Chemistry of Natural Compounds, Vol. 40, No. 3, 2004

ALKALOIDS FROM *Arundo donax*. XVII. STRUCTURE OF THE DIMERIC INDOLE ALKALOID ARUNDAPHINE

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UDC 547.944/945+548.737

The new dimeric alkaloid arundaphine, a tryptamine—tryptamine base, was isolated from roots and rhizomes of Arundo donax *(Poaceae). Spectral data and an x-ray structure analysis established its structure as 1-[3-(2-dimethylaminoethyl)-5-hydroxy-1H-4-indolyl]-3-hydroxy-3-(2-methylaminoethyl)-2-indolinone.*

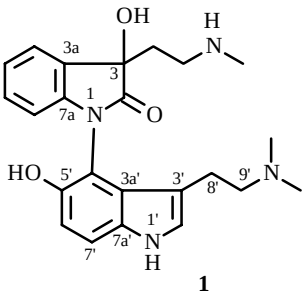
Key words: *Arundo donax*, Poaceae, *bis*-indole alkaloid, arundaphine, isolation, structure, x-ray structure analysis.

We previously isolated from the roots and rhizomes of *Arundo donax* L. (Poaceae) a new alkaloid of composition $C_{23}H_{28}N_4O_3$ and called it arundaphine (**1**) [1].

The IR spectrum of **1** exhibits absorption bands (cm^{-1}) of active H (NH, OH) at 3320 and 3200, amide carbonyl at 1630, and an aromatic ring (1610, 1520).

The mass spectrum of **1** contains peaks for the protonated molecular ion $[M + 1]^+$ with *m*/*z* 409 and ions with *m*/*z* 390 (17%) [M - 18], 391 (7%) [M - 17], and 372 (7%) [M - 36]. These are consistent with the presence in the alkaloid of at least two hydroxyls. A peak with *m*/*z* 332 (6%) indicates that **1** has a *bis*-indole structure. A peak with *m*/*z* 348 is formed from the molecular ion via loss of 17 amu with further cleavage of $N(CH_3)_2$. Peaks at low mass are found with *m*/*z* 130, 115, 103, 97, and 95, which are typical of an indole ring [2].

The spectral properties of **1**, its high molecular weight, and comparison with *bis*-indole alkaloids of this plant (arundinine, arundamine [3], arundanine [4], arundavine [5]) are indicative of the dimeric nature of **1**.



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The structure of **1** was established by an x-ray structure analysis (XSA). Crystals of **1** contain two independent molecules of the alkaloid (**1a** and **1b**) related by a pseudo-center of symmetry.

Figure 1 shows the molecular structure of one molecule of **1** from the XSA. It can be seen that the dimer consists of a hydroxyindole (**A**) and the known alkaloid bufotenine (**B**) [6]. They are joined through N1 and C4′ (from **A** and **B**, respectively), similar to arundamine [3] and arundavine [5]. The relative configurations of asymmetric center C3 in **A** of **1**, in alline [7], and in arundavine [5], are the same.

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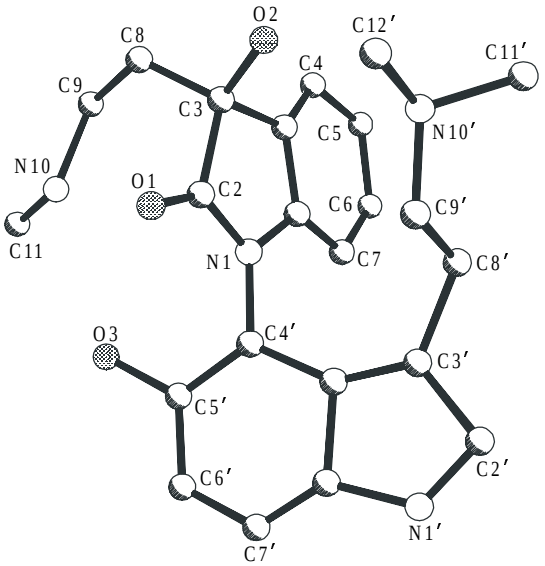

Fig. 1. Molecular structure of arundaphine (**1**).

