ISSN 1070-4280 Russian Journal of Organic Chemistry, 2006, Vol. 42, No. 5, pp. 742–747. © Pleiades Publishing, Inc. 2006.
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# Synthesis and Conformational Study of 1,2,3,4,5,6,7,8-Octahydro-1,6-naphthiridines

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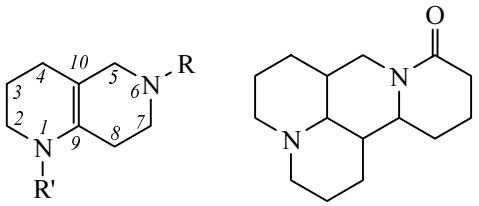
Received January 17, 2005

**Abstract**—A new class of endocyclic enamines, 1,6-disubstituted 1,2,3,4,5,6,7,8-octahydro-1,6-naphthiridines, was synthesized from 4-piperidone imines by successive subjecting the latter to lithiation with lithium diethylamide, to alkylation with 1-bromo-3-chloropropane, and to intramolecular cyclization. All stages were carried out as a unique process without isolation of the intermediate compounds. A thorough optimization of the process conditions, workup, and product storage was carried out. The conformational study of 1,6-disubstituted 1,2,3,4,5,6,7,8-octahydro-1,6-naphthiridines was performed.

**DOI:** 10.1134/S1070428006050162

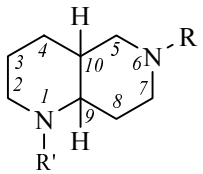
1,2,3,4,5,6,7,8-Octahydro-1,6-naphthiridines are interesting as synthons for preparation of new physiologically active compounds. We formerly developed a convenient synthetic procedure for previously non-studied bicyclic endoenamines, 1,2,3,4,5,6,7,8-octahydro-1,6-naphthiridines, whose structure includes two fused piperidine rings [1]. The study of the reactivity of *endo*-enamines and their derivatives opens a prospect of a synthesis therefrom of unknown earlier decahydro-1,6-naphthiridines that are biomimetics of matrine alkaloids, for instance, matridine. The matridine alkaloids N-oxides control the intensity of the respiratory process in plant tissue: at decrease in their amount the respiration sharply gets slower [2]. The synthesis of cyclic *endo*-enamines from acyclic ketone imines was first introduced by D. Evans [3, 4].



Octahydro-1,6-naphthiridine



Matridine



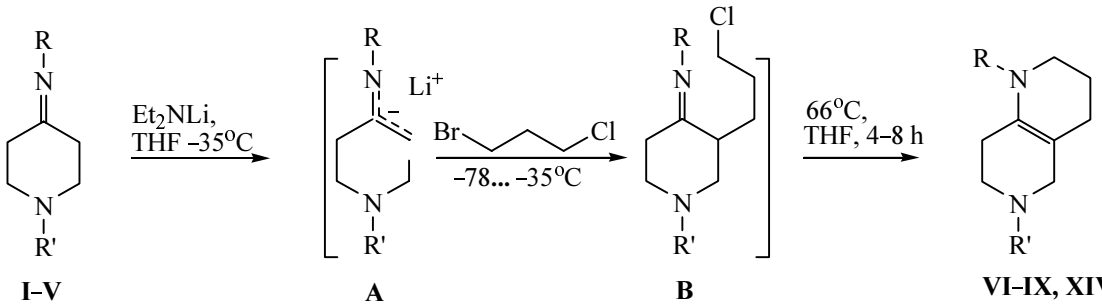
Decahydro-1,6-naphthiridine

Endocyclic enamines, 1,6-disubstituted 1,2,3,4,5,6,7,8-octahydro-1,6-naphthiridines, were obtained by subjecting piperidone imines **I–V** in succession to lithiation with lithium diethylamide, to alkylation of azaenolates (intermediate **A**) with 1-bromo-3-chloropropane yielding intermediate **B,** and to intramolecular cyclization of the latter affording the target 1,6-disubstituted 1,2,3,4,5,6,7,8-octahydro-1,6-naphthiridines **VI–IX** and **XIV**. All reaction sequence was carried out without isolation of the intermediate compounds [1] (Scheme 1) .

Octahydro-1,6-naphthiridines similarly to common enamines proved to be relatively unstable and difficult to isolate. Therefore virtually in every instance the synthesis conditions, workup, and storage required a thorough adjustment [1].

