ISSN 1070-4280, Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 6, pp. 922–928. © Pleiades Publishing, Inc., 2006.
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cis- and *trans*-Decahydro-1,6-naphthyridines. Stereoselective Synthesis and Stereochemistry

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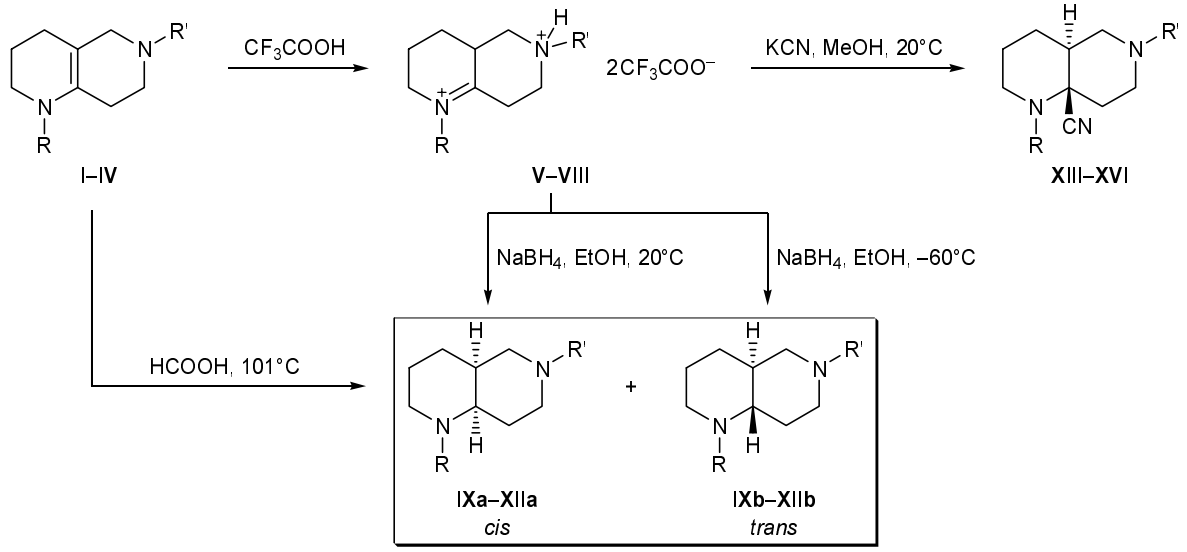
Received October 4, 2004

Abstract—New 1,6-disubstituted *trans*-decahydro-1,6-naphthyridines were synthesized by stereoselective nucleophilic addition of hydride and cyanide ions to 1,2,3,4,5,6,7,8-octahydro-1,6-naphthyridines, and their predominant conformations were determined. Some *trans*-decahydro-1,6-naphthyridine derivatives were found to exhibit anti-HIV activity.

DOI: 10.1134/S1070428006060194

Piperidine ring is an important pharmacophoric fragment which constitutes a structural unit of many natural and synthetic biologically active compounds and medicines. The decahydro-1,6-naphthyridine system including two fused piperidine rings was almost unknown previously. This system may be regarded is a biomimetic of piperidine, matrine, and neurotoxin alkaloids [1]; therefore, it attracts interest as a synthon for the preparation of biologically active substances. In this connection, search for convenient methods of synthesis of *cis*- and *trans*-decahydro-1,6-naphthyridines and study of their stereochemistry and biological activity seem to be quite promising. In the present communication we report on the stereoselective synthesis of *trans*-decahydro-1,6-naphthyridines, including optically active derivatives, by nucleophilic addition of hydride and cyanide ions to cyclic enamines, iminium salts derived from 1,2,3,4,5,6,7,8-octahydro-1,6-naphthyridines **I**–**IV** which were prepared previously [2, 3]. Nucleophilic addition of hydride ($NaBH_4$/EtOH, boiling formic acid [4]) and cyanide ions (KCN/MeOH) to 2,3,4,4a,5,6,7,8-octahydro-1,6-naphthyridine-1,6-diium bis(trifluoroacetates) **V**–**VIII** occurred in a stereoselective fashion to give the corresponding decahydro-

Scheme 1.



I, **V**, **IX**, **XIII**, R = Ph, R' = $PhCH_2$; **II**, **VI**, **X**, **XIV**, R = Ph, R' = Me; **III**, **VII**, **XI**, **XV**, R = 4-MeC_6H_4, R' = $PhCH_2$; **IV**, **VIII**, **XII**, **XVI**, R = 4-$MeOC_6H_4$, R' = $PhCH_2$.

Table 1. Product yields and diastereoselectivity (%) in the addition of nucleophiles to iminium salts **V–VIII**

Parameter	HCOOH, 101°C								$NaBH_4$, 20°C, ethanol		$NaBH_4$, –60°C, ethanol			KCN, methanol			
	IX		**X**		**XI**		**XII**		**IXb**	**XIIb**	**IXb**	**XIb**	**XIIb**	**XIII**	**XIV**	**XV**	**XVI**
	a	**b**	**a**	**b**	**a**	**b**	**a**	**b**									
Yield, %	8	45	5	36	7	42	–	42	50	20	46	52	30	58	37	75	55
Diastereoselectivity, %		78		78		83		81	94	90	97	98	95	100	100	100	100

Table 2. Intensities of fragment ions in the mass spectra of compounds **X–XII**

Compound no.	Fragment ion intensity I_{rel}, %				
	$[M-91]^+$ (F_1)	$[M-119]^+$ (F_2)	$[M-120]^+$ (F_3)	$[M-134]^+$ (F_4)	$[M-146]^+$ (F_5)
IXa/IXb	100/39.2	25.6/9.6	68.8/33.6	19.2/41.6	6.4/10.4
XIa/XIb	100/12.1	21.2/ –	65.7/1.5	28.3/19.2	2.0/2.0
XIIa/XIIb	100/60.3	24.1/1.3	65.8/14.1	26.6/39.7	2.5/14.1
	$[M-15]^+$ (F_1)	$[M-43]^+$ (F_2)	$[M-44]^+$ (F_3)	$[M-58]^+$ (F_4)	$[M-70]^+$ (F_5)
Xa/Xb	7.8/1.5	79.4/8.8	77.5/11.8	60.8/30.4	4.9/7.8

