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SYNTHESIS AND STRUCTURE OF HYDRAZONE DERIVATIVES OF HARMINE

Abstract. The present paper deals with chemical synthesis based on 8-acetylharmine. It was established that interaction of 8-acetylharmine with hydrazine hydrate produces (*E*)-8-(1-hydrazonoethyl)-7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole in a yield of 69%. It was shown, that reaction of (*E*)-8-(1-hydrazonoethyl)-7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole with functionally substituted aromatic aldehydes (anisaldehyde, 2-fluorobenzaldehyde, 2,4- dimethoxybenzaldehyde) by boiling in methanol leads to the formation of the corresponding *N*-arylidenehydrazones with 56-82% yields. The structure of the synthesized compounds was characterized on the basis of one-dimensional ^{1}H, ^{13}C and DEPT NMR methods, as well as data from two-dimensional COSY, HMQC, and HMBC spectra, elemental analysis and mass spectra. Correlation spectroscopic methods provided information for identification of three bond protons-protons and one bond protons-carbons correlations COSY (^{1}H -^{1}H) and HMQC (^{1}H-^{13}C, ^{1}H-^{15}N). Homo- and heteronuclear interactions, confirming the structures of new derivatives of harmine, are determined. The use of modern physicochemical and spectroscopic research methods in the present work allowed reliable and unambiguous characterization of the structure and properties of the obtained compounds.

Key words: harmine, hydrazone derivative of 8-acetylharmine, N-arylidenehydrazones, ^{1}H-, ^{13}C-NMR spectra, two-dimensional NMR spectra.

Introduction. It is well known that modification of alkaloids gives a wide opportunity to obtain compounds whose biological activity spectrum is significantly expanded and modified in comparison with the starting substance.

In order to search for new synthons and biologically active compounds and to find effective drugs of a given spectrum of activity, a chemical modification of the alkaloid harmine was carried out [1]. Alkaloid of β-carboline type harmine **1** is contained in the plant *Peganum harmala* L., widely distributed on the territory of Republic of Kazakhstan.

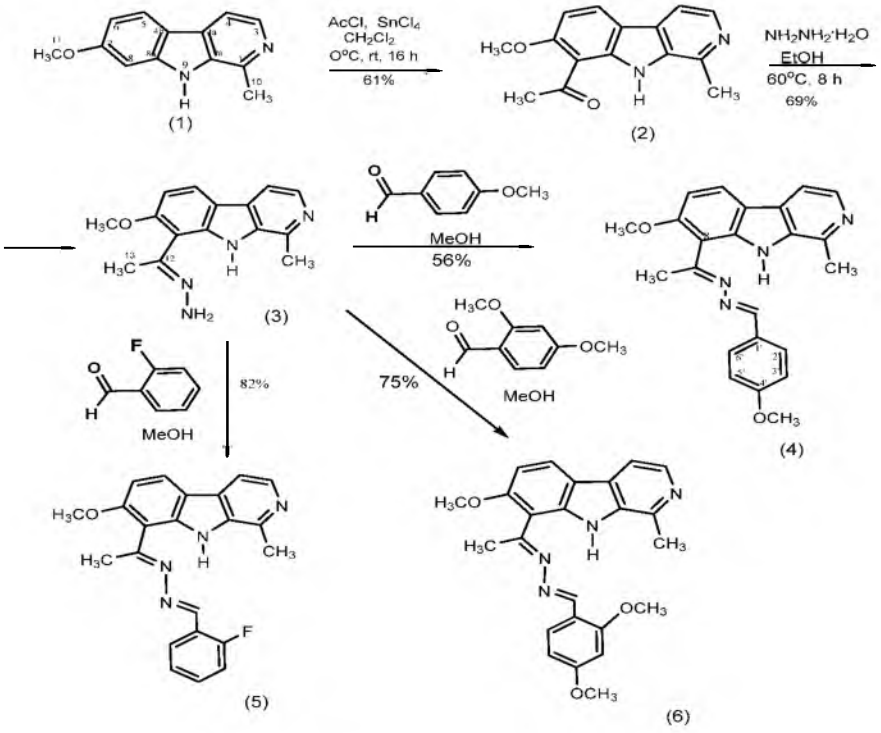
According to the literature data, the indole alkaloid harmine **1** has a wide spectrum of pharmacological activity. Harmine affects the central nervous system, showing neuroprotective activity in neurological diseases. Derivatives of harmine have neurotropic activity, and its water-soluble form, harmine hydrochloride, has antidepressant, antihypoxic (hypobaric hypoxia) and anti-Parkinson effects [1-6].

