Synthetic Derivatives of Natural Alkaloid Harmine

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Abstract

The indole alkaloid harmine was extracted from underground part of *Peganum harmala* L. With the purpose of obtaining the new biological active derivatives on base of alkaloid harmine the chemical modification was carried out. The p-toluolsulfochlorid, p-toluolsulfoacid, hydrochloric, sulfuric, nitric acids, dioxide selenium and phthalic anhydride have been chosen as modifiers. For the first time quaternary ammonium salts, derivatives of N-oxide and N (2)-oxyharminiumphthalate harmine are synthesized. The structure of the synthesized compounds is determined by methods of the spectral analysis and X-ray analysis. Antimicrobic and phagocytosis stimulating activities of isolated alkaloids and their derivatives are investigated.

Introduction

Among the renewed sources of biologically active substances the plants, traditionally used in folk and official medicine, have been taken a special place. In flora of Kazakhstan there is totally over 100 species of alkaloid plants having a wide area of distribution in territory of Republic. There are particular groups of plants, which are the most widespread or dominate over greater territories and thereof, are of interest for the chemical and pharmacological study. Such plants which belong to species of *Peganaceae* harmala family, are taking extensive covers in natural flora of region in Kazakhstan`s territory and are being a source of indole and chinasolinic alkaloids. They have been widely applied for treatment of cardiovascular diseases and also can be used as anti-tumor, antibacterial, anticholinesterase, antitussive and psychotropic drugs [1-7].

In a number of indole the alkaloids with tricyclic structure (carbolinic atom) of harmine and its derivatives takes important place and shows the expressed biological activity, and are accessible and convenient for synthesis of new physiologically active substances and effective medical drugs with a wide spectrum of action.

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Experimental

The control of reactions has been carried out by method of thin-layer chromatography on plates of «Sorbfil AF-A». Reagents of qualification «ch» have been used for work. Melting points of individual compounds has been measured on "Boetius". UF-spectra have been taken with spectrophotometer Helios-b V-4.60 in an interval of wavelength 190-500 nm. IR-spectra have been taken with Fourier spectrophotometer Vector - 22 in KBr tablets. ^{1}H and ^{13}C NMR - spectra have been obtained on spectrometers Bruker AC-300 [working frequencies 400.13 (^{1}H) and 125.76 MHz (^{13}C)] and Bruker DRX 500 [working frequencies 500.13 (^{1}H) and 125.76 MHz (^{13}C)] for 5% solutions of CD_3OD or $(CD_3)_2SO$. X-ray experiment have been carried out with diffractometer Bruker P4 (Mo Kα-radiation with graphite monochromator, 2θ/θ-scanning in the field of 2θ <52°).

High-performance liquid chromatography (HPLC) of alkaloids derivatives has been carried out on "Hewlett-Packard Agilent 1100 Ser." with a column in length 4,6x150 mm, filled with phase Sorbax C_{18}-CB with the size of particles 5μм. Mobile phase has been acetonitrile. Detection has been carried out at wave length 224 nm.

Synthesis of N(2)-n-toluene sulfonic harmine chloride (2): 0.03 g (0.14 millimole) harmine (1) has been dissolved in 7 ml methanol and then 0.026 g (0.14 millimole)p-toluene sulfonic chloride has

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been added into the obtained solution. Prepared composition has been mixed at room temperature (25°C) for 16 hours and steamed with rotocione evaporator. The remained weight has been re-crystallized from methanol. White crystal substance (2) has been obtained with m.p. 164-166°C, R_f 0.43 (methanol - chloroform 6:1), yield of 57 %, HPLC 98.91 %.

IR - spectrum: 3416, 3121 (>N-H), 2925 (-C=C-, -C-C-), 1638 (CH_3O), 1463 ($C=N^+$), 1347, 1285, 1123 (SO_2Cl), 1029, 1006 ($C-SO_2$), 814, 797 (S-O), 683, 567 (C-S).