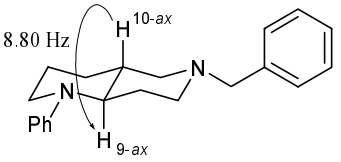
1,6-naphthyridines **IX–XII** (yield ~50%) and **XIII–XVI** (37–75%) (Scheme 1. Table 1). According to the GC–MS data, compounds **IX–XII** were formed as mixtures of two stereoisomers **IXa–XIIa** and **IXb–XIIb**, the latter strongly prevailing (up to 90–94%). Both isomers were characterized by similar fragmentation patterns but different intensities of fragment ion peaks. In the mass spectra of minor isomers **IXa**, **XIa**, and **XIIa**, the most abundant ions were F_1 ($[M-91]^+$, elimination of CH_2Ph), F_2 (elimination of $CH_2{=}NCH_2Ph$), and F_3 (elimination of CH_2NHCH_2Ph), while ions F_5 {$[M-146]^+$, elimination of $CH_2{=}N^+(CH_2Ph)CH{=}CH_2$} were the most intense in the spectra of isomers **b** (Table 2).

The stereoselectivity of the hydride reduction with $NaBH_4$ increased to 98% when the reaction was carried out at –60°C. The reduction of octahydro-1,6-naphthyridines **I–IV** with formic acid gave diastereoisomer mixtures in which the fraction of isomers **IXb–XIIb** was greater by 78–83%. Pure stereoisomers **IXa–XIIa** and **IXb–XIIb** were isolated by column chromatography on silica gel, and their composition was proved by elemental analysis.

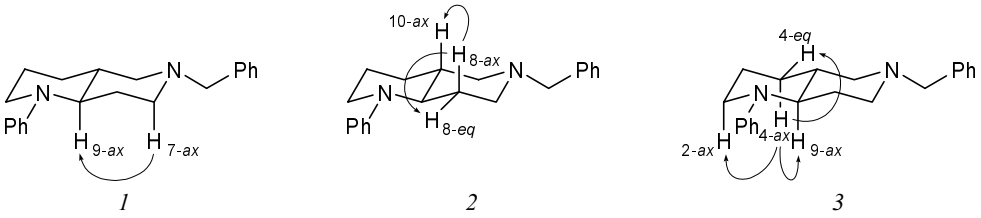
The addition of cyanide ion to bis(trifluoroacetates) **V–VIII** in methanol at room temperature resulted in formation of 9-cyanodecahydro-1,6-naphthyridines **XIII–XVI** (yield 37–75%) as a single stereoisomer, as followed from the GC–MS data; i.e., the reaction was strictly stereoselective. The structure of nitriles **XIII** and **XIV** was proved by the high-resolution mass spectra (electrospray ionization). In the mass spectra of **XIII–XVI** only $[M-27]^+$ and $[M-26]^+$ ions (corresponding to loss of HCN and CN) were observed. The IR spectra of nitriles **XIII–XVI** contained an absorption band at about 2230 cm^{-1}, which belongs to stretching vibrations of the cyano group, and the C≡N carbon signal appeared in the ^{13}C NMR spectra at δ_C 107.50 ppm.

The steric structure of compounds **IXa–XIIa** and **IXb–XIIb** was determined by analysis of their ^{13}C and ^1H NMR spectra using spin–echo sequence (APT), nuclear Overhauser effect (NOE), and a series of double resonance experiments. To determine the mode of ring junction it was necessary to estimate the coupling constant between protons at the bridgehead carbon atoms (C^9 and C^{10}), i.e., $^3J_{9,10}$. For this purpose, all signals observed in the spectrum were assigned on the basis of the double resonance data. The $^3J_{9,10}$ value for major isomer **IXb** is 8.80 Hz, which corresponds to *trans*-diaxial orientation of the 9-H and 10-H protons, i.e., isomer **IXb** has the structure of *trans*-6-benzyl-1-phenyldecahydro-1,6-naphthyridine (Scheme 2).

Scheme 2.

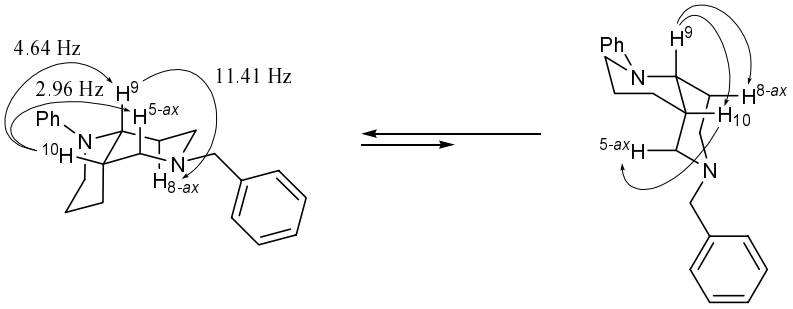


Scheme 3.



1 *2* *3*

Scheme 4.

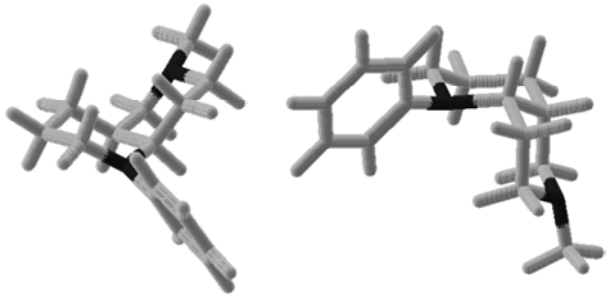


A **B**

An additional proof for the *trans* configuration of **IXb** was obtained by measuring the nuclear Overhauser effects. Successive irradiation at frequencies corresponding to resonance of 7-H_{ax}, 8-H_{ax}, and 4-H_{ax} gave responses (increase in the signal intensity) on (*1*) 9-H_{ax} (5.4%) and 7-H_{eq} (17.0%); (*2*) 10-H_{ax} (5.0%) and 8-H_{eq} (13.9%); and (*3*) 9-H_{ax} (4.0%), 2-H_{ax} (6.6%), and 4-H_{eq} (30.3%) (Scheme 3).

