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Synthesis of (3*RS*)- and (3*SR*)-Acetoxy-(3a*RS*,8b*SR*)-*N*-acetyl-5-methoxy-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indoles

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Abstract—Stereoisomeric 3-acetoxy-5-methoxy-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indoles differing by the configuration of the C^3 atom were synthesized. The reaction of *N*-acetyl-6-(cyclopent-2-en-1-yl)-2-methoxyaniline with 50% hydrogen peroxide in the presence of Na_2WO_4–H_3PO_4 in AcOH gave (3*RS*,3a*RS*,8b*SR*)-*N*-acetyl-3-hydroxy-5-methoxy-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole which was converted into the corresponding 3-*O*-acetyl derivative by treatment with acetic anhydride in pyridine. *N*-Acetyl-6-(cyclopent-2-en-1-yl)-2-methoxyaniline reacted with iodine in methylene chloride in the presence of $NaHCO_3$ to produce (3*SR*,3a*RS*,8b*SR*)-3-acetoxy-5-methoxy-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole which was subjected to acetylation at the nitrogen atom by reaction with acetic anhydride. The structure of (3*RS*,3a*RS*,8b*SR*)-*N*-acetyl-3-hydroxy-5-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole was proved by X-ray analysis.

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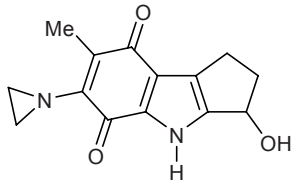
Some compounds of the cyclopenta[*b*]indole series exhibit strong biological activity and therefore attract researchers' attention [1, 2]. Several procedures have been proposed for the preparation of functionalized cyclopenta[*b*]indole derivatives. An example is cyclization of 2-(cyclopent-2-en-1-yl)anilines by the action of electrophilic reagents [3], which ensures synthesis of functionally substituted cyclopenta[*b*]indoles in good yields.

In the present article we report the results of our studies aimed at synthesizing structural analogs of 6-(aziridin-1-yl)-3-hydroxy-7-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indole-5,8-dione (**I**) which was shown to exhibit antimelanoma activity [2]. Oxidation of anilides **IIa** [4] and **IIb** with hydrogen peroxide in acetic acid in the presence of Na_2WO_4–H_3PO_4 gave

