

Synthesis of 1'-Substituted 4',4'-Dimethyl-6'-methoxy-4'H-spiro[cyclohexane-1,3'-isoquinolines]

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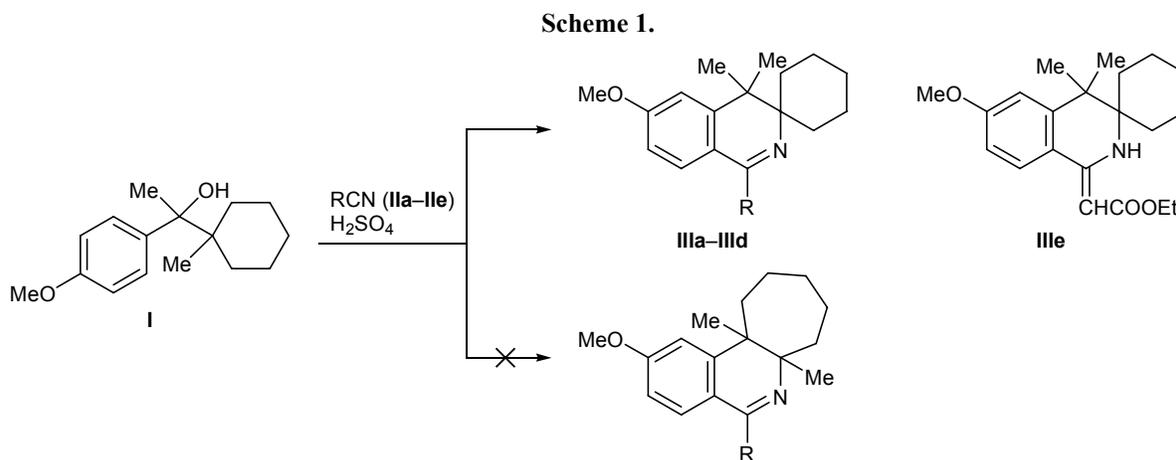
Received February 3, 2014

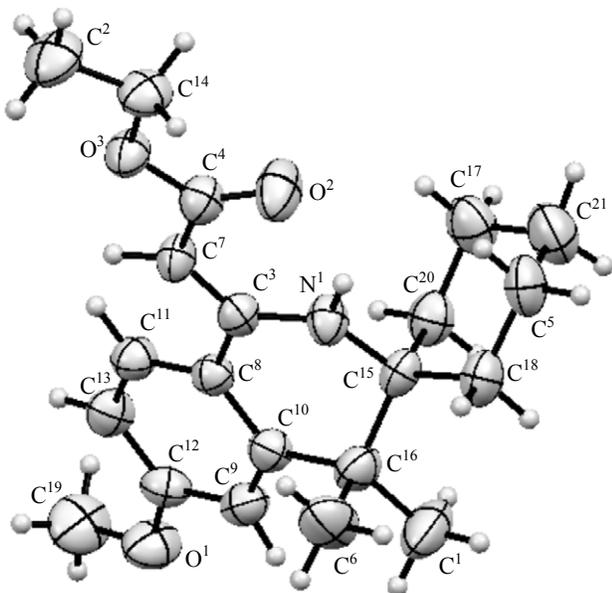
Abstract—The reaction of 1-(4-methoxyphenyl)-1-(1-methylcyclohexyl)ethanol with nitriles in concentrated sulfuric acid afforded 1'-substituted 6'-methoxy-4',4'-dimethyl-4'H-spiro[cyclohexane-1,3'-isoquinolines] as a result of consecutive Wagner–Meerwein rearrangement and Ritter reaction.

