SYNTHESIS OF QUATERNARY SALTS OF *Peganum harmala* ALKALOIDS

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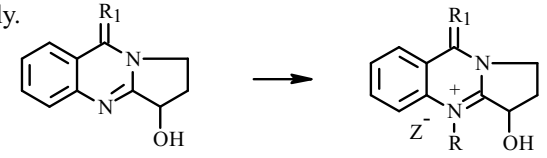
In continuation of research on alkaloids of *Peganum harmala* L. [1–4] and the search for new biologically active quinazoline, quinazolone, and indole compounds, we studied *N*-alkylation of (±)-peganine (**1**), (±)-vasicinone (**2**), and harmine (**3**), respectively, with methyliodide, boric acid chelated to ethyleneglycol, and protonation by dilute H_2SO_4. These alkaloids were isolated from common *P. harmala* collected in Kurdaisk Region, Dzhambul Oblast′ (Republic of Kazakhstan) and were identified by the published physicochemical constants [5, 6].

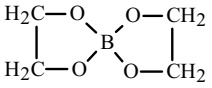
It was found that **1** reacted with methyliodide and boric acid chelated to ethyleneglycol in DMF or EtOH to form iminium salts **4** and **5**, respectively.



1, 2 **4 - 6**

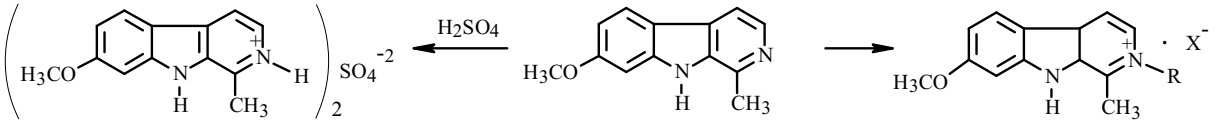
1, 4, 5: $R_1 = H_2$; **2, 6:** $R_1 = O$

4, 6: Z = I, R = CH_3

5: Z =  , R = H

Reaction of **2** with methyliodide under the above conditions also occurred at the azomethine N atom and gave iminium salt **6**. The results were interesting in view of a previous report [7] that salts of 1-acyldeoxyvasicinone form readily and can be used for further syntheses.

Harmine (**3**) reacted with methyliodide to give β-carbolinium salt **7**. Treatment of **3** with dilute H_2SO_4 in MeOH gave the *bis*-hydrate of *bis*-[*N*(2)-harminium]sulfate (**8**), the structure of which was elucidated by an x-ray structure analysis (XSA).



8 **3** **7, 9**

7: R = CH_3, X = I

9: R = H, X = Cl

The asymmetric unit of the unit cell contained two molecules of **8**, one SO_4^{-2}, and two waters of solvation. The closest structural analog of **8** was harmine hydrochloride (**9**) [5], the structure of which was studied by XSA [8]. The geometry of all three molecules of **8** (in our instance two independent ones) agreed within 3σ and had similar corresponding mean-square values [9]. Intermolecular interactions were analyzed using the program PLATON [10]. Molecules of **8** were bonded through H-bonds to SO_4^{-2} and waters of solvation (Fig. 1). Table 1 lists the H-bond parameters. Molecules of **8** were placed in stacks with a face-to-face shift through π...π-interaction with an interplanar distance 3.36Å and a distance between centers of five-membered rings of neighboring molecules in the stack 3.424(2) and 3.440(2) Å.

Harmine (**3**) is known to exhibit psychotomimetic activity [11]. We obtained some new data on the biological activity of **3** and its derivatives.

Harmine (**3**) and the *bis*-hydrate of *bis*-[*N*(2)-harminium]sulfate (**8**) exhibited pronounced anticholinesterase activity greater (0.182 μA and 0.125 μA) than the model inhibitor proserine (0.115 μA).