In keeping with the above stated, the second isomer (**IXa**) should be *cis*-6-benzyl-1-phenyldecahydro-1,6-naphthyridine. In fact, the vicinal coupling constant $^3J_{9,10}$ equal to 4.64 Hz indicates axial–equatorial orientation of protons at the bridgehead C^9 and C^{10} carbon atoms, i.e., *cis* configuration of isomer **IXa**. However, isomer **IXa** could also give rise to conformational equilibrium **A** $\rightleftharpoons$ **B**. Therefore, the next problem was to determine the predominant conformer of *cis*-6-benzyl-1-phenyldecahydro-1,6-naphthyridine in the equilibrium **A** $\rightleftharpoons$ **B** (Scheme 4).

Scheme 5.



A **B**

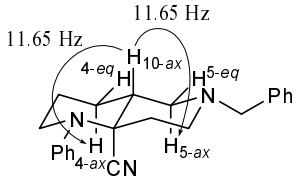
The ^{1}H NMR spectrum of *cis* isomer **IXa** at room temperature reflects an averaged conformational pattern and is fairly difficult to interpret. Therefore, both conformers **A** and **B** of **IXa** were simulated in terms of the HF/6-31G** method using PCMODEL 7 program; the minimal energies of conformers **A** and **B** were thus estimated at 0 and 1.99 kcal/mol, respectively (Scheme 5). These data suggest that conformer **A** should predominate in the equilibrium mixture. Using a series of double resonance experiments we succeeded in estimating the coupling constants $^3J_{9,8\text{-}ax}$ and $^3J_{10,5\text{-}ax}$ at 11.41 and 2.96 Hz, respectively. These values are also consistent with structure **A**. The value of $^3J_{9,10}$, calculated by the HF/6-31G** method for conformer (4.25 Hz), almost coincides with the experimental value (4.64 Hz).

The chemical shifts of the bridgehead carbon atoms C^9 and C^{10} in *cis*- and *trans*-decahydro-1,6-naphthyridines were determined using APT sequence. In the ^{13}C NMR spectra of *cis* isomers **IXa** and **XIa**, the signals from C^{10} (δ_C 36.55, 36.58 ppm) and C^9 (δ_C 56.78, 57.30 ppm) appear in a stronger field relative to the corresponding signals of *trans* isomers **IXb** and **XIb** (δ_C 41.5, 41.32 and 64.50, 65.50 ppm for C^{10} and C^9, respectively). These values are in a good agreement with the chemical shifts of the bridgehead carbon atoms in the series of *cis*- and *trans*-decahydroquinolin-4-ols [4].

Likewise, the *trans* configuration of nitrile **XIII** follows from the vicinal coupling constant $^3J_{10\text{-}ax,5\text{-}ax}$,

which is equal to 11.65 Hz (Scheme 6); this value is typical of *trans*-diaxial orientation of the 10-H_{ax} and 5-H_{ax} protons. A similar coupling constant, 11.65 Hz, was found for the 10-H_{ax} and 4-H_{ax} protons, indicating their *trans*-diaxial orientation. Thus analysis of the $^3J_{10\text{-}ax,5\text{-}ax}$ $^3J_{10\text{-}ax,4\text{-}ax}$ values shows that the proton on C^{10} occupies the axial position, i.e., molecule **XIII** has *trans* configuration. The axial orientation of 10-H in molecules **XIV–XVI** was determined in a similar way.

Scheme 6.



To conclude, we have developed a stereoselective method for the synthesis of *trans*-decahydro-1,6-naphthyridines and their 9-cyano derivatives, isolated a series of pure *cis*- and *trans*-decahydro-1,6-naphthyridines, and determined their steric structure and predominant conformations. It should be noted that some *trans*-decahydro-1,6-naphthyridine derivatives were found to exhibit a moderate anti-HIV activity.

EXPERIMENTAL

The IR spectra were recorded on a UR-20 spectrometer. The ^1H and ^{13}C NMR spectra were measured on Bruker WM-400 (400 MHz) and Varian VXR-400 (100.58 MHz) spectrometers, respectively, using TMS as internal reference. Gas chromatographic–mass spectrometric analysis was performed on HP 5989x-G, Jasco-980 (LC), and Fisons Instruments VG Platform 7031 (electron impact, 70 eV, positive ion detection). The high-resolution mass spectra (electrospray ionization) were run on a Bruker FT-ICR MS instrument. Thin-layer chromatography was performed using Silufol UV-254 plates (Czechia). Silica gel (60–40 μm) and aluminum oxide 90 (Merck) were used for column chromatography.