NMR ^1H - spectrum: 2.36 (s., 3H, Ph-CH_3), 3.33 (s., 3H, CH_3), 3.99 (s., 3H, CH_3O), 7.06 (d.d., 1H, H-6, J=2.0, 8.0 Hz,), 7.16 (d., 1H, H-8, J=2 Hz), 7.19 (d., 1H, H-2′), 7.22 (d., 1H, H-6′), 7.73 (d., 1H, H-3′), 7.75 (d., 1H, H-5′), 8.18 (d., 1H, H-4, J=4 Hz), 8.21 (d., 1H, H-5, J=4 Hz), 8.30 (d., 1H, H-3, J=4 Hz).

NMR ^{13}C - spectrum: 134.45 (s., (C-1)), 129.45 (d., (C-3)), 114.38 (d., (C-4)), 124.98 (d., (C-5)), 144.88 (d., (C-6)), 165.06 (s., (C-7)), 90.07 (d., (C-8)), 147.37 (s., (C-8a)), 141.62 (s., (C-9a)), 137.66 (s., (C-4a)), 115.08 (s., (C-4b), 56.29 (q., CH_3O), 21.30 (q., CH_3), 15.88 (q., (Ph-CH_3)), 142.09 (s., (C-1′)), 129.74 (d., (C-2′, C-6′)), 126.84 (d., (C-3′, C-5′)), 135.09 (s., (C-4′)).

Synthesis of N(2)-hydro harmine tozilat (3): 0.03 g (0.14 millimole) harmine **(1)** has been dissolved in 7 ml methanol and 0.024 g (0.14 millimole) of p-toluene sulfonic acid have been added into the obtained solution. Prepared composition has been mixed at room temperature for 11 hours, heated up to 35-40°C and steamed. Residue has been crystallized in methanol. White crystal substance **(3)** has been obtained with m.p. 172-176°C, R_f 0.54 (methanol -chloroform 6:1), yield of 66 %, HPLC 97.48 %.

UF - spectrum: 223, 249, 326 (lg ε 2.34, 2.39, 2.51).

IR - spectrum: 3418, 3120 (>N-H), 2925 (-C=C-, -C-C-), 2713 (N+-H), 1638 (CH_3O), 1461 ($C=N^+$), 1343, 1285, 1223, 1162, 1122 (O=S=O) 1029, 1006 ($C-SO_2^-$), 814, 797 ($S-O^-$), 683, 567 (C-S).

NMR ^1H - spectrum: 2.34 (s., 3H, Ph-CH_3), 2.97 (s., 3H, CH_3), 3.95 (s., 3H, CH_3O), 6.99 (d.d., 1H, H-6, J=2.0, 8.0 Hz), 7.1 (d., 1H, H-8, J=2 Hz), 7.17 (d., 1H, H-2′), 7.19 (d., 1H, H-6′), 7.71 (d., 1H, H-3′), 7.75 (d., 1H, H-5′), 8.07 (d., 1H, J=8 Hz, H-4), 8.09 (d., 1H, H-5, J=6 Hz), 8.17 (d., 1H, H-3, J=6 Hz).

NMR ^{13}C - spectrum: 132.36 (s., (C-1)), 127.41 (d., (C-3)), 112.47 (d., (C-4)), 122.89 (d., (C-5)), 112.85 (d., (C-6)), 162.92 (s., (C-7)), 93.23 (d., (C-8)), 145.33 (s., (C-8a)), 139.59 (s., (C-9a)), 135.45 (s., (C-4a)), 113.04 (s., (C- 4b), 54.49 (q., CH_3O), 21.70 (q., CH_3), 14.21 (q., (Ph-CH_3)), 141.17 (s., (C-1′)), 127.85 (d., (C-2′, C-6′)), 124.85 (d., (C-3′, C-5′)), 133.08 (s., (C-4′)).

