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ALKALOIDS OF *Arundo donax*. XI. NMR SPECTROSCOPIC STUDY OF THE STRUCTURE OF THE DIMERIC ALKALOID ARUNDAMINE

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The dimeric indole alkaloid arundamine is isolated from the total bases of Arundo donax *L. (Poaceae) roots. The structure of arundamine is investigated using ordinary one-dimensional ^{1}H and ^{13}C NMR, J-modulated ^{13}C NMR, and various types of two-dimensional spectra, COSY, NOESY, HSQC, and HMBC.*

Key words: *Arundo donax*, Poaceae, alkaloids, arundamine, two-dimensional NMR spectroscopies (COSY, NOESY, HSQC, HMBC).

The aerial part and roots of *Arundo donax* L. have been used since antiquity in folk medicine as diuretics and sudorifics and to cure female illnesses [1, 2]. The active principles of the plant extracts are alkaloids. A study of the chemical composition of *A. donax* L. isolated about 15 alkaloids [3, 4], including the dimeric bases arundinine [5] and arundamine.

Arundamine (**1**) is a while crystalline compound, mp 104-105°C. The UV spectrum exhibits maxima at 222 and 285 nm (log ε 4.36 and 3.74). The IR spectrum has absorption bands for active H (NH, OH), $-CH_3$, $-CH_2$, and an aromatic ring. The mass spectrum has a peak for the molecular ion with *m*/*z* 376 $[M]^+$. Fragments characteristic of indole with *m*/*z* 130 and 115 are found in the mass spectrum of arundamine. The spectrum also exhibits a peak for an ion with *m*/*z* 204, indicative that the structure of the alkaloid includes a bufotenine moiety that is formed via fragmentation of the molecular ion of arundamine and loss of an ion with *m*/*z* 173. The presence of a peak for an ion with *m*/*z* 174 in the mass spectrum indicates that the structure of the second half of arundamine is similar to the dipterin core [6]. An x-ray structure analysis of arundamine has been reported [7, 8]. It was noted that it is a combination of the two known indole bases dipterin and bufotenine, which are bonded at N1′ and C4, respectively. It seemed interesting to study the structure of arundamine as a model compound for NMR spectroscopy.

The structure of arundamine was studied using a wide range of experimental methods. These included ordinary one-dimensional ^{1}H and ^{13}C NMR spectroscopies, J-modulated ^{13}C NMR, and various types of two-dimensional (2D) spectra, COSY, NOESY, HSQC, and HMBC. The use of such a global approach in the NMR spectral study provides an exhaustive and unambiguous determination of the main NMR spectral parameters such as chemical shifts of ^{1}H and ^{13}C and spin—spin coupling constants (SSCC), assignment of all NMR signals to the correpsonding atoms, and establishment of the complete through-space coupling of ^{1}H nuclei, the nuclear Overhauser effect (NOE) coupling scheme. Reliable assignment of all proton signals and reconstruction of the NOE scheme are very important for the study of arundamine. The presence of cross-peaks between aromatic protons of one half of the dimer and substituents in the other half indicates that the spatial structure of the alkaloid is remarkable because the structural fragments can approach each other through space.

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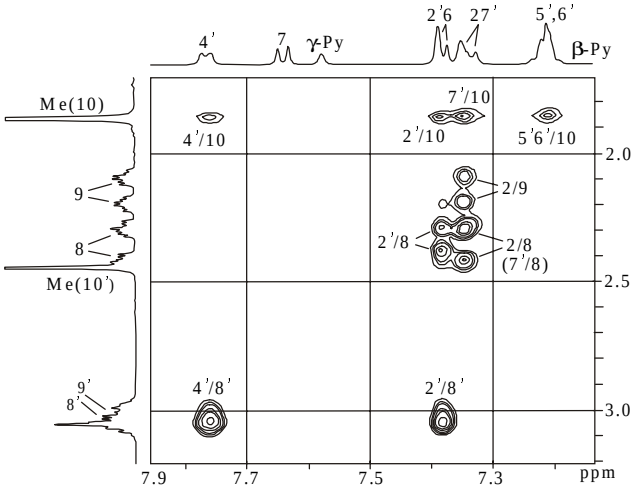

Fig. 1. NOESY spectrum of arundamine.

