hz), 7.20–7.30 m (5H, ArH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 22.09 (3-CH_3), 25.52 (C^5), 45.61, 56.56, 57.65, 62.04 (C^2, C^4, C^6, Ph$\underline{C}H_2$), 56.71 (C^3), 126.88, 128.04 (2C), 128.85 (2C), 137.78 (ArC). Picrate, mp 168–169°C (EtOH). Mass spectrum, *m/z* (I_{rel}, %): 203 (6) [*M*]$^+$, 202 (7), 188 (3), 186 (11) 174 (2), 146 (5), 133 (7), 132 (10), 126 (2), 120 (3), 118 (4), 112 (16), 104 (3), 98 (2), 92 (9), 91 (100). Found, %: C 53.18; H 4.68; N 12.34. $C_{18}H_{18}N_4O_8$. Calculated, %: C 52.78; H 4.66; N 12.96.

1-Benzyl-3,4-epoxy-4-methylpiperidine (Vc) was prepared similarly to compound **Va** from 0.410 g (2.2 mmol) of 1-benzyl-4-methyl-1,2,5,6-tetrahydropyridine (**VIc**). Yield of epoxide **Vc** 0.230 g (60%). Colorless oily substance, R_f 0.59 (Silufol, hexane–acetone, 2:1). IR spectrum (thin film), ν, cm^{-1}: 865 (epoxide). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.34 s (CH_3), 1.90 m [2H, 5-CH_2, ^3J(5-CH_2H^{6a}) 7.2, ^3J(5-CH_2H^{6e}) 4.6 Hz], 2.14 d.t [1H, H^{6a}, ^2J(H^{6a}H^{6e}) 11.4, ^3J(5-CH_2H^{6a}) 7.2 Hz], 2.38 d.d.t [1H, H^{6e}, ^2J(H^{6e}H^{6a}) 11.4, ^3J(5-CH_2H^{6e}) 4.6, ^5J(H^{5e}H^{2e}) 1.3 Hz], 2.57 d [1H, H^{2a}, ^2J(H^{2a}H^{2e}) 13.2 Hz], 3.02 d [1H, H^3, ^3J(H^{3}H^{2e}) 4.7 Hz], 3.08 d.d.d [1H, H^{2e}, ^2J(H^{2e}H^{2a}) 13.2, ^3J(H^{2e}H^3) 4.7, ^4J(H^{2e}H^{6e}) 1.4 Hz], 3.43 d (1H, PhC$\underline{H}_2$N, ^2J 12.9 Hz), 3.46 d (1H, PhC$\underline{H}_2$N, ^2J 13.2 Hz), 7.21–7.32 m (5H, ArH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 22.08 (3-$\underline{C}H_3$), 30.65 (C^5), 46.25, 52.48, 58.32, 62.12 (C^2, C^3, C^6, Ph$\underline{C}H_2$), 56.35 (C^4), 126.96, 128.12 (2C), 128.92 (2C), 137.93 (ArC). Picrate, mp 150–151°C (EtOH). Mass spectrum, *m/z* (I_{rel}, %): 203 (3) [*M*]$^+$, 188 (3), 186 (16) 160 (2), 144 (5), 133 (4), 132 (7), 120 (5), 112 (9), 98 (3), 92 (10), 91 (100). Found, %: C 53.08; H 4.62; N 12.91. $C_{18}H_{18}N_4O_8$. Calculated, %: C 52.78; H 4.66; N 12.96.

Diastereomers of 1-benzyl-3,4-epoxy-6-methylpiperidine (Vd, e) were prepared similarly to compound **Va** from a mixture of products obtained by reduction of 1-benzyl-2-methylpyridinium bromide with sodium borohydride that contained according to ^{1}H NMR spectrum 16% of 1-benzyl-2-methylpiperidine, 6% of 1-benzyl-2-methyl-1,2,5,6-tetrahydropyridine, and 78% (0.320 g, 1.7 mmol) of 1-benzyl-6-methyl-1,2,5,6-tetrahydropyridine (**VId**). Yield 0.230 g (67%) of a mixture of *cis*- and *trans*-1-benzyl-3,4-epoxy-6-methylpiperidines (**Vd, Ve**) in the ratio 1:1 according to ^{1}H NMR spectrum. Colorless oily substance, R_f 0.72 (Silufol, hexane–acetone, 4:1). IR spectrum (thin film), ν, cm^{-1}: 830, 1265 (epoxide). ^{1}H NMR spectrum (400 MHz, $CDCl_3$, for isomers mixture), δ, ppm: 1.08 d [3H, CH_3, ^3J(CH_3H^6) 6.4 Hz], 1.10 d [3H, CH_3, ^3J(CH_3H^6) 6.5 Hz], 1.71 d.d.d [1H,