We communicate in this paper a detailed optimization of the synthetic conditions, and adjustment of the isolation and storage procedures for the target compounds. Then in the conditions developed we carried out the synthesis and conformational investigation of new octahydro-1,6-naphthiridines **VI–IX** and **XIV**. We found that the synthesis of octahydro-1,6-naphthiridines **VI–IX** was successful only when at each stage of the process the monitoring showed that the reaction completion was attained; also the factors affecting the course of the

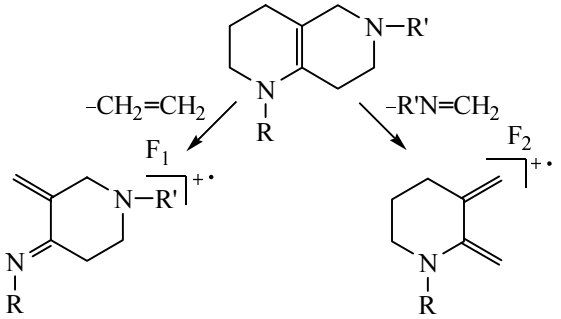
**Scheme 1.**




**I–V** **A** **B** **VI–IX, XIV**

R = $C_6H_5$, R' = $CH_2C_6H_5$ (**I, VI**), $CH_3$ (**II, VII**); R' = $CH_2C_6H_5$, R = $C_6H_4CH_3$-*p* (**III, VIII**), $C_6H_4OCH_3$-*p* (**IV, IX**), $C_6H_5CH(CH_3)$ (**V, XIV**).

**Scheme 2.**




reaction (variation of solvents, temperature, and the reaction time) should be accurately controlled. The chromatographic monitoring by sampling the reaction mixture at all the process stages showed that in the range –78...–50°C practically no alkylation of azaenolate **A** with 1-bromo-3-chloropropane occurred, and intermediate **B** started to form at –18°C, and its formation totally completed within 12 h. The 4-piperidone imines are unstable at the chromatography on $SiO_2$ and suffer decomposition into the initial amine and 4-piperidone. Therefore the completion of the alkylation and consequently the completion of intermediate **B** formation is indicated by total disappearance of the corresponding initial 1-benzyl-4-piperidone (**X**) and by appearance of the respective 1-benzyl-3-(3-chloropropyl)-4-piperidone (**XI**). The completion of the final stage, intramolecular cyclization of intermediate **B** affording the target 1,2,3,4,5,6,7,8-octahydro-1,6-naphthiridines **VI–IX**, also in all cases was chromatographically monitored.

In the preparation of octahydro-1,6-naphthiridines with 1-aralkyl substituents, for instance, 1-(1-phenylethyl)-octahydro-1,6-naphthiridine **XIV**, the alkylation of the azaenolate of 1-benzyl-4-(1-phylethylimino)piperidine (**V**) occurred completely, and the intramolecular cyclization, according to GC-MS data proceeded only to 50%, therefore in the reaction mixture alongside the target naphthiridine **XIV** was present the practically inseparable intermediate **B**. The prolonging of the process to 48 h, replacement THF by toluene or dioxane was unsuccessful. In this case the microwave irradiation of 180W power efficiently promoted cyclization of intermediate **B** in the absence of solvent: The cyclization was complete within 3-3.5 min affording the target 1-(1-phenylethyl)-6-benzyl-1,2,3,4,5,6,7-octahydro-1,6-naphthiridine in a 58% yield. Another possible way to perform the cyclization of 1-benzyl-3-(3-chloropropyl)-4-(1-phenylethylimino)-piperidine was a solid-phase synthesis on an activated aluminum oxide at 135°C within 30 min.However the yield of 1-(1-phenylethyl)-6-benzyl-1,2,3,4,5,6,7-octahydro-1,6-naphthiridine in this case was only 27%. The application of the microwave irradiation to the synthesis of all octahydro-1,6-naphthiridines at the stage of intermediate **B** cyclization efficiently accelerated the process and shortened the time of the last stage, e.g., for naphthiridine **VI** actually 240-fold.

The composition of endocyclic enamines **VI–IX** and **XIV** was established by GC-MS method from the existence of their molecular ions corresponding to the respective empirical formulas. In all series the fragmentation under the electron impact occurrs in a characteristic fashion, and it can be used further for identification of the structures of new *endo*-enamine. The main patterns of octahydro-1,6-naphthiridines fragmentation involve elimination of substituents from both nitrogen atoms and two ways of retrodiene decomposition giving fragment ions $F_1$ and $F_2$ (Scheme 2).

