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ISOLATION AND CHEMICAL TRANSFORMATIONS OF VASICINONE

M. T. Agedilova,[1] A. Zh. Turmukhambetov,[1] A. V. Kazantsev,[1]
E. E. Shul′ts,[2] M. M. Shakirov,[2] and S. M. Adekenov[1]

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Vasicinone and peganine were isolated from Peganum harmala *L. Vasicinone 2,4-dinitrophenylhydrazone and vasicinone ketal were prepared.*

Key words: *Peganum harmala*, alkaloids, vasicinone, peganine, 2,4-dinitrophenylhydrazine, ketal.

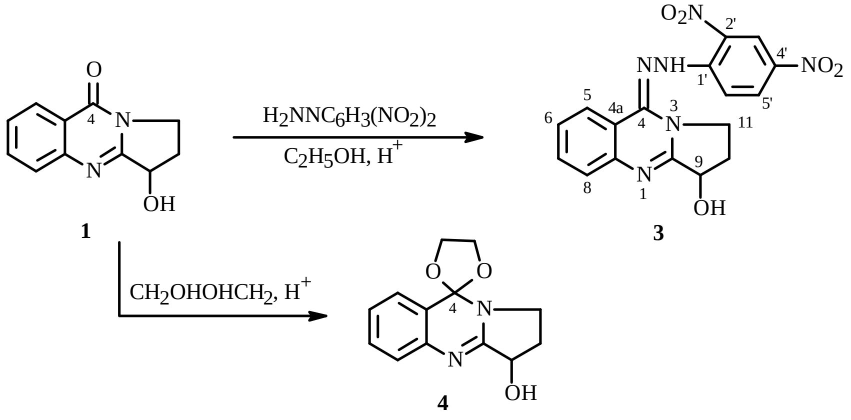
Quinazoline alkaloids are the active principles of plants of the harmala family (Peganaceae Tiegh.), which are popular in alternative medicine [1-3]. We investigated alkaloids of common harmala (*Peganum harmala* L.) collected in Karaganda region (Kazakhstan) during flowering and fruiting.

Extraction with $CHCl_3$ of stems, flowers, and leaves produced extracts that were separated by column chromatography over Al_2O_3. Elution of the column isolated compounds identical to the quinazoline alkaloids (-)-vasicinone (**1**) and peganine (**2**), which have been previously obtained from this plant [1, 2, 4, 5].

In order to prepare new derivatives potentially with biological activity, we studied the reaction of **1** with hydrazine hydrate, hydrazinium sulfate, phenylhydrazine, 2,4-dinitrophenylhydrazine, and ethyleneglycol.

We found that hydrazine hydrate, hydrazinium sulfate, and phenylhydrazine do not react with **1** under normal conditions.

2,4-Dinitrophenylhydrazine reacts with **1** in aqueous-alcoholic H_2SO_4 at room temperature and gives the desired vasicinone 2,4-dinitrophenylhydrazone (**3**) in 80% yield.



Heating **1** with ethyleneglycol in the presence of H_3PO_4 forms vasicinone ketal **4** in 53% yield.

The structures of these compounds were confirmed by PMR, ^{13}C NMR, IR, and UV spectra.

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1) Institute of Phytochemistry, Ministry of Education and Science, Republic of Kazakhstan, Karaganda, ul. Gazalieva, 4, Kazakhstan; 2) Novosibirsk Institute of Organic Chemistry, Siberian Division, Russian Academy of Sciences, Novosibirsk, Russia. Translated from Khimiya Prirodnykh Soedinenii, No. 3, pp. 230-231, May-June, 2004. Original article submitted April 19, 2004.

TABLE 1. ^{13}C NMR Spectra of Vasicinone 2,4-Dinitrophenylhydrazone (**3**) and Vasicinone Ketal (**4**)

Atom	δ, ppm	
	3	**4**
2	160.5	160.3
4	160.2	46.8
4a	127.4	121.0
5	126.2*	126.6
6	127.4*	127.4
7	134.2	134.2
8a	148.6	148.6
8	126.5*	129.8
9	71.9	71.9
10	29.4	29.4
11	43.4	43.3
1′	129.8	77.5
2′	118.7	76.4
3′	126.8*	
4′	121.0	
5′	126.8*	
6′	126.5*	

Signals marked by asterisks may be interchanged within one column.

EXPERIMENTAL

Melting points were determined on a Boetius instrument. IR spectra were recorded on a Vector-22 Fourier-spectrophotometer in KBr disks. PMR and ^{13}C NMR spectra were obtained on Bruker AC-200 [working frequencies 200.13 (PMR) and 50.32 MHz (^{13}C)] and Bruker DRX-500 [working frequencies 500.13 (PMR) and 125.76 MHz (^{13}C)] in CDCl$_3$ (5%) solutions.