Synthesis of hydrochloride harmine (4): 15 g (70.75 millimole) harmine **(1)** have been dissolved in 7 ml methanol and 9,37 ml (3.79 millimole) of concentrated hydrochloric acid have been added into the obtained solution at mixing. White residue has been filtered and dried up. Hydrochloride harmine **(4)** has been obtained with m.p. 272-275°C (decomposition), yield of 99 %, HPLC 99.42 %.

NMR ^1H - spectrum: 2.94 (s., 3H, CH_3), 3.95 (s., 3H, OCH_3), 4.95 (wid.s., 1H, N^+-HCl^-), 7.0 (t., 2H, H-6, H-8, $J_{1/2}$ =2.0, 4.0 Hz), 8.16 (d.d., 3H, H-4, H-3, H-5, J=1.2, 4.5, 5.5 Hz), 11.40 (s., 1H, Ind. N-H).

NMR ^{13}C - spectrum: 134.32 (s., (C-1)), 137.71 (d., (C-3)), 114.32 (d., (C-4)), 124.95 (d., (C-5)), 114.32 (d., (C-6)), 165.04 (s., (C-7)), 95.02 (d., (C-8)), 147.26 (s., (C-8a)), 135.08 (s., (C-9a)), 129.49 (s., (C-4a)), 149.96 (s., (C-4b)), 56.36 (q., (CH_3O)), 15.95 (q., (CH_3)).

Mass spectrum m/z (%): 28 (M^+100), 32 (28.44), 51 (2.34), 63.0 (3.98), 75 (3.85), 77.1 (3.82), 91 (2.36), 101 (3.46), 106 (9.03), 115 (5.29), 127 (3.73), 140 (4.64), 169 (52.89), 183 (73.10), 197 (27.41), 212 (84.63).

Elemental analysis: it has been determined in %: C 73.19; H 5.55; N 13.02. $C_{13}H_{13}N_2OCl$: it has been calculated in %: C 73.21; H 5.50; N 13.05.

Synthesis of bis-hydrate bis [N(2)-harmine] sulfate (5): 0.1 g (0.47 millimole) harmine **(1)** have been dissolved in 7 ml of methanol and 0.035 ml (0.0654 millimole) of sulfuric acid have been added into the obtained solution. Prepared composition has been mixed at room temperature (25°C) for 40 min. White residue has been filtered and filtrate has been steamed in vacuum. Residue has been washed with methanol and dried up. Crystal substance **(5)** has been obtained with m.p. 260-264°C, R_f 0.11 (methanol-chloroform 6:1), yield of 47 %, HPLC 96.3 %.

UF-spectrum: 209 (4.16), 245 (3.88), 327 (3.41).

IR-spectrum: 3418, 3120 (>N-H), 2889 (-C=C-, -C-C-), 2713 (N^+-H), 1648 (CH_3O), 1461 ($C=N^+$), 1330 (SO_4).

NMR ^1H-spectrum: 2.97 (s., 3H, CH_3), 3.93 (s., 3H, CH_3O), 7.03 (d.d., 1H, J = 8.8, 2.1, H-6), 7.15 (d., 1H, J = 2.1, H-8), 8.30 (d.,1H, J = 8.8, H-5), 8.36

(d., 1H, J=5.6, H-4), 8.43 (d, 1H., J=5.6 Hz, H-3), 12.65 (s., 1H, N-H).

NMR ^{13}C-spectrum: 15.83 (к., CH_3), 55.73 (к., CH_3O), 94.42 (d., (C-8)), 112.47 (d., (C-4)), 113.63 (s., (C-4b)), 114.02 (d., (C-6)), 124.51 (d., (C-5)), 128.90 (d., (C-3)), 132.09 (c., (C-4a)), 133.67 (s., (C-9a)), 137.23 (s., (C-1)), 145.40 (s., (C-8a)), 161.68 (d., (C-7)).