H^{5a}, $^2J(H^{5a}H^{5e})$ 14.8, ^3J 8.2, ^3J 3.1 Hz], 1.85 d.d [1H, H^{5a}, $^2J(H^{5a}H^{5e})$ 15.2, ^3J 7.6 Hz], 2.00 d.d.d [1H, H^{5e}, $^2J(H^{5e}H^{5a})$ 15.2, ^3J 5.3, ^3J 4.4 Hz], 2.09 d.d [1H, H^{5e}, $^2J(H^{5a}H^{5e})$ 14.7 Hz], 2.56–2.66 m (4H), 2.97–3.12 m (4H), 3.20–3.26 m (3H), 3.40 d (1H, PhC$\underline{H}_2$, ^2J 13.2 Hz), 3.78–3.84 m (2H, PhC$\underline{H}_2$), 7.20–7.33 m (10H, ArH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 17.02, 17.86 (6-$\underline{C}H_3$), 31.42, 32.45 (C^5), 48.58 (2C), 49.48 (2C), 50.63, 50.92, 50.95, 56.55, 56.81 (C^2, C^3, C^4, C^6, Ph$\underline{C}H_2$), 126.73, 126.76, 128.13 (4C), 128.69 (2C), 128.77 (2C), 138.98, 139.19 (ArC). Picrate, mp 164–165°C (EtOH). Mass spectrum, *m/z* (I_{rel}, %): 203 (5) $[M]^+$, 187 (13), 188 (84), 146 (3), 92 (8), 91 (100). Found, %: C 52.86; H 4.68; N 12.84. $C_{18}H_{18}N_4O_8$. Calculated, %: C 52.78; H 4.66; N 12.96.

1-Benzyl-1,2,3,6-tetrahydropyridin-3-ol (IVa). Into a round-bottom flask of 25 ml capacity equipped with a magnetic stirrer and a septum was introduced with a syringe under argon atmosphere 0.18 g (2.5 mmol) of diisopropylamine in 5 ml of anhydrous tetrahydrofuran. The mixture was cooled to –15°C, and 1.57 ml (2.5 mmol) of 1.6 M butyllithium solution in hexane was added. The temperature was gradually raised to –5°C, the solution was stirred for 20 min, and then into the reaction mixture was slowly added a solution of 0.195 g (1.0 mmol) of 1-benzyl-3,4-epoxypiperidine in 3 ml of anhydrous tetrahydrofuran, the cooling was removed, and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was treated with 10 ml of saturated water solution of ammonium chloride and extracted with methylene chloride (10×10 ml). The combined organic extracts were dried over sodium sulfate. The solvent was removed in a vacuum. The crude reaction product was applied to a column packed with silica gel in hexane. The elution was performed with a system hexane–ethyl acetate with ethyl acetate gradient from 0 to 40%. Chromatographically uniform fractions were combined. We obtained 0.155 g (79%) of 1-benzyl-3-hydroxy-1,2,3,6-tetrahydropyridine (**IVa**) as a colorless viscous oily substance, R_f 0.53 (Silufol, hexane–acetone, 5:1). IR spectrum (thin film), ν, cm^{-1}: 1660 (C=C), 3410 (bound OH). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 2.53 d.d.d [1H, H^2, $^2J(H^2H^2)$ 11.4, $^3J(H^2H^3)$ 3.6, J 0.6 Hz], 2.71 d.d [1H, H^2, $^2J(H^2H^2)$ 11.4, $^3J(H^2H^3)$ 3.8 Hz], 2.76 m [1H, H^6, $^2J(H^6H^6)$ 16.7 Hz], 2.93 br.s (1H, OH), 3.05 m [1H, H^6, $^2J(H^6H^6)$ 16.7 Hz], 3.59 d (1H, PhC$\underline{H}_2$, ^2J 13.2 Hz), 3.57 d (1H, PhC$\underline{H}_2$, ^2J 13.2 Hz), 4.05 m (1H, H^3), 5.76 m [1H, H^5, $^3J(H^5H^4)$ 10.0 Hz], 5.85 m [1H, H^4, $^3J(H^4H^5)$ 10.0 Hz], 7.21–7.33 m (5H, ArH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 52.43, 57.49, 62.31 (C^2, C^6, Ph$\underline{C}H_2$), 64.37 (C^3), 127.93, 128.25 (C^4, C^5), 127.11, 128.16 (2C), 128.99 (2C), 137.47 (ArC). Picrate, mp 152–153°C (EtOH). Found, %: C 51.80; H 4.37; N 13.28. $C_{18}H_{18}N_4O_8$. Calculated, %: C 51.68; H 4.34; N 13.39.