Moreover, it should be noted that in recent years, the synthesis of hydrazones has attracted great attention not only because of the significant biological activity of the target compounds, but also because the possible synthesis of various heterocycles based on them, including energy-intensive materials.

In this regard, our aim was to continue research on the transformation of the available alkaloid harmine in order to obtain new biologically active compounds.

Experimental part. Earlier, we published effective methods for the synthesis of derivatives of β-carboline alkaloids 8-formylharmine and 8-acetylharmine. By the condensation of 8-acetylharmine **2** with aromatic aldehydes the corresponding chalcones were synthesized, the reaction of which with hydrazine hydrate in acetic acid resulted in 3-substituted 1-acetylpyrazolines [7-11].

In continuation of our work, new derivatives of the alkaloid harmine **1** were synthesized; on the basis of 8-acetylharmine **2**, 8-acetylhydrazone harmine **3** was synthesized and a number of *N*-arylidenehydrazones harmine **4-6** were obtained with a yield of 56-82% (scheme 1).



The structure of the synthesized compounds was characterized by the complex of physicochemical methods: IR, UV, one-dimensional NMR ^{1}H, ^{13}C and DEPT and two-dimensional COSY spectroscopy (^{1}H -^{1}H), HMQC, HMBC (^{1}H-^{13}C, and ^{1}H-^{15}N), mass spectrometry and elemental analysis data.

Materials and research methods. The ^{1}H and ^{13}C NMR spectra were recorded on a JEOL JNM-ECZR 500 MHz spectrometer (500 MHz ^{1}H and 125 MHz ^{13}C). The ^{19}F NMR spectrum of compound **5** was recorded on a JEOL JNM-ECZR 500 MHz spectrometer (282 MHz) in $CDCl_3$. The ^{15}N NMR spectra were obtained on a JEOL JNM-ECZR 500 MHz (60.84 MHz) in CD_3OD using CH_3NO, as monitor sample δ_N 167,6 ppm.

Different types of proton-proton and carbon-proton correlation spectroscopy were used to assign signals in the NMR spectra (COSY, DEPT, HMBC, HMQC). High-resolution mass spectra were recorded on a DFS Thermo Scientific mass spectrometer, evaporator's temperature 150-240 °C, EI ionization (70 eV). Melting points were determined on Opti Melt apparatus. The reaction progress was monitored by TLC method on Silufol UV-254 plates. For the detection of alkaloids derivatives the Dragendorff's reagent was used. The reaction products were isolated by column chromatography on Al_2O_3 (stage II act.).

Results of the study. We have established that the interaction of 8-acetylharmine **2** with an excessive amount of hydrazine hydrate in ethanol leads to the formation of (*E*)-8-(1-hydrazonoethyl)-7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole **3**, yield 69%, composition $C_{15}H_{16}N_4O$, melting point 207-209 °C, $[\alpha]^{24}_D$ -187.5 (*c* 0.16; $CHCl_3$).

N-arylidenehydrazones of harmine **4-6** were prepared (yield 65-83%) starting from (*E*)-8-(1-hydrazonoethyl)-7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole **3** which easily reacted with functionally substituted aromatic aldehydes (anisaldehyde, 2-fluorobenzaldehyde, 2,4-dimethoxybenzaldehyde).

The IR-spectrum of compounds **3–6** contain intense stretching bands at 3327–3220 cm^{-1}, which belong to the (–NH) group, and at 3178–2827 cm^{-1} (C–H aromatic and methoxy groups). In the spectra of all compounds, a set of absorption bands was observed in the region of 1617–1606, and 1569–1418 cm^{-1}, corresponding to the presence of aromatic groups in the structure (C=N) and (C=C). The bending vibrations of the C=N-N groups correspond to bands 1293–1202 and 1113 cm^{-1}.

In the ^{1}H NMR spectrum of (*E*)-8-(1-hydrazonoethyl)-7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole **3**, singlet signals were observed in the region of δ 2.71 and 2.12 ppm, corresponding to proton signals of the methyl groups at C-1 and C-12. Signals of protons of the methoxy group at C-7 were observed in the region of δ 3.86 ppm in a form of singlet. The proton signals H-3, H-4, H-5, H-6 of the β-carboline core appear at δ 8.15, 7.81, 8.12 and 7.04 ppm, with coupling of 5.8; 5.8; 8.2; 8.2 Hz, respectively. The characteristic signal of NH_2 groups was observed in the low field in the region of δ 8.03 and 8.05 ppm. The proton signal of the N-H group of the pyrrole ring was observed in the low magnetic field at δ 10.51 ppm.