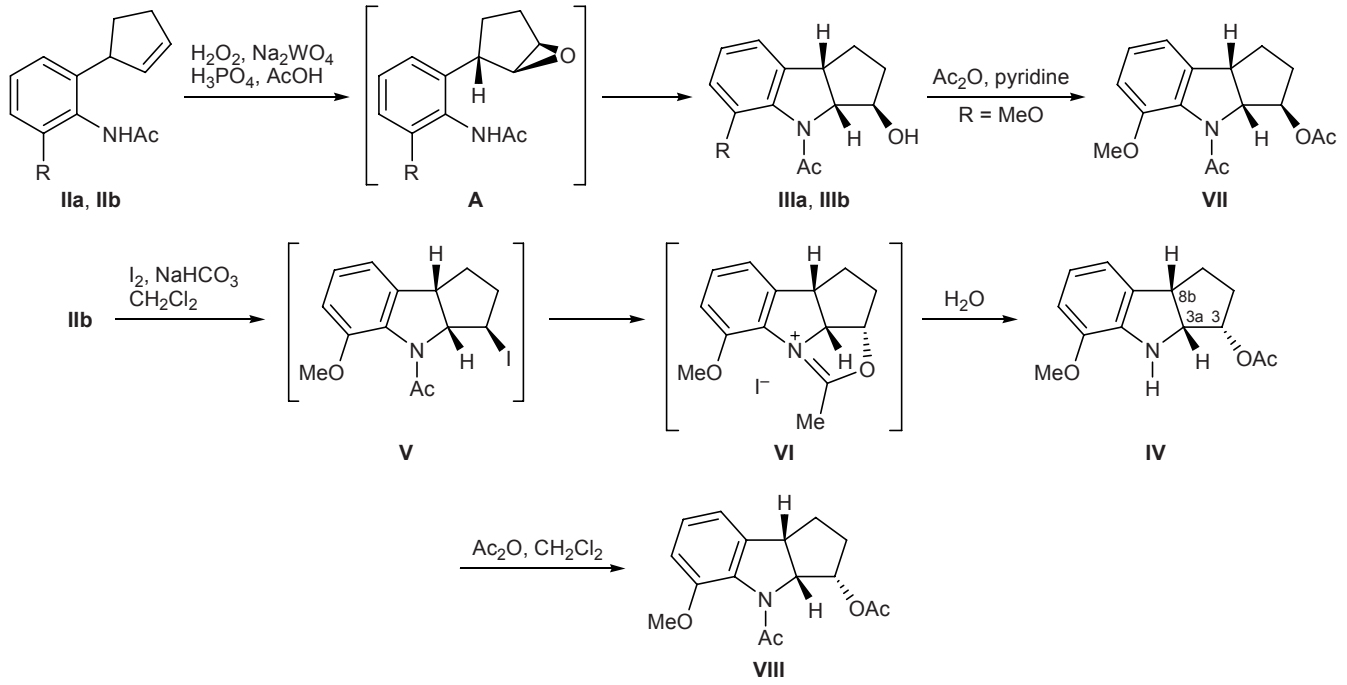


I

compounds **IIIa** [4] and **IIIb** in good yields. Here, the most probable intermediate is likely to be epoxycyclopentyl-substituted anilide **A** (Scheme 1). By reaction of anilide **IIb** with iodine in methylene chloride in the presence of $NaHCO_3$ we obtained acetoxycyclopenta[*b*]indole **IV** which is isomeric to **IIIb**. Compound **IV** is likely to be formed as a result of a series of consecutive transformations, including cyclization of **IIb** to *N*-acetyl-3-iodohexahydrocyclopenta[*b*]indole **V**, isomerization of **V** to tetracyclic compound **VI** (an analogous product was described by us previously [5]), and hydrolytic cleavage of the oxazolium ring. Hydrogen iodide liberated during the process is neutralized with $NaHCO_3$. By treatment with acetic anhydride compounds **IIIb** and **IV** were converted into the corresponding *N*,*O*-diacetyl derivatives **VII** and **VIII** (Scheme 1).

The molecular and crystalline structures of cyclopenta[*b*]indole **IIIa** [4] was determined by X-ray analysis (Fig. 1). The principal bond lengths and bond angles are given in Table. The indole fragment in molecule **IIIa** is nonplanar, and the five-membered nitrogen-containing ring has a distorted *envelope* conformation with the N^4 atom deviating by 0.23 Å from

Scheme 1.



R = Me (**a**), MeO (**b**).

the base plane. Presumably, the observed conformation in crystal is stabilized by intermolecular contacts C^{11}–$H^{11b}\cdots O^{2'}$ ($C^{11}\cdots O^{2'}$ 2.834(3), $H^{11}\cdots O^{2'}$ 2.43 Å, $\angle C^{11}H^{11b}O^{2'}$ 103°). According to published data, conformation of the five-membered nitrogen-containing ring is determined by the nature of the ring fused at the C^{8b}–C^{3a} bond, as well as of the substituent in the benzene ring [6, 7].

The N^4 atom is slightly pyramidalized: the sum of the bond angles at N^4 is 354.2°. The N^4–C^{4a} bond is shorter than N^4–C^{3a} by 0.06 Å (see table), indicating conjugation between the lone electron pair on the nitrogen atom and fused benzene ring. By contrast, the N^4–C^{3a} bond length approaches a value typical of standard single C–N bond [8]. The cyclopentane fragment is disordered, presumably as a result of restricted inversion of the C^2 atom with respect to the $C^{11}C^8C^1C^3$ plane. Different populations of the C^{2A} and C^{2B} positions suggest appreciable energy difference between the corresponding conformers. Molecules **IIIa** in crystal are linked to form chains parallel to the 001 crystallographic axis (Fig. 2). Weak intermolecular C–H$\cdots$O contacts give rise to a three-dimensional network (O$\cdots$H 2.36–2.71 Å).

We failed to determine the coupling constant for the 8b-H proton in the ^{1}H NMR spectrum of compound **IV**, for its signal was overlapped by those from the OCH_3 and NH groups. In the ^{13}C NMR spectrum of **IV** we observed signals from the acetyl methyl carbon

