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Indole type akuammiline from *Vinca erecta*: Crystal structure of 10-OAc-Akuammine

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ABSTRACT

Single crystal X-ray diffraction has established the absolute configuration of the indole alkaloids from *Vinca erecta* such as akuammiline-o-acyl derivative of akuammine with a 3D stable polycyclic framework. Crystal data for $C_{24}H_{28}N_2O_5$: orthorhombic, space group $P2_12_12_1$ (no. 19), a = 7.349(3) Å, b = 16.099(5) Å, c = 17.323(5) Å, V = 2049.5(12) Å^3, Z = 4, T = 293(2) K, μ(CuKα) = 0.789 mm^{-1}, *Dcalc* = 1.376 g/cm^3, 1742 reflections measured (7.496° ≤ 2Θ ≤ 119.792°), 1742 unique (R_{sigma} = 0.0374) which were used in all calculations. The final R_1 was 0.0608 (I > 2σ(I)) and wR_2 was 0.1680 (all data). The polycyclic framework of the well-known picrinine and akuammine is compared. The ether bridges located in different positions of the framework and forming five-membered cycles do not change the conformation of the polycyclic akuammiline framework. In *V. erecta* alkaloids, the exomethylene fragment (C18-C19=C20-C21) of the polycyclic backbone always takes on the E-condition.

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1. Introduction

Vinca erecta Rgl. et Schmalh. (fam. Apocynaceae) perennial herb spread in the mountainous and foothill regions of Central Asia [1,2], and this plant contains a large number of indole alkaloids [3,4]. Plant alkaloids are biologically active substances and are used in medicine as important medicines [5].

The handbook [4] notes the isolation from *V. erecta* of five indoline alkaloids such as akuammiline (according to the systematics of Lee Men [6]): picrinine (**1**) [7,8], vincaricine (**2**) [9,10], vinkarinine (**3**) [11], akuammine (**4**) [12], 10-o-methylakuammine (**5**) [13], which differs in the location of the ether bridge in the akuammiline skeleton (Figure 1). Essential oxygen atoms in the case of 1-3 bind the atoms of the polycyclic framework C2 and C5, and in the case of 4,5-C2 and C22. In compound **1** and **2**, the carbon atom C22 is absent, but the polycyclic skeleton of akuammiline is preserved.

In order to compare the conformations of the akuammiline polycyclic skeleton and unambiguously determine the absolute configuration (the values of R and S chirality descriptors), X-ray structural analysis (XRD) of the indoline alkaloid 10-OAc-akuammine molecule (**6**) was carried out. Compound **6** is formed by processing the amount of alkaloids with 5% acetic acid in the process of isolating them from the plant.

2. Experimental

2.1. Materials and apparatus

Plants of *V. erecta* were grown in natural conditions in the mountain of Piskent, Tashkent region, Uzbekistan. Dried material was powdered and kept in a desiccator at room temperature, in the dark, until the analysis. Compound **6** is formed as a result of processing the amount of alkaloids with 5% acetic acid in the process of isolating them from the plant, *V. erecta*. Single-crystal X-ray diffraction data were collected on a STOE Stadi-4 four-circle diffractometer using CuKα-radiation (λ = 1.54184 Å) (T =293 K, θ/2θ-scan) equipped with a graphite monochromator.

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Table 1. Crystal data and details of the structure refinement for compound **6**.