The ^{13}C NMR spectrum of compound **3** contained 6 singlet signals at 116.47, 123.36, 135.64, 138.67, 141.58, 156.81 ppm, characteristic for carbon atoms C-4a and C-4b, C-9a, C-8a, C- 1, C-7, as well as 5 doublet signals at δ 105.00, 105.82, 129.02, 137.24 ppm related to carbon atoms C-6, C-8, C-4, C-5, C-3, respectively. The signals of carbon atoms related to CH_3CN, $-CH_3$, $-OCH_3$, were observed at δ 18.51, 21.94, 55.55 ppm, in the form of quartets. The carbon atom C=N appears as a singlet at δ 145.95 ppm.

For assignment of all ^{1}H and ^{13}C NMR signals, a number of two-dimensional spectroscopic methods were used: ^{1}H–^{1}H COSY, ^{1}H–^{13}C HSQC, ^{1}H–^{13}C HMBC, and ^{1}H–^{15}N HMBC.

The ^{1}H and ^{13}C NMR spectra of synthesized derivatives of harmine **4-6** contained a set of characteristic signals of protons and carbon atoms of the β-carboline core and the corresponding substituent. The proton CH= of side chain in the ^{1}H NMR spectrum of compounds **4-6** resonated as a broadened singlet in the region of δ 8.73-8.32 ppm. Signals, characteristic for the protons of the aromatic ring H-3'-5' appeared at δ 6.18-8.69 ppm, respectively. The characteristic signals of carbon atoms in the ^{13}C NMR spectra belonging to $-CH_3C=N$, $-CH_3$, $(-OCH_3)$, $(-OCH_3)_2$ groups occurred in the regions of δ 19.84-19.94, 20.21-20.42, 55.56-56.43 ppm, respectively, as quartets. Doublet (d) signal related to the CH=N substituent was observed at δ 150.43-157.20 ppm. The singlet signal of the -C=N group in the C-8 substituent shifted to the low magnetic field relative to the location in the spectrum of hydrazone **3** and were detected at δ 163.59-167.68 ppm.

The correct assignment of signals in the ^{1}H NMR spectrum of compound **3** confirm the two-dimensional ^{1}H–^{1}H COSY correlation spectra (Fig. 1).

For compound **3**, the ^{1}H–^{1}H COSY spectrum shows the spin-spin correlation between the protons of methine groups: H-3 and H-4 of the pyridine ring with a cross peak of 8.15, 7.81 ppm (doublets with J = 5.8 Hz) and between H-5 and H-6 of the aromatic ring with the correlation of signals at δ 8.12, 7.04 ppm (J coupling of 8.2 Hz).

