Chemistry of Natural Compounds, Vol. 37, No. 4, 2001

SYNTHESIS AND STEREOCHEMISTRY OF NEW N-SUBSTITUTED CYTISINE DERIVATIVES

T. V. Khakimova, O. A. Pukhlyakova, G. A. Shavaleeva, A. A. Fatykhov, E. V. Vasil'eva, and L. V. Spirikhin

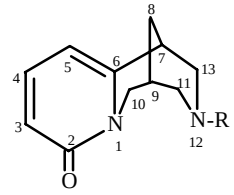
UDC 547.94;543422.25;541.620; 547.834.2;547.514.472.1

A series of new N-substituted cytisine derivatives was synthesized. The ^{1}H and ^{13}C NMR spectra of certain compounds exhibit a doubled set of signals. This is explained by formation of diastereomeric pairs in compounds containing an asymmetric center in the substituents. The signal splitting in -COHC=CHCO$_2$H and HC=O (formyl) derivatives is explained by the existence of Z and E invertomers. Their stereochemical features are discussed. Amide conjugation is confirmed by temperature experiments.

Key words: cytisine, derivatives, amide conjugation, ^{1}H and ^{13}C NMR spectra.

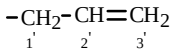
The alkaloid cytisine is a representative of natural 3,7-diazabicyclo[3.3.1]nonanes. It is used in medicine [1] because it possesses a wide spectrum of biological activity. Its derivatives are interesting for studying the biological activity of chiral 3,7-diazabicyclo[3.3.1]nonanes and in structural studies.

We synthesized a series of N-substituted cytisines: N-methylcytisine (**1**) [2], N-allylcytisine (**2**), N-formylcytisine (**3a** and **b**), dimethyl-2-(N-cytisinyl)succinate [3] (**4a** and **b**), N-(γ-nitrilopropyl)-cytisine (**5**) [2], 1,4-dioxa-7-chloro-6-N-cytisinylspiro[4.4]non-6-en-8-one (**6**), 1,4-dioxa-7,9-dichloro-6-N-cytisinylspiro[4.4]non-6-en-8-one (**7a** and **b**), 2-N-cytisinyl-1,4-naphthoquinone [3] (**8**), and 4-oxo-4-(N-cytisinyl)butenoic acid (**9a** and **b**) [3].



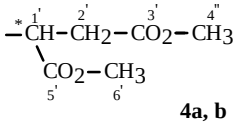
R= –CH$_3$ (1')

1

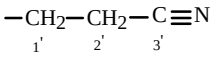


2

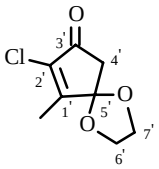
3a, b



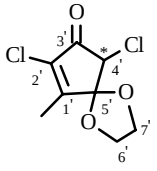
4a, b



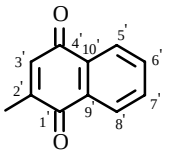
5



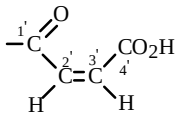
6



7a, b



8



9a, b

*Asymmetric center

Institute of Organic Chemistry, Ufa Scientific Center of the Russian Academy of Sciences, 450054, Ufa, Prospekt Oktyabrya 71, fax (3472) 35 60 66, e-mail: chemorg@anrb.ru. Translated from Khimiya Prirodnykh Soedinenii, No. 4, pp. 301-305, July-August, 2001. Original article submitted May 11, 2001.