Reduction of 6-benzyl-1-phenyl-1,2,3,4,5,6,7,8-octahydro-1,6-naphthyridine-1,6-diium bis(trifluoroacetate) (V) with sodium tetrahydridoborate. *a*. Sodium tetrahydridoborate, 0.185 g (0.004 mol), was added in portions under stirring to a solution of 0.535 g (0.001 mol) of compound **V** in 10 ml of ethanol, cooled to –78°C. The mixture was stirred for 1 h at –60°C, excess reducing agent was decomposed with water, the solvent was evaporated, the residue was adjusted to pH 11–12 by adding sodium hydroxide and extracted with diethyl ether (5×5 ml), and the extract was dried over Na_2SO_4. The *cis–trans* ratio of the crude product was 1:57. A 300-mg portion of the product was applied to a column charged with silica gel in petroleum ether, and the column was eluted with petroleum ether–ethyl acetate (8:1 to 3:1) to isolate 0.14 g (46%) of *trans*-6-benzyl-1-phenyldecahydro-1,6-naphthyridine (**IXb**) as light yellow crystals, R_f 0.50 (hexane–acetone, 2:1), mp 57.4–57.9°C. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.07 d.m (1H, 4-H_{ax}, $^2J_{4\text{-}ax,4\text{-}eq} = {}^3J_{4\text{-}ax,3\text{-}ax} = 12.61$, $^3J_{4\text{-}ax,3\text{-}eq} = 4.16$ Hz), 1.40 d.d.d.d (1H, 8-H_{ax}, $^2J_{8\text{-}ax,8\text{-}eq} = 12.84$, $^3J_{8\text{-}ax,7\text{-}ax} = {}^3J_{8\text{-}ax,9\text{-}ax} = 11.18$, $^3J_{8\text{-}ax,7\text{-}eq} = 3.81$ Hz), 1.54 d.m (1H, 8-H_{eq}, $^2J_{8\text{-}ax,8\text{-}eq} = 12.84$, $^3J_{8\text{-}eq,7\text{-}ax} = 2.61$, $^3J_{8\text{-}eq,9\text{-}ax} = 3.69$ Hz), 1.61 d.m (1H, 4-H_{eq}, $^2J_{4\text{-}ax,4\text{-}eq} = 12.61$, $^3J_{4\text{-}eq,3\text{-}ax} = 4.04$ Hz), 1.68 d.m (1H, 3-H_{eq}, $^2J_{3\text{-}eq,3\text{-}ax} = 11.89$, $^3J_{3\text{-}eq,4\text{-}ax} = 4.16$, $^3J_{3\text{-}eq,2\text{-}ax} = 3.09$ Hz), 1.70–1.77 m (2H, 10-H_{ax}, 5-H_{ax}), 1.79 d.m (1H, 3-H_{ax}, $^2J_{3\text{-}ax,3\text{-}eq} = 11.89$, $^3J_{3\text{-}ax,2\text{-}ax} = 12.8$, $^3J_{3\text{-}ax,4\text{-}ax} = 12.61$, $^3J_{3\text{-}ax,4\text{-}eq} = 4.04$ Hz), 1.95 d.d.d (1H, 7-H_{ax}, $^2J_{7\text{-}ax,7\text{-}eq} = 11.90$, $^3J_{7\text{-}ax,8\text{-}ax} = 11.18$, $^3J_{7\text{-}ax,8\text{-}eq} = 2.61$ Hz), 2.70 d.d.d (1H, 9-H_{ax}, $^3J_{9\text{-}ax,8\text{-}ax} = 11.18$, $^3J_{9\text{-}ax,10\text{-}ax} = 8.80$, $^3J_{9\text{-}ax,8\text{-}eq} = 3.69$ Hz), 2.90 d.d.d (1H, 2-H_{ax}, $^2J_{2\text{-}ax,2\text{-}eq} = 11.65$, $^3J_{2\text{-}ax,3\text{-}ax} = 11.89$, $^3J_{2\text{-}ax,3\text{-}eq} = 3.09$ Hz), 2.77 d.d (1H, 5-H_{eq}, $^2J_{5\text{-}eq,5\text{-}ax} = 11.42$, $^3J_{5\text{-}eq,10\text{-}ax} = 1.90$ Hz), 2.81 d.m (1H, 7-H_{eq}, $^2J_{7\text{-}eq,7\text{-}ax} = 11.90$ Hz), 3.11 d.m (1H, 2-H_{eq}, $^2J_{2\text{-}eq,2\text{-}ax} = 11.65$ Hz), 3.43 q (2H, C**H**$_2$C$_6$H$_5$, *AB* system), 7.00–7.20 m (10H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 26.5 (C^3); 29.0 (C^4); 31.0 (C^8); 41.5 (C^{10}); 53.5 (C^2); 57.5 (C^7); 59.0 (C^5); 63.0 (**C**H$_2$Ph); 64.5 (C^9); 124.5, 126.0, 127.0, 128.5, 129.0, 129.5, 139.0, 152.5 (C_{arom}). Mass spectrum (ES): found *m*/*z* 307.21688 $[M + H]^+$; calculated 307.21688. GC–MS data: R_t 20.389 min; *m*/*z* (I_{rel}, %): 306 (8.8) $[M]^+$, 215 (100) $[M - 91]^+$, 187 (25.6) $[M - 119]^+$, 186 (68.8) $[M - 120]^+$, 172 (19.2) $[M - 134]^+$, 160 (6.4) $[M - 146]^+$, 158 (8.8) $[M - 148]$. Found, %: C 51.95; H 4.23; N 14.71. $C_{33}H_{32}N_8O_{14}$ (dipicrate). Calculated, %: C 51.83; H 4.22; N 14.65

b. Following a similar procedure, the reaction was carried out at room temperature. The *cis–trans* isomer ratio was 1:33. The *trans* isomer was isolated by column chromatography on silica gel using petroleum ether–ethyl acetate (8:1 to 3:1) as eluent. Yield of **IXb** 0.15 g (50%).

Reduction of 6-benzyl-1-(*p*-tolyl)-1,2,3,4,5,6,7,8-octahydro-1,6-naphthyridine-1,6-diium bis(trifluoroacetate) (VII) with sodium tetrahydridoborate. The reaction was carried out at –60°C. The *cis–trans* isomer ratio was 1:88.5. *trans*-6-Benzyl-1-