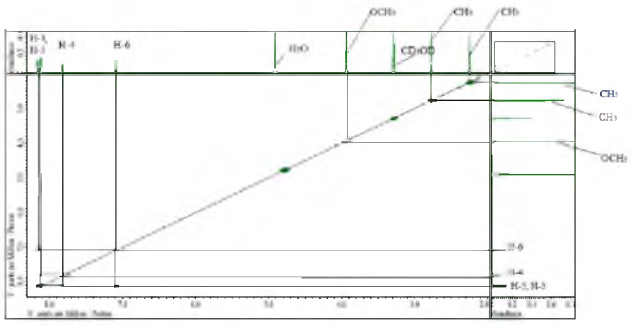


Figure 1 - Two-dimensional ^{1}H-^{1}H COSY spectrum of compound **3**

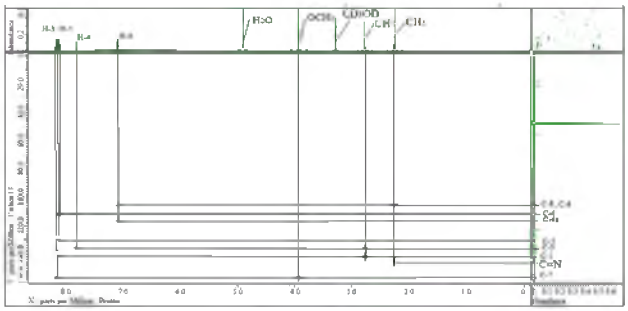


Figure 2 - Two-dimensional spectrum HMBC (^{1}H-^{13}C) of compound **3**

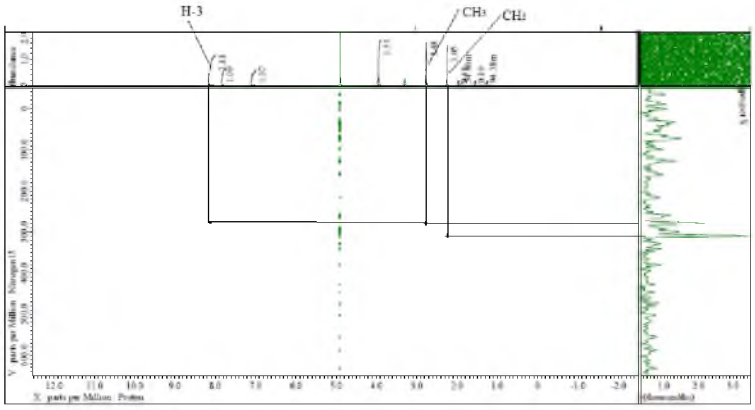


Figure 3 - Two-dimensional spectrum HMBC (^{1}H-^{15}N) of compound **3**

The assignment of signals in the ^{15}N NMR spectra was carried out according to the two-dimensional spectrum of the inverse correlation of ^{1}H–^{15}N on the long-range interactions (HMBC). To assign the chemical shifts of carbon atoms that are not related to hydrogen atoms, heteronuclear correlation methods for long-range bonds were applied: ^{1}H–^{13}C HMBC (Fig. 2) and ^{1}H–^{15}N HMBC (Fig. 3) [19]. With the help of the correlation spectra for long-range bonds all carbon atoms that are not connected with hydrogen atoms in the molecule were uniquely determined, thereby completely confirming the structure of the obtained compounds **3-6**.

The ^{1}H–^{13}C HMBC showed correlation peaks of the CH_3 protons (C-13) with C-8 and C=N atoms. CH_3 protons (C-10) interacted with atoms C-1 and C-3. Protons of OCH_3 (C-11) correlated with the C-7 atom. This experiment confirmed the assignment of the methyl groups.

An analysis of the ^{1}H–^{15}N HMBC spectra showed that the CH_3 proton (C-13) (δ 2.12 ppm), showed correlation with the nitrogen atom of the group C=N at 310 ppm. Proton H-3 (doublet, δ 8.15 ppm), and the CH_3 protons (C-10) (δ 2.71 ppm), showed interaction with a nitrogen atom in position 2 of the pyridine ring (δ_N 280 ppm).

All of these data suggest that the synthesized compound has the following structure (figure 4).

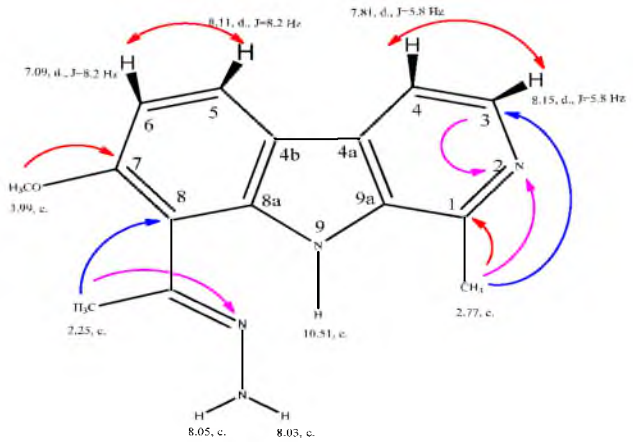


Figure 4 - The main correlations in the ^{1}H-^{13}C and ^{1}H-^{15}N HMBC spectra of compound **3**

Experimental part. (*E*)-8-(1-hydrazonoethyl)-7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole (3). Solution of 0.5 g (1.96 mol) 8-acetylharmine **2** in 25 ml of ethanol was stirred, and meanwhile 2.94 g (0.06 mol) of hydrazine hydrate was added dropwise in excess. The reaction mixture was stirred for 7-8 hours at a temperature of 60 °C. The precipitate formed was filtered and recrystallized from EtOH. Yield 69%, yellow paurocrystalline powder, melting point 207-209 °C, $[\alpha]^{24}_{D}$ -187.5 (*c* 0.16; $CHCl_3$). UV-spectrum (EtOH), λ_{max}/nm (log ε): 213 (2.85), 243 (2.99), 302 (2.66), 328 (2.22), 341 (2.17). IR-spectrum (KBr, ν, cm^{-1}): 3327, 3220, (-NH), 3170, 3096, 2890, 2827 (-C-H), 2983, 2927, 2915, (-OCH_3 of phenyl fragment), 1617 (-C=N), 1569, 1446, 1418 (-C-C), 1293, 1222, 1202 (-C=N-N), 1113 (-N-N).

