Chemistry of Natural Compounds, Vol. 41, No. 4, 2005

ALKALOIDS FROM *Papaver angrenicum*. II. CRYSTAL AND MOLECULAR STRUCTURE OF THE NEW DIISOQUINOLINE ALKALOID PANGRENINE

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UDC 547.944/945+548.737

The structure of pangrenine, a new diisoquinoline alkaloid representing salts of protoberberine bases that was isolated from the aerial part of Papaver angrenicum *as the nitrate, was established. Spectral and x-ray structural data of the isolated compound were presented.*

Key words: *Papaver*, diisoquinoline alkaloids, pangrenine, x-ray structure analysis.

Papaver angrenicum P. (Papaveraceae) is a perennial herbaceous plant growing in the Tian-Shan, Pamir-Alai, and mountainous regions of Samarkand and Tashkent districts [1]. The chemical composition of *P. angrenicum* has not been reported. We investigated the alkaloid content of plants collected in Tashkent district near the village Ertosh during full flowering.

The content of total alkaloids (0.19%) was determined in the $CHCl_3$ extract of the plant. Total bases were divided into phenolic and nonphenolic parts. Chromatography of the phenolic part of the alkaloid mixture over a silica-gel column isolated a crystalline compound with mp 281-283°C [2].

The IR spectrum of the alkaloid contained an absorption band for active H and an aromatic ring. According to PMR spectroscopy, the alkaloid contained three aromatic methoxyls that appeared as singlets at δ 4.14, 4.06, and 4.02 ppm. The region of aromatic protons showed two 1H and one 2H signals at 6.67 (1H, s), 6.06 (2H, s), and 5.07 ppm (1H, s). A 2H singlet for methylenedioxy protons was found at 4.80 ppm. Methylene protons were observed as poorly resolved multiplets at 1.8-2.8 ppm.

However, the spectral data and properties together did not enable the structure of the isolated compound to be established unambiguously. Therefore, we performed a single-crystal x-ray structure analysis (XSA). According to the XSA, the compound was a diisoquinoline alkaloid representing salts of protoberberine bases. We called it pangrenine (**1**). Its 7,8,13,14-tetrahydro derivative is known in the literature as mecambridine, which was isolated as the base from *P. bracteatum* [3, 4].

Figure 1 shows pangrenine, which contains the protoberberine skeleton and is a salt consisting of the alkaloid cation and a nitrate anion (nitric-acid residue). These ions are bonded in the crystal by an O–H...O H-bond. A nitrate (translated by 0.5 + x, 0.5 - y, 0.5 + z) approaches the hydroxyl (O9H) on C19 through O2 and O1. The O2...H-O9 H-bond has the following parameters: O2...O9, 3.06 Å; O2...H–O9, 1.89 Å; angle O2...H–O9, 161°. However, the O1...H–O9 H-bond is weaker (3.18, 2.24, 132). Furthermore, there is a weak intermolecular contact C8–H...O3 (3.24, 2.33, 165) near the positively charged N7 although N7 is planar (bond-angle sum 359.6°) and is not involved in "direct" intermolecular interactions, in contrast with mecambridine.