(*p*-tolyl)decahydro-1,6-naphthyridine (**XIb**) was isolated by column chromatography on silica gel using petroleum ether–ethyl acetate (8:1 to 4:1) as eluent. Yield 52%, light yellow crystals, R_f 0.54 (hexane–acetone, 2:1), mp 83.1–83.5°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.07 d.m (1H, 4-H_{ax}, $^2J_{4\text{-}ax,4\text{-}eq}$ = $^3J_{4\text{-}ax,3\text{-}ax}$ = 12.60, $^3J_{4\text{-}ax,3\text{-}eq}$ = 4.10 Hz), 1.39 d.d.d.d (1H, 8-H_{ax}, $^2J_{8\text{-}ax,8\text{-}eq}$ = 12.60,* $^3J_{8\text{-}ax,7\text{-}ax}$ = $^3J_{8\text{-}ax,9\text{-}ax}$ = 11.14, $^3J_{8\text{-}ax,7\text{-}eq}$ = 4.10 Hz), 1.51 d.m (1H, 8-H_{eq}, $^2J_{8\text{-}eq,8\text{-}ax}$ = 12.90,* $^3J_{8\text{-}eq,7\text{-}ax}$ = 2.93, $^3J_{8\text{-}eq,9\text{-}ax}$ = 3.52 Hz), 1.61 d.m (1H, 4-H_{eq}, $^2J_{4\text{-}eq,4\text{-}ax}$ = 12.60 Hz), 1.65–1.85 m (5H, 3-H_{eq}, 5-H_{ax}, 10-H_{ax}, 3-H_{ax}), 1.95 d.d.d (1H, $^2J_{7\text{-}ax,7\text{-}eq}$ = 11.72, $^3J_{7\text{-}ax,8\text{-}ax}$ = 11.14, $^3J_{7\text{-}ax,8\text{-}eq}$ = 2.64 Hz), 2.23 d.d.d (1H, 9-H_{ax}, $^3J_{9\text{-}ax,8\text{-}ax}$ = 11.14, $^3J_{9\text{-}ax,10\text{-}ax}$ = 8.79, $^3J_{9\text{-}ax,8\text{-}eq}$ = 3.81 Hz), 2.29 s (3H, CH_3), 2.70 d.d.d (1H, 2-H_{ax}, $^2J_{2\text{-}ax,2\text{-}eq}$ = $^3J_{2\text{-}ax,3\text{-}ax}$ = 11.73, $^3J_{2\text{-}ax,3\text{-}eq}$ = 2.93 Hz), 2.77 d.d (1H, 5-H_{eq}, $^2J_{5\text{-}eq,5\text{-}ax}$ = 10.54, $^3J_{5\text{-}eq,10\text{-}ax}$ = 2.06 Hz), 2.81 d.m (1H, 7-H_{eq}, $^2J_{7\text{-}eq,7\text{-}ax}$ = 11.72 Hz), 3.08 d.m (1H, 2-H_{eq}, $^2J_{2\text{-}eq,2\text{-}ax}$ = 11.73 Hz), 3.43 q (2H, C**H**$_2$C$_6$H$_5$, *AB* system), 6.81 d (2H, C_6H_4, *J* = 8.79 Hz), 7.03 d (2H, C_6H_4, *J* = 8.21 Hz), 7.20–7.35 m (5H, CH_2C_6**H**$_5$). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.94 (CH_3); 26.25 (C^3); 29.19 (C^4); 31.14 (C^8); 41.32 (C^{10}); 53.40 (C^2); 57.73 (C^7); 59.09 (C^5); 63.22 (**C**H_2Ph); 65.21 (C^9); 126.14, 127.54, 128.81, 129.72, 130.03, 134.74, 139.29, 150.34 (C_{arom}). GC–MS data: R_t 22.223 min; *m*/*z* (I_{rel}, %): 320 (50.6) $[M]^+$, 229 (100) $[M-91]^+$, 201 (21.2) $[M-119]^+$, 200 (65.7) $[M-120]^+$, 186 (28.3) $[M-134]^+$, 174 (2.0) $[M-146]^+$. Found, %: C 52.64; H 4.45; N 14.59. $C_{34}H_{34}N_8O_{14}$ (dipicrate). Calculated, %: C 52.44; H 4.40; N 14.39.

Reduction of 6-benzyl-1-(4-methoxyphenyl)-1,2,3,4,5,6,7,8-octahydro-1,6-naphthyridine-1,6-diium bis(trifluoroacetate) (VIII) with sodium tetrahydridoborate. *a. At –60°C.* The *cis–trans* isomer ratio was 1:36. *trans*-6-Benzyl-1-(4-methoxyphenyl)-decahydro-1,6-naphthyridine (**XIIb**) was isolated by column chromatography on silica gel using petroleum ether–ethyl acetate (8:1 to 4:1) as eluent. Yield 30%, light yellow crystals.

b. At 20°C. cis–trans Ratio 1:18.4. *trans* Isomer **XIIb** was isolated by column chromatography on silica gel using petroleum ether–ethyl acetate (8:1 to 4:1) as eluent. Yield 20%, R_f 0.52 (hexane–acetone, 2:1), mp 63.5–64.5°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.06 d.m (1H, 4-H_{ax}, *J* = 12.60, 4.40 Hz), 1.31–1.46 m (2H, 8-H_{ax}, 8-H_{eq}), 1.61 d.m (1H, 4-H_{eq}), 1.65–1.81 m (4H, 3-H_{eq}, 10-H_{ax}, 5-H_{ax}, 3-H_{ax}), 1.91 d.d.d (1H, 7-H_{ax}, *J* = 11.72, 11.72, 3.22 Hz), 2.19 d.d.d (1H, 9-H_{ax}, *J* = 10.55, 9.08, 4.10 Hz), 2.71 d.d.d (1H, 2-H_{ax}, *J* = 11.72, 11.72, 2.93 Hz), 2.73 d.d (1H, 5-H_{eq}, *J* = 10.55, 2.93 Hz), 2.81 d.m (1H, 7-H_{eq}, *J* = 11.43 Hz), 3.04 d.m (1H, 2-H_{eq}, *J* = 11.43 Hz), 3.47 q (2H, C**H**$_2$C$_6$H$_5$, *AB* system), 3.76 s (3H, OCH_3), 6.82 d (2H, C_6H_4, *J* = 9.08 Hz), 7.07 d (2H, C_6H_4, *J* = 8.79 Hz), 7.29 m (5H, CH_2C_6**H**$_5$). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 26.58 (C^3); 29.53 (C^4); 31.50 (C^8); 41.71 (C^{10}); 53.72 (C^2); 55.94 (OCH_3); 58.00 (C^7); 59.38 (C^5); 63.54 (**C**H_2Ph); 66.05 (C^9); 114.83, 127.63, 127.88, 129.14, 130.06, 139.61, 146.17, 157.85 (C_{arom}). GC–MS data: R_t 33.611 min; *m*/*z* (I_{rel}, %): 336 (70.9) $[M]^+$, 245 (100) $[M-91]^+$, 217 (24.1) $[M-119]^+$, 216 (65.8) $[M-120]^+$, 202 (26.6) $[M-134]^+$, 190 (2.5) $[M-146]^+$. Found, %: C 51.37; H 4.50; N 14.14. $C_{34}H_{34}N_8O_{15}$ (dipicrate). Calculated, %: C 51.39; H 4.31; N 14.10.