Mass spectra were recorded on a Finnigan MAT-8200 high-resolution mass spectrometer (electron ionization potential 70 eV). Column chromatography used Al$_2$O$_3$ (activity standard II); TLC, Silufol UV-254 plates and silica gel on alumina (20X) with I$_2$ vapor developer. Table 1 lists the ^{13}C NMR spectra.

Isolation of Native Alkaloids. Air dried raw material from the aerial part of common harmala was exhaustively extracted with CHCl$_3$ (40°C). The extracts were chromatographed over an Al$_2$O$_3$ column (activity standard II). The yield of **1** from the stem extract upon elution by benzene:ethylacetate (2:1) was 0.02%; flowers (ethylacetate), 0.05%; leaves (benzene), 0.06%. The leaf extract upon elution by benzene:ethylacetate (2:1) afforded **2** in 0.004% yield from the air-dried raw material.

Vasicinone 2,4-Dinitrophenylhydrazone (3). Vasicinone (**1**, 0.5 g) in ethanol (20 mL) was treated at 20°C with an aqueous alcohol solution of 2,4-dinitrophenylhydrazine, which was prepared from 2,4-dinitrophenylhydrazine (0.4 g), conc. H$_2$SO$_4$ (2 mL), H$_2$O (3.0 mL), and ethanol (10 mL). The reaction mixture was kept at room temperature until the hydrazone precipitation was complete. The precipitate was filtered off and recrystallized from alcohol to afford **3** (0.75 g, 80%), mp 159-162°C, R_f 0.31 (benzene:alcohol:NH$_3$ 1:4:0.1), $[\alpha]_{580}$ -62° (*c* 0.08, ethanol). UV spectrum (EtOH, λ_{max}, nm): 225, 205, 265, 351, 316, 303 (log ε 3.6055, 3.6073, 3.9626, 4, 4.2441, 4.3468).

IR spectrum (KBr, ν, cm^{-1}): 3365 (OH); 3227, 1668 (NH); 1623 (C=N); 1519, 1343 (NO$_2$); 1594 (C$_6$H$_5$).

PMR spectrum (CD$_3$OD, δ, ppm, J/Hz): 2.30 (1H, m, H-10a), 2.78 (1H, m, H-10b), 4.10 (1H, m, J$_{gem}$ = 17.2, H-11a), 4.40 (1H, m, J$_{gem}$ = 17.2, H-11b), 5.48 (1H, t, J = 7.5, H-9), 7.69 (1H, dt, J = 7.8, 1.5, H-7), 7.72 (1H, dd, J = 7.5, 2.5, H-8), 7.82 (1H, dd, J = 7.5, 2.5, H-5′), 7.95 (1H, dt, J = 7.8, 2.0, H-6), 8.32 (1H, dd, J = 7.8, 1.8, H-5), 8.31 (1H, d, J = 7.5, H-1$^{6'}$), 9.05 (1H, d, J = 2.5, H-3′).

Vasicinone Ketal (4). Vasicinone (**1**, 0.1 g, 0.001 mmol) was placed in a flask and treated with stirring with ethyleneglycol (6 mL, pH 8) and H_3PO_4 (1 drop, 87%). The reaction mixture was stirred at 61°C for 2 h with TLC monitoring, cooled, treated with saturated NaCl solution, and extracted with $CHCl_3$. The $CHCl_3$ was evaporated. The solid was distilled in vacuum to afford **4** (53% yield), R_f 0.4. The product solidified upon storage in a refrigerator. Recrystallization from alcohol gave crystals, mp 188-190°C, $[\alpha]_{580}$ -110° (*c* 0.1, ethanol).

IR spectrum (KBr, ν, cm^{-1}): 3300 (OH); 3136, 1684, 1668 (NH); 1633 (C=N); 1211, 1042 ($–O–CH_2–CH_2–O–$).

PMR spectrum ($CDCl_3$, δ, ppm, J/Hz): 2.30 (1H, m, H-10a), 2.62 (1H, m, H-10b), 3.73 (s, $O–C\underline{H}_2–C\underline{H}_2–O$), 3.98 (1H, m, H-11b), 4.33 (1H, m, H-11a), 5.23 (1H, t, J = 7, H-9, OH), 7.45 (1H, m, H-7), 7.71 d, 7.73 d (1H each, H-5,8), 8.26 (1H, m, H-6).

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