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 0009-3130/05/4104-0442

TABLE 1. Bond Lengths (r, Å) and Angles (w, deg) in **1**

Bond	r	Angle	w	Angle	w
C(1)-C(2)	1.353 (10)	C(2)-C(1)-O(4)	120.9 (7)	C(8a)-C(12a)-C(12)	119.1 (7)
C(1)-O(4)	1.379 (8)	C(2)-C(1)-C(1a)	117.6 (7)	C(13)-C(12a)-C(12)	122.1 (6)
C(1)-C(1a)	1.431 (9)	O(4)-C(1)-C(1a)	121.5 (7)	C(14)-C(13)-C(12a)	123.4 (7)
C(1a)-C(4a)	1.416 (10)	C(4a)-C(1a)-C(1)	117.7 (7)	C(13)-C(14)-N(7)	115.7 (7)
C(1a)-C(14)	1.470 (10)	C(4a)-C(1a)-C(14)	120.2 (7)	C(13)-C(14)-C(1A)	126.8 (7)
C(2)-C(3)	1.375 (10)	C(1)-C(1a)-C(14)	122.1 (7)	N(7)-C(14)-C(1A)	117.6 (7)
C(2)-O(5)	1.386 (8)	C(1)-C(2)-C(3)	123.5 (7)	O(6)-C(16)-O(5)	107.2 (6)
C(3)-O(6)	1.365 (9)	C(1)-C(2)-O(5)	126.5 (8)	O(9)-C(19)-C(12)	111.8 (6)
C(3)-C(4)	1.367 (10)	C(3)-C(2)-O(5)	110.0 (7)	C(1)-O(4)-C(15)	113.7 (6)
C(4)-C(4a)	1.386 (10)	O(6)-C(3)-C(4)	129.4 (8)	C(2)-O(5)-C(16)	103.6 (6)
C(4a)-C(5)	1.505 (10)	O(6)-C(3)-C(2)	109.4 (7)	C(3)-O(6)-C(16)	105.2 (6)
C(5)-C(6)	1.490 (10)	C(4)-C(3)-C(2)	121.1 (8)	C(10)-O(7)-C(17)	117.0 (6)
C(6)-N(7)	1.489 (9)	C(3)-C(4)-C(4a)	117.4 (8)	C(11)-O(8)-C(18)	114.1 (6)
N(7)-C(8)	1.323 (9)	C(4)-C(4a)-C(1a)	122.6 (7)	O(1)-N(1)-O(3)	123.0 (12)
N(7)-C(14)	1.395 (8)	C(4)-C(4a)-C(5)	120.2 (7)	O(1)-N(1)-O(2)	115.8 (11)
C(8)-C(8a)	1.401 (10)	C(1a)-C(4a)-C(5)	117.1 (7)	O(3)-N(1)-O(2)	119.8 (9)
C(8a)-C(12a)	1.396 (9)	C(6)-C(5)-C(4a)	110.7 (7)		
C(8a)-C(9)	1.415 (10)	N(7)-C(6)-C(5)	109.3 (6)		
C(9)-C(10)	1.348 (10)	C(8)-N(7)-C(14)	122.5 (7)		
C(10)-O(7)	1.351 (9)	C(8)-N(7)-C(6)	117.1 (6)		
C(10)-C(11)	1.446 (10)	C(14)-N(7)-C(6)	120.3 (6)		
C(11)-O(8)	1.366 (8)	N(7)-C(8)-C(8a)	122.7 (7)		
C(11)-C(12)	1.374 (10)	C(12a)-C(8a)-C(8)	117.0 (7)		
C(12)-C(12a)	1.433 (9)	C(12a)-C(8a)-C(9)	122.1 (7)		
(C12)-C(19)	1.517 (9)	C(8)-C(8a)-C(9)	120.9 (7)		
C(12a)-C(13)	1.400 (9)	C(10)-C(9)-C(8a)	119.1 (7)		
C(13)-C(14)	1.375 (10)	C(9)-C(10)-O(7)	125.6 (7)		
C(15)-O(4)	1.440 (9)	C(9)-C(10)-C(11)	119.7 (7)		
C(16)-O(6)	1.422 (9)	O(7)-C(10)-C(11)	114.7 (7)		
C(16)-O(5)	1.439 (9)	O(8)-C(11)-C(12)	120.1 (7)		
C(17)-O(7)	1.440 (8)	O(8)-C(11)-C(10)	117.6 (7)		
C(18)-O(8)	1.441 (9)	C(12)-C(11)-C(10)	122.1 (7)		
C(19)-O(9)	1.426 (9)	C(11)-C(12)-C(12a)	117.7 (7)		
N(1)-O(1)	1.160 (9)	C(11)-C(12)-C(19)	120.7 (7)		
N(1)-O(3)	1.223 (10)	C(12a)-C(12)-C(19)	121.6 (7)		
N(1)-O(2)	1.224 (11)	C(8a)-C(12a)-C(13)	118.7 (7)		

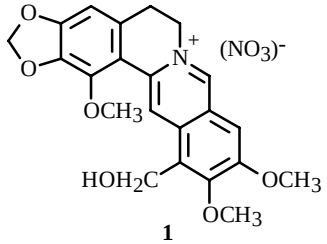

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TABLE 2. Crystallographic Data, Experimental Conditions, and Refinement Parameters for **1**

Empirical formula	$C_{22}H_{22}NO_6*NO_3$
Molecular weight	458.42
Temperature, K	293
Space group	$P2_1/n$, Z = 4
a, Å	9.454 (2)
b, Å	12.072 (2)
c, Å	18.482 (4)
β	104.21 (3)
V, Å^3	2044.8 (7)
ρ, g/cm^3	1.489
Absorption coefficient, μ (Mo)	0.0019 (3)
Crystal dimensions, mm	0.50×0.25×0.15
Angle range, θ, deg	2.03 to 24.99
Total number of reflections	2783
Number of reflections [$I > 2\sigma(I)$]	1650
R-factor [$I > 2\sigma(I)$]	R1 = 0.115, wR2 = 0.151
R-factor (whole data set)	R1 = 0.179, wR2 = 0.1730
GOOF	1.151
Electron-density difference peaks	0.31 and -0.25 e Å^{-3}

