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ALKALOIDS FROM *Arundo donax*. XVI. STRUCTURE OF THE NEW DIMERIC INDOLE ALKALOID ARUNDAVINE

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The new bis-*indole alkaloid arundavine, a tryptamine—tryptamine base, was isolated from roots of* Arundo donax. *The dimer consists of monomeric units of two known indole alkaloids, alline and bufotenine, joined through the N1 and C4′ atoms, respectively, to give the structure 8-[3-(2-dimethylaminoethyl)-5-hydroxy-1H-indol-4-yl]-1-methyl-2,3,8,8a-tetrahydro-1H-pyrrolo[2,3-b]indol-3a-ol.*

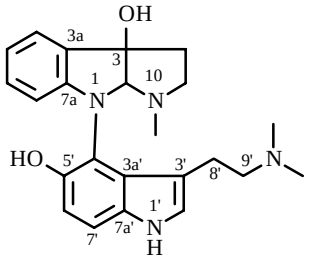
Key words: *Arundo donax*, Poaceae, *bis*-indole alkaloid, arundavine, isolation, structure, x-ray structure analysis.

In continuation of systematic studies of alkaloids from *Arundo donax* L. (Poaceae, grasses), we studied the alkaloid content of *A. donax* roots from Fergan district (Uzbekistan). Column chromatography of the total bases over aluminum oxide isolated N-methyl-tetrahydro-β-carboline [1], arundamine [2], arundanine [3], and arundacine [4]. Rechromatography of the individual fractions isolated a new alkaloid of composition $C_{23}H_{28}N_4O_2$, named arundavine (**1**).

The IR spectrum of **1** has absorption bands (cm^{-1}) for active H at 3343 and 3247 (N–H, O–H), an aromatic ring (1606, 1540), and an ether (950).

The mass spectrum of **1** shows a peak for a molecular ion with *m*/*z* 392 and a protonated peak $[M + 1]^+$ with *m*/*z* 393. The spectrum also shows peaks for fragment ions. Thus, peaks of ions with *m*/*z* 375 and 374 (98%) correspond to loss by the molecular ion of 17 and 18 amu, respectively. This is consistent with a hydroxyl in the alkaloid. Fragment peaks of ions with *m*/*z* 347 $[M - 45]^+$, 334 $[M - 58]^+$, and 320 $[M - 72]^+$ correspond to sequential cleavage of a side N-dimethylaminoethyl group, analogously to other dimeric indole alkaolids of this plant, e.g., arundamine and arundanine [2, 3]. The base peak in the spectrum is that with *m*/*z* 57 (100%), which corresponds to cleavage of the CH_2–$N(CH_3)_2$ fragment with migration of one proton. Peaks typical of an indole ring are also observed in the mass spectrum at *m*/*z* 130, 115, 103, 97, and 95 [5].

The spectral properties of arundavine, its high molecular weight, and a comparison with dimeric alkaloids of this plant (arundinine [6], arundamine, arundanine, arundarine) are consistent with its dimeric structure.



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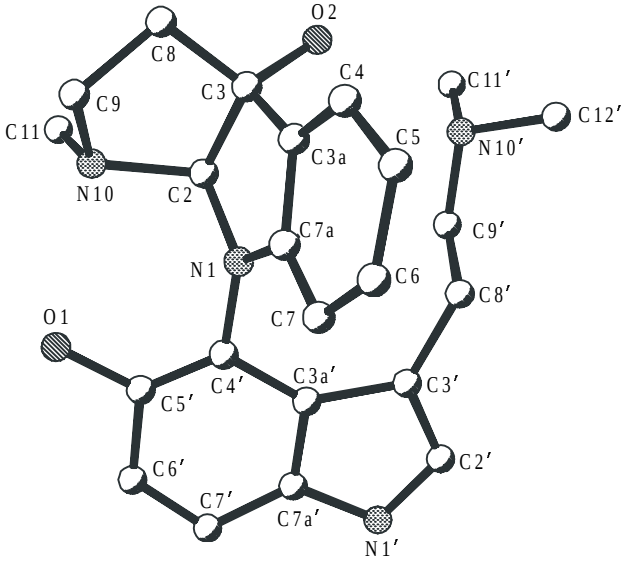

Fig. 1. Molecular structure of arundavine.

