MOLECULAR STRUCTURE OF 5′-BROMOLAPPACONITINE

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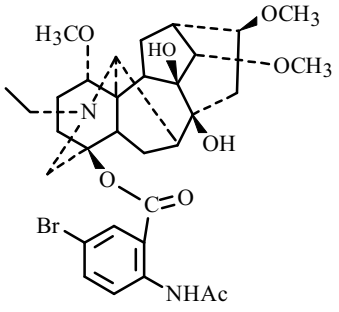
The structure of 5′-bromolappaconitine that was synthesized by an alternate method was solved by XSA.

Key words: lappaconitine, 5′-bromolappaconitine, pyridinium dichlorobromate, XSA, ring conformations, gas-phase quantum-chemical calculations.

The synthesis of 5′-bromolappaconitine (**1**) has been reported [1]. Its antiarrhythmic activity has been investigated [2, 3]. It was found that the hydrobromide of **1** is practically an order of magnitude more effective than the hydrobromide of lappaconitine **2** (preparation Allapinine [4]) as an antiarrhythmic in $CaCl_2$ and adrenaline arrhythmia models. The hydrobromide of 5′-bromolappaconitine is 4.8 times less toxic than Allapinine [3, 4]. Therefore, the search for alternate pathways for preparing **1** and the study of its structure seemed timely.



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Herein a method for preparing **1** by bromination of lappaconitine (**2**) using pyridinium dichlorobromate ($PyHBrCl_2$), a new stable brominating agent for bromination of aromatic compounds [5], is described. Bromination of an acetylanilide by an equivalent amount of this reagent resulted in rapid formation of bromo derivatives, including *o*-substituted ones [5]. This last feature prompted us to use $PyHBrCl_2$ in our work with the hope of synthesizing the still unknown 3′-bromolappaconitine. However, as it turned out, bromination of **2** by 1 eq. of this reagent in CH_2Cl_2 was unsuccessful. Bromination in ethanol gave a complicated mixture of products [*N*-deacetyllappaconitine, 5′-bromolappaconitine (**1**), *N*-deacetyl-5′-bromolappaconitine, etc.]. Compound **1** was isolated in 32% yield using $PyHBrCl_2$ only with 5 eq. of the reagent in CH_2Cl_2. 3′-Bromolappaconitine was apparently not formed. An x-ray structure analysis (XSA) was carried out for the synthesized 5′-bromolappaconitine (**1**).

Figures 1a and 1b show the structures of two crystallographically independent molecules of **1** that differ in the orientation of the C16 methoxyl. The bond lengths are similar to those of starting lappaconitine (**2**) [6]. Six-membered rings A (C1-C5, C11), B (C7-C11, C17), and E (C4, C5, C11, C17-C19) had the chair conformation with a distortion toward the envelope/chair. The distorted boat conformation of ring A is usually observed due to formation of an intramolecular H-bond by the protonated N atom (hydrobromide of lappaconitine [7]) or by replacing the C1 methoxyl by hydroxyl (e.g., condelphine [8]).

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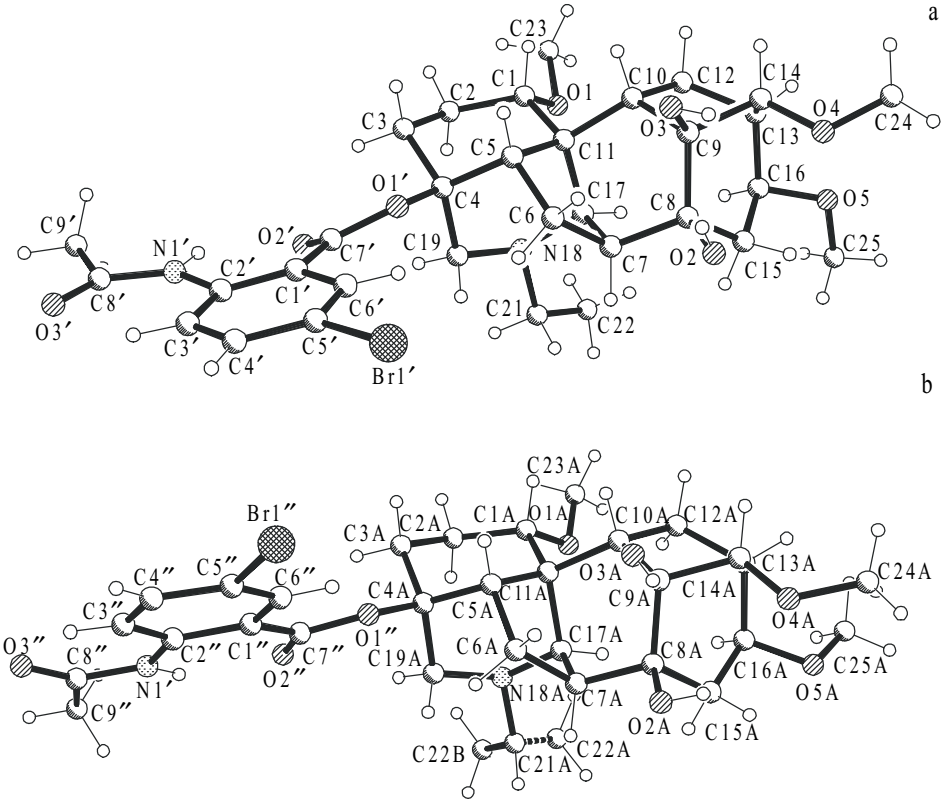

Fig. 1. Molecular structure of 5′-bromolappaconitine (**1**) (structures of two crystallographically independent molecules *a* and *b* are shown).