X-ray research of compound 5*. For experiment the crystal sample of salt compound 5 with size 0.50 × 0.50 × 0.10 mm has been selected. Monoclinic crystals: a = 6.7389(7), b = 17.9250(9), c = 11.3023(8) Å, β = 104.475(7)°, V = 1321.9(2) Å^3, spatial group $P2_1$, Z = 4, $C_{13}H_{13}N_2O$+ 1/2 SO_4^{-2} + H_2O, d_{cal} = 1.403 g/sm^3, μ = 0.180 mm^{-1}. Intensity 2684 of independent reflections has been measured. The amendment of absorption has not been entered. Structure has been decoded with direct method on program SIR2002 [11]. Specification of structure parameters has been carried out with method of the least squares in full matrix anisotropic approach on program SHELXL-97 [12]. Parameters of the majority of atoms H have been counted in each cycle of specification on coordinates of corresponding carbon atoms (model "rider"). Atoms H at N2 and N9 and also in molecules of water have been localized from difference synthesis, their parameters have been specified isotropically. Final structure specification have been carried on F^2 up to wR_2 = 0.0972, S = 1.04, specified 384 parameters (R = 0.0357 для 2434 F > 4σ).

Synthesis of N-oxide harmine (6): 0.05 g (0.022 millimole) of harmine (1) has been dissolved in 12 ml of methanol and 0.0783 g (0.705 millimole) of dioxide selenium have been added into the obtained solution. The reactionary composition has been mixed for 4 days, residue has been filtered, solvent has been distilled off. Crystal substance (6) has been obtained with m.p. 90-93°C, HPLC 99.0 %.

UF - spectrum: 207, 249, 327 (lgε 2,31, 2,39, 2,51).

IR - spectrum: (KBr, ν, sm^{-1}): 3159 (NH), 2938, 2373 (-C=C-, -C-C-), 1704, 1632, 1576 (CH_3O), 1463, 1442 (C=N<), 1392, 1335, 1282, 1263, 1212, 1143, 1114, 1074, 1030.

NMR ^{1}H - spectrum: 3.01 (3H, s., H-1, >N-CH_3), 3.95 (3H, s., H-7, CH_3O), 6.96 (1H, d., J=8.8 Hz, H-6), 7.12 (1H, d., H-8), 7.98 (1H, d., J=5.6, J=8.8 Hz, H-5), 8.18 (1H, d., J=5.6 Hz, H-3).

Mass spectrum m/z (%): 226 (M^+, 7.93), 213 (39.84), 212 (82.24), 197 (19.56), 169 (51.52), 114 (17.95), 112 (77.02), 96 (51.52), 80 (24.70), 44 (100), 19 (23.06).

Synthesis of N(2)-hydroxy harmine chloride (7): 0.11 g (0.48 millimole) N-oxide harmine (6) has been dissolved in 7 ml of methanol and 0.02 ml (0.72 millimole) hydrochloric acid have been added into the obtained solution. The reactionary composition has been mixed at room temperature (20-25°C) for 22 hours and steamed. Residue has been washed by chloroform with water and dried up. Light yellow crystal substance (7) has been obtained with m.p. 108-111°C, R_f 0.53 (methanol-chloroform 6:1), yield of 72 %, HPLC 97.48 %.

UF - spectrum: 207, 248, 327 (lg ε 2.31, 2.39, 2.51).

IR - spectrum: 3501 (OH), 3131 (NH), 2722 (-C=C-, -C-C-), 1631 (CH_3O), 1463 (C=N^+), 676 (Cl).

NMR ^{1}H - spectrum: 2.46 (s., 1H, OH), 3.01 (s., 3H, CH_3), 3.93 (s., 3H, CH_3O), 7.0 (d.d., 1H, H-6, J=4.4, 9.0 Hz), 7.13 (d., 1H, H-8, J =4 Hz), 8.29 (d., 1H, H-4, J =9 Hz), 8.31 (d., 1H, H-5, J =5.0 Hz), 8.40 (d., 1H, H-3, J=4.0 Hz), 12.9 (s., 1H, Ind. N-H).