The complete structure of **1** was established by an x-ray structure analysis (XSA), which was performed on two crystal modifications as the solvate (**A**) and the solvent-free form (**B**). Crystals with different unit-cell constants were found in selecting a crystal for the XSA. Form **A** (mp 231-233°C) includes one acetone molecule, i.e., the crystallographically asymmetric unit has the composition $C_{23}H_{28}N_4O_2 \cdot C_3H_6O$. However, the acetone in the crystal lies at two equivalent positions relative to its central C atom. In crystal form **B** (mp 250-252°C), the acetone is absent. Therefore, the XSA enables the geometry of two independent arundavine molecules to be analyzed.

The XSA showed that the isolated compound is dimeric and is a *bis*-indole alkaloid of the tryptamine—tryptamine type. Figure 1 shows the molecular structure of **1** (solvate form) from the XSA. The molecular structure is practically the same in both **A** and **B**. It can be seen that the dimer consists of two monomeric moieties of the known indole alkaloids alline (**a**) [7] and bufotenine (**b**) [8] joined at N1 and C4′ (of **a** and **b**, respectively), similar to that observed in arundamine [2]. The stereochemistry, i.e., the relative configuration of the asymmetric centers and the fusion of the five-membered heterocycles (*cis*) in part **a** of **1**, are the same as those observed in alline.

The bicyclic pseudoaromatic indole nuclei in **1** are practically planar within ±0.03-0.04 Å in the two independent molecules. However, the indole in the alline part of **1** (form **B**) is noticeably distorted. The middle five-membered heterocycle adopts the C2β-envelope conformation with C2 deviating from the plane of the remaining four atoms by 0.21 Å. The reason for this is the condensation of the indole nucleus to the third five-membered ring (loses aromaticity). The distortions in crystalline **A** are somewhat averaged out (deviations of atoms from the plane average ±0.078 Å). This may be due to the poor statistics of the experiment (see Experimental section).

The alline (**a**) and bufotenine (**b**) parts of **1** are situated relative to each other differently in the two crystalline forms. The indole nuclei in **A** make an angle of 68.7°; in **B**, 82.8°. The difference in the placement of the **a**/**b** fragments in **A** and **B** is probably a function of packing factors, i.e., the effects of the crystal field, which is also reflected in the geometry of the intramolecular H-bonds. Whereas in **A** two rather strong intramolecular H-bonds (distances O2...N10′ 2.72 and O1...N10 2.62 Å) are formed, they are weak in **B** (2.81 and 2.75 Å, respectively). Atoms N10 and N10′ with unshared electron pairs are directed toward hydroxyl H atoms of O1–H and O2–H, respectively, and have tetrahedral configurations. Figure 1 and the bond angles show this.

The weak statistics of the experiment for **A** and the higher values of the agreement factors prevent a more detailed discussion of the geometric parameters of the two independent arundavine molecules because the uncertainties in the bond distances reach 0.03 Å, and in solvate molecule where acetone is some more - to 0.07 Å. However, the bond lengths and angles in both crystallin forms are in general similar to those in alline [7] and arundamine [2].

The crystal packing shows that molecules in **A** that are related by a glide plane form a H-bond (N1′–H...O2, N1′...O2 = 2.92 Å) and form an infinite chain along the *a*,*c* diagonal. However, the intermolecular H-bonds in **B** (N1′–H...O1) are weaker and are formed by molecules related by a two-fold screw axis (N1′...O1 = 3.03 Å).

TABLE 1. Chemical Shifts of ^{1}H and ^{13}C and SSCC of Arundavine in DMSO-d_6

Atom	^{1}H (SSCC, Hz)	^{13}C	Atom	^{1}H (SSCC, Hz)	^{13}C
2	4.558 (s)	97.37	2′	7.061 (J = 2.0)	124.24
3		88.13	3′		108.93
3a		131.05	3′a		124.48
4	7.316 (d, J = 7.3)	123.71	4′		116.35
5	6.662 (t, J = 7.3)	117.05	5′		149.35
6	6.959 (t, J = 7.6)	129.16	6′	7.235 (J = 8.6)	112.85
7	5.712	106.11	7′	6.776 (J = 8.6)	111.96
7a	(d, J = 7.8)	149.70	7′a		132.02
8	2.525 (m)	38.19	8′	2.653 (m)	22.05
	2.197			2.626	
9	2.950 (m)	53.36	9′	2.779 (m)	58.17
	2.863			2.625	
10	2.463 (s)	42.46	10′	2.250 (br.s)	42.46