DOI: 10.1134/S1070428014040125

Wagner–Meerwein rearrangement is a cationic rearrangement typical of systems possessing several geminal alkyl substituents. It is used in the synthesis and transformations of carbocyclic compounds [1–4]. Wagner–Meerwein rearrangement can be accompanied by Ritter reaction since intermediate carbocation is capable of reacting with nitriles. For example, we previously showed that 3,3-dimethyl-2-phenylbutan-2-ol in the presence of nitriles under acidic conditions can be converted into 1-substituted 3,3,4,4-tetramethyl-3,4-dihydroisoquinoline derivatives as a result of successive Wagner–Meerwein rearrangement and Ritter reaction [5].

If a tertiary alcohol contains a carbocyclic fragment, its Wagner–Meerwein rearrangement may be accompanied by expansion of the aliphatic ring [6, 7]. With a view to explore the behavior of carbinols of the 1-(1-methylcycloalkyl)-1-phenylethanol series under the Ritter reaction conditions, 1-(4-methoxyphenyl)-1-(1-methylcyclohexyl)ethanol (**I**) was brought into reaction with nitriles **IIa–IIe** in concentrated sulfuric acid. It was expected that compound **I** will undergo rearrangement involving both migration of methyl group with formation of a spiro isoquinoline system and expansion of the six-membered ring to produce previously unknown homophenanthridine derivatives.





Structure of the molecule of ethyl 2-[6'-methoxy-4',4'-dimethyl-2'*H*-spiro[cyclohexane-1,3'-isoquinolin]-1'(4'*H*)-ylidene]acetate (**IIIe**) according to the X-ray diffraction data.

In fact, we isolated for the first time 1-substituted 6'-methoxy-4',4'-dimethyl-4'*H*-spiro[cyclohexane-1,3'-isoquinolines] **IIIa–IIIe** in 66–84% yield (Scheme 1).

The structure of compounds **IIIa–IIIe** was proved by their IR, ^1H and ^{13}C NMR, and mass spectra and elemental analyses. The ^1H NMR spectra of **IIIa–IIIe** contained a three-proton singlet in the region δ 3.82–3.86 ppm due to the 6'-methoxy group. The 5'-H signal appeared as a doublet at δ 6.85–6.95 ppm ($^4J = 2.4$ –2.7 Hz). A doublet of doublets at δ 6.66–6.73 ppm ($^3J = 8.4$ –8.7, $^4J = 2.4$ –2.7 Hz) was assigned to 7'-H. The 8'-H proton resonated as a doublet at δ 7.39–7.59 ppm ($^3J = 8.4$ –8.7 Hz) in the spectra of **IIIa**, **IIIb**,

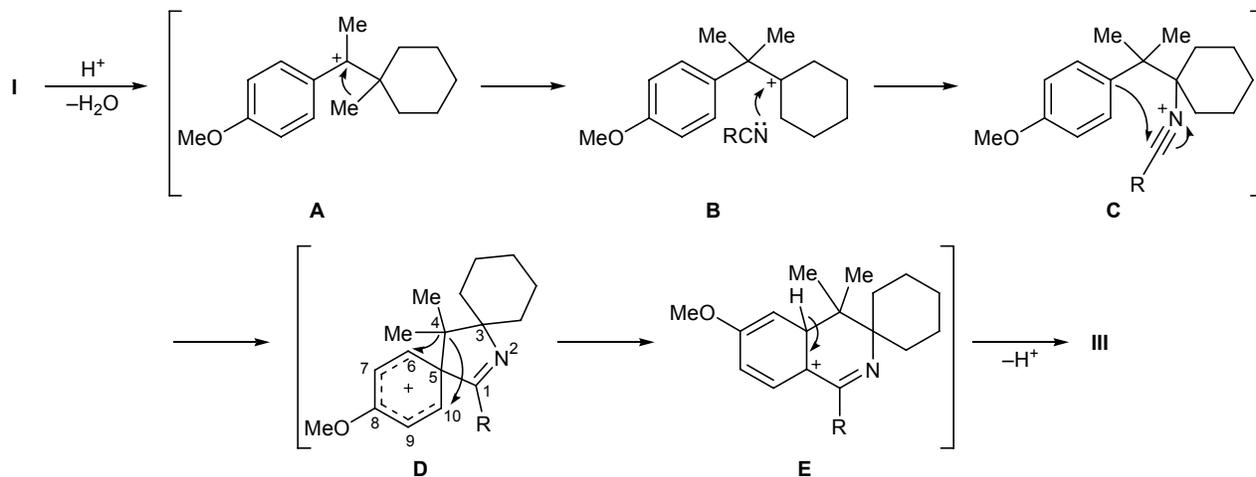
and **IIIe** or at δ 7.07–7.18 ppm ($^3J = 8.4$ Hz) in the spectra of isoquinolines **IIIc** and **IIId** having an aromatic substituent on C¹. In the latter case, the upfield position of the 8'-H signal is determined by shielding effect of the aromatic substituent.