Parameters	Compound 6
Empirical formula	$C_{24}H_{28}N_2O_5$
Formula weight	423.47
Temperature (K)	293.15
Crystal system	Orthorhombic
Space group	$P2_12_12_1$
a, (Å)	7.349(3)
b, (Å)	16.099(5)
c, (Å)	17.323(5)
Volume (Å^3)	2049.5(12)
Z	4
ρ_{calc} (g/cm^3)	1.376
μ (mm^1)	0.789
F(000)	904.0
Crystal size (mm^3)	0.2 × 0.3 × 0.7
Radiation	CuKα (λ = 1.54184)
2Θ range for data collection (°)	5.1 to 119.8
Index ranges	$0 \le h \le 8$, $0 \le k \le 18$, $0 \le l \le 19$
Reflections collected	1742
Independent reflections	1403 [R_{int} = 0.00, R_{sigma} = 0.0374]
Data/restraints/parameters	1742/0/282
Goodness-of-fit on F^2	1.130
Final R indexes [I≥2σ (I)]	R_1 = 0.0608, wR_2 = 0.1438
Final R indexes [all data]	R_1 = 0.0841, wR_2 = 0.1690
Largest diff. peak/hole (e.Å^{-3})	0.194/-0.304
Flack parameter	0.3(8)

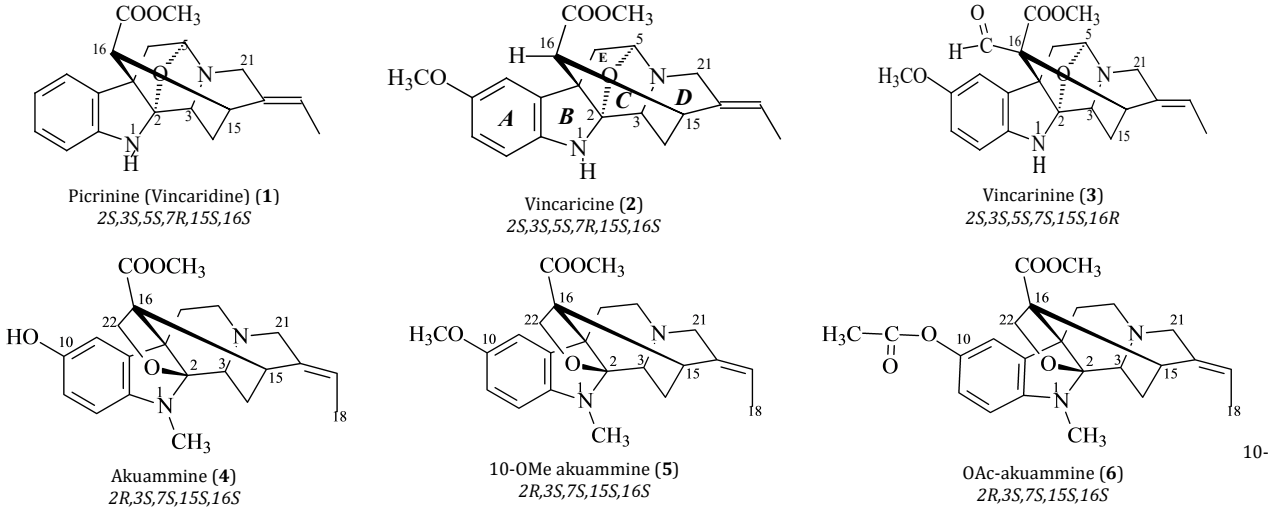

Figure 1. The structure of akuammine alkaloids from *Vinca erecta.*

2.2. X-ray crystal structure determination of compound 6

Single-crystal X-ray diffraction experiment of compound **6** was performed on a STOE Stadi-4 four-circle diffractometer using CuKα-radiation. The unit cell parameters of the crystal were determined and refined on this diffractometer. The crystals possessed rhombic space group $P2_12_12_1$, Z = 4. A three-dimensional set of reflections for crystal was obtained on this diffractometer. Table 1 shows the main parameters of X-ray diffraction experiments and calculations of the refinement of the crystal structure of compound **6**. The structural parameters including bond distances and bond angles for compound 6 are listed in Table 2.

The structure was deciphered by direct methods within the SHELXS-97 program [14], calculations to refine the structure were performed using the SHELXL-2014/7 program [15]. All non-hydrogen atoms were refined by the least squares method (F^2) in the full-matrix anisotropic approximation. Hydrogen atoms at carbon atoms are set geometrically and refined according to the rider's scheme with fixed isotropic displacement parameters U_{iso}=nU_{eq}, where n = 1.5 for methyl groups and 1.2 for the others (U_{eq} is the equivalent isotropic parameter for the displacement of the corresponding carbon atoms).