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TABLE 1. H-Bond Parameters in the Crystal

H-bond	D–H (Å)	H…A (Å)	D…A (Å)	Angle (°)
N2-H1N...O2S	0.96(5)	1.69(5)	2.654(4)	175(5)
O1R-H1R...O4S	0.89(6)	1.94(7)	2.793(5)	161(7)
N9-H2N...O1R	0.84(4)	1.99(3)	2.806(4)	165(3)
O1R-H2R...O3S	0.89(6)	1.94(6)	2.829(5)	170(5)
O2R-H4R...O3S	0.84(8)	2.19(8)	2.994(6)	160(8)
N9A-H2NA...O1S	0.94(4)	1.88(4)	2.815(3)	169(3)
N2A-H1NA...O3S	0.85(4)	1.90(4)	2.750(4)	176(4)

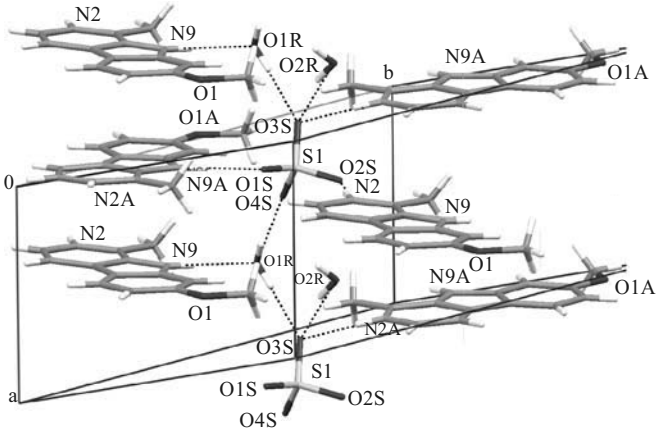

Fig. 1. Molecular packing of **8** in the crystal (dashed lines show H-bonds).

The antimicrobial activity of **3** and its hydrochloride **9** was studied toward strains of Gram-positive bacteria *Staphylococcus aureus* and *Bacillus subtilis*, Gram-negative strain *Escherichia coli*, *Pseudomonas aeruginosa*, and yeast fungus *Candida albicans* using the agar diffusion (well) method. The reference preparations were gentamicin (for bacteria) and nystatin (for *C. albicans*). The results showed that **3** and **9** exhibited moderate antimicrobial activity toward Gram-positive strains and that **3** had fungicidal activity toward *C. albicans*.

1-Methylpeganinium Iodide (4). Peganine (**1**, 0.10 g, 0.53 mmol) was dissolved in DMF (3 mL), treated with freshly distilled MeI (0.06 mL, 0.64 mmol), left for 10 h, and evaporated. The solid was worked up with ether. Recrystallization from alcohol afforded **4** (0.0919 g, 52.5%), $C_{12}H_{15}N_2OI$, mp 290°C. HPLC: retention time t_R = 1.17 min, purity 95.51%. UV spectrum (EtOH, λ_{max}, nm, log ε): 221 (5.02), 286 (3.26), 293 (3.12). IR spectrum (KBr, ν, cm^{-1}): 3299, 3259, 2928, 2763, 1668, 1496, 1311, 1040, 777, 712. PMR spectrum (300 MHz, CD_3OD, δ, ppm, J/Hz): 2.24 (1H, m, H-10), 2.64 (1H, m, H-10), 3.73 (3H, s, $NC\underline{H}_3$), 3.82 (1H, m, H-11), 4.08 (1H, m, H-11), 4.92 (1H, d, J = 10.5, H-4), 5.06 (1H, d, J = 10.5, H-4), 5.51 (1H, m, H-9), 7.22-7.47 (4H, m, H-5,6,7,8). ^{13}C NMR spectrum (75 MHz, CD_3OD, δ, ppm): 30.01 (t, C-10), 35.28 (q, N–CH_3), 47.45 (t, C-11), 53.24 (t, C-4), 73.43 (d, C-9), 116.65 (d, C-8), 119.59 (s, C-4a), 128.17 (d, C-5), 128.74 (d, C-6), 130.56 (d, C-7), 135.02 (s, C-8a), 164.8 (s, C-2).