Isoquinoline **IIIe** has enamine structure, as follows from the presence in its ^1H NMR spectrum of a singlet at δ 5.03 ppm from the vinylic proton and a broadened singlet at δ 9.34 ppm from the NH proton. In the IR spectrum of **IIIe** we observed an absorption band at 3269 cm^{-1} , typical of NH stretching vibrations. During GC/MS analysis compound **IIIe** underwent thermal decomposition, and only the peak corresponding to 1'-methyl derivative **IIIa** was detected [8]. The structure of isoquinoline **IIIe** was unambiguously determined by X-ray analysis (see figure).

According to the X-diffraction data, compound **IIIe** crystallizes in a non-centrosymmetric space group. The bond lengths and bond angles in molecule **IIIe** do not differ from the expected values. In particular, conjugation with the ester group leads to leveling of bonds at the C⁷ and C³ atoms. The difference between the formally double and formally single bonds in that fragment does not exceed 0.05 Å. The spiro-fused cyclohexane fragment adopts a *chair* conformation, and the dihydropyridine ring has *sofa* structure. No any specific intermolecular interactions were detected in the crystal packing of compound **IIIe**.

A probable mechanism of the described reaction includes Wagner–Meerwein rearrangement with formation of carbocation **B** which takes up nitrile molecule to give nitrilium ion **C**. Intramolecular cyclization of the latter at the *ipso* position yields spiro σ -complex **D**, and 1,2-migration of the C⁴–C⁵ bond in intermediate **D** leads to the final product (Scheme 2).

Scheme 2.



EXPERIMENTAL

The ^1H and ^{13}C (DEPT) NMR spectra were recorded from solutions in CDCl_3 on a Varian Mercury Plus 300 spectrometer at 300.06 and 75.46 MHz, respectively, using hexamethyldisiloxane as internal reference. The IR spectra were measured on a Bruker IFS-66/S spectrometer from thin films. The mass spectra were obtained on an Agilent Technologies 6890N–5975B GC/MS system (HP-5ms column, $30\text{ m} \times 0.25\text{ mm}$, film thickness $0.25\text{ }\mu\text{m}$; carrier gas helium, flow rate 1 mL/min ; electron impact, 70 eV). The elemental compositions were determined on a Leco CHNS-932 analyzer. The progress of the reactions and the purity of products were monitored by TLC on Sorbfil plates; spots were developed by treatment with a 0.5% solution of chloranil in toluene or under UV light. Silica gel (70–230 mesh, Lancaster) was used for column chromatography. The melting points were measured on a PTP melting point apparatus.

Commercially available reagents and solvents (Alfa Aesar, Sigma–Aldrich, Reakhim) were used.