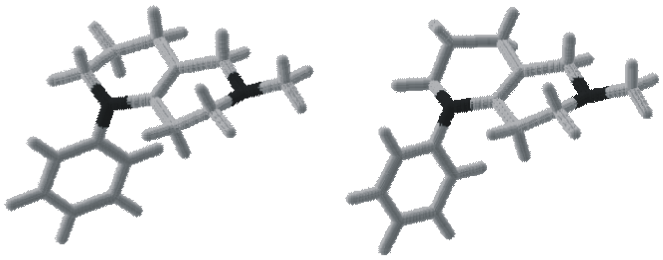
The most suitable storage form of the endocyclic enamines are their iminium salts, octahydro-1,6-naphthiridiniums trifluoroacetates. According to the data of mass spectrometry (direct admission, chemical ionization) and high resolution mass spectrometry applying electrospray

**Table 1.** Chemical shifts in $^{13}C$ NMR spectra of 1,6-naphthiridines **VI–IX** and **XIV**

| Compd. no. | $C^{10}$ | $C^{9}$ |
|---|---|---|
| **VI** | 112.85 | 133.41 |
| **VIII** | 112.01 | 133.66 |
| **IX** | 110.53 | 138.71 |
| **XIV** | 126.37 | 128.77 |

**Scheme 3.**

(a) (b)



**VI**

ionization (ESI) obtained on 1-phenyl-6-benzyl- **XV** and 1-phenyl-6-methyloctahydro-1,6-naphthiridinium **XVI** trifluoroacetates the spectra contained the corresponding molecular ions $[M]^+$ 304 and 228 respectively. Also in the ESI mass spectrum of trifluoroacetate **XV** $[M\text{H}]^+$ 305.20133 and $[M2\text{H}]^{++}$ 306.20470 ions are present in a ratio 4:1 corresponding to a monoprotonated form (with the more nucleophilic enamine nitrogen protonated) and a biprotonated form (the monoprotonated form of 1-phenyl-6-benzyl-1,2,3,4,5,6,7,8-octahydro-1,6-naphthiridine is presumably stabilized with the second enamine molecule). The ESI mass spectrum of trifluoroacetate **XVI** turned out to be even more complicated. Alongside the monoprotonated ion $[M\text{H}]^+$ 229.17005 an ion is present with a mass $[M\text{H}]^+$ 571.32595 (their ratio 2:1). This ion may originate from association of a trifluoroacetate anion with two monoprotonated forms (e.g., 229.170052 + 113.01535 = 571.35545). Quite possible, that this complex structure of iminium salts can affect their reactivity.

The presence of the enamine moiety in all members of the series of octahydro-1,6-naphthiridines **VI–IX** and **XIV** was proved by the appearance in the IR spectra of a strong band of the stretching vibrations of the N–C=C group in the region 1690 $cm^{-1}$. In the $^{13}C$ NMR spectra of compounds **VI, VIII, IX**, and **XIV** the downfield signals of atoms $C^9$ and $C^{10}$ correspond to the enamine fragment (Table 1).

In the $^1H$ NMR spectra of octahydro-1,6-naphthiridines **VI–IX** six multiplets were observed belonging to coupled protons of all methylene groups. To reveal the conformational features of enamines **VI–IX** a complete assignment was perforemed of the observed multiplets to the definite proton groups by means of the double resonance technique using successive irradiation of the separate groups of signals. However we succeeded only in estimating the coupling constants between the protons attached to $C^7$ and $C^8$, therefore the conformational fashion in general remained indeterminate (Table 2).

Therefore with the use of software PCMODEL v7 by HF/6-31G** method we carried out a computer simulation of the molecule of 1-phenyl-6-methyl-1,2,3,4,5,6,7,8-octahydro-1,6-naphthiridine (**VI**). According to the results of the quantum-chemical calculations the molecule of 1,6-naphthiridine **VI** exists in a fast conformational equilibrium of forms (**VI*a***)<=>(**VI*b***) with the minimum energies of the preferred conformations equal to 0 and 0.115 kcal $mol^{-1}$ respectively (Scheme 3). Further the comparison of the experimental and calculated for the *a* and *b* conformations $^3J_{Hw\ Hx}$ values revealed that the experimental $^3J_{Hw\ Hx}$ values exactly equaled the sum of the coupling constants for the pseudoaxial and pseudoequatorial protons at $C^7$ and $C^8$. Consequently the complicated pattern of the $^1H$ NMR spectra of the total series of the octahydro-1,6-naphthiridines is due to the fast conformational equilibrium between practically degenerate semichair-like *a* and *b* conformations.