3. Results and discussion

3.1. Crystal structure of compounds 6

Indoline alkaloids **1**, **2**, and **3** are of the type of the skeleton of akuammiline. Alkaloid **2** differs from compound **1** by the presence of the 10-exo OCH_3-group in the position, and in compound **3** the aldehyde CHO-group is added to the position C16. The spatial structure of compound **1** was previously defined by the single crystal X-ray diffraction analysis [16]. The CCDC base contains its 3D structure, where all six-membered boat-shaped cycles, ring C (C2-C3-N4-C5-C6-C7) is divided by the ether bridge into two five-membered cycles, the C/D-*cis* junction (C3-C14-C15-C20-C21-N4). Only the six-membered cycle formed by the C2-C3-C14-C15-C16-C7 links exists in the form of a chair. Ring B (C2-C7-C8-C13-N1) takes the form of a 2α envelope. Nitrogen atoms N1 and N4 in sp^3 hybridization. Molecule of compound **1** forms a three-dimensional rigid framework, and it is possible that, in the natural derivatives **2** and **3**, the stereochemistry of the polycyclic framework remains.

Table 2. Bond lengths and angles for compound **6**.

Atom-Atom	Bond length (Å)	Atom-Atom	Bond length (Å)
O1-C25	1.300(9)	C6-C7	1.541(8)
O1-C10	1.420(8)	C7-C8	1.516(8)
O2-C25	1.150(9)	C7-C16	1.541(8)
O3-C22	1.444(7)	C8-C9	1.373(8)
O3-C2	1.475(8)	C8-C13	1.392(8)
O4-C17	1.196(7)	C9-C10	1.388(9)
O5-C17	1.343(8)	C10-C11	1.361(9)
O5-C26	1.441(8)	C11-C12	1.390(9)
N1-C13	1.395(8)	C12-C13	1.372(9)
N1-C2	1.438(8)	C14-C15	1.537(9)
N1-C23	1.442(8)	C15-C20	1.529(9)
C2-C7	1.525(8)	C15-C16	1.575(8)
C2-C3	1.529(9)	C16-C17	1.483(8)
C3-N4	1.500(9)	C16-C22	1.532(8)
C3-C14	1.527(10)	C18-C19	1.464(11)
N4-C5	1.447(8)	C19-C20	1.321(9)
N4-C21	1.468(9)	C20-C21	1.510(9)
C5-C6	1.511(8)	C24-C25	1.424(10)
Atom-Atom-Atom	**Bond angles (°)**	**Atom-Atom-Atom**	**Bond angles (°)**
C25-O1-C10	124.0(6)	C11-C10-C9	122.4(6)
C22-O3-C2	108.4(4)	C11-C10-O1	123.3(6)
C17-O5-C26	116.8(6)	C9-C10-O1	114.1(6)
C13-N1-C2	105.3(5)	C10-C11-C12	119.2(6)
C13-N1-C23	120.9(6)	C13-C12-C11	119.0(6)
C2-N1-C23	120.6(6)	C12-C13-C8	121.3(6)
N1-C2-O3	106.8(4)	C12-C13-N1	128.7(6)
N1-C2-C7	104.5(5)	C8-C13-N1	110.0(5)
O3-C2-C7	103.6(5)	C3-C14-C15	107.6(6)
N1-C2-C3	120.6(5)	C20-C15-C14	104.5(6)
O3-C2-C3	108.2(5)	C20-C15-C16	116.8(5)
C7-C2-C3	111.9(5)	C14-C15-C16	110.4(5)
N4-C3-C14	109.7(6)	C17-C16-C22	112.9(5)
N4-C3-C2	111.6(5)	C17-C16-C7	113.7(5)
C14-C3-C2	105.6(6)	C22-C16-C7	100.3(5)
C5-N4-C21	110.1(5)	C17-C16-C15	111.0(5)
C5-N4-C3	113.5(5)	C22-C16-C15	105.8(5)
C21- N4-C3	112.7(6)	C7-C16-C15	112.4(5)
N4-C5-C6	112.8(5)	O4-C17-O5	122.3(6)
C5-C6-C7	109.8(5)	O4-C17-C16	125.7(6)
C8-C7-C2	98.4(5)	O5-C17-C16	111.9(6)
C8-C7-C6	108.6(5)	C20-C19-C18	130.0(7)
C2-C7-C6	113.1(5)	C19-C20-C21	121.9(6)
C8-C7-C16	118.5(5)	C19-C20-C15	124.3(6)
C2-C7-C16	97.4(5)	C21-C20-C15	113.4(6)
C6-C7-C16	118.3(5)	N4-C21-C20	116.8(5)
C9-C8-C13	119.7(6)	O3-C22-C16	104.4(5)
C9-C8-C7	131.8(6)	O2-C25-O1	119.3(8)
C13-C8-C7	108.0(5)	O2-C25-C24	124.6(8)
C8-C9-C10	118.3(6)	O1-C25-C24	116.0(7)