The X-ray diffraction data were obtained at 295(2) K from a $0.25 \times 0.20 \times 0.15\text{-mm}$ fragment of a colorless prismatic single crystal of **IIIe** on an Xcalibur-3 automatic diffractometer with a CCD detector (Oxford Diffraction). The data were acquired according to standard procedure [ω -scanning through a step of 1° , $\lambda = 0.71073\text{ }\text{\AA}$ (MoK_α)]. Rhombic crystal system, space group $Pca2_1$; unit cell parameters: $a = 12.5844(13)$, $b = 9.2785(8)$, $c = 16.3834(10)\text{ }\text{\AA}$; $V = 1913.0(3)\text{ }\text{\AA}^3$; $Z = 4$; $d_{\text{calc}} = 1.189\text{ g/cm}^3$. Total of 5746 reflection intensities were collected, 1995 of which were independent ($R_{\text{int}} = 0.0291$), and 1131 reflections were characterized by $I > 2\sigma(I)$; completeness 98% in the range $2.73 < \Theta < 26.38$. The structure was solved by the direct method and was refined against F^2 in anisotropic approximation for non-hydrogen atoms using SHELXTL software package [9]. The positions of hydrogen atoms were refined according to the riding model in isotropic approximation with dependent thermal parameters. No correction for absorption was applied because of its insignificance ($\mu = 0.079\text{ mm}^{-1}$); the absolute structural parameter was not estimated. The final divergence factors were $R_1 = 0.0305$, $wR_2 = 0.0562$ for reflections with $I > 2\sigma(I)$ and $R_1 = 0.0624$, $wR_2 = 0.0591$ for all reflections; goodness of fit $S = 1.003$; maximum and minimum residual electron density peaks 0.095 and $-0.123\text{ e}/\text{\AA}^3$. The crystallographic data for compound **IIIe** were deposited to

the Cambridge Crystallographic Data Centre (entry no. CCDC 983915).

(4-Methoxyphenyl)(1-methylcyclohexyl)methanone was synthesized according to the procedure described in [10] from 8.03 g (50 mmol) of 1-methylcyclohexane-1-carbonyl chloride and 15.36 g (142 mmol) of anisole in the presence of 6.67 g (50 mmol) of AlCl_3 . Yield 7.93 g (68%), colorless liquid, bp $175\text{--}178^\circ\text{C}$ (6.5 mm); published data [10]: mp $172\text{--}172.5^\circ\text{C}$ (5 mm). IR spectrum, ν , cm^{-1} : 1665, 1609. ^1H NMR spectrum, δ , ppm: 1.10–1.70 m (13H, Me, CH_2), 3.83 s (3H, OMe), 6.87 d.d (2H, 3-H, 5-H, $^3J = 6.9$, $^4J = 1.8$ Hz), 7.77 d.d (2H, 2-H, 6-H, $^3J = 6.9$, $^4J = 2.4$ Hz). Mass spectrum, m/z (I_{rel} , %): 232 [M] $^+$ (6.3), 136 [$M - \text{C}_7\text{H}_{13} + \text{H}$] $^+$ (12.3), 135 [$M - \text{C}_7\text{H}_{13}$] $^+$ (100), 77 [C_6H_5] $^+$ (11.5), 55 [C_4H_7] $^+$ (12.4). Found, %: C 77.72; H 8.45. $\text{C}_{15}\text{H}_{20}\text{O}_2$. Calculated, %: C 77.55; H 8.68. M 232.32.