^{1}H NMR spectrum (500 MHz, DMSO, δ, ppm, *J*/Hz): 2.12 (3H, s, CH_3CN), 2.71 (3H, s, CH_3), 3.86 (3H, s, OCH_3), 7.04 (1H, d, *J*=8.2, H-6), 7.81 (1H, d, J=5.8, H-4), 8.03, 8.05 (2H, s, NH_2), 8.12 (1H, d, *J*=8.2, H-5), 8.15 (1H, d, *J*=5.8, H-3), 10.51 (1H, br. s, NH). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): s. 141.58 (C-1); d. 137.24 (C-3); d. 112.1 (C-4); s. 116.47 (C-4a); s. 129.02 (C-4b); d. 123.31 (C-5); d. 105.0 (C-6); s. 156.81 (C-7); s. 105.82 (C-8); s. 138.67 (C-8a); s. 135.64 (C-9a); q. 18.51 (CH_3C=N); q. 55.55 (-OCH_3); q. 21.94 (-CH_3); s. 145.95 (C=N). Mass-spectrum, *m/z* (I_{rel}, %): 277 (100), 308 (37), 237 (22), 278 (18), 236 (15). Found, *m/z*: 268.1319 $[M]^+$. $C_{15}H_{16}N_4O$. Calculated, *m/z*: 268.1298. Elemental analysis: found, %: C 69.10; H 7.17; N 17.8. $C_{15}H_{16}N_4O$. Calculated, %: C 67.16; H 7.00; N 17.87.

7-Methoxy-8-((*E*)-1-((*E*)-(4-methoxybenzylidene)hydrazono)ethyl)-1-methyl-9*H*-pyrido[3,4 *b*]indole (4). To a solution of 0.1 g (0.37 mol) of (*E*)-8-(1-hydrazonoethyl)-7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole **3** in 10 ml of methanol, while stirring 0.151 g (1.12 mol) of anisaldehyde was added dropwise in 5 ml of methanol. The reaction mixture was stirred for 4 hours at 60-65 °C. The precipitate formed was filtered off and recrystallized from ethanol. $C_{23}H_{22}N_4O_2$, yield 56%, melting point 171-172 °C, $[\alpha]^{24}_D$ +250 (*c* 0.16; $CHCl_3$). UV-spectrum (EtOH, λ_{max}/nm (log ε): 215 (2.78), 238 (2.82), 305 (2.74). IR-spectrum (KBr, ν, cm^{-1}): 3235 (-NH), 3006, 2841 (-C-H), 2964, 2927, (-OCH_3 of phenyl fragment), 1618, 1605 (-C=N), 1572, 1513, 1462, 1424 (-C-C), 1293, 1249 (-C=N-N), 1175 (-N-N).

^{1}H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 2.72, (3H, s, CH_3CN), 2.79 (3H, s, -CH_3), 3.89 (3H, s, -OCH_3), 4,00 (3H, s, -OCH_3), 6,96 (1H, d, *J*=8.7, H-6), 6.99 (1H, q, *J*=6.8, H-3'), 7.01 (1H, q, *J*=6.8, H-5'), 7.73 ppm (1H, d, *J*=5.3, H-4), 7.84 (1H, q, *J*=8.8, H-2'), 7.86 (1H, q, *J*=8.8, H-6'), 8.07 (1H, d, *J*=8.7, H-5), 8.32 (1H, d, *J*=5.3, H-3), 8.32 (1H, br. s, H-16), 10.51 (1H, br. s, NH). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): s. 141.6 (C-1); d. 139.0 (C-3); d. 112.3 (C-4); s. 116.9 (C-4a); s. 128.14 (C-4b); d. 124.29 (C-5); d. 105.44 (C-6); s.162.05 (C-7); s. 110.22 (C-8); s. 140.33 (C-8a); s. 134.86 (C-9a); q. 19.84 (CH_3CN); q. 55.56 (OCH_3); q. 56.44 (OCH_3); q. 20.42 (CH_3); s. 167.24 (C=N); d. 157.2 (CH=N); s. 128.1 (C-1'); d. 114.40 (C-3',5'); d. 130.27 (C-2',6'). Mass-spectrum, *m/z* (I_{rel}, %): 355 (100), 356 (22), 386 (20), 387 (8). Found, *m/z*: 386.1739 $[M]^+$. $C_{23}H_{22}N_4O_2$. Calculated, *m/z*: 386.1737. Elemental analysis: found, %: C 71.07; H 6.13; N 14.32. $C_{23}H_{22}N_4O_2$. Calculated, %: C 71.45; H 5.72; N 14.51.