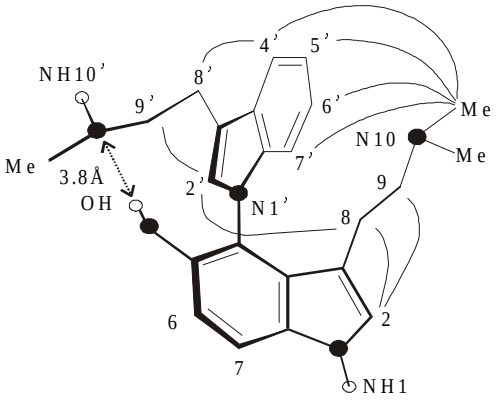

Fig. 2. Spatial structure of arundamine.

The reason that this unique conformation is stable may be the presence of intramolecular H-bonds between the C5 hydroxyl and N10′ on the other half of the dimer. According to the x-ray structure analysis, this interaction in the crystalline state is achieved through an additional water molecule. Molecular modeling of this conformation of the dimer (semi-empirical PM3 method, HyperChem program) did in fact reveal an energy minimum with the appropriate placement of the hydroxyl and the substituent C8′–C9′–N10′. However, the length of the probable H-bond OH...N is 3.8 Å; its energy, 0.10 eV. This is insufficient to stabilize the structure. The lack of an OH–N10′ H-bond in pyridine solution was confirmed by the lack in the spectrum of a signal for the hydroxyl proton, which probably exchanges with residual water in the pyridine (broad signal at 4.9 ppm). The main reason that the conformation noted above is stabilized is the significant barrier to rotation around the C4–N1′ bond. The calculated value of this barrier is 15.5 kcal/mole.

The PMR spectrum of arundamine in Py-d_5 exhibits two main groups of signals for the aromatic protons in the range 7.2-7.8 ppm (8 protons) and aliphatic protons in the range 1.8-3.1 ppm (18 protons). The NH1 proton appears as a 1H singlet at 11.88 ppm. The signals of the aromatic protons of the five-membered rings, H2 and H2′, appear as two singlets at 7.35 and 7.38 ppm, respectively. The singlet for H2 is slightly broadened relative to that for H2′ due to coupling with NH1. This is confirmed in the COSY and NOESY spectra. An AB system for H6 and H7 appears as two doublets with SSCC J = 8.6 Hz at 7.38 and 7.64 ppm, respectively. A correlation for 7.64/11.88 ppm in the NOESY spectrum corresponds to the NOE between H7 and NH1.

The four-spin system of aromatic protons H4′—H7′ gives three signals that can be assigned on the basis of the 2D COSY and NOESY spectra. The central protons H5′ and H6′ form a common 2H multiplet at 7.21 ppm. The edge protons H4′ and H7′ appear as two broad doublets with J = 7.5 Hz at 7.76 and 7.33 ppm, respectively. The SSCC of the second doublet could not be reliably measured because it overlaps the signal for H2. The NOESY spectrum contains a characteristic correlation 7.76/3.02 ppm for H4′/H8′ coupling, which enables the doublets for H4′ and H7′ to be assigned.

The aliphatic part of the spectrum contains two singlets for methyls [$N(Me)_2$, 1.86; NMe, 2.44 ppm] and five multiplets for methylene protons of substituents. The presence of 2D homo- and heterocorrelation spectra simplifies the assignment of these multiplets. The four methylene protons of the substituent C8′ and C9′ form one common multiplet at 3.02 ppm. The elevated intensity of this multiplet and the correlation in the NOESY spectrum of the multiplet at 3.02 ppm and the methyl on N10′ suggests that the NMR is also sensitive to the NH10′ proton. The NOESY spectrum has only two correlations for this multiplet with aromatic protons that are naturally the coupling of methylene H8′ and H9′ with H4′ (3.02/7.76 ppm) and H2′ (3.02/7.38 ppm) (Fig. 1). The lack of other distant NEO couplings of this substituent indicates that it has a peripheral orientation in the structure.