1-(4-Methoxyphenyl)(1-methylcyclohexyl)ethanol (I). A solution of 7.93 g (34 mmol) of (4-methoxyphenyl)(1-methylcyclohexyl)methanone in 10 mL of diethyl ether was added dropwise under stirring to a freshly prepared solution of methylmagnesium iodide {from 1.03 g (42 mmol) of magnesium turnings and 6.03 g (42 mmol) of methyl iodide in 20 mL of diethyl ether [11]} so that to maintain the mixture slightly boiling. The mixture was then heated for 2 h under reflux and hydrolyzed by slowly adding a mixture of 35 mL of a saturated solution of ammonium chloride and 15 mL of crushed ice. The organic phase was separated, the aqueous phase was extracted with diethyl ether ($3 \times 15\text{ mL}$), the extracts were combined with the organic phase, dried over MgSO_4 , and evaporated, and the residue was crystallized from hexane. Yield 6.91 g (82%), colorless crystals, mp 70°C . IR spectrum, ν , cm^{-1} : 3452, 2929, 2858, 1607, 1509. ^1H NMR spectrum ($\text{DMSO-}d_6$), δ , ppm: 0.82 s (3H, CH_3COH), 0.88–1.70 m (13H, 1-Me, CH_2), 3.76 s (3H, OMe), 4.60 s (1H, OH), 6.85 d (2H, m -H, $^3J = 9.0$ Hz), 7.33 d (2H, o -H, $^3J = 8.7$ Hz). ^{13}C NMR spectrum, δ_{C} , ppm: 17.49 (1-Me); 22.02, 22.12, 26.00, 31.07, 31.12 (CH_2); 24.70 (CH_3COH), 40.28 (C^1), 55.10 (OMe), 78.93 (COH), 112.17 (C^m), 128.47 (C^o), 138.20 (C^i), 157.91 (C^p). Mass spectrum, m/z (I_{rel} , %): 248 (0.01) [M] $^+$, 230 (2.9) [$M - \text{H}_2\text{O}$] $^+$, 215 (3.9) [$M - \text{H}_2\text{O} - \text{CH}_3$] $^+$, 151 (100) [$M - \text{C}_7\text{H}_{13}$] $^+$, 43 (31.3). Found, %: C 77.10; H 9.69. $\text{C}_{16}\text{H}_{24}\text{O}_2$. Calculated, %: C 77.38; H 9.74. M 248.36.

Compounds IIIa–IIIe (general procedure). A mixture of 1 mmol of alcohol **I** and 1 mmol of nitrile **IIa**–

IIe was added dropwise under vigorous stirring to 1 mL of 92% H₂SO₄ on cooling with ice water. The mixture was then stirred for 30 min at room temperature, poured into a mixture of crushed ice and 4 mL of aqueous ammonia, and extracted with methylene chloride (3×5 mL). The combined extracts were washed with water, dried over MgSO₄, and evaporated, and the product was isolated by column chromatography (**IIIc**) or recrystallization (**IIIa**, **IIIb**, **IIId**, **IIIe**).

6'-Methoxy-1',4',4'-trimethyl-4'H-spiro[cyclohexane-1,3'-isoquinoline] (IIIa). Yield 0.23 g (84%), mp 73–74°C (from acetone). IR spectrum, ν , cm⁻¹: 2958, 2915, 2854, 1614, 1576. ¹H NMR spectrum, δ , ppm: 0.60–2.10 m (16H, CH₂, 4'-Me), 2.37 s (3H, 1'-Me), 3.83 s (3H, OMe), 6.71 d.d (1H, 7'-H, ³J = 8.7, ⁴J = 2.4 Hz), 6.85 d (1H, 5'-H, ⁴J = 2.4 Hz), 7.39 d (1H, 8'-H, ³J = 8.4 Hz). ¹³C NMR spectrum, δ_C , ppm: 22.13 (1'-Me, 4'-Me), 26.18 and 30.35 (CH₂), 39.85 (C^{4'}), 55.15 (MeO), 61.58 (C^{3'}), 109.49 and 110.73 (C^{5'}, C^{7'}), 121.15 (C^{8a'}), 126.18 (C^{8'}), 148.74 (C^{4a'}), 160.64 and 161.76 (C^{1'}, C^{6'}). Mass spectrum, m/z (I_{rel} , %): 271 (88.3) [M]⁺, 256 (100) [M - CH₃]⁺, 228 (34.4) [M - C₃H₇]⁺, 189 (88.8) [M - CH₃CN - C₃H₅]⁺, 174 (77.4) [M - CH₃CN - C₄H₈]⁺. Found, %: C 79.54; H 9.08; N 5.35. C₁₈H₂₅NO. Calculated, %: C 79.66; H 9.28; N 5.16. *M* 271.40.