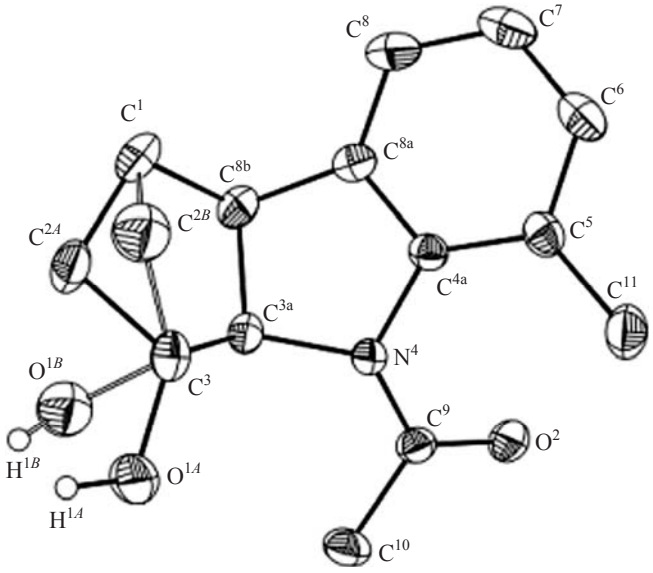


Fig. 1. Structure of the molecule of *N*-acetyl-5-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indol-3-ol (**IIIa**) according to the X-ray diffraction data. Non-hydrogen atoms are shown as thermal vibration ellipsoids with a probability of 30%. Hydrogen atoms (except for H^{1A} and H^{1B}) are not shown.

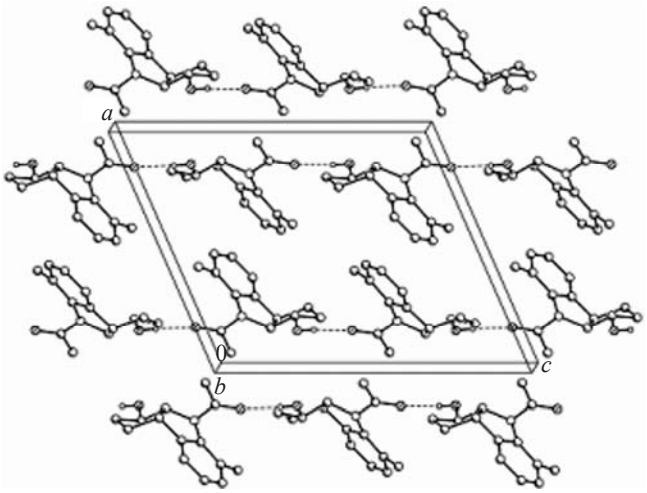


Fig. 2. Hydrogen bond chains formed by molecules **IIIa** in crystal. Interatomic distances $H^{1A}\cdots O^2$ 1.96, $O^{1A}\cdots O^2$ 2.779(2) Å, $\angle O^{1A}H^{1A}O^2$ 174°. The positions of C^{2B} and O^{1B} are not shown. The O^{1B} atom is involved in analogous hydrogen bond ($H^{1B}\cdots O^2$ 1.96, $O^{1B}\cdots O^2$ 2.786(2) Å, $\angle O^{1B}H^{1B}O^2$ 176.4°). The position of the O^2 atom is determined by the symmetry transformation $x, -y + 3/2, z - 1/2$.

Principal bond lengths and bond angles in the molecule of *N*-acetyl-5-methyl-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]-indol-3-ol (**IIIa**)

Bond	*d*, Å	Bond angle	ω, deg
O^{1a}–C^3	1.416(2)	$C^9N^4C^{4a}$	123.1(1)
O^{1b}–C^3	1.463(7)	$C^9N^4C^{3a}$	122.6(1)
O^2–C^9	1.224(2)	$C^{4a}N^4C^{3a}$	108.5(1)
N^4–C^9	1.366(2)	$C^{2b}C^1C^{8b}$	102.4(4)
N^4–C^{4a}	1.427(2)	$C^3C^{2a}C^1$	103.2(2)
N^4–C^{3a}	1.482(2)	$C^3C^{2b}C^1$	105.8(6)
C^1–C^{2b}	1.496(6)	$O^{1a}C^3O^{1b}$	52.3(3)
C^1–C^{2a}	1.534(3)	$O^{1a}C^3C^{2b}$	142.2(4)
C^1–C^{8b}	1.548(2)	$O^{1b}C^3C^{2b}$	110.6(5)
C^{2a}–C^3	1.510(2)	$O^{1a}C^3C^{2a}$	116.0(2)
C^{2b}–C^3	1.495(1)	$O^{1b}C^3C^{2a}$	68.4(3)
C^3–C^{3a}	1.525(2)	$C^{2b}C^3C^{2a}$	44.1(4)
C^{3a}–C^{8b}	1.546(2)	$O^{1a}C^3C^{3a}$	110.7(1)
C^{4a}–C^{8a}	1.388(2)	$O^{1b}C^3C^{3a}$	102.8(3)
C^{4a}–C^5	1.395(2)	$N^4C^{3a}C^3$	115.03(1)
C^5–C^6	1.399(2)	$N^4C^{3a}C^{8b}$	105.0(1)
C^5–C^{11}	1.498(2)	$C^{8a}C^{4a}N^4$	110.0(1)
C^6–C^7	1.377(3)	$C^5C^{4a}N^4$	127.2(1)
C^7–C^8	1.380(3)	$C^{4a}C^{8a}C^{8b}$	110.3(1)
C^8–C^{8a}	1.384(2)	$O^2C^9N^4$	121.6(1)
C^{8a}–C^{8b}	1.505(2)	$O^2C^9C^{10}$	121.2(1)
C^9–C^{10}	1.495(2)	$N^4C^9C^{10}$	117.2(1)