NMR ^{13}C - spectrum: 15.87 (q., CH_3), 55.76 (q., CH_3O), 94.42 (d., (C-8)), 112.47 (d., (C-4)), 113.63 (s., (C-4b)), 114.02 (d., (C-6)), 124.51 (d., (C-5)), 136.90 (d., (C-3)), 132.47 (s., (C-4a)), 133.67 (s., (C-9a)), 129.23 (s., (C-1)), 145.40 (s., (C-8a)), 161.68 (s., (C-7)).

Synthesis of N(2)-hydroxy harmine nitrate (8): 0.072 g (0.31 millimole) N-oxide harmine **(6)** has been dissolved in 7 ml of methanol and 0.02 ml (0.47 millimole) of nitric acid have been added into the obtained solution. Prepared composition has been mixed at room temperature (20-25°C) for 40 min. Residue has been filtered, filtrate has been steamed, residue have been washed with methanol and dried up. Crystal substance **(8)** has been obtained with m.p. 284-288°C, R_f 0.71 (methanol-chloroform 6:1), yield of 44.4 %, HPLC 97.0 %.

UF - spectrum: 207, 245, 304, 326 (lg ε 2.31, 2.38, 2.48, 2.51).

IR - spectrum: 3538 (OH), 3110 (NH), 2722 (-C=C-, -C-C-), 1636 (CH_3O), 1462 (C=N^+), 1359 (NO^-_3).

NMR ^{1}H - spectrum: 2.5 (s., 1H, OH), 2.97 (s., 3H, CH_3), 3.95 (s., 3H, CH_3O), 7.05 (d.d., 1H, H-6, J=4, 10 Hz), 7.13 (d., 1H, H-8, J =4 Hz), 8.32 (d., 1H, H-4, J =9 Hz), 8.35-8.39 (d., 1H, H-5, J =4 Hz), 8,45 (d., 1H, H-3, J=5.0 Hz), 12.63 (s., 1H, Ind. N-H).

NMR ^{13}C - spectrum: 129.75 (s., (C-1)), 136.71 (d., (C-3)), 113.32 (d., (C-4)), 124.95 (d., (C-5)),

114.32 (d., (C-6)), 165.04 (s., (C-7)), 94.02 (d., (C-8)), 147.26 (s., (C-8a)), 135.08 (d., (C-9a)), 132.49 (d., (C-4a)), 114.96 (d., (C-4b), 55.36 (q., (CH_3O)), 15.77 (q., (CH_3)).

Synthesis of N (2)-oxyharmine phthalate (9): 0.127 g (0.55 millimole) of N-oxide harmine (6) has been dissolved in 6 ml of methanol and 0.082 g (0.55 millimole) of phthalate anhydride has been added into the obtained solution. The reactionary composition has been mixed at room temperature (20-25°C) for 40 min. Residue has been filtered, filtrate has been steamed, residues have been combined, washed with methanol and dried up. Crystal substance (9) has been obtained with m.p. 260-264°C, R_f 0.10 (methanol-chloroform 6:1), yield of 21 %, HPLC 97.0 %.

IR - spectrum: 3120 (NH), 3081, 2938 (-C=C-, -C-C-), 1880 (C=O), 1539 (CH_3O), 1463 (C=N<), 1212 (N→O).