6'-Methoxy-4',4'-dimethyl-1'-methylsulfanyl-4'H-spiro[cyclohexane-1,3'-isoquinoline] (IIIb). Yield 0.20 g (66%), mp 131–132°C (from hexane). IR spectrum, ν , cm⁻¹: 2956, 2937, 2857, 1605, 1557. ¹H NMR spectrum, δ , ppm: 1.00–2.00 m (16H, CH₂, 4'-Me), 2.45 s (3H, SMe), 3.82 s (3H, OMe), 6.70 d.d (1H, 7'-H, ³J = 8.4, ⁴J = 2.4 Hz), 6.85 d (1H, 5'-H, ⁴J = 2.7 Hz), 7.57 d (1H, 8'-H, ³J = 8.4 Hz). ¹³C NMR spectrum, δ_C , ppm: 12.40 (SMe), 22.10 (4'-Me), 26.38 and 30.99 (CH₂), 39.51 (C^{4'}), 55.25 (MeO), 61.88 (C^{3'}), 109.52 and 110.93 (C^{5'}, C^{7'}), 121.31 (C^{8a'}), 126.21 (C^{8'}), 148.47 (C^{4a'}), 157.60 and 161.86 (C^{1'}, C^{6'}). Mass spectrum, m/z (I_{rel} , %): 303 [M]⁺ (6.1), 288 [M - CH₃]⁺ (100), 191 (3.9), 159 (4.0), 115 (3.3), 41 (3.4). Found, %: C 71.54; H 8.08; N 4.85; S 10.36. C₁₈H₂₅NOS. Calculated, %: C 71.24; H 8.30; N 4.62; S 10.57. *M* 303.46.

6'-Methoxy-4',4'-dimethyl-1'-phenyl-4'H-spiro[cyclohexane-1,3'-isoquinoline] (IIIc). Yield 0.26 g (78%), yellow oily substance (eluent hexane–ethyl acetate, 15:1). IR spectrum, ν , cm⁻¹: 2943, 2854, 1607, 1566. ¹H NMR spectrum, δ , ppm: 0.70–2.50 m (16H, CH₂, 4'-Me), 3.84 s (3H, OMe), 6.66 d.d (1H, 7'-H, ³J = 8.4, ⁴J = 2.7 Hz), 6.93 d (1H, 5'-H, ⁴J = 2.7 Hz), 7.18 d (1H, 8'-H, ³J = 8.4 Hz), 7.30–7.70 m (5H,

C₆H₅). ¹³C NMR spectrum, δ_C , ppm: 22.61 and 22.65 (4'-Me); 26.46, 29.66, 30.42 (CH₂); 39.10 (C^{4'}), 55.19 (MeO), 60.32 (C^{3'}), 109.09 and 110.97 (C^{5'}, C^{7'}), 121.02 (C^{8a'}); 128.03, 128.13, 128.98, 129.10, 129.62, 131.09 (C^{8'}, C^o, C^m, C^p); 140.07 and 150.26 (C^{1'}, Cⁱ), 161.68 and 163.36 (C^{4a'}, C^{6'}). Mass spectrum, m/z (I_{rel} , %): 333 [M]⁺ (100), 318 [M - CH₃]⁺ (66.4), 290 (12.1), 262 (10.0), 251 (18.6), 250 (25.7), 237 (88.8), 236 (68.8), 222 (15.4), 221 (29.2), 178 (19.3). Found, %: C 82.94; H 8.08; N 4.35. C₂₃H₂₇NO. Calculated, %: C 82.84; H 8.16; N 4.20. *M* 333.47.