atom at δ_C 20.9 ppm and carbonyl carbon atom at δ_C 170.8 ppm. Diacetyl derivative **VIII** displayed in the ^{13}C NMR spectrum two sets of signals from the acetyl groups (δ_C 18.8, 169.8 and 20.6, 168.8 ppm). No other appreciable differences were found in the ^{13}C NMR spectra of **IV** and **VIII**. As follows from the spectra of diacetyl derivatives **VII** and **VIII**, acetylation does not change the positions of the 8b-H and OCH_3 signals in the ^1H NMR spectra (the signals were overlapped). The C^{3a} and C^3 signals turned out to be the most sensitive to orientation of the acetoxy group on C^3 in heterocycles **VIII** and **VII**. The C^{3a} chemical shifts differ by 3 ppm (δ_C 67.2 ppm for **VIII** and 70.8 ppm for **VII**), and the C^3 chemical shifts differ by 6 ppm (δ_C 74.6 and 80.4 ppm, respectively).

EXPERIMENTAL

Reflection intensities for a single crystal of compound **IIIa** ($0.5 \times 0.4 \times 0.3$ mm; $C_{14}H_{17}NO_2$) were measured at 293(2) K on a Siemens P3/PC diffractometer (λMoK_α 0.71073 Å). Unit cell parameters: a = 12.335(3), b = 7.2320(14), c = 14.799(3) Å; β = 113.56(3)°; space group $P2_1/c$; M 231.29; $\mu(MoK_\alpha)$ = 0.85 cm^{-1}. Total of 2763 reflections were measured, and 2641 independent reflections ($2\Theta_{max}$ = 54.12°) were used in the refinement procedure. The structure was solved by the direct method and was refined in anisotropic approximation for non-hydrogen atoms. The hydroxy group and the C^2 atom are disordered by two positions denoted as *A* and *B* (O^{1A}, O^{1B}, C^{2A}, and C^{2B}) with a population ratio of 1:4. Hydrogen atoms in the methyl, methylene, and phenyl groups were visualized by the Fourier difference synthesis of electron density, and their positions were refined in isotropic approximation. The hydrogen atom in the hydroxy group was localized by the Fourier difference synthesis of electron density, and its position was refined with the O–H bond length constrained to 0.82 Å. The final divergence factors were R_1 = 0.0531 [2300 reflections with $I > 2\sigma(I)$], wR_2 = 0.1491 (all reflections); goodness of fit 1.053.

The IR spectra were recorded on a UR-20 spectrometer. The ^1H and ^{13}C NMR spectra were measured on a Bruker AM-300 instrument at 300.13 and 75.47 MHz, respectively, using TMS as internal reference. The elemental compositions were determined on an M-185B CHN Analyzer. Silica gel LS (40–100 μm; Lancaster) was used for column chromatography. Qualitative thin-layer chromatography was performed

using Sorbfil plates (*Sorbpolimer* Ltd., Krasnodar, Russia); detection by treatment with iodine vapor.