Peganine *bis*(Dioxolano)borate (5). Peganine (**1**, 0.10 g, 0.53 mmol) was dissolved in EtOH (3 mL) and treated with boric acid chelated to ethyleneglycol (0.035 g, 0.56 mmol). After 35 min the precipitate was filtered off and washed with EtOH to afford **5**, $C_{15}H_{21}N_2O_5B$, mp 250°C (dec.), yield 0.095 g (59.7%). HPLC: t_R = 6.17 min, purity 92.47%. IR spectrum (KBr, ν, cm^{-1}): 3224, 1616, 1578, 1317, 1228, 1090, 1163, 1037, 812, 723. ^{11}B NMR spectrum (500 MHz, CD_3OD) δ 18.91 ppm. PMR spectrum (500 MHz, CD_3OD, δ, ppm, J/Hz): 2.11 (1H, m, H-10a), 2.61 (1H, m, H-10b), 3.34 (2H, m, H-11), 4.77-4.85 [m, 8H, (–O–CH_2–CH_2–O)$_2$], 4.96 (1H, br.t, H-9), 7.13 (1H, dt, J = 7.6, 7.8, H-6), 7.22 (1H, d, J = 7.6, H-5), 7.24 (1H, d, J = 8.0, H-8), 7.34 (1H, dt, J = 7.8, 8.0, H-7). ^{13}C NMR spectrum (125 MHz, CD_3OD, δ, ppm): 30.26 (t, C-10), 47.38 (t, C-11), 51.39 (t, C-4), 64.23 (d, C-9), 72.19 (t, 4 × CH_2–O), 118.42 (s, C-4a), 119.39 (d, C-8), 127.05 (d, C-5), 127.99 (d, C-6), 130.21 (d, C-7), 134.27 (s, C-8a), 164.63 (s, C-2).

1-Methylvasicinonium Iodide (6). $C_{12}H_{13}N_2O_2I$, yield 86%, mp 240-243°C (dec.). IR spectrum (KBr, ν, cm^{-1}): 3490, 3260, 1675, 1668, 1653, 1312, 1280, 1040, 840, 777, 712. PMR spectrum [$(CD_3)_2SO$, 300 MHz, δ, ppm, J/Hz]: 2.04 (2H, m, H-10), 4.02 (1H, m, H-11), 4.21 (1H, m, H-11), 3.73 (3H, s, N–CH_3), 5.10 (1H, br.t, J = 7.5, H-9), 7.67-8.27 (4H, m,

H-5,6,7,8). ^{13}C NMR spectrum (75 MHz, DMSO-d_6, δ, ppm): 29.3 (t, C-11), 37.9 (q, NCH_3), 43.4 (t, C-10), 70.3 (d, C-9), 121.4 (d, C-8), 126.5 (s, C-6), 127.3 (s, C-4a), 128.5 (d, C-5), 133.5 (d, C-7), 146.0 (s, C-8a), 164.9 (d, C-2), 167.2 (s, C-4).