6'-Methoxy-4',4'-dimethyl-1'-(4-nitrophenyl)-4'H-spiro[cyclohexane-1,3'-isoquinoline] (IIIId). Yield 0.30 g (79%), mp 135–136°C (from acetone). IR spectrum, ν , cm⁻¹: 2935, 2854, 1603, 1569, 1520. ¹H NMR spectrum, δ , ppm: 0.80–1.80 m (16H, CH₂, 4'-Me), 3.86 s (3H, OMe), 6.68 d.d (1H, 7'-H, ³J = 8.4, ⁴J = 2.4 Hz), 6.95 d (1H, 5'-H, ⁴J = 2.7 Hz), 7.07 d (1H, 8'-H, ³J = 8.4 Hz), 7.80 d (2H, *o*-H, ³J = 8.7 Hz), 8.27 d (2H, *m*-H, ³J = 8.7 Hz). ¹³C NMR spectrum, δ_C , ppm: 22.51 and 22.54 (4'-Me), 26.32 and 30.32 (CH₂), 39.20 (C^{4'}), 55.33 (MeO), 61.13 (C^{3'}), 109.45 and 111.43 (C^{5'}, C^{7'}), 120.18 (C^{8a'}), 123.42 (C^o), 129.03 and 130.01 (C^{8'}, C^m); 146.23, 148.25, 150.29 (C^{1'}, Cⁱ, C^p); 161.89 and 162.20 (C^{4a'}, C^{6'}). Mass spectrum, m/z (I_{rel} , %): 378 [M]⁺ (84.2), 377 [M - H]⁺ (40.6), 363 [M - CH₃]⁺ (48.4), 296 [M - C₆H₁₀]⁺ (16.9), 295 [M - C₆H₁₁]⁺ (18.4), 282 (100), 281 (81.6), 266 (20.9), 236 (9.7), 235 (9.3), 220 (8.6), 219 (9.6), 191 (12.4), 189 (11.5), 178 (10.9), 165 (9.2), 98 (23.0), 41 (18.4). Found, %: C 72.85; H 6.89; N 7.31. C₂₃H₂₆N₂O₃. Calculated, %: C 72.99; H 6.92; N 7.40. *M* 378.46.

Ethyl 2-[6'-methoxy-4',4'-dimethyl-2'H-spiro[cyclohexane-1,3'-isoquinolin]-1'-(4'H)-ylidene]-acetate (IIIe). Yield 0.29 g (77%), mp 97–98°C (from acetone). IR spectrum, ν , cm⁻¹: 3269, 2982, 2848, 1701, 1637, 1591. ¹H NMR spectrum, δ , ppm: 0.70–2.00 m [19H, OCH₂Me, (CH₂)₅, 4'-Me], 3.83 s (3H, OMe), 4.17 q (2H, OCH₂, ³J = 7.2 Hz), 5.03 s (1H, C^{1'}=CH), 6.73 d.d (1H, 7'-H, ³J = 8.7, ⁴J = 2.4 Hz), 6.87 d (1H, 5'-H, ⁴J = 2.7 Hz), 7.59 d (1H, 8'-H, ³J = 8.7 Hz), 9.34 br.s (1H, NH). ¹³C NMR spectrum, δ_C , ppm: 14.73 (OCH₂Me), 21.65 and 25.48 [(CH₂)₅], 29.53 (4'-Me), 40.95 (C^{4'}), 55.20 (MeO), 55.99 (C^{3'}), 58.30 (OCH₂), 75.64 (C^{1'}=CH), 110.43 and 111.10 (C^{5'}, C^{7'}), 120.80 (C^{8a'}), 126.87 (C^{8'}), 147.57 (C^{4a'}), 154.96 and 161.88 (C^{1'}, C^{6'}), 171.41 (C=O). Found, %: C 73.62; H 8.48; N 4.23. C₂₁H₂₉NO₃. Calculated, %: C 73.44; H 8.51; N 4.08. *M* 343.46.

This study was performed under financial support by the Presidium of the Russian Academy of Sciences

(program "Development of Methods for the Synthesis of Chemical Substances and Design of New Materials," project no. 12-P-3-1007) and by the Ural Branch of the Russian Academy of Sciences (Research Project for Young Scientists and Post-graduate Students, no. 14-3-NP-14) .

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