Accordingly, we developed a simple and convenient synthesis of a series of 1,6-disubstituted 1,2,3,4,5,6,7,8-

**Table 2.** Chemical shifts in $^1H$ NMR spectra of naphthiridines **VI–IX**, δ, ppm ($CDCl_3$)

| Compd. no. | 3-$CH_2$ | 4-$CH_2$ | 8-$CH_2$ | 7-$CH_2$ | 5-$CH_2$ | 2-$CH_2$ | 1-$CH_2C_6H_5$ | Other |
|---|---|---|---|---|---|---|---|---|
| **VI** | 1.69 m | 1.94 m | 2.10 m | 2.57 t ($J_{Hw\,Hx}$ 5.70 Hz) | 2.98 s | 3.45 m | 3.62 | – |
| **VII**[a] | 1.47 m | 1.77 m | 2.22 m | 2.36 t ($J_{Hw\,Hx}$ 5.70 Hz) | 2.84 s | 3.31 m | – | 2.23 s (N-C$\underline{H}_3$) |
| **VIII** | 1.68 m | 1.96 m | 2.07 m | 2.38 t ($J_{Hw\,Hx}$5.72 Hz) | 2.98 s | 3.40 m | 3.60 | 2.55 s (C$\underline{H}_3$) |
| **IX** | 1.70 m | 1.93 m | 2.00 m | 2.52 t ($J_{Hw\,Hx}$ 5.71 Hz) | 2.97 s | 3.35 m | 3.59 | 3.75 s (OC$\underline{H}_3$) |

[a] $C_6D_6$

octahydro-1,6-naphthiridines **VI–IX** and **XIV** that consisted in a sequence of reactions performed without isolation of intermediate compounds. The target octahydro-1,6-naphthiridines **VI–IX** and **XIV** are convenient synthons for preparation of new biologically active compounds.

## EXPERIMENTAL

IR spectra were recorded on a spectrophotometer UR-20. $^1$H and $^{13}$C NMR spectra were registered respectively on spectrometers Bruker WM-400 (400 MHz) and Varian VXR-400 (100.58 MHz) using TMS as an internal reference. GC-MS measurements were performed on instruments HP5989x-G, Jasco-980 (LC), Fisons Instruments VG Platform 7031 (electron impact ionization, 70 eV, defector of positive ions) (GC/MS). High-resolution mass spectra were measured on spectrometer Bruker FT-ICR MS [electrospray ionization (ESI)].

Thin-layer chromatography was carried out on Silufol UV-254 plates (Kavaler, Czechia). The column chromatography was done using Silica gel 60-40 and Aluminiumoxid 90 standardisiert Merck (Germany).

**1-Benzyl-4-(phenylimino)piperidine (I).** Into a flask equipped with a Dean-Stark trap was charged 10 g (53.0 mmol) of 1-benzyl-4-piperidone, 7.4 g (79.5 mmol) of freshly distilled aniline, and 100 ml of anhydrous toluene. The reaction mixture was boiled till the amount of eliminated water was equal to the calculated quantity. The toluene was evaporated, the excess aniline was distilled off in a vacuum, bp 35–36°C (2 mm Hg). The red-brown oily substance was purified by crystallization from hexane. We obtained 8.5 g (61%) of compound **I** as light-brown crystals, mp 43.9–45.5°C (from hexane). IR spectrum (mull in mineral oil), ν, cm$^{-1}$: 1680 (C=N).

**1-Methyl-4-(phenylimino)piperidine (II).** In the same way from 5.65 g (50.0 mmol) of 1-methyl-4-piperidone and 7.44 g (80.0 mmol) of aniline was obtained 5.63 g (60%) of compound **II** as a light-yellow oily substance, bp 118–119°C (1.5 mm Hg). IR spectrum (thin film), ν, cm$^{-1}$: 1680 (C=N).

**1-Benzyl-4-(*p*-tolylimino)piperidine (III).** Similarly from 7.02 g (37.0 mmol) of 1-benzyl-4-piperidone and 6.0 g (56.0 mmol) of *p*-toluidine we obtained 6.61 g (64%) of compound **III** as light-brown crystals, mp 50.7–51.2°C (from hexane). IR spectrum (mull in mineral oil), ν, cm$^{-1}$: 1670 (C=N).