Reduction of 6-benzyl-1-(*p*-tolyl)-1,2,3,4,5,6,7,8-octahydro-1,6-naphthyridine-1,6-diium bis(trifluoroacetate) (III) with formic acid. A mixture of 0.550 g (0.0017 mol) of compound **III** and 5 ml of 99.7% formic acid was heated for 8 h at 101°C (under reflux). The mixture was evaporated, the residue was treated with 3 ml of a saturated solution of NaCl, adjusted to pH 11–12 by adding potassium carbonate, and extracted with diethyl ether (7×5 ml), and the extracts were combined and dried over Na_2SO_4. The *cis–trans* isomer ratio in the product was 1:11; a 0.550-g portion of the crude product was applied to a column charged with silica gel in petroleum ether, and the column was eluted with petroleum ether–ethyl acetate (8:1 to 4:1) to isolate 0.230 g (42%) of *trans*-6-benzyl-1-(4-methylphenyl)decahydro-1,6-naphthyridine (**XIb**) and 0.04 g (7.2%) of *cis*-6-benzyl-1-(4-methylphenyl)decahydro-1,6-naphthyridine (**XIa**).

Compound **XIa**. Light yellow crystals, R_f 0.63 (hexane–acetone, 2:1), mp 81.7–82.6°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.26 m (1H, 8-H_{ax}), 1.47 d.m (1H, 8-H_{eq}, *J* = 12.89, 3.52 Hz), 1.63 d.m (1H, 3-H_{ax}, *J* = 12.90, 4.25 Hz), 1.82 d.m (1H, 3-H_{eq}, $^2J_{3\text{-}eq,3\text{-}ax}$ = 12.89, *J* = 3.22 Hz), 1.89–2.00 m (3H, 10-H, 4-H_{ax}, 4-H_{eq}), 2.07 d.d.d (1H, 7-H_{ax}, *J* = 12.75, 12.75, 3.51 Hz), 2.16 d.d (1H, 5-H_{ax}, $^2J_{5\text{-}ax,5\text{-}eq}$ = 11.43, $^3J_{5\text{-}ax,10}$ = 3.23 Hz), 2.24 s (3H, CH_3), 2.74 d.d (1H, 5-H_{eq}, $^2J_{5\text{-}eq,5\text{-}ax}$ = 11.43, $^3J_{5\text{-}eq,10}$ = 2.05 Hz), 2.82 m (1H, 7-H_{eq}), 2.88 d.d.d (1H, 2-H_{ax}, *J* = 12.16, 12.16, $^3J_{2\text{-}ax,3\text{-}eq}$ = 2.93 Hz), 3.32 m (1H, 2-H_{eq}), 3.43 q (2H, C**H**$_2$Ph, *AB* system), 3.75 d.d.d (1H, 9-H, $^3J_{9,8\text{-}ax}$ = 10.55, $^3J_{9,10}$ = 4.40, *J* = 4.40 Hz), 7.00–7.20 m (9H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.40

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(CH_3); 20.46 (C^3); 24.22 (C^4); 25.77 (C^8); 36.58 (C^{10}); 42.63 (C^2); 53.82 (C^7); 57.30 (C^9); 59.22 (C^5); 63.22 (**C**H_2Ph); 117.15, 127.48, 128.43, 128.82, 129.37, 130.30, 139.12, 149.30 (C_{arom}). GC–MS data: R_t 23.680 min; *m*/*z* (I_{rel}, %): 320 (38.4) $[M]^+$, 229 (12.1) $[M - 91]^+$, 200 (1.5) $[M - 120]^+$, 186 (19.2) $[M - 134]^+$, 174 (2.0) $[M - 146]^+$. Found, %: C 52.57; H 4.28; N 14.39. $C_{34}H_{34}N_8O_{14}$ (dipicrate). Calculated, %: C 52.44; H 4.40; N 14.39;

Reduction of 6-benzyl-1-phenyl-1,2,3,4,5,6,7,8-octahydro-1,6-naphthyridine (I) with formic acid. The *cis*–*trans* isomer ratio was 1:8. The stereoisomers were separated by column chromatography on silica gel using petroleum ether–ethyl acetate (8:1 to 3:1) as eluent. We isolated 45% of *trans*-6-benzyl-1-phenyldecahydro-1,6-naphthyridine (**IXb**) and 8% of *cis*-6-benzyl-1-phenyldecahydro-1,6-naphthyridine (**IXa**).

Compound **IXa**. Light yellow crystals, R_f 0.66 (hexane–acetone, 2:1), mp 93.9–94.9°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.34 m (1H, 8-H_{ax}), 1.48 d.m (1H, 8-H_{eq}, $^2J_{8\text{-}eq,8\text{-}ax}$ = 13.10, J = 3.81 Hz), 1.63 d.m (1H, 3-H_{ax}, $^2J_{3\text{-}ax,3\text{-}eq}$ = 13.10, $^3J_{3\text{-}ax,2\text{-}ax}$ = 10.98, $^3J_{3\text{-}ax,2\text{-}eq}$ = 4.65, $^3J_{3\text{-}ax,4\text{-}eq}$ = 4.01 Hz), 1.84 d.m (1H, 3-H_{eq}, $^2J_{3\text{-}eq,3\text{-}ax}$ = 13.10, J = 3.38 Hz), 1.91–1.99 m (3H, 10-H, 4-H_{ax}, 4-H_{eq}), 2.10 d.m (1H, 7-H_{ax}, $^2J_{7\text{-}ax,7\text{-}eq}$ = 13.10, $^3J_{7\text{-}ax,8\text{-}ax}$ = 12.68, $^3J_{7\text{-}ax,8\text{-}eq}$ = 3.81 Hz), 2.18 d.d (1H, 5-H_{ax}, $^2J_{5\text{-}ax,5\text{-}eq}$ = 11.41, $^3J_{5\text{-}ax,10\text{-}eq}$ = 2.96 Hz), 2.75 d.d (1H, 5-H_{eq}, $^2J_{5\text{-}eq,5\text{-}ax}$ = 11.41, $^3J_{5\text{-}eq,10}$ = 2.32 Hz), 2.85 d.d.d (1H, 7-H_{eq}, $^2J_{7\text{-}eq,7\text{-}ax}$ = 13.10, J = 2.54, 2.54 Hz), 2.89 d.d.d (1H, 2-H_{ax}, $^2J_{2\text{-}ax,2\text{-}eq}$ = 11.83, $^3J_{2\text{-}ax,3\text{-}ax}$ = 10.98, $^3J_{2\text{-}ax,3\text{-}eq}$ = 2.96 Hz), 3.32 d.m (1H, 2-H_{eq}, $^2J_{2\text{-}eq,2\text{-}ax}$ = 11.83, $^3J_{2\text{-}eq,3\text{-}ax}$ = 4.65 Hz), 3.44 q (2H, C**H**$_2$Ph, *AB* system), 3.83 d.m (1H, 9-H, $^3J_{9,8\text{-}ax}$ = 11.41, $^3J_{9,10}$ = 4.64 Hz), 7.00–7.20 m (10H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.59 (C^3); 24.12 (C^4); 25.79 (C^8); 36.55 (C^{10}); 41.99 (C^2); 53.85 (C^7); 56.78 (C^9); 59.26 (C^5); 63.18 (**C**H_2Ph); 116.56, 118.85, 127.47, 128.82, 129.35, 129.77, 139.88, 151.42 (C_{arom}). Mass spectrum (ES): found *m*/*z* 307.21780 $[M + H]^+$; calculated 307.21688. GC–MS data: R_t 21.607 min; *m*/*z* (I_{rel}, %): 306 (19.2) $[M]^+$, 215 (39.2) $[M - 91]^+$, 187 (9.6) $[M - 119]^+$, 186 (33.6) $[M - 120]^+$, 172 (41.6) $[M - 134]^+$, 160 (10.4) $[M - 146]^+$, 158 (12.8) $[M - 148]^+$.