1-Benzyl-3-methyl-1,2,3,6-tetrahydropyridin-3-ol (IVb) was prepared in the same way as compound **IVa** from 0.140 g (0.69 mmol) of 1-benzyl-3-methyl-3,4-epoxypiperidine (**Vb**). Yield of compound **IVb** 0.112 g (80%). Light-yellow oily substance, R_f 0.82 (Silufol, hexane–acetone, 4:1). IR spectrum (thin film), ν, cm^{-1}: 1660 (C=C), 3435 (bound OH). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.20 C (3H, CH_3), 2.24 d [1H, H^2, $^2J(H^2H^2)$ 11.2 Hz], 2.67 m [1H, H^6, $^2J(H^6H^6)$ 17.3 Hz], 2.73 d [2H, H^2 $^2J(H^2H^2)$ 11.1 Hz and OH], 3.15 d.d [1H, H^6, $^2J(H^6H^6)$ 16.4, $^3J(H^6H^5)$ 3.8 Hz], 3.62 s (2H, PhC$\underline{H}_2$), 5.67 m [1H, H^5, $^3J(H^5H^4)$ 10.0, $^3J(H^5H^6)$ 4.0 Hz], 5.72 m [1H, H^4, $^3J(H^4H^5)$ 10.0 Hz], 7.23–7.36 m (5H, ArH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 24.67 (3-$\underline{C}H_3$), 52.63, 62.28, 63.09 (C^2, C^6, Ph$\underline{C}H_2$), 67.37 (C^3), 126.42, 127.19, 128.28 (2C), 128.92 (2C), 132.73, 137.84 (C^4, C^5, ArC). Picrate, mp 160–161°C (EtOH). Mass spectrum, *m/z* (I_{rel}, %): 203 (1) $[M]^+$, 121 (5), 120 (62), 94 (1), 92 (8), 91 (100). Found, %: C 52.74; H 4.67; N 12.84. $C_{18}H_{18}N_4O_8$. Calculated, %: C 52.78; H 4.66; N 12.96.

1-Benzyl-4-methyl-1,2,3,6-tetrahydropyridin-3-ol (IVc). was prepared in the same way as compound **IVa** from 0.190 g (0.94 mmol) of 1-benzyl-4-methyl-3,4-epoxypiperidine (**Vc**). Yield of compound **IVc** 0.116 g (61%). Light-yellow oily substance, R_f 0.51 (Silufol, hexane–acetone, 2:1). IR spectrum (thin film), ν, cm^{-1}: 1655 (C=C), 3410 (bound OH). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.78 m (3H, CH_3), 2.43 d.d.d [1H, H^2, $^2J(H^2H^2)$ 11.5, $^3J(H^2H^3)$ 3.0, J 0.9 Hz], 2.66 m [2H, H^6, $^2J(H^6H^6)$ 16.4 Hz and 3-OH], 2.83 d.d.d [1H, H^2, $^2J(H^2H^2)$ 11.7, $^3J(H^2H^3)$ 3.0, J 0.9 Hz], 3.08 m [1H, H^6, $^2J(H^6H^6)$ 16.4 Hz], 3.57 s (2H, PhC$\underline{H}_2$), 3.78 m (1H, H^3), 5.44 m (1H, H^5), 7.22–7.32 m (5H, ArH). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 20.21 (4-$\underline{C}H_3$), 52.74, 57.81, 62.30 (C^2, C^6, Ph$\underline{C}H_2$), 68.15 (C^3), 122.50 (C^5), 134.97 (C^4), 127.11, 128.21 (2C), 129.00 (2C), 137.79 (ArC). Picrate, mp 155–157°C (EtOH). Found, %: C 52.72; H 4.77; N 12.66. $C_{18}H_{18}N_4O_8$. Calculated, %: C 52.78; H 4.66; N 12.96.