**1-Benzyl-4-(*p*-methoxyimino)piperidine (IV).** Similarly from 6.5 g (34.0 mmol) of 1-benzyl-4-piperidone and 6.34 g (51.0 mmol) of *p*-anisidine we obtained 8.82 g (88%) of compound **IV** as light-brown crystals, mp 36.9–38.9°C (from hexane). IR spectrum (mull in mineral oil), ν, cm$^{-1}$: 1665 (C=N).

**1-Benzyl-4-(1-phenylethylimino)piperidine (V).** In a flat-bottom flask was mixed 3.57 g (19 mmol) of 1-benzyl-4-piperidone and 4.58 g (38 mmol) of 1-phenylethylamine in 10 ml of anhydrous benzene. The mixture was stirred for 10 h at room temperature with activated molecular sieves 3 Å (5 ml) in an argon flow. Benzene was evaporated, excess 1-phenylethylamine was distilled off in a vacuum, bp 44–45°C (2 mm Hg). We obtained 5.2 g (94%) of crude compound **V** as a yellow oily substance. IR spectrum (thin film), ν, cm$^{-1}$: 1670 (C=N).

**1-Phenyl-6-benzyl-1,2,3,4,5,6,7,8-octahydro-1,6-naphthiridine (VI).** To a solution of 1.75 ml (17.0 mmol) of diethylamine in 10 ml of anhydrous THF was slowly added at –10°C 10.6 ml (17.0 mol) of 1.6 M solution of *n*-butyllithium in hexane under an argon atmosphere. The reaction mixture was stirred for 30 min at –10°C, cooled to –35°C, a solution of 3 g (11.4 mmol) of compound **I** in 10 ml of THF was added, and the mixture was stirred for 2 h at –35°C. Then the reaction mixture was cooled to –78°C, and a solution of 2.7 g (17.0 mmol) of 1-bromo-3-chloropropane in 5 ml of THF was added, and the resulting mixture was stirred for 2 h at –50...–35°C. The temperature was slowly raised to –18°C, the reaction mixture was maintained at this temperature for 12 h, then it was slowly warmed to room temperature, and boiled for 12 h at 66°C. The solvent was evaporated, the residue was treated with 1 ml of water, acidified with diluted HCl till pH 3, extracted with ether (3×5 ml), alkalinized with 20% NaOH till pH 11–12, again extracted with ether (7×5 ml), the extract was dried with $Na_2SO_4$. The solvent was evaporated to give 2.1 g (60%) of compound **VI** as yellow crystals, mp 68.4–69.0°C (from hexane), $R_f$ 0.61 (hexane–acetone, 2:1). IR spectrum (mull in mineral oil), ν, cm$^{-1}$: 1690 (N–C=C). $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 1.69 m (2H, $3CH_2$), 1.94 m (2H, $4CH_2$), 2.10 m (2H, $8CH_2$), 2.57 t (2H, $7CH_2$, *J* 5.70 Hz), 2.98 m (2H, $5CH_2$), 3.45 m (2H, $2CH_2$), 3.62 s (2H, $C\underline{H}_2C_6H_6$), 7.20 m (10H, $C_6\underline{H}_5$ and $CH_2C_6\underline{H}_5$). $^{13}$C NMR spectrum ($CDCl_3$), δ, ppm: 20.46 ($C^3$), 25.62 ($C^8$), 27.58 ($C^4$), 50.23 ($C^2$), 52.81 ($C^7$), 56.84 ($C^5$), 62.70 ($\underline{C}H_2$-Ph), 112.85 ($C^{10}$), 122.38 ($C_6H_5$), 124.64 ($C_6H_5$), 127.37 ($C_6H_5$), 128.56 ($C_6H_5$), 128.96 ($C_6H_5$), 129.57 ($C_6H_5$), 133.41 ($C^9$), 138.64 ($C_6H_5$), 149.1 ($C_6H_5$). Mass spectrum, *m/z* ($I_{rel}$, %): 304 (39.2) $[M]^+$, 276 (1.0) $[M-28]^+$, 213 (17.7) $[M-91]^+$, 185 (11.4) $[M-119]^+$.