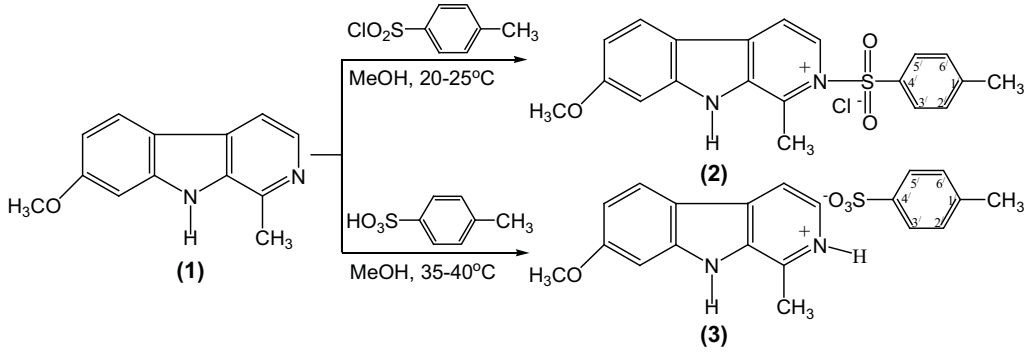
NMR ^{1}H - spectrum: 2.86 (s., 3H, CH_3), 3.91 (s., 3H, CH_3O), 6.95 (d.d., 1H, H-6, J=2.0, 9.0 Hz), 7.08 (d., 1H, H-8, J=2 Hz), 7.51 (d., 1H, H-2′, J=2 Hz), 7.53 (d., 1H, H-5′, J=2 Hz), 7.93 (d., 1H, H-3′, J=2 Hz), 7.95 (d., 1H, H-4′, J=2 Hz), 8.14 (d., 1H, H-4, J=5.0 Hz), 8.19 (d., 1H, H-5, J=8.0 Hz), 8.27 (d., 1H, H-3, J=6 Hz), 12.10 (s., 1H, Ind. N-H).

NMR ^{13}C - spectrum: 130.45 (s., (C-1)), 131.84 (d., (C-3)), 111.40 (d., (C-4)), 123.85 (d., (C-5)), 113.30 (d., (C-6)), 161.81 (s., (C-7)), 94.39 (d., (C-8)), 144.19 (s., (C-8a)), 138.55 (s., (C-9a)), 133.98 (s., (C-4a)), 113.98 (s., (C-4b), 129.10 (s.,(C-1′), (C-6′)), 130.68 (d., (C-2′), (C-5′)), 131.12 (d., (C-3′), (C-4′)), 168.57 (s., (C=O)), 55.57 (q., (CH_3O)), 17.23 (q.,(CH_3)).

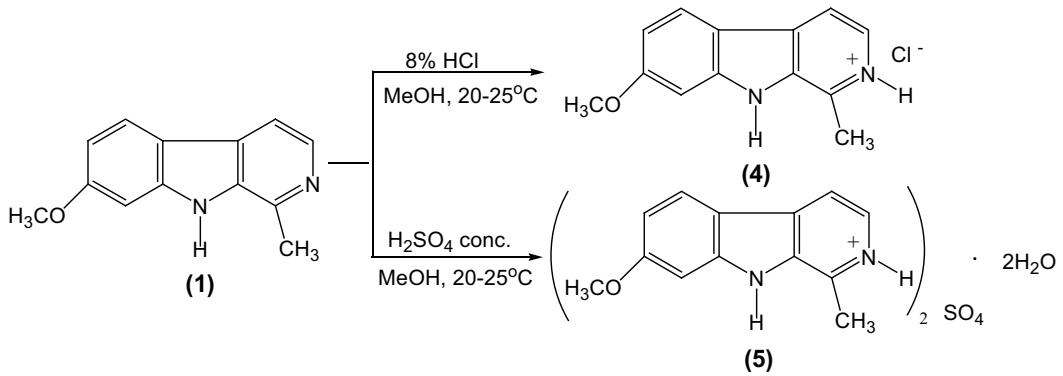
Results and Discussion

With this purpose we have extracted indole alkaloid harmine from spirit extract of Peganum harmala L. roots and investigated its chemical modification. The p-toluene sulfonic acid, p-toluene sulfonic chloride, hydrochloric, sulfuric acids and dioxide selenium have been chosen as modifiers.