Reduction of 6-methyl-1-phenyl-1,2,3,4,5,6,7,8-octahydro-1,6-naphthyridine (II) with formic acid. The *cis*–*trans* isomer ratio was 1:8. The stereoisomers were separated by column chromatography on aluminum oxide using petroleum ether–ethyl acetate (6:1 to pure ethyl acetate) as eluent. Yield of *trans*-6-methyl-1-phenyldecahydro-1,6-naphthyridine (**Xb**) 36%, yellow oily substance, R_f 0.22 (benzene–acetone, 1:1). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.10 d.m (1H, 4-H_{ax}, J = 12.40, 4.34 Hz), 1.25 m (1H), 1.30 d.m (1H, 8-H_{ax}, J = 12.45, 3.72 Hz), 1.55 m (1H), 1.65–1.85 m (3H), 1.90 d.d.d (1H, 7-H_{ax}, J = 10.95, 10.95), 2.05 s (3H, NCH_3), 2.2–2.3 m (3H), 2.7–2.8 m (2H), 3.15 m (1H), 4.15 q (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 26.0 (C^3); 29.0 (C^4); 31.0 (C^8); 41.0 (C^{10}); 45.0 (NCH_3); 55.0 (C^2); 57.0 (C^7); 61.0 (C^5); 64.0 (C^9); 124.0, 125.0, 129.0, 151.0 (C_{arom}). Mass spectrum (ES): found *m*/*z* 231.18556 $[M + H]^+$; calculated 231.18558. GC–MS data: R_t 7.653 min; *m*/*z* (I_{rel}, %): 230 (100) $[M]^+$, 215 (7.8) $[M - 15]^+$, 187 (79.4) $[M - 43]^+$, 186 (77.5) $[M - 44]^+$, 172 (60.8) $[M - 58]^+$, 160 (4.9) $[M - 70]^+$.

***cis*-6-Methyl-1-phenyldecahydro-1,6-naphthyridine (Xa).** Yield 5.3%, yellow oily substance, R_f 0.37 (benzene–acetone, 1:1). Mass spectrum (ES): found *m*/*z* 231.18565 $[M + H]^+$; calculated 231.18558. GC–MS data: R_t 8.343 min; *m*/*z* (I_{rel}, %): 230 (86.3) $[M]^+$, 215 (1.5) $[M - 15]^+$, 187 (8.8) $[M - 43]^+$, 186 (11.8) $[M - 44]^+$, 172 (30.4) $[M - 58]^+$, 160 (7.8) $[M - 70]^+$.

Reduction of 6-benzyl-1-(4-methoxyphenyl)-1,2,3,4,5,6,7,8-octahydro-1,6-naphthyridine (IV) with formic acid. The *cis*–*trans* isomer ratio was 1:9.6. The stereoisomers were separated by column chromatography on silica gel using petroleum ether–ethyl acetate (8:1 to 4:1) as eluent. Yield of *trans*-6-benzyl-1-(4-methoxyphenyl)decahydro-1,6-naphthyridine 42%.

***cis*-6-Benzyl-1-(4-methoxyphenyl)decahydro-1,6-naphthyridine (XIIa).** R_f 0.52 (hexane–acetone, 2:1). GC–MS data: R_t 35.606 min; *m*/*z* (I_{rel}, %): 336 (91) $[M]^+$, 245 (60.3) $[M - 91]^+$, 217 (1.3) $[M - 119]^+$, 216 (14.1) $[M - 120]^+$, 202 (39.7) $[M - 134]^+$, 190 (14.1) $[M - 146]^+$.

6-Benzyl-1-phenyldecahydro-1,6-naphthyridine-9-carbonitrile (XIII). A solution of potassium cyanide in 10 ml of methanol was added to a solution of 2.04 g (0.0038 mol) of compound **V** in 10 ml of methanol. The mixture was stirred for 1 h and evaporated, the residue was treated with 3 ml of water, adjusted to pH 10–12, and extracted with diethyl ether (5×5 ml), and the extracts were combined and dried over Na_2SO_4. After removal of the solvent, 1.2 g of the crude product was applied to a column charged with silica gel in petroleum ether, and the column was eluted with petroleum ether–ethyl acetate (25:1 to 10:1). Yield

0.730 g (58%), yellowish oily substance. IR spectrum (film): ν(C≡N) 2230 cm^{-1}. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.43–1.61 m (3H), 1.66–1.82 m (3H), 2.0 d.d.d.d (1H, 10-H_{ax}, J = 11.65, 11.65, 3.47, 3.47 Hz), 2.05 d.d (1H, 5-H_{ax}, J = 11.65, 11.65 Hz), 2.25 m (1H), 2.7 d.d (1H, 5-H_{eq}, J = 11.65, 1.73 Hz), 2.9 m (1H), 3.4 m (1H), 3.5 m (C**H**$_2$Ph), 7.17–7.35 m (10H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 25.45 (C^3); 25.84 (C^4); 35.62 (C^8); 44.53 (C^{10}); 50.69 (C^2); 51.75 (C^7); 55.97 (C^5); 62.81 (**C**H_2Ph); 64.86 (C^9); 107.50 (CN); 119.10, 127.18, 127.83, 128.99, 129.56, 129.68, 138.94, 148.57 (C_{arom}). Mass spectrum (ES): found m/z 332.21220 $[M + H]^+$; calculated 332.21212. Mass spectrum, m/z (I_{rel}, %): 331 50.7) $[M]^+$, 304 (25.7) $[M - 27]^+$ (F_1), 303 (57.1) $[M - 28]^+$, 275 (5.7) $[F_1 - 29]^+$, 227 (5.0) $[F_1 - 77]^+$, 213 (39.3) $[F_1 - 91]^+$, 185 (16.8) $[F_1 - 119]^+$.