8-((*E*)-1-((*E*)-(2-fluorobenzylidene)hydrazono)ethyl)-7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole (5). To a solution of 0.1 g (0.37 mol) of (*E*)-8-(1-hydrazonoethyl)-7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole **3** in 10 ml of methanol, while stirring 0.092 g (2 mol) of 2-fluorobenzaldehyde was added dropwise in 5 ml of methanol. The reaction mixture was stirred for 4 hours at 60-65 °C. The precipitate formed was filtered and recrystallized from ethanol. Yield 82%, $C_{22}H_{19}N_4OF$, melting point 166-168 °C, $[\alpha]^{24}_D$ +62.5 (*c* 0.16; chloroform). UV-spectrum (EtOH), λ_{max}/nm (log ε): 209 (3.03), 245 (3.08), 300 (2.87), 342 (2.69) nm. IR-spectrum (KBr, ν, cm^{-1}): 3274 (-NH), 3044, 2840 (-C-H), 2997, 2977 (-OCH_3 of phenyl fragment), 1622, 1604 (-C=N), 1577, 1484, 1459 (-C-C), 1295, 1283 (-C=N-N), 1236 (-C-F), 1170 (-N-N). ^{1}H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 2.72, (3H, s, CH_3CN), 2.81 (3H, s, CH_3), 4,01 (3H, s, OCH_3), 6,97 (1H, d, *J*=8.7, H-6), 7.16 (1H, ddd, *J*=10.3, 8.4, 0.9, H-3'), 7.27 (1H, td, *J*=7.6, 0.9, H-5'), 7.46 (1H, dddd, *J*=8.4, 7.6, 5.4, 1.6, H-4'), 7.74 (1H, d, *J*=5.4, H-4), 8.09 (1H, d, *J*=8.7, H-5), 8.19 (1H, td, *J*=7.6, 1.6, H-6'), 8.34 (1H, d, *J*=5.4, H-3), 8.73 (1H, br.s, H-16), 10.53 (1H, br.s, NH). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): s.141.6 (C-1); d. 139.0 (C-3); d. 112.3 (C-4); s. 116.97 (C-4a); s. 128.20 (C-4b); d. 124.61 (C-5); d. 105.47 (C-6); s. 160.10 (C-7); s. 109.94 (C-8); s. 140.40 (C-8a); s. 134.86 (C-9a); q. 19.94 (CH_3CN); q. 20.21 (CH_3); q. 56.43 (OCH_3); s. 167.68 (C=N); d. 150.43 (CH=N); s. 122.49 (C-1', J_F=9.8); s. 162.16 (C-2', J_F=5.2), d. 116.14 (C-3', J_F=2.1); d. 132.60 (C-4', J_F=8.5); d. 124.56 (C-5', J_F=3.8); d. 127.77 (C-6', J_F=2.5). In the ^{19}F NMR spectrum, the only signal of the fluorine phenyl fragment of the compound (E)-1-(2-fluorophenyl)hydrazone)ethyl)-7-methoxy-1-methyl-9H-pyrido[3,4-b]indole-8-yl **5** was observed. Mass spectrum, *m/z* (I_{rel}, %): 343 (100), 374 (58), 344 (23), 237 (21), 375 (15). Found, *m/z*: 374.1537 $[M]^+$. $C_{22}H_{19}FN_4O$. Calculated, *m/z*: 374.1535. Elemental analysis: found, %: C 69.61; H 5.61; N 14.40. $C_{22}H_{19}FN_4O$. Calculated, %: C 70.47; H 5.11; N 14.96.

8-((*E*)-1-((*E*)-(2,4-dimethoxybenzylidene)hydrazono)ethyl)-7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*]indole (6). To a solution of 0.15 g (0.56 mol) of (*E*)-8-(1-hydrazonoethyl)-7-methoxy-1-methyl-9*H*-pyrido[3,4-*b*] indole **3** in 20 ml of methanol 0.186 g (1.12 mol) of 2,4-dimethoxybenzaldehyde was added

dropwise with stirring in 5 ml of methanol. The reaction mixture was stirred for 4 hours at a temperature of 60-65 °C. The precipitate formed was filtered and recrystallized from ethanol. Yield 75%, $C_{24}H_{24}N_4O_3$, $[\alpha]^{24}_D$ +125 (*c* 0.16; chloroform). UV-spectrum (EtOH, λ_{max}/nm (log ε): 216 (2.78), 236 (3.26), 293 (2.26), 317 (2.17). IR-spectrum (KBr, ν, cm^{-1}): 3220 (-NH), 3178, 3107, 3004, 2851, 2837 (-C-H), 2970, 2926 (-OCH_3 of phenyl fragment), 1623, 1606 (-C=N), 1570, 1462, 1421 (-C-C), 1290, 1271, 1226 (-C=N-N), 1173 (-N-N).