The boat conformation of ring A in **1** was less favorable by 2.3 kcal/mol (gas-phase DFT/PBE/3z calculations). Ring D (C8, C9, C13-C16) had the boat conformation with a distortion toward an envelope that is often seen for similar alkaloids. Deviations of C14 and C15 from the plane of the remaining atoms were 0.83, 0.88 and 0.37, 0.28 Å, respectively, for the two independent molecules. The chair conformation for this ring (e.g., in talatisamine [9]) in our instance was not a local minimum. Five-membered ring C (C9, C10, C12-C14) had the envelope conformation with C14 deviating from the plane of the other atoms by 0.75 and 0.67 Å; ring F (C5-C7, C11, C17), the twist conformation with C11 and C17 deviating by 0.44, –0.38 and 0.37, –0.47 Å, respectively, for the two independent molecules.

The different orientation of the C16 methoxyl in the two independent molecules (Fig. 1) produced different C13C16O5C25 torsion angles of –162.7 and –65.0°, respectively. This angle in lappaconitine (**2**) [6] is –165.8°; in lappaconitine hydrobromide [7], disordered over two positions (–150.1 and –97.2°). Disorder of the N18 ethyl group was observed in the second molecule of **1** (0.4:0.6 ratio). The C17N18C21C22 torsion angles were –73.1 and –144.3°. This angle in lappaconitine hydrobromide was –66.3; in lappaconitine, –164.6°. According to gas-phase calculations, changing the orientation of the C16 methoxyl and the N18 ethyl in **1** changes the energy by about 0.2 kcal/mol. The 2-(acetylamino)benzoate moiety is nearly planar (deviation of atoms in the range ±0.41 and ±0.13 Å) with an intramolecular H-bond N1′–H...O2′ (H...O, 2.02 and 2.01 Å; N–H...O, 135 and 136°).

According to the hydroxyl H-atom positions found by the SHELXL-97 program [10], all OH groups form bifurcated H-bonds, both intra- and intermolecular. The intramolecular H-bonds were O2–H...O3 (H...O, 2.21 Å, O–H...O, 118°), O3–H3...O4 (H...O, 2.59 Å, O–H...O, 107°), O2A–H...O4A (H...O, 2.39 Å, O–H...O, 127°), O3A–H...O2A (H...O, 2.30 Å, O–H...O, 108°). The intermolecular H-bonds O2–H...O4A (H...O, 2.19 Å, O–H...O, 147°), O3–H...O3A (H...O, 2.28 Å, O–H...O, 177°), 02A–H...O2 (H...O, 2.31 Å, O–H...O, 138°), O3A–H...O4 (H...O, 2.34 Å, O–H...O, 118°) linked the two independent molecules into dimers that were combined into ribbons along diagonals in the *b*-*c* plane through C25A–H...O5 (H...O, 2.21 Å, C–H...O, 167°) interactions. Dimers were not observed in the crystal of starting lappaconitine (**2**) [7].

EXPERIMENTAL

NMR spectra in $CDCl_3$ were recorded on a Bruker AV-300 instrument at operating frequency 300.13 MHz. The course of reactions and the purity of products were monitored by TLC on Silufol UV-254 plates using $CHCl_3$:C_2H_5OH. Pyridinium dichlorobromate was prepared by the literature method [5].

Synthesis of 5′-Bromolappaconitine using $PyHBrCl_2$. A mixture of lappaconitine (**2**, 584 mg, 1 mmol) and $PyHBrCl_2$ (1155 mg, 5 mmol) was dissolved in CH_2Cl_2 (20 mL), stirred at room temperature for 4 d, and treated with ammonia solution (25%) until the pH was ~10. The aqueous layer was separated. The organic layer was dried over anhydrous $MgSO_4$. Solvent was distilled in a rotary evaporator. The mixture was separated by column chromatography over SiO_2 with elution by $CHCl_3$:C_2H_5OH (50:1). Yield of 5′-bromolappaconitine, 32% of theoretical (215 mg). The melting point and PMR spectrum agreed with those published [1].

X-ray structure analysis of **1** was performed at room temperature by the standard method on a Bruker P4 diffractometer using Mo Kα-radiation (λ = 0.71073 Å) and a graphite monochromator. Intensities of reflections were measured by θ/2θ-scanning. Absorption was calculated by integrating along the crystal faces (transmission 0.781-0.889). The structure was solved by direct methods using the Sir2002 program and was refined by full-matrix anisotropic and isotropic (for H atoms) least-squares methods using the SHELXL-97 program. Coordinates of H atoms were calculated geometrically and refined using the rider model. The hydroxyl H atoms could not be found in difference syntheses. Therefore, the capabilities of the SHELXL-97 program were used to examine three orientations and select the version giving the best H-bond. The crystallographic data are $C_{32}H_{42}BrN_2O_8$, MW = 662.59, triclinic system, space group *P*1, a = 10.970(2), b = 12.983(2), c = 13.136(2) Å, α = 62.41(1), β = 86.10(1), γ = 74.03(1)°, V = 1590.3(5) Å^3, Z = 2, d_{calc} = 1.384 g/cm^3, μ = 1.345 mm^{-1}, crystal size 0.1 × 0.2 × 0.3 mm, 5755 independent reflections, $2\theta_{max}$ = 51°, R_1 = 0.0617 for 2739 observed ($I > 2\sigma$) reflections, wR_2 = 0.1595 and GooF = 1.004 for all reflections. The absolute structure factor was 0.008(14).

Crystallographic data for **1** and data from the x-ray structure analysis were deposited in the Cambridge Crystallographic Data Centre (number CCDC 692647). Gas-phase quantum-chemical calculations (DFT method, functional PBE, 3z basis) were performed using the PRIRODA program [11].

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