***cis*- and *trans*-Isomers of 1-benzyl-6-methyl-1,2,3,6-tetrahydropyridin-3-ol (IVd, IVe)** were obtained from 0.200 g (0.99 mmol) of the equimolar mixture of *cis*- and *trans*-isomers of 1-benzyl-6-methyl-3,4-epoxypiperidine (**Vd, Ve**).

***cis*-1-Benzyl-6-methyl-1,2,3,6-tetrahydropyridin-3-ol (IVd)** was isolated as a light-yellow oily substance, R_f 0.6 (Silufol, hexane–acetone, 4:1), yield 30%. IR spectrum (thin film), ν, cm^{-1}:1665 (C=C), 3410 (bound OH). ^{1}H (400 MHz, $CDCl_3$), δ, ppm: 1.28 d [3H, C$\underline{H}_3$, J(CH$_3$H^6) 6.4 Hz], 2.38 br.s (1H, OH) 2.40 d.d [1H, H^2, ^2J(H^{2}H^2) 11.7, ^3J (H^{2}H^3) 2.6 Hz], 2.85 d.d.d [1H, H^2, ^2J(H^{2}H^2) 11.8, ^3J (H^{2}H^3) 3.0, ^4J(H^{2}H^4) 0.9 Hz), 3.01 m (1H, H^6), 3.33 d (1H, PhC$\underline{H}_2$, ^2J 13.5 Hz), 3.91 m (1H, H^3), 4.08 d (1H, PhC$\underline{H}_2$, ^2J 13.5 Hz), 5.65 d.d [1H, H^5, ^3J(H^{5}H^4) 10.0, ^3J(H^{5}H^6) 2.0 Hz], 5.78 m [1H, H^4 ^3J(H^{4}H^5) 9.6, ^3J(H^{4}H^3) 5.0, ^4J(H^{4}H^6) 2.2, ^4J(H^{4}H^2) 1.0 Hz], 7.22–7.32 m (5H, ArH). ^{1}H NMR spectrum (500 MHz, DMSO-d_6), δ, ppm: 1.09 d [3H, C$\underline{H}_3$, J(CH$_3$H^6) 6.6 Hz], 2.50–2.51 m (2H, 2-CH$_2$), 3.08–3.10 m (1H, H^6), 3.54 d (1H, PhC$\underline{H}_2$, ^2J 13.8 Hz), 3.74 d (1H, PhC$\underline{H}_2$, ^2J 13.8 Hz), 3.99 br.s (1H, H^3), 4.56 br.s (1H, OH), 5.63–5.66 m (2H, H^4, H^5), 7.23–7.25 m (1H, H$^{4'}$), 7.31–7.36 m (4H, H$^{2'}$, H$^{3'}$, H$^{5'}$, H$^{6'}$). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 19.19 (6-$\underline{C}$H$_3$), 55.24, 55.50, 57.94 (C^2, C^6, Ph$\underline{C}$H$_2$), 63.80 (C^3), 126.98 (2C), 128.21 (2C), 128.84 (2C), 135.14, 138.36 (C^4, C^5, ArC). ^{13}C NMR spectrum (125 MHz, DMSO-d_6), δ, ppm: 15.43 (6-$\underline{C}$H$_3$), 51.93 (C^2), 53.01(C^6), 57.36 (Ph$\underline{C}$H$_2$), 62.86 (C^3), 126.62 (C$^{4'}$), 128.01 (C$^{3'}$, C$^{5'}$), 128.35 (C$^{2'}$, C$^{6'}$), 128.89 (C^4), 132.60 (C^5), 139.19 (C$^{1'}$). Mass spectrum, *m/z* (I_{rel}, %): 203 (1) [M]$^+$, 188 (10), 170 (1), 121 (5), 120 (50), 92 (8), 91 (100).