(3*S*,3a*R*,8b*S*)-*N*-Acetyl-5-methoxy-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indol-3-ol (IIIb). Cyclopentenylanilide **IIb**, 2.31 g (10 mmol), was dissolved in 8 ml of acetic acid, 0.68 g (10 mmol) of 50% hydrogen peroxide and a solution of 150 mg of $Na_2WO_4 \cdot 2H_2O$ and 100 mg of 85% H_3PO_4 in 0.5 ml of water were added, and the mixture was kept for 5 h at a temperature not exceeding 40°C. The mixture was treated with 80 ml of chloroform, the extract was washed with 10% aqueous $Na_2S_2O_3$ (20 ml) and water (20 ml), dried over $MgSO_4$, and evaporated, and the residue was subjected to chromatography on silica gel. Yield 1.01 g (41%), mp 161–162°C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.55–1.75 m (3H, CH_2, 2-H, 4-H), 2.25 s (3H, CH_3), 2.30–2.40 m (1H, 2-H), 3.80 s (4H, OH, OCH_3), 3.90 d.d.t (1H, 8b-H, J = 3.5, 9.4, 10.0 Hz), 4.07 d.t (1H, 3-H, J = 4.5, 6.3 Hz), 4.61 d.d (1H, 3a-H, J = 4.5, 9.4 Hz), 6.71 d.d (1H, H_{arom}, J = 1.0, 7.0 Hz), 6.75 d.d (1H, H_{arom}, J = 1.0, 7.0 Hz), 7.08 t (1H, 7-H, J = 7.0 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 24.0 (CH_3), 30.6 and 31.7 (C^1, C^2), 43.0 (C^{8b}), 55.3 (OCH_3), 74.6 (C^{3a}), 78.9 (C^3), 111.2 (C^6), 117.1 and 125.9 (C^7, C^8), 129.2 and 140.1 (C^{4a}, C^{8a}), 147.9 (C^5), 172.5 (C=O). Found, %: C 67.71; H 6.77; N 5.49. $C_{14}H_{17}NO_3$. Calculated, %: C 68.00; H 6.93; N 5.66.

(3*R*,3a*R*,8b*R*)-5-Methoxy-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indol-3-yl acetate (IV). Anilide **IIb**, 2.31 g (10 mmol), was dissolved in 50 ml of methylene chloride, 2.72 g (10.7 mmol) of iodine and 9 g of $NaHCO_3$ were added, and the mixture was stirred for 48 h at 20°C. The mixture was then diluted with 150 ml of methylene chloride, 50 ml of 5% aqueous $Na_2S_2O_3$ was added, and the mixture was stirred for 1 h. The organic phase was separated, washed with water (2×50 ml), and dried over Na_2SO_4. The solvent was distilled off under reduced pressure, and the residue was purified from tarry products by chromatography on silica gel using benzene as eluent. Yield 1.48 g (60%), light brown viscous material, R_f 0.8 (C_6H_6–EtOAc, 2:1). IR spectrum: ν 3385 cm^{-1} (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.65–1.85 m (4H, CH_2), 2.07 s (3H, CH_3), 3.70–3.90 m (5H, NH, OCH_3, 8b-H), 4.45 d.d (1H, 3a-H, J = 5.8, 8.6 Hz), 5.01 d.t (1H, 3-H, J = 5.8, 9.6 Hz), 6.65–6.72 m (3H, H_{arom}). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 20.9 (CH_3); 28.0, 30.1 (C^1, C^2); 45.8 (C^{8b}); 55.0 (OCH_3); 63.0 (C^{3a}); 77.6 (C^3); 109.1, 116.2, 118.9 (C^6, C^7, C^8); 133.6, 140.0, 144.4 (C^5, C^{4a}, C^{8a}); 170.8 (C=O). Found, %: C 67.79; H 6.73; N 5.51. $C_{14}H_{17}NO_3$. Calculated, %: C 68.00; H 6.93; N 5.66.

(3*S*,3a*R*,8b*S*)-*N*-Acetyl-5-methoxy-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indol-3-yl acetate (VII). Compound **IV**, 0.49 g (2 mmol), was dissolved in 5 ml of methylene chloride, 0.41 g (4 mmol) of acetic anhydride was added, and the mixture was left to stand for 24 h. The mixture was then treated with 10 ml of water, stirred for 20 min, and extracted with 100 ml of methylene chloride. The organic phase was washed with a 5% solution of sodium hydrogen carbonate until carbon dioxide no longer evolved and with water (20 ml) and dried over Na_2SO_4. The solvent was removed under reduced pressure, and the residue was subjected to chromatography on silica gel. Yield 0.43 g (74%), transparent thick material. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.60–2.00 m (4H, CH_2), 1.95 s (3H, CH_3), 2.15 s (3H, CH_3), 3.87 s (4H, OH, OCH_3), 3.96 t (1H, 8b-H, J = 8.0 Hz), 4.48 d.d (1H, 3a-H, J = 2.0, 8.0 Hz), 5.10 q (1H, 3-H, J = 2.0 Hz), 6.70 d (1H, H_{arom}, J = 7.9 Hz), 6.80 d (1H, H_{arom}, J = 7.7 Hz), 7.10 d.d (1H, H_{arom}, J = 7.7, 7.9 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 21.2 (CH_3), 23.5 (CH_3), 29.6 and 30.3 (C^1, C^2), 44.1 (C^{8b}), 55.5 (OCH_3), 70.8 (C^{3a}), 80.4 (C^3), 111.7 (C^6), 116.6 and 126.3 (C^7, C^8), 130.5 and 139.1 (C^{4a}, C^{8a}), 148.7 (C^5), 170.2 and 171.3 (2C=O). Found, %: C 66.20; H 6.44; N 4.72. $C_{16}H_{19}NO_4$. Calculated, %: C 66.42; H 6.62; N 4.84.