^{1}H NMR spectrum (500 MHz, $CDCl_3$, δ, ppm, *J*/Hz): 2.54, (3H, s, CH_3CN); 2.68 (3H, s, -CH_3); 3.70 (3H, s, -OCH_3); 3.71 (3H, s, -OCH_3); 3.95 (3H, s, OCH_3); 6.18 (1H, dd, *J* = 8.7, H-3'), 6.32 (1H, d, *J* = 8.8, H-6'), 6,94 (1H, d, *J*=8.7, H-6); 7.73 (1H, d, *J* = 5.3, H-4), 8.04 (1H, d, *J* = 8.7, H-5), 8.32 (1H, d, *J* = 5.3, H-3), 8.69 (1H, d, *J* = 6.8, H-5'), 8.76 (1H, br. s, H-16), 10.56 (1H, br. s, NH). ^{13}C NMR spectrum (125 MHz, $CDCl_3$, δ, ppm): s.129.1 (C-1'); d.139.28 (C-3); d.112.43 (C-4); s.115.49 (C-4a); s.117.07 (C-4b); d.123.31 (C-5); d.105.34 (C-6); s.162.34 (C-7); s.110.60 (C-8); s.141.73 (C-8a); s.135.65 (C-9a); q.24.33 (CH_3CN); q.56.40 (OCH_3); q.55.57 (OCH_3); q.56.52 (OCH_3); q.20.31 (CH_3); d.98.39 (C-6'); d.28.52 (C-3',5'); d.155.01 (CH=N); s.163.59 (C=N). Mass spectrum, *m/z* (I_{rel}, %): 385 (100), 416 (32), 386 (26), 237 (11), 417 (9). Found, *m/z*: 416.1843 $[M]^+$. $C_{24}H_{24}N_4O_3$. Calculated, *m/z*: 416.1840. Elemental analysis: found, %: C 68.99; H 6.34; N 13.03. $C_{24}H_{24}N_4O_3$. Calculated, %: C 69.21; H 5.82; N 13.45.

In conclusion, new methods for the preparation of harmine derivatives substituted at position C-8 were elaborated which allow subsequent modification of 8-acetylharmine to new *N*-arylidenehydrazones of harmine, the molecular structure of which was established on the basis of elemental analysis and spectral data (IR-, UV-, ^{1}H-, ^{13}C-, ^{19}F-, ^{15}N- NMR).

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ГАРМИН ГИДРАЗОН ТУЫНДЫЛАРЫНЫҢ СИНТЕЗІ ЖӘНЕ ҚҰРЫЛЫСЫ

Аннотация. Алкалоидтардың молекулаларын түрлендіру биологиялық белсенділік спектрі бастапқы затпен салыстырғанда айтарлықтай кеңейетін әрі түрі өзгеретін қосылыстарды алуға кең мүмкіндік беретіні белгілі.

Жаңа синтондар мен биологиялық белсенді қосылыстарды іздеу және олардың негізінде әсер ету спектрі белгіленген тиімді дәрілік құралдарды іздестіру мақсатында гармин алкалоидының химиялық түрлендірілуі жүргізілді. β-карболин типтес гармин алкалоиды Оңтүстік Қазақстанда кеңінен таралған кәдімгі адыраспан (*Peganum harmala* L.) шикізатының құрамында кездеседі.

Әдеби деректерге сәйкес гармин индолды алкалоиды кең фармакологиялық белсенділік спектріне ие. Гармин нейрологиялық аурулар кезінде нейропротекторлық белсенділік танытып, орталық жүйке жүйесіне әсер етеді, А моноаминоксидазаны тежейді. Гармин туындылары микробқа қарсы белсенділікке ие, ал оның суда еритін түрі – гармин гидрохлоридінің депрессияға, гипоксияға (гипобариялық гипоксия) және паркинсонизмге қарсы әсері бар.

Соңғы жылдары гидразондар синтезі нысаналы қосылыстардың айтарлықтай биологиялық белсенділігімен ғана емес, олардың негізінде әртүрлі гетероциклдерді, оның ішінде энергия сыйымды материалдарды синтездеу мүмкіндігімен де назар аударатынын атап өткен жөн.

Осыған байланысты біздің тарапымыздан жаңа биологиялық белсенді қосылыстар алу мақсатында қолжетімді гармин алкалоидын трансформациялау жөніндегі зерттеулер жалғасуда.