***trans*-1-Benzyl-6-methyl-1,2,3,6-tetrahydropyridin-3-ol (IVe)** was isolated as a light-yellow oily substance, R_f 0.5 (Silufol, hexane–acetone, 4:1), yield 33%. IR spectrum (thin film), ν, cm^{-1}:1660 (C=C), 3380, 3440 (OH). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.12 d [3H, CH$_3$ ^3J(CH$_3$H^6) 6.7 Hz], 2.25 br.s (1H, OH) 2.36 d.d [1H, H^2, ^2J(H^{2}H^2) 11.6, ^3J(H^{2}H^3) 5.1 Hz], 2.94 d.d [1H, H^2, ^2J(H^{2}H^2) 11.6, ^3J(H^{2}H^3) 4.0 Hz], 3.22 m (1H, H^6), 3.56 d (1H, PhC$\underline{H}_2$, ^2J 13.4 Hz), 4.07 d (1H, PhC$\underline{H}_2$, ^2J 13.5 Hz), 4.05 m (1H, H^3), 5.67 d.d.d [1H, H^5, ^3J(H^{5}H^4) 10.0, ^3J(H^{5}H^6) 3.4, ^4J(H^{5}H^3) 0.8 Hz], 5.78 d.d.d [1H, H^4, ^3J(H^{4}H^5) 10.0, ^3J(H^{4}H^3) 3.5, ^4J(H^{4}H^6) 2.1 Hz], 7.22–7.36 m (5H, ArH). ^{1}H (500 MHz, DMSO-d_6), δ, ppm: 1.15 d [3H, C$\underline{H}_3$, J(CH$_3$H^6) 6.5 Hz], 1.95 t [1H, H^{2a}, ^2J(H^{2a}H^{2e}) 10.0, ^3J(H^{2a}H^3) 8.9 Hz], 2.83 d.d [1H, H^{2e}, ^2J(H^{2e}H^{2a}) 10.6, ^3J(H^{2e}H^3) 5.1 Hz], 2.92 br.s (1H, H^6), 3.26 d (1H, PhC$\underline{H}_2$, ^2J 13.8 Hz), 3.97–4.00 m (2H, PhC$\underline{H}_2$, H^3), 4.67 br.s (1H, 3OH), 5.52 d [1H, H^5, ^3J(H^{5}H^4) 9.9 Hz], 5.61 d [1H, H^4, ^3J(H^{4}H^5) 10.3 Hz], 7.24–7.26 m (1H, H$^{4'}$), 7.32 m (4H, H$^{2'}$, H$^{3'}$, H$^{5'}$, H$^{6'}$). ^{13}C NMR spectrum (100 MHz, $CDCl_3$), δ, ppm: 14.46 (6-$\underline{C}$H$_3$), 53.03, 53.07, 57.79 (C^2, C^6, Ph$\underline{C}$H$_2$), 64.84 (C^3), 127.11, 127.40, 128.28 (2C), 128.89 (2C), 134.44, 138.48 (C^4, C^5, ArC). ^{13}C NMR spectrum (125 MHz, DMSO-d_6), δ, ppm: 18.95 (6-$\underline{C}$H$_3$), 54.50 (C^6), 55.66 (C^2), 57.11 (Ph$\underline{C}$H$_2$), 64.14 (C^3), 126.67 (C$^{4'}$), 128.03 (C$^{3'}$, C$^{5'}$), 128.58 (C$^{2'}$, C$^{6'}$), 129.84 (C^4), 131.92 (C^5), 139.00 (C$^{1'}$). Mass spectrum, *m/z* (I_{rel}, %): 203 (1) [M]$^+$, 189 (3), 188 (20), 170 (1), 121 (4), 120 (45), 96 (1), 92 (8), 91 (100).

Picrate of the isomer mixture **IVd, IVe**, mp 145–146°C (EtOH). Found, %: C 53.01; H 4.67; N 12.98. $C_{18}H_{18}N_4O_8$. Calculated, %: C 52.78; H 4.66; N 12.96.

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