 0009-3130/01/3704-0356$25.00

TABLE 1. ^{13}C NMR Parameters of Cytisine and Its Derivatives

C	Cytisine	**1**	**2**	**3a**	**3b**	**4a**	**4b**	**5**	**6**	**7a**	**7b**	**8**	**9a**	**9b**
2	163.37	163.44	163.48	163.20	163.05	163.34	163.34	163.25	164.01	165.4	165.31	163.49	163.1	163.2
3	116.38	116.38	116.37	117.65	117.34	116.63	116.50	116.47	116.01	117.43	117.43	117.70	117.05	116.81
4	138.53	138.47	138.44	138.59	138.96	138.66	138.66	138.46	139.92	141.39	141.34	138.80	139.42	139.43
5	104.70	104.54	104.35	105.75	105.00	104.62	104.62	104.39	104.10	105.11	105.30	105.49	105.17	105.29
6	150.89	151.32	151.46	147.93	147.93	151.07	150.75	150.61	148.93	149.91	149.91	153.98	150.56	150.87
7	35.32	35.16	35.35	33.68	34.40	34.40	34.29	34.98	34.93	36.26	36.03	35.10	35.16	35.16
8	26.03	25.13	25.77	26.12	26.17	25.62	25.62	25.31	24.97	26.14	26.06	28.08	26.07	25.96
9	27.50	27.69	27.88	26.92	26.54	28.25	27.59	27.57	27.91	29.26	29.03	25.97	27.91	27.91
10	49.48	49.77	49.83	48.73	48.48	49.77	49.54	49.55	48.52	48.76	48.76	48.88	49.58	49.39
11	52.72	61.93	59.73	51.99	45.88	60.40	60.23	59.65	53.98	56.36	55.63	55.38	54.20	48.83
13	53.69	62.24	60.11	46.94	53.24	63.17	62.97	59.11	53.14	54.74	55.43	55.87	47.85	52.82
1′	-	45.99	134.87	160.97	161.09	53.58	52.98	52.65	63.81	63.78	63.78	183.85	166.86	167.14
2′	-	-	117.03	-	-	34.40	34.29	15.32	62.07	63.58	63.58	148.76	137.31	137.81
3′	-	-	-	-	-	171.12	171.12	118.19	107.51	108.91	109.11	113.38	125.25	125.42
4′	-	-	-	-	-	51.44	51.44	-	160.05	160.11	159.97	182.05	166.18	166.50
5′	-	-	-	-	-	170.71	170.82	-	107.51	109.71	109.65	125.53; 126.83 (C8)		
6′	-	-	-	-	-	51.85	51.73	-	191.68	187.26	187.09	132.70; 133.85 (C7)		
7′	-	-	-	-	-	-	-	-	45.08	66.59	66.41	132.01; 132.55 (C10)		

In the present article, we discuss the spectral properties of these compounds. The physicochemical properties of **1** and **5**, which have been previously synthesized, correspond to those published [4, 5]. Thus, reaction of cytisine with allylbromide or formic acid gives N-allylcytisine **2** or N-formylcytisine **3a** and **b** in yields of 87 and 95%, respectively; reaction of 1,4-dioxa-6,7,9-trichlorospiro[4.4]non-6-en-8-one [6] or 1,4-dioxa-7,9-dichlorospiro[4.4]non-6-en-8-one [7] with cytisine gives 1,4-dioxa-7,9-dichloro-6-N-cytisinylspiro[4.4]non-6-en-8-one (**7a** and **b**) or 1,4-dioxa-7-chloro-6-N-cytisinylspiro[4.4]non-6-en-8-one (**6**) in yields of 75 and 64%, respectively.

Analysis of the ^{1}H and ^{13}C NMR spectra revealed that a doubled set of signals is observed for **3**, **4**, **7**, and **9** (Table 1 lists ^{13}C NMR spectral data of the studied compounds). According to the literature [8-10], adding substituents to the N has no effect on the conformation of the cytisine core. This is confirmed by the fact that the chemical shifts of bridging C-8, which are sensitive to conformational changes, are practically the same.

Compounds **4a** and **b** and **7a** and **b** are pairs of diastereomers that are formed when addition of a substituent creates an asymmetric center. Signals for stereoisomeric **4a** and **b** and **7a** and **b** were assigned based on integrated intensities in the ^{1}H and ^{13}C NMR spectra [11, 12].