TABLE 1. ^{1}H and ^{13}C Chemical Shifts in **1**

Atom	^{1}H	^{13}C	Atom	^{1}H	^{13}C
2	7.35	125.29	2′	7.38	129.03
3	-	113.28	3′	-	114.15
3a	-	133.13	3′a	-	117.10
4	-	128.84	4′	7.76	111.66
5	-	149.04	5′	7.21	119.25
6	7.38	113.09	6′	7.21	122.01
7	7.64	113.14	7′	7.33	119.41
7a	-	126.81	7′a	-	139.58
8	2.42/2.28	24.10	8′	3.02	26.19
9	2.20/2.08	61.35	9′	3.02	52.90
10	1.46	45.12	10′	2.44	36.45

The methylene protons of substituent C8 and C9 form four separate multiplets: H8, 2.42 and 2.28; H9, 2.20 and 2.08 ppm. These give well resolved correlations in the NOESY and COSY spectra for H2. The correlation in the NOESY spectrum of the N10 methyl protons with all aromatic protons of the other half of the dimer is remarkable: $N(CH_3)_2$→H2′,H4′-H7′ (Fig. 1). The presence of an H8/H2′ correlation (and possibly H8,H9/H7′) and the unusual high-field position of signals for $N(CH_3)_2$ (1.86 ppm) indicate that the C8–C9–N10 substituent has a specific placement. Atom N10 should be located above the aromatic part of the second half of the dimer. This stereochemistry of the dimer provides additional shielding of the $N(CH_3)_2$ protons and further NOE coupling of the substituent with the aromatic fragment of the other half. The planes of the aromatic fragments of the dimer should be twisted by about 90° relative to each other (Fig. 2). Shielding of the $N(CH_3)_2$ protons is noted both for a pyridine solution of the alkaloid (spectrum under discussion) and in $CDCl_3$ and DMSO solutions (1.73 and 1.67 ppm). The substituent C8′–C9′–N10′ is free and oriented along the periphery of the molecule. It is sufficiently free to rotate. This may be why the signals of the five protons of the linear chain coalesce into one rather sharp (Δw = 52 Hz) multiplet. The signal of NH10′ can be assigned only to the multiplet at 3.02 ppm, which is at rather high field for an NH proton.

Signals of the ^{13}C NMR were assigned using J-modulated ^{13}C NMR spectra and 2D heterocorrelation HSQC and HMBC spectra. The chemical shifts are listed in Table 1.

EXPERIMENTAL

IR spectra were recorded on a Perkin—Elmer Model 2000 Fourier spectrometer in KBr pellets; mass spectra, in an MX 1310 spectrmeter equipped with a direct probe into the ion source. NMR spectra were recorded on a Bruker AM-500 spectrometer at working frequency 500 MHz for protons and 125.8 MHz for ^{13}C.

We used aluminum oxide (neutral) 100/160 μm for column chromatography; aluminum-oxide 5/40 μm plates and system 1 ($CHCl_3$—CH_3OH, 9:1) for TLC.

Arundamine (1). The isolation of **1** has been reported [8]. $C_{23}H_{28}N_4O_2$. **1** is freely soluble in methanol and ethanol; moderately, in acetone; poorly, in $CHCl_3$ and benzene. R_f = 0.4 (TLC, aluminum oxide, system 1).

IR spectrum: 3334-3049, 2935-2799, 1459-1390, 1612-1505, 764-744 cm^{-1}.

Mass spectrum: 376 $[M]^+$, 346, 322, 276, 259, 204, 174, 173, 146, 130, 115, 103, 58, 44.

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