TABLE 2. Correlation Peaks for SSCC $^{2}J_{H\text{-}C}$ and $^{3}J_{H\text{-}C}$ in the HMBC Spectrum of Arundavine in DMSO-d_6

Atoms			
^{1}H	^{13}C	^{1}H	^{13}C
2	N1-CH_3, 3, 3a, 7a, 9	2′	3′, 3′a, 7′a,8′
4	3, 6, 7a		
6	4, 7a	6′	4′, 5′, 7a
7	5, 3a	7′	3′a, 5′
8	2, 3, 3a, 9	8′	3′, 3′a, 9′
9	2, 3, 8, 10	9′	10′
10	2, 9	10′	9′

PMR spectra of arundavine in DMSO-d_6 exhibit two groups of characteristic signals for aromatic atoms at 6.65-7.30 ppm and aliphatic protons at 2.20-3.00 ppm. Furthermore, two more 1H signals appear at positions unusual for them. These are a doublet (J = 7.9 Hz) at 5.71 ppm and a singlet at 4.56 ppm. The COSY spectrum enables all partners to be assigned easily, including the signal at 5.71 ppm, as four aromatic protons of the ortho-substituted benzene ring H4-H7. The signal at 5.71 ppm belongs to H7. Its unusually large strong-field shift can be explained only by effects of the substituent on N1. In this instance, it is the aromatic system of the second half of the dimer, which is situated at a large angle to the aromatic ring of protons H4-H7 and exerts on H7 a strong positive inductive effect, greater than 1.0 ppm. Signals of the remaining protons of this group were assigned using the COSY spectrum (Table 1).

In addition to the signals for H4-H6, the aromatic part of the spectrum also contains two coupled doublets (J = 8.6 Hz at 7.24 and 6.78 ppm) that belong to aromatic protons H7′ and H6′. A poorly resolved doublet (J = 2.0 Hz) for H2′ appears at 7.06 ppm. The poorly resolved SSCC apparently belongs to N1′–H.

The singlet at 4.56 ppm can probably be assigned to H2, which is situated between two N atoms and quaternary C3. The geminal position of H2 and C3 was confirmed by the peak in the two-dimensional HMBC spectrum (Table 2). The HMBC peaks for H2 also indicate that it is coupled with C3a, C7a, C9, and N10–H.

The aliphatic part of the spectrum shows very interesting distortions for the signals of the two N10′ methyls. Apparently, two H-bonds of N-methyls with hydroxyls exist in both solution and the crystal. However, whereas this has no noticeable effects on N10 (the signal remains a narrow singlet), the signal for N10′ broadens significantly. Apparently, the two methyls are not completely equivalent, causing their signal to broaden whereas the total amplitude of the 6H signal becomes 1.5 times less than the singlet for the three N10–CH_3 protons.

TABLE 3. Principal Crystallographic Parameters and Properties for the XSA of Arundavine (in **A** and **B** Forms)

Structure	**A**	**B**
Molecular formula	$C_{23}H_{28}N_4O_2 \cdot C_3H_6O$	$C_{23}H_{28}N_4O_2$
System	Monoclinic	Trigonal
Space group	$P2_1/n$	$P3_212$
Z	4	6
a, Å	16.351 (7)	8.527 (1)
b, Å	9.154 (5)	8.527 (1)
c, Å	17.613 (9)	50.10 (1)
α	90	90
β	108.16 (19)	90
γ	90	120
V, Å^3	2504.9 (34)	3154.7 (9)
r, g/cm^3	1.197	1.240
Dimensions, mm	0.15×0.40×0.60	0.11×0.40×1.20
Scan range, 2θ	$2.1 \le \theta \le 22.5^\circ$	$2.4 \le \theta \le 25.0^\circ$
μ_{exp}, cm^{-1}	0.79	0.80
Number of reflections	22.93	2041
Number of reflections with I>2σ (I)	1125	1294
R1 [I>2σ (I) and total]	0.143 (0.197)	0.072 (0.114)
wR2	0.284 (0.346)	0.174 (0.212)
Difference electron-density peaks	0.363 and -0.386 e. Å^3	0.233 and -0.218 e. Å^3

The remaining signals in the aliphatic part of the spectrum are complicated multiplets with poorly resolved SSCC typical of strongly coupled four-spin systems. Table 1 gives the chemical shifts of these signals. Their values were found by analyzing two-dimensional NMR COSY, HSQC, and HMBC correlation spectra. Table 2 gives a list of the principal peaks in the HMBC spectrum.