It is interesting that the chiral centers in **7a** and **b** are located six bonds from each other. Nevertheless, the diastereomeric splitting reaches 0.3 ppm. The N atom located between the chiral centers probably intensifies the transfer of magnetic shielding by the asymmetric nuclei [13, 14]. Diastereomerism was not observed previously in cytisine derivatives with an asymmetric center in the substituent [15, 16]. Formation of **3** and **9** also produces two stereoisomers. The maximum difference for C-11 and C-13 in these instances is 1-2 ppm. Invertomers with hindered rotation around the N–C bond, which are considered to be *Z* and *E* isomers, appear because of the formation of amide conjugation [17, 18]. Assignments were made for **3** and **9**. The chemical shifts of H-8, H-9, and H-7 in the ^{1}H NMR of **3a** and **b** are the same. All other give a pair of signals of equal intensity. The major and minor resonances of the formyl proton occur as two singlets (3:2) at 7.88 and 7.65 ppm, respectively, i.e., they have an unusual strong-field shift compared with that expected (~11 ppm). Crystals of the pure compound dissolve in dry $CDCl_3$. The difference $\Delta\delta = 7.88 - 7.65$ is independent of solvent. Therefore, the difference in the chemical shifts is explained only by the different stereochemistry. Double resonance, integration by parts, and 2D experiments were

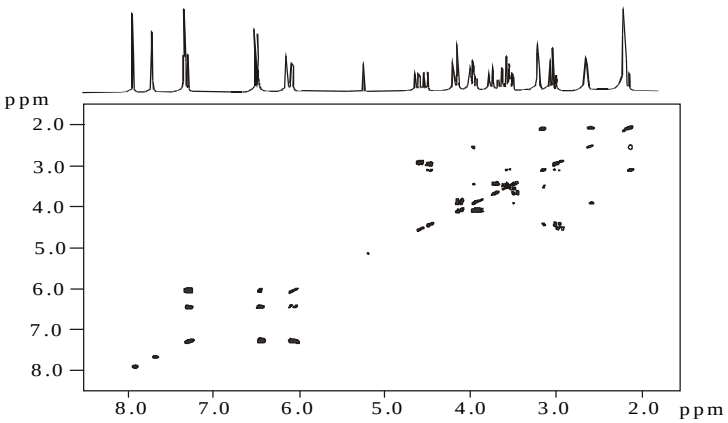


Fig. 1. Two-dimensional COSYHH-45 spectrum of formylcytisine (**3a**, **3b**).

performed to determine unambiguously all interactions in each isomer. The 2D COSY-45 (Fig. 1) and COSYLR-45 spectra include two subspectra for each isomer. The pairs of geminal protons at 2.95-4.58 and 2.9-4.52 ppm have the greatest difference in chemical shifts. They correspond to the C atoms at 45.88 and 46.94, respectively, as expected from the 2D heteronuclear correlation spectra. Such a diastereotopic shift is due to the presence of a *cis*-carbonyl in the substituent on N [19]. Therefore, one pair of geminal protons in the *Z*-isomer should belong to C-13; in the *E*-isomer, to C-11. The axial proton on C-11 is broadened owing to through-space coupling with the axial proton on C-10, which in the one-dimensional spectrum has a constant of 1.1 and 1.3 Hz in different isomers. Therefore, the minor component is the *E*-isomer with C-11 at 45.88 ppm and H_a (2.95 ppm) and H_e (4.58 ppm). Other pairs of protons H_a (3.45 ppm) and H_e (3.56 ppm) on C (53.24 ppm) and H_a (3.44 ppm) and H_e (3.53 ppm) on C (51.99 ppm) belong to C-13 in the *E*-isomer and C-11 in the *Z*-isomer, respectively. This agrees with the literature [20, 21]. The signal in similar systems with the C atom *trans* to a carbonyl is located at weaker field and to a greater extent in the *E*-isomer [19]. The resonance of an axial proton *trans* to a carbonyl in the *Z*-isomer is also at weaker field relative to that in the *E*-isomers [19]. In COSYLR, where through-space couplings have stronger cross-peaks, the following couplings are seen: for the *Z*-isomer [H-1′ with H_a-13], for the *E*-isomer [H-1′ with H_a-11].