2-Methylharminium Iodide (7). Harmine (**3**, 0.1 g, 0.47 mmol) was dissolved in DMF (3 mL), treated with freshly distilled MeI (0.04 mL, 0.47 mmol), left for 3 h, and evaporated. The solid was recrystallized from alcohol to afford $C_{14}H_{15}N_2OI$, yield 0.095 g (55.9%), mp 280°C. HPLC: t_R = 4.63 min, purity 98%. UV spectrum (λ_{max}, nm, log ε): 209 (4.12), 220 (4.23), 252 (4.62), 331 (3.66). IR spectrum (KBr, ν, cm^{-1}): 3420, 3142, 1660, 1627, 1565, 1500, 1484, 1312, 1160, 1025, 975, 770, 740, 712. PMR spectrum [$(CD_3)_2SO$, δ, ppm, J/Hz]: 2.78 (3H, s, CH_3), 3.70 (3H, s, CH_3), 4.02 (3H, s, CH_3), 7.18 (1H, dd, J = 7.8, 1.6, H-6), 7.28 (1H, d, J = 1.6, H-8), 8.39 (1H, d, J = 7.8, H-5), 8.47 (1H, d, J = 4.6, H-3), 8.59 (1H, d, J = 4.6, H-4). ^{13}C NMR spectrum (DMSO-d_6, δ, ppm): 16.28 (q, CH_3), 34.08 (q, CH_3), 55.91 (q, CH_3O), 98.54 (d, C-8), 111.32 (d, C-4), 113.39 (d, C-6), 115.28 (s, C-4b), 124.13 (d, C-5), 129.78 (d, 3), 131.32 (s, C-4a), 132.27 (s, C-9a), 138.56 (s, C-1), 144.98 (s, C-8a), 161.92 (d, C-7).

***Bis*-Hydrate of *bis*-[*N*(2)-Harminium]sulfate (8).** Yield 47%, mp 260–264°C (MeOH), HPLC 96.3%. UV spectrum (λ_{max}, nm, log ε): 209 (4.16), 245 (3.88), 327 (3.41). IR spectrum (KBr, cm^{-1}): 3412, 3380, 3312, 3179, 3114, 1648, 1632, 1627, 1512, 1500, 1312, 1275, 1100, 1078, 1021, 956, 858, 825, 800, 771, 720. PMR spectrum (DMSO-d_6, δ, ppm, J/Hz): 2.97 (3H, s, CH_3 on C′), 3.93 (3H, s, CH_3O), 7.03 (1H, dd, J = 8.8, 2.1, H-6), 7.15 (1H, d, J = 2.1, H-8), 8.30 (1H, d, J = 8.8, H-5), 8.36 (1H, d, J = 5.6, H-4), 8.43 (1H, d, J = 5.6, H-3), 12.65 (1H, s, N–H). ^{13}C NMR spectrum (DMSO-d_6, δ, ppm): 15.83 (q, CH_3), 55.73 (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), 128.90 (d, 3), 132.09 (s, C-4a), 113.67 (s, C-9a), 137.23 (s, C-1), 145.40 (s, C-8a), 161.68 (d, C-7).

X-ray Structure Analysis (XSA) of 8. The XSA was performed on a Bruker P4 diffractometer (Mo Kα-radiation, graphite monochromator, 2θ/θ-scanning, 2θ < 52°). A crystal of **8** of size 0.50 × 0.50 × 0.10 mm was selected for the experiment. The crystal was monoclinic, a = 6.7389(7), b = 17.9250(9), c = 11.3023(8) Å, β = 104.475(7)°, V = 1321.9(2) $Å^3$, space group $P2_1$, Z = 4, $C_{13}H_{13}N_2O^+ + 1/2\ SO_4^{-2} + H_2O$, d_{calc} = 1.403 g/cm^3, μ = 0.180 mm^{-1}. Intensities of 2684 independent reflections were measured. Absorption corrections were not applied. The structure was solved by direct methods using the SIR2002 program [12]. Structure factors were refined by anisotropic full-matrix least-squares methods using the SHELXL-97 program [13]. Parameters of most H atoms were calculated in each refinement cycle using coordinates of the corresponding C atom (rider model). A difference synthesis located the H atoms on N2 and N9 and water molecules. Their parameters were refined isotropically. The final refinement of the structure over all F^2 gave wR_2 = 0.0972, S = 1.04. A total of 384 parameters were refined (R = 0.0357 for 2434 F > 4σ).

The structure of **8** was registered in the Cambridge Crystallographic Data Centre (CCDC 693264).

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