**1-Phenyl-6-methyl-1,2,3,4,5,6,7,8-octahydro-1,6-naphthiridine (VII).** Similarly from 2.0 g (18.0 mmol) of compound **II** and 2.2 ml (22.0 mmol) of 1-bromo-3-chloropropane we obtained 2.8 g (70%) of compound **VII** as an orange oily substance, $R_f$ 0.31 (benzene–acetone, 1:1). IR spectrum (thin film), ν, cm$^{-1}$: 1690 (N–C=C). $^1$H NMR spectrum ($C_6D_6$), δ, ppm: 1.47 m (2H, 3C$H_2$), 1.77 m (2H, 4C$H_2$), 2.22 m (2H, 8C$H_2$), 2.23 s (3H, N–C$\underline{H}_3$), 2.36 t (2H, 7C$H_2$, $^3J_{Hw\ Hx}$ 5.7 Hz), 2.84 m (2H, 5C$H_2$), 3.31 m (2H, 2C$H_2$), 7.20 m (5H, $C_6\underline{H}_5$). Mass spectrum, *m/z* ($I_{rel}$, %): 228 (46.2) [*M*]$^+$, 200 (3.8) [*M* – 28]$^+$, 213 (3.8) [*M* – 15]$^+$, 213 (9.6) [*M* – 43]$^+$.

**1-(*p*-Tolyl)-6-benzyl-1,2,3,4,5,6,7,8-octahydro-1,6-naphthiridine (VIII)** was obtained similarly from 2.0 g (7.2 mmol) of compound **III** and 1.42 ml (14.4 mmol) of 1-bromo-3-chloropropane as an orange oily substance. Yield of crude compound 96%, $R_f$ 0.60 (hexane–acetone, 2:1). $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 1.68 m (2H, 3C$H_2$), 1.96 m (2H, 4C$H_2$), 2.07 m (2H, 8C$H_2$), 2.38 t (2H, 7C$H_2$, $^3J_{Hw\ Hx}$ 5.72 Hz), 2.55 s (3H, C$\underline{H}_3$), 2.98 m (2H, 5C$H_2$), 3.40 m (2H, 2C$H_2$), 3.60 s (2H, C$\underline{H}_2C_6H_6$), 6.87 d (2H, $C_6\underline{H}_4$-*p*-$CH_3$, *J* 8.50 Hz), 7.05 d (2H, $C_6\underline{H}_4$-*p*-$CH_3$, *J* 8.50 Hz), 7.32 m (5H, $CH_2C_6\underline{H}_5$). $^{13}$C NMR spectrum ($CDCl_3$), δ, ppm: 20.40 (–$\underline{C}H_3$), 20.47 ($C^3$), 25.64 ($C^8$), 27.70 ($C^4$), 50.30 ($C^2$), 53.03 ($C^7$), 56.98 ($C^5$), 62.78 ($\underline{C}H_2$–Ph), 112.01 ($C^{10}$), 124.90 ($C_6H_5$), 127.31 ($C_6H_5$), 128.55 ($C_6H_5$), 129.54 ($C_6H_5$), 129.62 ($C_6H_5$), 132.23 ($C_6H_5$), 133.66 ($C^9$), 138.83 ($C_6H_5$), 146.72 ($C_6H_5$). Mass spectrum, *m/z* ($I_{rel}$, %): 318 (38.1) [*M*]$^+$, 290 (0.5) [*M* – 28]$^+$, 227 (28.6) [*M* – 91]$^+$, 199 (12.5) [*M* – 119]$^+$.

**1-(4-Methoxyphenyl)-6-benzyl-1,2,3,4,5,6,7,8-octahydro-1,6-naphthiridine (IX)** was obtained similarly from 3 g(10.2 mmol) of compound **IV** and 2.0 ml (20.4 mmol) 1-bromo-3-chloropropane as an orange oily substance. Yield of crude compound 60%, $R_f$ 0.60 (hexane–acetone, 2:1). $^1$H NMR spectrum ($CDCl_3$), δ, ppm: 1.70 m (2H, 3C$H_2$), 1.93 m (2H, 4C$H_2$), 2.00 m (2H, 8C$H_2$), 2.52 t (2H, 7C$H_2$, $^3J_{Hw\ Hx}$ 5.70 Hz), 2.97 m (2H, 5C$H_2$), 3.35 m (2H, 2C$H_2$), 3.59 s (2H, C$\underline{H}_2C_6H_6$), 3.75 s (3H, OC$\underline{H}_3$), 6.79 d (2H, $C_6\underline{H}_4$-*p*-$CH_3$, *J* 8.79 Hz), 6.93 d (2H, $C_6\underline{H}_4$-*p*-$CH_3$, *J* 8.80 Hz), 7.32 m (5H, $CH_2C_6\underline{H}_5$). $^{13}$C NMR spectrum ($CDCl_3$), δ, ppm: 20.92 ($C^3$), 26.01 ($C^8$), 28.21 ($C^4$), 50.63 ($C^2$), 53.56 ($C^7$), 55.67 (O–$\underline{C}H_3$), 57.29 ($C^5$), 63.03 ($\underline{C}H_2$–Ph), 110.53 ($C^{10}$), 114.22 ($C_6H_5$), 126.58 ($C_6H_5$), 127.32 ($C_6H_5$), 128.43 ($C_6H_5$), 129.42 ($C_6H_5$), 133.79 ($C_6H_5$), 138.71 ($C^9$), 142.36 ($C_6H_5$), 155.90 ($C_6H_5$). Mass spectrum, *m/z* ($I_{rel}$, %): 334 (65.6) [*M*]$^+$, 243 (24.6) [*M* – 91]$^+$, 215 (13.1) [*M* – 119]$^+$.