Thus, the signal for an aldehyde proton in the *Z*-isomer is shifted to weaker field compared with that for the *E*-isomer apparently due to deshielding of the magnetically anisotropic C-2 carbonyl because the molecular symmetry is destroyed only by the pyridone ring. Assignments were made for 4-oxo-4-(N-cytisinyl)butenoic acid (**9a** and **b**) as follows. Amide conjugation occurs also in this instance. However, *cis* and *trans* isomerization around the C=C double bond is absent. This is confirmed by the identical spin—spin coupling constants between protons on C-2′ and C-3′ (11.9 Hz). However, the *E*-isomer predominates in this instance (3:2). Furthermore, the ^{1}H NMR spectra of **9a** and **b** show that the vicinal protons on C-2′ and C-3′ of one isomer are located at weaker field. The signal of one of them is shifted to weak field up to 6.5 ppm. Such magnetic deshielding can be explained by the *Z*-conformation. We can exclude H-bonding because the IR spectrum lacks the characteristic absorption band. The presence of amide conjugation was confirmed by varying temperature. Thus, heating **9a** and **b** to 100°C causes the signals to coalesce in the ^{13}C NMR because of free rotation of the substituent around the N–COCHCHCO$_2$H bond.

EXPERIMENTAL

NMR spectra were recorded on a Bruker AM-300 spectrometer (^{1}H, 300.13; ^{13}C, 75.47 MHz). Chemical shifts are given vs. $CDCl_3$, 77.1 ppm; $(CD_3)_2CO$, 28.83; DMSO-d_6, 39.43 (^{13}C) and 7.27, 2.07, and 2.50 ppm (^{1}H). IR spectra were recorded on a UR-20 instrument as thin layers or in mineral oil. Mass spectra were obtained in a MX-1300 spectrometer with source temperature 100°C and ionizing-electron energy 70 and 12 eV.

N-Allylcytisine (2). A mixture of cytisine (3.39 g) and K_2CO_3 (4.5 g) in acetone (75 mL) was stirred under N_2 and treated with N-allylbromide (1.56 mL, 0.2-mL portions) over 10 min. The mixture was boiled for 11 h. After the reaction was finished K_2CO_3 was filtered off and washed with acetone. The filtrate was evaporated. The solid was purified by dissolving

in CH_2Cl_2 and passing through a layer of Al_2O_3. Solvent was evaporated to give 4.85 g (87%) of a white crystalline powder of N-allylcytisine, mp 117-118°C.

Found (%): C 73.08, H 8.00, N 12.15. $C_{14}H_{18}N_2O$. Calc. (%): C 73.01, H 7.88, N 12.16.

IR spectrum (KBr, ν/cm^{-1}): 2900-2980 (CH_2), 2870, 2810, 1660 (N–C=O), 1585 (C=C–C=O), 1560, 960, 820, 760 (C=C).

^{1}H NMR ($CDCl_3$, δ, ppm, J/Hz): 1.68 [1H, dt, H′C(8), ^2J = -12.7, $^3J_{8-9}$ = $^3J_{8-7}$ = 3.0], 1.8 [1H, dt, H″C(8), ^2J = -12.7, $^3J_{8-9}$ = $^3J_{8-7}$ = 3.0], 2.18 [2H, m, HC(13)], 2.45 [1H, m, HC(9)], 2.75-2.95 [5H, m, H_2C(1′), H_2C(11), HC(7)], 3.82 [1H, dd, H_aC(10), ^2J = -15.4, $^3J_{10-9}$ = 6.7], 3.94 [1H, d, H_eC(10), ^2J = -15.4], 4.94 [2H, m, HC(3′)], 5.45-5.60 [1H, m, HC(2′), $^3J_{2-1}$ = 6.1], 5.90 [1H, d, HC(5), $^3J_{5-4}$ = 6.8], 6.36 [1H, dd, HC(3), $^3J_{3-4}$ = 9.0, $^4J_{3-5}$ = 1.1], 7.19 [1H, dd, HC(4), $^3J_{3-4}$ = 9.0, $^3J_{5-4}$ = 6.8].