It has been determined that bonding of harmine (1) with n-toluene sulfonic chloride and p-toluene sulfonic acid in methanol is due to presence of azomethine atom of nitrogen with formation of N(2)-p-toluene sulfonic harmine chloride **(2)** and N(2)-hydro harmine tozilat **(3)**, accordingly:



Bonding of harmine **(1)** with diluted hydrochloric and sulfuric acids in methanol at room temperature has been coursed in position of atom N(2) and resulted in formation of hydrochloride harmine **(4)** and bis-hydrate bis [N(2)-harmine] sulfate **(5)**:



The spatial structure of molecule of compound **(5)** according to X-ray analysis is showed in figure 1. In an independent part of an elementary cell there were 2 molecules of compound **(5)**, one molecule of SO_4^{-2} and two solvate molecules of H_2O. Most close analogue on structure of compound **(5)** is hydrochloride harmine **(4)** which structure has been studied by method of X-ray analysis in work [8]. The geometry of all three molecules **(5)** (in our case two independent) within the limits of 3s has coincided and close to corresponding average sizes [9]. The analysis of intermolecular correlations has been carried out by program PLATON [10]. Molecules of compound **(5)** are connected by hydrogen bonds with molecules SO_4^{-2} and with solvate molecules of water (figure 2). Parameters of hydrogen bonds are showed in the Table 1. While a molecule of compound **(5)** are put in a pile «side-to-side with shift» due to p…p- correlations with interplane distance 3.36 Å and distance between centers of pentamerous cycles of the next molecules in a pile 3.424 (2) and 3.3.440 (2) Å.

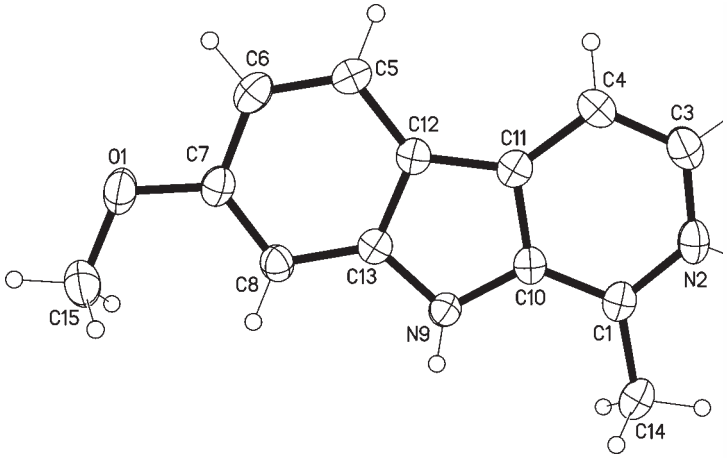


Fig. 1. The spatial structure of compound (5) according to X-ray analysis

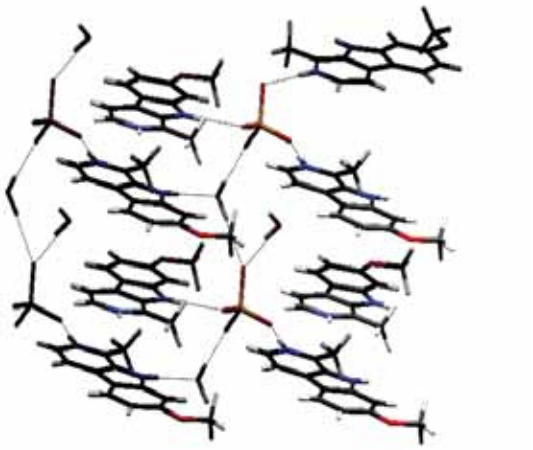


Fig. 2. Fragment of molecules packing of compound (5) in crystal (hydrogen bonds are shown by dotted lines).