Thus, spectral data and an XSA of arundavine established the structure 8-[3-(2-dimethylaminoethyl)-5-hydroxy-1H-indol-4-yl]-1-methyl-2,3,8,8a-tetrahydro-1H-pyrrolo[2,3-b]indol-3a-ol.

EXPERIMENTAL

UV spectra were obtained on a Lambda-16 spectrometer; IR spectra, on a Perkin—Elmer System 2000 FT IR in KBr disks; mass spectra (EI, 70 eV), on an MX-1310 spectrometer with direct sample introduction into the ion source at ionization chamber temperature 150°C. NMR spectra were recorded on AM 300 (C) and DRX 500 (H and 2D spectra) spectrometers.

Column chromatography used aluminum oxide (neutral) 100/160 μm. TLC was performed on Al_2O_3 (5/40 μm) plates using $CHCl_3$:CH_3OH (**1**, 2:1), ether (**2**), and benzene (**3**).

Isolation of Arundavine. Total alkaloids from *A. donax* L. roots (18 g) collected during rapid growth in Fergan district were chromatographed over an Al_2O_3 column with elution by benzene, $CHCl_3$, and $CHCl_3$:CH_3OH mixtures in various proportions. The second fraction of $CHCl_3$ eluates (total 6) was rechromatographed over a silica-gel column with elution by $CHCl_3$ (5-mL fractions). Fractions 6-30 were combined and rechromatographed over Al_2O_3 with elution by benzene (25 fractions of 5 mL). Fractions 3-15 of the benzene eluates afforded crystals of arundavine (**1**, TLC, Al_2O_3), R_f 0.35 (system **1**), R_f 0.10 (system **2**), R_f 0.25 (system **3**).

IR spectrum (cm^{-1}): 3343, 3247, 1606, 1540, 1481, 1463, 1385, 1289, 1241, 1142, 1101, 1054, 1001, 950, 827, 755.

Mass spectrum: 392 $[M]^+$, 393 [M + 1], 375, 374 (98%), 347, 334, 331, 292, 288, 273, 247, 173, 171, 145, 130, 115, 97, 95, 92, 58, 57 (100%).

X-ray Structure Analysis. As noted above, two crystals of the alkaloid were collected from a single crystallization medium.

The small amount of isolated compound did not give single crystals of the required quality and size to perform an XSA. Therefore, several crystals had to be selected on the diffractometer. It was noted that the selected crystals had different unit-cell constants. Visual inspection and a check of the melting points showed that the crystallization medium contained two crystalline forms of a single compound. Crystals obtained from a mixture of ethanol and acetone had different habits. The needle-like transparent crystals located on the bottom of the vessel were the solvate **A** (mp 231-233°C) whereas the planar transparent crystals located on the side walls of the vessel were form **B** (mp 250-252°C).

The selected crystals were examined by XSA. The unit-cell constants of **A** and **B** crystals were determined and refined on a Stoe Stadi-4 diffractometer (T = 295 K, graphite monochromator). Intensities of reflections were measured on the same diffractometer using $\omega/2\theta$-scanning for **A** and ω-scanning for **B** and Mo Kα-radiation (graphite monochromator). Table 3 lists the principal parameters of the XSA and calculations. Absorption corrections were not applied.

Structures were solved by direct methods using the SHELXS-97 program and were refined by least-squares (LS) methods using the same program. All nonhydrogen atoms were refined by anisotropic full-matrix LS (on F^2). Peaks of the acetone of crystallization were observed in the initial stage of the structure solution for **A**. The solvate molecule was disordered. The three atoms from C1A (O and two methyl C) occupy six equivalent positions.

The positions of H atoms were found geometrically and refined with fixed isotropic displacements $U_{iso} = nU_{eq}$, where n = 1.5 for methyls and 1.2 for the others and U_{eq} is the equivalent isotropic displacement of the corresponding C or N atoms. The positions of hydroxyl H atoms were found from a difference electron-density synthesis only for **B**.

The poor quality of the data set obtained from the crystal of unsatisfactory size and quality and the disordering of the acetone solvate caused the agreement factor for refinement of **A** to remain above the commonly accepted value.

Data from the XSA were deposited as a CIF file in the Cambridge Crystallographic Database (CCDC238865 and CCDC238866).

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