Mass spectrum (EI, 70 eV), *m*/*z* [I_{rel} (%)]: 230 $[M]^+$ (50), 189 (7), 147 (15), 146 (30), 169 (30), 84 (100).

N-Formylcytisine (3a and b). A solution of cytisine (0.2 g, 1 mmole) in acetic acid (2 mL) was treated with formic acid (90%, 6 mL, 5 mmole) and boiled for 2 h (TLC monitoring). The solvent was evaporated. The product was isolated by column chromatography on SiO_2 ($CHCl_3$:CH_3OH, 1:1). Yield 0.22 g (95%) of **3a** and **b** as a white crystalline powder, mp 169-171°C. Found (%): C 60.72, H 6.39, N 11.61. $C_{12}H_{14}N_2O_2$. Calc. (%): C 66.04, H 6.47, N 12.84.

IR spectrum (KBr, ν/cm^{-1}): 1648 (N–C=O), 1632 (N–C=O), 1540, 1440, 1416, 804, 744 (C=C).

Mass spectrum (EI, 70 eV), *m*/*z* [I_{rel} (%)]: 218 $[M]^+$ (100), 190 (14), 189 (12), 147 (30), 146 (80).

^{1}H NMR (**3a**, *Z*-isomer) ($CDCl_3$, δ, ppm, J/Hz): 2.09 [2H, m, H_2C(8)], 2.50 [1H, m, HC(9)], 2.95 [1H, d, H_a(13), ^2J = -13.0], 3.09 [1H, m, HC(7)], 3.44 [1H, dd, H_a(11), ^2J = -13.4, ^4J = 1.1], 3.53 [1H, d, H_eC(11), ^2J = -13.4], 3.88 [1H, ddd, H_aC(10), ^2J = -15.73, $^3J_{10-9}$ = 6.4, $^3J_{10-11}$ = 1.1], 4.06 [1H, d, H_eC(10), ^2J = -15.73], 4.52 [1H, d, H_eC(13), ^2J = -13.0], 6.00 [1H, dd, HC(5), $^3J_{5-4}$ = 6.8, $^4J_{5-3}$ = 1.6], 6.40 [1H, dd, HC(3), $^3J_{3-4}$ = 9.1, $^4J_{3-5}$ = 1.6], 7.25 [1H, dd, HC(4), $^3J_{4-5}$ = 6.8, $^3J_{3-4}$ = 9.1], 7.88 [1H, s, COH].

^{1}H NMR (**3b**, *E*-isomer) ($CDCl_3$, δ, ppm, J/Hz): 2.09 [2H, m, H_2C(8)], 2.50 [1H, m, HC(9)], 2.90 [1H, dd, H_aC(11), ^2J = -13.4], 3.09 [1H, m, HC(7)], 3.45 [1H, m, H_aC(13), ^2J = -13.0], 3.56 [1H, d, H_eC(13), ^2J = -13.0, $^3J_{10-11}$ = 1.3], 3.82 [1H, ddd, H_aC(10), ^2J = -13.0, $^3J_{10-9}$ = 6.2, $^3J_{10-11}$ = 1.3], 4.06 [1H, d, H_eC(10), ^2J = -13.4], 4.58 [1H, d, H_eC(11), ^2J = -13.4], 6.08 [1H, dd, HC(5), $^3J_{5-4}$ = 6.8, $^4J_{5-3}$ = 1.6], 6.41 [1H, dd, HC(3), $^3J_{3-4}$ = 9.1, $^4J_{3-5}$ = 1.6], 7.25 [1H, dd, HC(4), $^3J_{4-5}$ = 6.8, $^3J_{3-4}$ = 9.1], 7.65 [1H, s, COH].