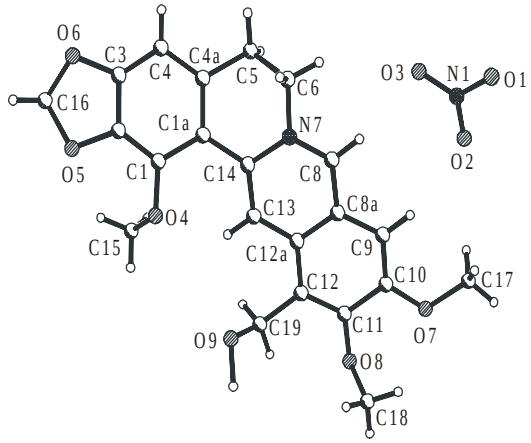

Fig. 1. Molecular structure and atomic numbering in **1**.

The cation of **1** contains a five-membered heterocycle as an envelope flattened at C16. An unsaturated six-membered heterocycle that links the two planar fragments of the molecule has the twisted-boat conformation with C_2 symmetry. As a result, the planar fragments, an aromatic ring with a fused five-membered ring and a heteroaromatic ring with another aromatic ring, form an angle of 14.7°. The active hydroxyls and methoxyls have the same relative positions as those observed in mecambridine [5].

The nitrate is approximately planar (±0.03 Å). The sum of the angles around N1 is 358.6°. The N–O1 bond length [1.160(9) Å] is shorter than the other two N–O2 and N–O3 [1.224(11) and 1.223 (10) Å, respectively] (Table 1). However, they are identical within experimental uncertainty (3σ) (Table 2) and agree with the usual values [6].

EXPERIMENTAL

Melting points were measured on a Boetius apparatus. IR spectra were recorded on a Model 2000 Fourier spectrometer (Perkin—Elmer) in KBr disks. PMR spectra were recorded on a Tesla spectrometer at working frequency 100 MHz for protons

in CD_3OD. Chemical shifts were measured relative to HMDS. Column chromatography used KSK silica gel and a 1:30 compound:sorbent ratio.

Extraction of Total Alkaloids from *P. angrenicum*. The air-dried and ground aerial part of the plant (1 kg) was moistened with NH_4OH solution (5%), soaked for 2 h, and treated with $CHCl_3$. Liquid was decanted every day. A total of six decantations was made. The $CHCl_3$ extracts were combined, condensed, and treated with H_2SO_4 solution (5%). The acidic solution was made basic with conc. NH_4OH. Alkaloids were exhaustively extracted with $CHCl_3$. The combined extracts were dried over anhydrous Na_2SO_4 and condensed to afford the total alkaloids (1.9 g).

Isolation of Pangrenine. The mixture of bases (1.9 g) was dissolved in benzene (200 mL) and treated with KOH (5%, 3×25 mL). The combined alkaline solutions were washed with $CHCl_3$, made basic with conc. NH_4OH, and treated with $CHCl_3$ (3×200 mL). The $CHCl_3$ extracts were condensed and dried to afford a mixture of bases (0.9 g) that was placed on a column of silica gel (27 g) and eluted by $CHCl_3$ and $CHCl_3$:CH_3OH. The $CHCl_3$:CH_3OH effluents afforded **1** (0.02 g), R_f 0.18 (TLC, silica gel, $CHCl_3$:CH_3OH, 9:1).

X-ray Structure Analysis. Single crystals of **1** were grown from acetone solution by slow evaporation at room temperature. The crystals were transparent elongated prisms. Unit-cell constants and intensities of reflections were determined on a STOE Stadi-4 four-circle diffractometer ($\theta/2\theta$-scanning) using Mo Kα-radiation (graphite monochromator). Absorption corrections were not applied. Table 2 gives the principal crystallographic data and experimental conditions.

The structure was solved by direct methods using the SHELXS-97 program set and refined by full-matrix isotropic and anisotropic least-squares methods (LS) using the SHELXL-97 program. All nonhydrogen atoms were refined by anisotropic full-matrix LS (over F^2). Positions of H atoms were found geometrically and refined with fixed isotropic thermal parameters $U_{iso} = nU_{eq}$, where n = 1.5 for methyls and 1.2 for others and U_{eq} is the equivalent isotropic parameter of the corresponding C atoms. The hydroxyl H atom was found from a difference electron-density synthesis and refined isotropically.

The XSA data were deposited as a CIF file in the Cambridge Crystallographic Database (CCDC 273902).

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