Table 1.
Parameters of hydrogen bonds in crystal

№	Hydrogen bond	D-H (Å)	H…A (Å)	D…A (Å)	Angle (°)
1.	N2-H1N...O2S	0.96(5)	1.69(5)	2.654(4)	175(5)
2.	O1R-H1R...O4S	0.89(6)	1.94(7)	2.793(5)	161(7)
3.	N9-H2N...O1R	0.84(4)	1.99(3)	2.806(4)	165(3)
4.	O1R-H2R...O3S	0.89(6)	1.94(6)	2.829(5)	170(5)
5.	O2R-H4R...O3S	0.84(8)	2.19(8)	2.994(6)	160(8)
6.	N9A-H2NA...O1S	0.94(4)	1.88(4)	2.815(3)	169(3)
7.	N2A-H1NA...O3S	0.85(4)	1.90(4)	2.750(4)	176(4)

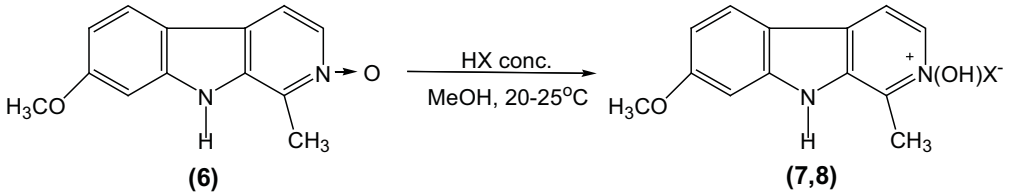
N-oxide harmine **(6)** has been formed due to effect of dioxide selenium on harmine **(1)** in methanol at moderate heating and practically with quantitative yield:

(1) **(6)**

The easy way of reaction and high yield of N-oxide harmine have been found which opens a wide opportunities of synthesis of new biologically active compounds and development of effective medical drugs with a wide spectrum of action on their basis.

The reactions of N-oxide harmine with anhydrides of dicarboxylic acids, hydrochloric and nitric acids were investigated and various derivatives of harmine with the expressed biological activity have been synthesized on their basis for the first time.

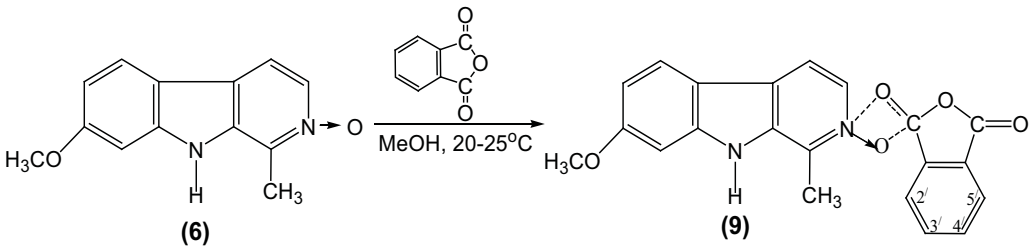
Thus it was determined that bonding of N-oxide harmine **(6)** with hydrochloric and nitric acids passes regiospecifically with formation of N(2)-hydroxy harmine chloride **(7)** and N(2)-hydroxy harmine nitrate **(8)**:



(6) **(7,8)**

X=Cl **(7)**; NO_3 **(8);**

Reactions of N-oxide harmine (6) with phthalic anhydride in methanol passed mainly in N-oxide grouping and led to formation of N (2)-oxyharmine phthalate (9):



(6) **(9)**

Conclusions

The investigations of antimicrobic activity of harmine (1) and its derivatives in relation to strains of gram-positive bacteria of Staphylococcus aureus, Bacillus subtilis, gram-negative strains of Escherichia coli, Pseudomonas aeruginosa and yeasty mushroom Candida albicans by a method of diffusion in agar (lunules) have been carried out in laboratory of bioscreening of JSC "IRPH "Phytochemistry". Gentamycin (for bacteria) and nystatin (for yeasty mushroom Candida albicans) have been used for comparison. Thus it was determined that alkaloid harmine has moderatel antimicrobic action concerning strains of gram-positive bacteria of Staphylococcus aureus, Bacillus subtilis and fungicidal activity in relation to yeasty mushroom Candida albicans.

Bioscreening on phagocytic activity showed that harmine (1) and N-oxide harmine (6) have dose-dependent phagocytosis-stimulating action, and hydrochloride harmine (4) has antibacterial activity.

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