Жұмыста 8-ацетилгармин молекуласы негізіндегі синтездің нәтижелері ұсынылған. 8-ацетилгарминнің гидразин гидратымен өзара әрекеттесуі кезінде шығымы 69% (*E*)-8-(1-гидразоноэтил)-7-метокси-1-метил-9*H*-пиридо[3,4-*b*]индол алынды. Метанолда қайнатқан кезде (*E*)-8-(1-гидразоноэтил)-7-метокси-1-метил-9*H*-пиридо[3,4-*b*]индолдың функционалдық түрде алмастырылған ароматикалық альдегидтермен (анис альдегиді, 2-фторбензальдегид, 2,4-диметоксибензальдегид) реакциясы шығымдары 56-82% тиісті N-арилиденгидразондардың туындауына алып келетіні көрсетілді. Синтезделген қосылыстардың құрылысы

бір өлшемді ^{1}H, ^{13}C және DEPT ЯМР әдістерімен, сондай-ақ COSY, HMQC, HMBC екі өлшемді спектрлерінің, элементтік талдау және масс-спектрлердің деректерімен сипатталған. Протондардың үш байланыс арқылы протондармен корреляция схемалары және протондардың COSY (^{1}H-^{1}H) және HMQC (^{1}H-^{13}C, ^{1}H-^{15}N) бір байланыс арқылы көміртекті атомдармен корреляция схемалары ұсынылған, гарминнің жаңа туындыларының құрылымдарын растайтын гомо және гетероядролық өзара әрекеттесулер анықталды. Жұмыста заманауи физика-химиялық және спектроскопиялық зерттеу әдістерін қолдану алынған қосылыстардың құрылысы мен қасиеттерін сенімді әрі бірмағыналы сипаттауға мүмкіндік берді.

Түйін сөздер: гармин, 8-ацетилгармин гидразонтуындысы, N-арилиденгидразон туындылары, ЯМР спектрлер, екі өлшемді спектрлері.

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СИНТЕЗ И СТРОЕНИЕ ГИДРАЗОНПРОИЗВОДНЫХ ГАРМИНА

Аннотация. Известно, что модификация молекул алкалоидов дает широкую возможность получения соединений, спектр биологической активности которых значительно расширяется и видоизменяется по сравнению с исходным веществом.

С целью поиска новых синтонов и биологически активных соединений и изыскания на их основе эффективных лекарственных средств заданного спектра действия проведена химическая модификация алкалоида гармина. Алкалоид β-карболинового типа гармин содержится в сырье гармалы обыкновенной (*Peganum harmala* L.), широко распространённом в Южном Казахстане.

Согласно литературным данным, индольный алкалоид гармин обладает широким спектром фармакологической активности. Гармин оказывает влияние на центральную нервную систему, проявляя нейропротекторную активность при нейрологических заболеваниях, ингибирует моноаминоксидазу А. Производные гармина обладают антимикробной активностью, а его водорастворимая форма –гидрохлорид гармина обладает антидепрессивным, противогипоксическим (гипобарическая гипоксия) и антипаркинсоническим действием.

Следует отметить, что в последние годы синтез гидразонов привлекает внимание не только значительной биологической активностью целевых соединений, но и возможностью синтеза на их основе разнообразных гетероциклов, в том числе энергоемких материалов.

В связи с этим нами продолжаются исследования по трансформации доступного алкалоида гармина с целью получения новых биологически активных соединений.

В работе представлены результаты синтеза на основе молекулы 8-ацетилгармина. При взаимодействии 8-ацетилгармина с гидразин гидратом получено (*E*)-8-(1-гидразоноэтил)-7-метокси-1-метил-9*H*-пиридо [3,4-*b*]индол с выходом 69%. Показано, что реакция (*E*)-8-(1-гидразоноэтил)-7-метокси-1-метил-9*H*-пиридо[3,4-*b*]индола с функционально замещёнными ароматическими альдегидами (анисовый альдегид, 2-фторбензальдегид, 2,4-диметоксибензальдегид) при кипячении в метаноле приводит к образованию соответствующих N-арилиденгидразонов с выходами 56-82%. Строение синтезированных соединений охарактеризованы методами ЯМР одномерной ^{1}H, ^{13}C и DEPT, а также данными двумерных спектров COSY, HMQC, HMBC, элементного анализа и масс-спектров. Представлены схемы корреляций протонов с протонами через три связи и схемы корреляций протонов с углеродными атомами через одну связи COSY (^{1}H -^{1}H) и HMQC (^{1}H-^{13}C, ^{1}H-^{15}N), установлены гомо- и гетероядерные взаимодействия, подтверждающие структуры новых производных гармина. Применение в работе современных физико-химических и спектроскопических методов исследования позволили надежно и однозначно охарактеризовать строение и свойства полученных соединений.

Ключевые слова: гармин, гидразонпроизводное 8-ацетилгармина, N-арилиденгидразоны, ЯМР спектры, двумерные спектры.

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