The bicyclic pseudoaromatic indole fragments in **1** are planar with small distortions (deviations of atoms from the plane are ±0.08-0.09 Å in **1a** and ±0.04-0.06 Å in **1b**). The planar fragments in the two monomers of **1a** and **1b** are distorted because of the poor statistics of the data set (see Experimental). The indole fragments in **1a** and **1b** make angles of 77.8 and 75.6° to each other, respectively. This is close to the orientation observed in arundamine (79.7°) and arundavine (82.7°). Such positions of the monomers of **A** and **B** in **1a** and **1b** favors formation of two intramolecular H-bonds. This can be seen in the distances O2...N10′ [2.83 Å (**1a**) and 2.69 Å (**1b**)] and O3...N10 [2.82 Å (**1a**) and 2.80 Å (**1b**)]. Here N10′ with an unpaired electron pair is directed toward the hydroxyl O2–H and is tetrahedral. The nature of the second H-bond is still unclear because the positions of the H atoms on N10 and O3 were not determined experimentally.

A comparison of the geometries of arundamine, arundavine, and arundaphine shows that the intramolecular H-bond is typical for these *bis*-indole alkaloids and has practically no effect on the mutual orientation of the indole nuclei (the angle between the two planar fragments). The H-bond is stabilized by the mobility of the linear exocyclic $–CH_2–CH_2–NR–CH_3$ moiety.

The poor quality of the data set do not enable a more detailed discussion of the geometric parameters of arundaphine because the uncertainties in the bond lengths reach 0.05 Å. However, the bond lengths and angles are in general similar to those observed in arundavine [5] and arundamine [3].

The packing in the structure of **1** shows that analogous molecules translated by a glide plane are related by a N–H...O H-bond (N1′...O1 distance 2.95 Å) and form an infinite chain along the *c* axis.

NMR spectra of **1** were recorded in a mixture of two solvents, CD_3OD and $CDCl_3$. The qualitative set and the positions of the signals in the spectrum of **1** are very similar to those of arundavine [5]. Signals of aromatic protons form a four-spin system for *o*-substituted benzene (H4-H7), an AB-system for *o*-located protons (H6′ and H7′), and a singlet for H2′. Like in arundavine, H7 has an unusually large strong-field shift, the reason for which is the stereochemistry of the dimer. Thus, H7, like N-methyls, winds up over the aromatic systems and experiences a positive inductive shift.

The aliphatic part of the spectrum has more changes when compared with that of arundavine. Opening of the third ring in the first half of the dimer and a slight change in the nature of N10 led to a collapse of the signals in the aliphatic region: 8 methylene protons and the NH10 methyl resonate near 0.6 ppm. However, 4 methylene protons appear as independent signals with the proper multiplicity (Table 1). Signals in this region were interpreted using homo- and heterocorrelation 2D NMR spectra. A slight relaxation of the stereochemical strain in the molecular structure removed the slight nonequivalency of the methyls on N10′. The signal for this group became a singlet of usual width with an amplitude twice that of the ordinary methyl on N10. However, the N10′–C3OH H-bond is preserved in solution. This was confirmed by the anomalously large strong-field shift of the N-methyl signal (1.88 ppm), i.e., the free C8′–C9′–N10′ side chain is oriented in space and remains over the plane of the first half of the dimer.

TABLE 1. ^{1}H and ^{13}C Chemical Shifts and SSCC of Arundaphine in CD_3OD and $CDCl_3$

Atom	^{1}H (SSCC, Hz)	^{13}C	Atom	^{1}H (SSCC, Hz)	^{13}C
2	s	180.38	2′	6.95	124.00
3		75.20	3′		111.47
3a		130.88	3′a		124.55
4	7.45 (d, J = 7.5)	124.24	4′		109.94
5	7.15 (t, J = 7.5)	124.94	5′		148.07
6	7.21 (t, J = 7.5)	130.17	6′	6.89 (d, J = 8.7)	112.70
7	6.44 (d, J = 7.5)	110.74	7′	7.34 (d, J = 8.7)	113.98
7a		144.06	7′a		133.10
8	2.54 (m)	35.93	8′	2.52 (m);	25.14
	2.70 (dt, J = 12.2, 8.3)			2.61 (m)	
9	2.30 (dt, J = 12.2, 8.3)	47.77	9′	2.13 (dt, J = 11.4, 5.5)	60.61
	2.46 (m)			2.19 (td, J = 11.4, 4.4)	
10	2.29 (s)	36.25	10′	1.88 (s)	44.37