**Preparation of 1-phenyl-6-benzyl-1,2,3,4,5,6,7,8-octahydro-1,6-naphthiridine (VI) with the use of microwave radiation.** To a solution of 1.75 ml (17.0 mmol) diethylamine in 10 ml of anhydrous THF was slowly added at –10°C 10.6 ml (17.0 mol) of 1.6 M solution of *n*-butyllithium in hexane under an argon atmosphere. The reaction mixture was stirred for 30 min at –10°C, cooled to–35°C, a solution of 3 g (11.4 mmol) of compound **I** in 10 ml of THF was added, and the mixture was stirred for 2 h at –35°C. Then the reaction mixture was cooled to–78°C, and a solution of 1.68 ml (17.0 mmol) of 1-bromo-3-chloropropane in 5 ml of THF was added, and the resulting mixture was stirred for 2 h at –50...–35°C. Then the temperature was slowly raised to –18°C, the reaction mixture was maintained at this temperature for 12 h, then it was slowly warmed to room temperature, and the solvent was evaporated. The dry residue was placed into a microwave oven by portions of 200 mg and subjected to irradiation of 90 W power by short intervals: 30 s + 60 s + 60 s. The powder mixture obtained was treated with 1 ml of water, acidified with diluted HCl till pH 3, extracted with ether (3×5 ml), alkalinized with 20% NaOH till pH 11–12, again extracted with ether (7×5 ml), the extract was dried with $Na_2SO_4$. The solvent was evaporated, the octahydro-1,6-naphthiridine was recrystallized from hexane to obtain 2.0 g (58%) of compound **VI** as yellow crystals.

**Preparation of 1-(1-phenylethyl)-6-benzyl–1,2,3,4,5,6,7,8-octahydro-1,6-naphthiridine (XIV) with the use of microwave radiation.** To a solution of 1.76 ml (17.0 mmol) of diethylamine in 10 ml of anhydrous THF at –10°C was slowly added 10.6 ml 17.0 mol) of 1.6 M solution of *n*-butyllithium in hexane under an argon atmosphere. The reaction mixture was stirred for 30 min at –10°C, cooled to –35°C, a solution of 3 g (10.3 mmol) of compound **V** in 10 ml of THF was added, and the mixture was stirred for 2 h at –35°C. Then the reaction mixture was cooled to–78°C, and a solution of 1.68 ml (17.0 mmol) of 1-bromo-3-chloropropane in 5 ml of THF was added, and the resulting mixture was stirred for 2 h at –50...–35°C. Then the temperature was slowly raised to –18°C, the reaction mixture was maintained at this temperature for 12 h, then it was slowly warmed to room temperature, and the solvent was evaporated. The dry residue was placed into a microwave oven by portions of 200 mg and subjected to irradiation of 180 W power for 3–3.5 min. The powder mixture obtained was treated with 1 ml of water, acidified with diluted HCl till pH 3,