***trans*-6-Methyl-1-phenyldecahydro-1,6-naphthyridine-9-carbonitrile (XIV).** Yield of chromatographically pure product 37%, yellowish oily substance. IR spectrum (film): ν(C≡N) 2230 cm^{-1}. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.20–1.30 m (1H), 1.45–1.70 m (2H), 1.75 m (2H), 2.00 d.d.d.d (1H, 10-H_{ax}, J = 11.65, 11.65, 3.46, 3.46 Hz), 2.10 d.d (1H, 5-H_{ax}, J = 11.65, 11.65), 2.20–2.45 m (2H), 2.30 s (3H, NCH_3), 2.70 d.d (1H, 5-H_{eq}, J = 11.65, 1.71 Hz), 2.80 m (1H), 3.00 m (1H), 3.40 m (1H). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 24.0 (C^3); 25.0 (C^4); 35.5 (C^8); 44.0 (C^{10}); 46 (NCH_3); 51.5 (C^2); 52.5 (C^7); 57.5 (C^5); 64.0 (C^9); 118.5 (CN); 126.0, 127.0, 128.0, 129.0 (C_{arom}). Mass spectrum (ES): found m/z 256.18101 $[M + H]^+$; calculated 256.18082. Mass spectrum, m/z (I_{rel}, %): 255 (16.4) $[M]^+$, 228 (14.3) $[M - 27]^+$ (F_1), 227 (37.1) $[M - 28]^+$, 213 (5.0) $[F_1 - 15]^+$, 199 (12.1) $[F_1 - 29]^+$, 184 (8.6) $[F_1 - 44]^+$, 151 (4.6) $[F_1 - 77]^+$.

***trans*-6-Benzyl-1-(*p*-tolyl)decahydro-1,6-naphthyridin-9-carbonitrile (XV).** Yield of chromatographically pure product 75%, yellowish crystals, mp 68.0–68.9°C. IR spectrum (film): ν(C≡N) 2225 cm^{-1}. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.45–1.60 m (3H), 1.70–1.83 m (3H), 1.98 d.d.d.d (1H, 10-H_{ax}, J = 11.72, 11.72, 3.52, 3.52 Hz), 2.09 d.d (1H, 5-H_{ax}, J = 11.72, 11.72 Hz), 2.25 m (1H), 3.21s (3H, CH_3), 2.70 d.d (1H, 5-H_{eq}, J = 11.72, 1.76 Hz), 2.88 m (1H), 2.97 m (1H), 3.38 m (1H), 3.49 m (C**H**$_2$Ph), 7.10 d (2H, C_6H_4, J = 8.21 Hz), 7.19 d (2H, C_6H_4, J = 7.91 Hz), 7.23–7.35 m (5H, C_6H_5). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.02 (CH_3); 25.48 (C^3); 25.85 (C^4); 35.68 (C^8); 44.54 (C^{10}); 50.74 (C^2); 51.78 (C^7); 56.00 (C^5); 62.83 (**C**H_2Ph); 64.96 (C^9); 119.18 (CN); 127.54, 127.79, 128.98, 129.65, 130.15, 136.87, 139.02, 145.95 (C_{arom}). GC–MS data: R_t 12.475 min; m/z (I_{rel}, %): 318 (36.9) $[M - 27]^+$ (F_1), 317 (100) $[M - 28]^+$, 289 (3.1) $[F_1 - 29]^+$, 241 (0.1) $[F_1 - 77]^+$, 227 (19.5) $[F_1 - 91]^+$, 199 (10.3) $[F_1 - 119]^+$.

***trans*-6-Benzyl-1-(4-methoxyphenyl)decahydro-1,6-naphthyridine-9-carbonitrile (XVI).** Yield of chromatographically pure product 55%. IR spectrum (film): ν(C≡N) 2225 cm^{-1}. ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.45–1.60 m (3H), 1.70–1.80 m (3H), 1.98 d.d.d.d (1H, 10-H_{ax}, J = 11.72, 11.72, 3.51, 3.51 Hz), 2.09 d.d (1H, 5-H_{ax}, J = 11.72, 11.72 Hz), 2.29 m (1H), 2.70 d.d (1H, 5-H_{eq}, J = 11.72, 1.76 Hz), 2.83 m (1H), 2.97 m (1H), 3.36 m (1H), 3.49 m (C**H**$_2$Ph), 3.77 s (3H, OCH_3), 6.80–7.35 m (11H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 25.50 (C^3); 25.84 (C^4); 35.69 (C^8); 44.53 (C^{10}); 50.76 (C^2); 51.85 (C^7); 55.64 (OCH_3); 56.02 (C^5); 62.84 (**C**H_2Ph); 65.21 (C^9); 119.29 (CN); 114.56, 127.80, 128.98, 129.66, 129.92, 139.05, 141.41, 158.84 (C_{arom}). GC–MS data: R_t 16.951 min; m/z (I_{rel}, %): 334 (45.5) $[M - 27]^+$ (F_1), 333 (100) $[M - 28]^+$, 305 (2.5) $[F_1 - 29]^+$, 257 (0.03) $[F_1 - 77]^+$, 243 (25.1) $[F_1 - 91]^+$, 215 (7.8) $[F_1 - 119]^+$.

The authors thank I.V. Trushkov for his inestimable help in performing quantum-chemical calculations. This study was performed under financial support by the Russian Foundation for Basic Research (project no. 05-03-32658a).

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