TABLE 2. Correlation Peaks from SSCC $^{2}J_{H\text{-}C}$ and $^{3}J_{H\text{-}C}$ in HMBC Spectrum of Arundaphine in CD_3OD and $CDCl_3$

Atoms			
^{1}H	^{13}C	^{1}H	^{13}C
4	3, 6, 7a	2′	3′, 3′a, 7′a, 8′
5	3a, 7		
6	4, 7a	6′	4′, 5′, 7a
7	3a, 5, 7a	7′	3′a, 5′
8	2, 3, 10	8′	3′, 3′a, 7′a, 9′
9	3	9′	3′, 8′, 10′
10	9	10′	9′

A more significant change in the C spectrum is the appearance of a signal for carbonyl C2 at 180.38 ppm. The positions of all other signals agree well with the ^{13}C NMR spectrum of arundavine.

The C skeleton, the position of quaternary C atoms in it, and the fusion of the characteristic fragments found from the PMR spectra were based on 2D heterocorrelation HMBC NMR spectra, like for arundavine. Table 2 lists the more characteristic key peaks in the HMBC spectrum.

EXPERIMENTAL

UV spectra were obtained on a Lambda-16 spectrometer; IR spectra, on a Perkin—Elmer System 2000 FT IR Fourier spectrometer in KBr disks; mass spectra (EI, 70 eV), in an MX-1310 spectrometer with direct sample introduction into the ion source at ionization-chamber temperature 150°C. NMR spectra were recorded on a DRX 500 spectrometer.

Column chromatography used Al_2O_3 (neutral, 100/160 μm). TLC was performed on plates (Al_2O_3, 5/40 μm) using solvent systems.

Isolation of Arundaphine. Column chromatography of total akaloids (18 g) from *A. donax* over Al_2O_3 separated benzene and $CHCl_3$ fractions. Then, the column was further eluted with $CHCl_3$:CH_3OH (7:3). Fractions of 100-mL volume (total 20 fractions) were collected. Fractions 5-13 were combined and rechromatographed with elution by $CHCl_3$:CH_3OH (7:3) to give 30 fractions (5-mL). Fractions 3-7 afforded arundaphine (100 mg), mp 205-207°C, R_f 0.46 ($CHCl_3$:CH_3OH, 9:1).

IR spectrum: 3320-3200, 1630, 1610, 1520 cm^{-1}.

Mass spectrum: 409 (100%) [M + 1], 391 (7%), 390 (17%), 372 (7%), 332 (6%), 295 (296), 272, 248 (249), 237, 204, 188, 170 (171), 145 (146), 130, 115, 112 (113), 103, 97, 95, 92, 81.

X-ray Structure Analysis. Prismatic and transparent crystals of **1** were obtained from a mixture of alcohol and acetone. The small amount of isolated compound did not yield a single crystal of the required quality and size for the XSA. Nevertheless, the XSA (at 295 K) was performed on crystals of approximate dimensions 0.1 × 0.3 × 0.4 mm. Crystals are orthorhombic: a = 16.436(3), b = 15.686(3), c = 16.536(3) Å, V = 4263.2(14) $Å^3$, d_{calc} = 1.273 g/cm^3, absorption coefficient μ = 0.86 cm^{-1}, space group $Pca2_1$, Z = 8. Intensities of 1685 independent non-zero reflections were measured on a Stoe Stadi-4 automated diffractometer (Mo Kα-radiation, graphite monochromator, $\theta/2\theta$-scanning, $2\theta_{max}$ = 40°). Absorption corrections were not applied.

The structure was solved by direct method using the SHELXS-97 program and refined by least-squares (LS) method using the same program. Nonhydrogen atoms were refined by anisotropic full-matrix LS (over $\mathbf{F}^2$). 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 thermal parameter of the corresponding C, N, or O. Positions of hydroxyl H atoms were not found.

The final agreement factors were: $R_1(F)$ = 0.127, $wR_2(F^2)$ = 0.159, GOF = 1.121 over all independent reflections [$R_1(F)$ = 0.083, $wR_2(F^2)$ = 0.136] calculated for 1077 reflections with $I > 2\sigma(I)$ and included in the final refinement stage.

Data from the XSA were deposited as a CIF file in the Cambridge Crystallographic Database (CCDC 237465).

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