extracted with ether (3×5 ml), alkalinized with 20% NaOH till pH 11–12, again extracted with ether (7×5 ml), the extract was dried with $Na_2SO_4$. The solvent was evaporated to obtain 2.0 g (58%) of compound **XIV** as an orange oily substance, $R_f$ 0.54 (hexane–acetone, 1:1). IR spectrum (thin film), ν, cm$^{-1}$: 1660 cm$^{-1}$. $^{13}$C NMR spectrum ($CDCl_3$, 100.58 MHz), δ, ppm: 15.49 ($C\underline{H}_3$), 22.36 (C3), 25.79 ($C^8$), 27.05 ($C^4$), 41.86 ($C^2$), 50.43 ($C^7$), 53.56 ($C^5$), 57.52 [$\underline{C}H(CH_3)Ph$], 62.66 ($\underline{C}H_2$-Ph), 126.37 ($C^{10}$), 126.48 ($C_6H_5$), 126.87 ($C_6H_5$), 127.30 ($C_6H_5$), 127.99 ($C_6H_5$), 128.12 ($C_6H_5$), 128.34 ($C_6H_5$), 128.77 ($C^9$), 129.03 ($C_6H_5$), 129.15 ($C_6H_5$). Mass spectrum, *m/z*: 332 $[M]^+$.

**1-(1-Phenylethyl)-6-benzyl-1,2,3,4,5,6,7,8-octahydro-1,6-naphthiridine (XIV).** To a solution of 1.35 ml diethylamine in 10 ml of anhydrous THF at –10°C was slowly added 8.0 ml (0.013 mol) of 1.6 M solution of *n*-butyllithium in hexane under an argon atmosphere. The reaction mixture was stirred for 30 min at –10°C, cooled to –35°C, a solution of 1.905 g (6.5 mmol) of compound **V** in 10 ml of THF was added, and the mixture was stirred for 2 h at –35°C. Then the reaction mixture was cooled to –78°C, and a solution of 1.3 ml (13.0 mmol) of 1-bromo-3-chloropropane in 5 ml of THF was added, and the resulting mixture was stirred for 2 h at –50...–35°C. Then the temperature was slowly raised to –18°C, the reaction mixture was maintained at this temperature for 12 h, then it was slowly warmed to room temperature, and the solvent was evaporated. The dry residue was dissolved in $CH_2Cl_2$, the solution was applied to an activated sorbent ($Al_2O_3$), then the solvent was evaporated, and the residue was heated to 135°C in an argon flow for 30 min. The sorbent was washed with EtOAc (3×5 ml), then with $CH_2Cl_2$ saturated with $NH_3$. The combined methylene extract was dried over $Na_2SO_4$. On evaporating the solvent we obtained 0.580 g (27%) of compound **XIV** as an orange oily substance.

**1-Phenyl-6-benzyl-1,2,3,4,5,6,7,8-octahydro-1,6-naphthiridinium trifluoroacetate (XV).** To a solution of 1 g (3.3 mmol) of compound **VI** in ether cooled to 0° was added dropwise at cooling a solution of 6.6 mmol of $CF_3COOH$ in anhydrous ether till pH 7. Then a 10% excess of $CF_3COOH$ (0.7 mmol) was added till pH 4. The solvent was evaporated. The salt was dried in a vacuum-desiccator over $P_2O_5$ and alkali. The residue obtained was crystallized from ether We obtained 0.88 g (50%) of compound **XV** as colorless crystals, mp 112.4–113.0°C. Mass spectrum, *m/z* ($I_{rel}$, %): 304 (7.8) $[M]^+$, 303 (13.5) $[M - H]^+$, 276 (1.4) $[M - 28]^+$, 227 (0.7) $[M - 77]^+$, 213 (5.7) $[M - 91]^+$, 185 (2.8) $[M - 119]^+$. Mass spectrum (ESI): $MH^+$ 305.20133, $MH^+_{calc}$ 305.19903, D 0.0023.

**1-Phenyl-6-methyl-1,2,3,4,5,6,7,8-octahydro-1,6-naphthiridinium trifluoroacetate (XVI)**. Similarly from 2.8 g (12.0 mmol) of compound **VII** and 2.85 g (24.0 mmol) of trifluoroacetic acid we obtained 5.40 g (99%)of trifluoroacetate of compound **XVI** as a red oil. Mass spectrum, *m/z* ($I_{rel}$, %): 228 (17.0) $[M]^+$, 227 (36.9) $[M - H]^+$, 213 (1.4) $[M - 15]^+$, 199 (4.3) $[M - 29]^+$, 184 (10.0) $[M - 44]^+$, 151 (0.7) $[M - 77]^+$. Mass spectrum (ESI): $MH^+$ 229.17005, $MH^+_{calc}$ 229.16993, D 0.00012.

The study was carried out under financial support of the Russian Foundation for Basic Research (grant no. 05-03-32658a).

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