1,4-Dioxa-7,9-dichloro-6-N-cytisinylspiro[4.4]non-6-en-8-one (7a and b). A solution of 1,4-dioxa-6,7,9-trichlorospiro[4.4]non-6-en-8-one (0.2 g, 0.82 mmole) and cytisine (0.23 g, 1.2 mmole) in benzene (5 mL) was boiled for 3 h. The solvent was evaporated. The solid was dissolved in aqueous NaCl (10 mL). The product was extracted by $CHCl_3$ (3×10 mL). The combined organic extracts were dried over $MgSO_4$ and evaporated. The product was purified by column chromatography over SiO_2 (benzene:methanol, 7:1). Yield 0.25 g (75%) of 1,4-dioxa-7,9-dichloro-6-N-cytisinylspiro[4.4]non-6-en-8-one.

Found (%): C 54.52, H 4.91, N 6.78, Cl 17.55. $C_{18}H_{18}O_4Cl_2N_2$. Calc. (%): C 54.45, H 4.63, N 7.08, Cl 17.80.

IR spectrum (KBr, ν/cm^{-1}): 1720 (C=O), 1660 (N–C=O), 1610, 1580 (C=C–C=O), 820, 760 (C=C).

^{1}H NMR (**7a**) ($CDCl_3$, δ, ppm, J/Hz): 1.90 [2H, m, HC(8)], 2.49 [1H, m, HC(9)], 3.12 [1H, m, HC(7)], 3.28 [1H, d, HC(11), ^2J = -12.4], 3.44 [1H, d, HC(13), ^2J = -13.0], 3.81 [1H, dd, HC(10), H_aC(10), ^2J = -15.4, $^3J_{10-9}$ = 5.7], 3.93-4.37 [7H, m, H_2C(6′), H_2C(7′), HC(4′), H_eC(10), H_eC(13)], 4.44 [1H, d, H_eC(11), ^2J = -12.4], 6.01 [1H, d, HC(5), ^3J = 6.8], 6.36 [1H, dd, HC(3), $^3J_{3-4}$ = 9.0, $^4J_{3-5}$ = 1.1], 7.19 [1H, dd, HC(4), $^3J_{3-4}$ = 9.0, $^3J_{5-4}$ = 6.8].

^{1}H NMR (**7b**): 1.90 [2H, m, HC(8)], 2.58 [1H, m, HC(9)], 3.08 [1H, m, HC(7)], 3.31 [1H, d, HC(11), ^2J = -12.4], 3.42 [1H, d, HC(13), ^2J = -13.0], 3.73 [1H, dd, HC(10), H_aC(10), ^2J = - 15.4, $^3J_{10-9}$ = 5.7], 3.93-4.37 [7H, m, H_2C(6′), H_2C(7′), HC(4′), H_eC(10), H_eC(13)], 4.44 [1H, d, H_eC(11)], 6.01 [1H, d, HC(5), ^2J = 6.8], 6.36 [1H, dd, HC(3), $^3J_{3-4}$ = 9.0, $^4J_{3-5}$ = 1.1], 7.19 [1H, dd, HC(4), $^3J_{3-4}$ = 9.0, $^3J_{5-4}$ = 6.8].

1,4-Dioxa-7-chloro-6-N-cytisinylspiro[4.4]non-6-en-8-one (6) was prepared analogously to **7a** and **b** from 1,4-dioxa-6,7-dichlorospiro[4.4]non-6-en-8-one. Yield 64%.

IR spectrum (KBr, ν/cm^{-1}): 1720 (C=O), 1660 (N–C=O), 1610, 1580 (C=C–C=O), 820, 760 (C=C).