(3*R*,3a*R*,8b*R*)-*N*-Acetyl-5-methoxy-1,2,3,3a,4,8b-hexahydrocyclopenta[*b*]indol-3-yl acetate (VIII). Compound **IIIb**, 0.49 g (2 mmol), was dissolved in 5 ml of pyridine, 0.41 g (4 mmol) of acetic anhydride was added, and the mixture was left to stand for 24 h. The mixture was diluted with water and extracted with 100 ml of methylene chloride, the extract was washed with a 5% solution of sodium hydrogen carbonate until carbon dioxide no longer evolved and with water (20 ml) and dried over Na_2SO_4, the solvent was removed under reduced pressure, and the residue was subjected to chromatography on silica gel. Yield 0.44 g (75%), transparent viscous material. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.20–1.60 m (3H, CH_2, 2-H), 1.17–1.95 m (1H, 2-H), 1.55 s (3H, CH_3), 2.00 s (3H, CH_3), 3.45–3.51 m (1H, 8b-H), 3.48 s (3H, OCH_3), 4.67 d.d (1H, 3a-H, J = 6.2, 8.6 Hz), 5.20 d.t (1H, 3-H, J = 5.0, 6.2 Hz), 6.47 d (1H, H_{arom}, J = 8.2 Hz), 6.52 d (1H, H_{arom}, J = 7.5 Hz), 6.79 d.d (1H, 7-H, J = 7.5, 8.2 Hz). ^{13}C NMR spectrum ($CDCl_3$), δ_C, ppm: 18.8, 20.6 (CH_3); 29.7, 29.8 (C^1, C^2); 43.9 (C^{8b}); 55.6 (OCH_3); 67.2 (C^{3a}); 74.6 (C^3); 111.9, 116.7, 125.8 (C^6,

C^7, C^8); 132.5, 140.7 (C^{4a}, C^{8a}); 148.7 (C^5); 168.8, 169.8 (C=O). Found, %: C 66.27; H 6.47; N 4.66. $C_{16}H_{19}NO_4$. Calculated, %: C 66.42; H 6.62; N 4.84.

REFERENCES

1. Smith, A.B., Kurti, L., and Davulcu, A.H., *Org. Lett*., 2006, vol. 8, p. 2167.
2. Xing, S., Wu, P., and Skibo, E.B., *J. Med. Chem*., 2000, vol. 43, p. 457.
3. Gataullin, R.R., Ishberdina, R.R., Shitikova, O.V., Spirikhin, L.V., Kazhanova, T.V., and Abdrakhmanov, I.B., *Mendeleev Commun*., 2004, no. 3, p. 219.
4. Ishberdina, R.R., Nasyrov, M.F., Gataullin, R.R., and Abdrakhmanov, I.B., *Bashkir. Khim. Zh*., 2004, vol. 11, no. 1, p. 90.
5. Likhacheva, N.A., Gataullin, R.R., and Abdrakhmanov, I.B., *Russ. J. Gen. Chem*., 2007, vol. 77, p. 654.
6. Adam, W., Ahrweiler, M., Peters, K., and Schmiedeskamp, B., *J. Org. Chem*., 1994, vol. 59, p. 2733.
7. Miyata, O., Takeda, N., Kimura, Y., Takemoto, Y., Tohnai, N., Miyata, M., and Naito, T., *Tetrahedron*, 2006, vol. 62, p. 3629.
8. Allen, F.H., Kennard, O., Watson, D.G., Brammer, L., Orpen, A.G., and Taylor, R., *J. Chem. Soc., Perkin. Trans. 2*, 1987, p. S1.