^{1}H NMR (acetone-d_6, δ, ppm, J/Hz): 1.68-1.87 [2H, m, HC(8)], 2.30 [1H, m, HC(9)], 2.97 [1H, m, HC(7)], 3.05-3.20 [2H, m, HC(13)], 3.40-3.55 [2H, dd, HC(10), ^2J = 15.4, $^3J_{10-9}$ = 6.8], 3.85-4.30 [6H, m, 2HC(11), 4H, O–CH_2–CH_2–O], 4.42 [1H, d, HC(4′), ^2J = -13.0], 4.63 [1H, d, HC(4′), ^2J = -13.0], 6.04 [1H, d, HC(5), $^3J_{4-5}$ = 6.6], 6.43 [1H, d, HC(3), $^3J_{3-4}$ = 9.0], 7.15 [1H, dd, HC(4), $^3J_{3-4}$ = 9.0, $^3J_{5-4}$ = 6.6]. Mass spectrum (EI, 70 eV), *m*/*z* [I_{rel} (%)]: 362 $[M]^+$, 345, 319, 216, 172, 146.

4-Oxo-4-(N-cytisinyl)butenoic Acid (9a and b). A solution of cytisine (0.190 g, 1 mmole) in toluene (5 mL) was

treated dropwise with maleic anhydride (0.196 g, 2 mmole). The mixture was stirred at room temperature for 24 h. The white precipitate was filtered off and washed with acetone. Yield 0.216 g (75%), mp 215-217°C. Found (%): C 64.65, H 5.91, N 9.79. $C_{15}H_{16}N_2O_4$. Calc. (%): C 62.49, H 5.59, N 9.72.

IR spectrum (KBr, ν/cm^{-1}): 3480, 3435, 3110 (OH), 1715 (C=C–CO_2H), 1660-1620 (N–C=O, C=C), 835, 770, 760, 720 (C=C).

Mass spectrum (EI, 70 eV), *m*/*z* [I_{rel} (%)]: 288 $[M]^+$ (15), 190 (70), 189 (30), 148 (50), 147 (75), 146 (85), 98 (60), 54 (100).

^{1}H NMR (**9a**, *E*-isomer) (DMSO, δ, ppm, J/Hz): 1.93 [2H, br.s, H_2C(8)], 2.50 [1H, br.s, H_aC(9)], 2.88 [1H, d, H_aC(11), ^{2}J = -13.2], 3.12 [1H, br.s, HC(7)], 3.22 [1H, d, H_aC(13), ^{2}J = -13.1], 3.27-3.50 [m, CO_2**H**], 3.60-3.80 [2H, m, H_aC(10), H_eC(13)], 3.88 [1H, d, H_eC(10), ^{2}J = -15.5], 4.48 [1H, d, H_eC(11), ^{2}J = -13.2], 5.84 [1H, d, HC(3′), $^3J_{3'-2'}$ = 11.9], 5.90 [1H, d, HC(2′), $^3J_{2'-3'}$ = 11.9], 6.16 [1H, d, HC(5), $^3J_{5-4}$ = 6.7], 6.21 [1H, d, HC(3), $^3J_{3-4}$ = 7], 7.27-7.37 [1H, m, HC(4)].

^{1}H NMR (**9b**, *Z*-isomer) (DMSO, δ, ppm, J/Hz): 1.93 [2H, br.s, H_2C(8)], 2.50 [1H, br.s, H_aC(9)], 2.91 [1H, d, H_aC(13), ^{2}J = -13.2], 3.17 [1H, br.s, HC(7)], 3.28-3.50 [2H, m, H_aC(11), CO_2H], 3.65 [3H, m, H_aC(10), H_eC(11), H_eC(10)], 4.31 [1H, d, H_eC(13), ^{2}J = 13.2], 5.92 [1H, d, HC(3′), $^2J_{3'-2'}$ = 11.9], 6.16 [1H, d, HC(5), $^2J_{5-4}$ 6.7], 6.23 [1H, d, HC(3), $^3J_{3-4}$ = 7], 6.49 [1H, d, HC(2′), $^2J_{2'-3'}$ = 11.9], 7.27-7.37 [1H, m, HC(4)].

The work was financed by the Russian Basic Research Foundation (Grant No. 00-15-973225).

REFERENCES

1. M. D. Mashkovskii, *Medicinal Preparations* [in Russian], Meditsina, Moscow (1998), Vol. 1, p. 127.
2. O. A. Pukhlyakova, T. V. Khakimova, N. Z. Baibulatova, V. A. Dokichev, and M. S. Yunusov, in: Abstracts of Papers of the Youth Scientific School of Organic Chemistry, Ekaterinburg, 1-5 May, 2000, p. 296.
3. O. A. Pukhlyakova, N. Z., Baibulatova, I. O. Maidanova, T. V. Khakimova, V. A. Dokichev, and M. S. Yunusov, *Zh. Org. Khim.*, **36**, 1404 (2000).
4. A. S. Sadykov, Kh. A. Aslanov, and Yu. K. Kushmuradov, *Quinolizidine Alkaloids* [in Russian], Nauka, Moscow (1975), p. 64.
5. A. S. Sadykov, Kh. A. Aslanov, and Yu. K. Kushmuradov, *Quinolizidine Alkaloids* [in Russian], Nauka, Moscow (1975), p. 54.
6. O. M. Kuznetsov, R. R. Akhmetvaleev, N. S. Vostrikov, and M. S. Miftakhov, *Izv. Akad. Nauk, Ser. Khim.*, 1027 (1996).
7. R. R. Akhmetvaleev, L. R. Imaeva, T. A. Belogaeva, and M. S. Miftakhov, *Izv. Akad. Nauk, Ser. Khim.*, 1699 (1997).
8. O. A. Nurkenov, A. M. Gazaliev, and B. Ibragimov, *Zh. Org. Khim.*, **66**, No. 2, 1212 (1996).
9. A. M. Gazaliev and K. M. Turdybekov, *Zh. Org. Khim.*, **62**, No. 2, 456 (1992).
10. O. A. Nurkenov, A. M. Gazaliev, and B. Ibragimov, *Zh. Org. Khim.*, **68**, No. 2, 328 (1998).
11. O. A. Subbotin and N. M. Sergeev, *Anal. Chem.*, **48**, 545 (1976).
12. I. K. O'Neill and M. A. Pringuer, *Org. Magn. Reson.*, **6**, 398 (1974).
13. T. T. Omarov, *Conformational Effects of Nitrogeneous Heterocycles* [in Russian], Nauka, Alma-Ata (1988), p. 81.
14. F. A. Alimirzoev, V. P. Lezina, and A. U. Stepanyants, *Khim. Geterotsikl. Soedin.*, No. 9, 1255 (1986).
15. I. A. Primukhamedov, Kh. A. Aslanov, and A. S. Sadykov, *Uzb. Khim. Zh.*, No. 4, 57 (1969).
16. R. A. Shaimardanov, S. Iskandarov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 383 (1971).
17. I. I. Chervin, Sh. S. Nasibov, V. F. Rudchenko, V. G. Stamburg, and R. G. Kostyanovskii, *Izv. Akad. Nauk, Ser. Khim.*, 544 (1981).
18. A. V. Patel, G. Blunden, and T. A. Grabb, *Magn. Reson. Chem.*, **29**, 794 (1991).
19. N. L. Allinger, *J. Am. Chem. Soc.*, **99**, 8127 (1977).
20. H. Fritz and T. Winkler, *Helv. Chem. Acta*, **59**, 903 (1976).
21. R. Glaser, M. A. Bernstein, and A. Balan, *Magn. Reson. Chem.*, **29**, 766 (1991).