Table 3. Intra- and inter-molecular interactions on the crystal structure **6**.

D—H...A	d(D—H), Å	d(H...A), Å	d(D...A), Å	∠(DHA), °	Symmetry
C5-H5A...N1	0.970	2.460	2.989(8)	114.0	-
C9-H9A...O4	0.930	2.580	3.244(8)	129.0	-
C11-H11A...O2	0.930	2.540	2.860(11)	101.0	-
C14-H14A...O2	0.970	2.560	3.126(15)	118.0	1-*x*, -1/2+*y*, 1/2-*z*
C14-H14B...O3	0.970	2.220	2.585(9)	101.0	-

This assumption confirms the spatial structure of compound **2** (*S*)-cathafoline (**1'**) [17], where the ether bridge is absent in the polyamine framework of akuammiline, but the conformation of the polycyclic framework remains (Figure 2).

Structure of the compound **4** and its 10-OMe derivative **5** was established on the basis of spectral data and an absolute configuration was proposed [12,13,18]. The spatial structure of compounds **4** and **5** is determined by single crystal XRD on the basis of its 10-OAc derivative (**6**), which is shown in Figure 2. The five-membered heterocyclic of the indoline core **B** (C13-N1-C2-C7-C8) and **E** (C2-O3-C22-C16-C7) take the 2β- and 7β-envelope form, respectively, and the six-membered cycles C (C2-C3-N4-C5-C6-C7) and **D** (C3-C14-C15-C20-C21-N4) take the boat conformation and they are *cis*-articulated. The flat (with an accuracy of ±0.04 Å) 10-O-acetyl group in the exo-position is slightly rotated by 14.1° relative to the benzene ring (±0.01 Å) and does not significantly affect the stereochemical parameters of the akuammine polycycle. Atom O2 of the carbonyl group has an abnormally large thermal parameter in the direction perpendicular to the plane of the OAc group, which is explained by the free oscillation of this atom in this direction. N1 nitrogen atoms (the sum of the internal valent angles is 347.7°) and N4 (336.1°) in sp^3 hybridization and the methyl group with N4β is oriented similarly to that observed in picrinine.

In akuammine and picrinine (skeletons that differ in the location of the ether bridge), the conformation of the cycles (polycyclic framework) is practically the same. In indolines of *V. erecta*, the skeletons of the akuammiline type are observed in the Z-states of the exomethylene group (fragment C18-C19=C20-C15). However, in the CCDC database there are examples of indolines (the same types of skeletons) isolated from other plants with E-states of the exomethyl fragment [16]. In the crystal structure of compound **6**, the molecules are connected via weak non classic hydrogen bonds (Table 3).

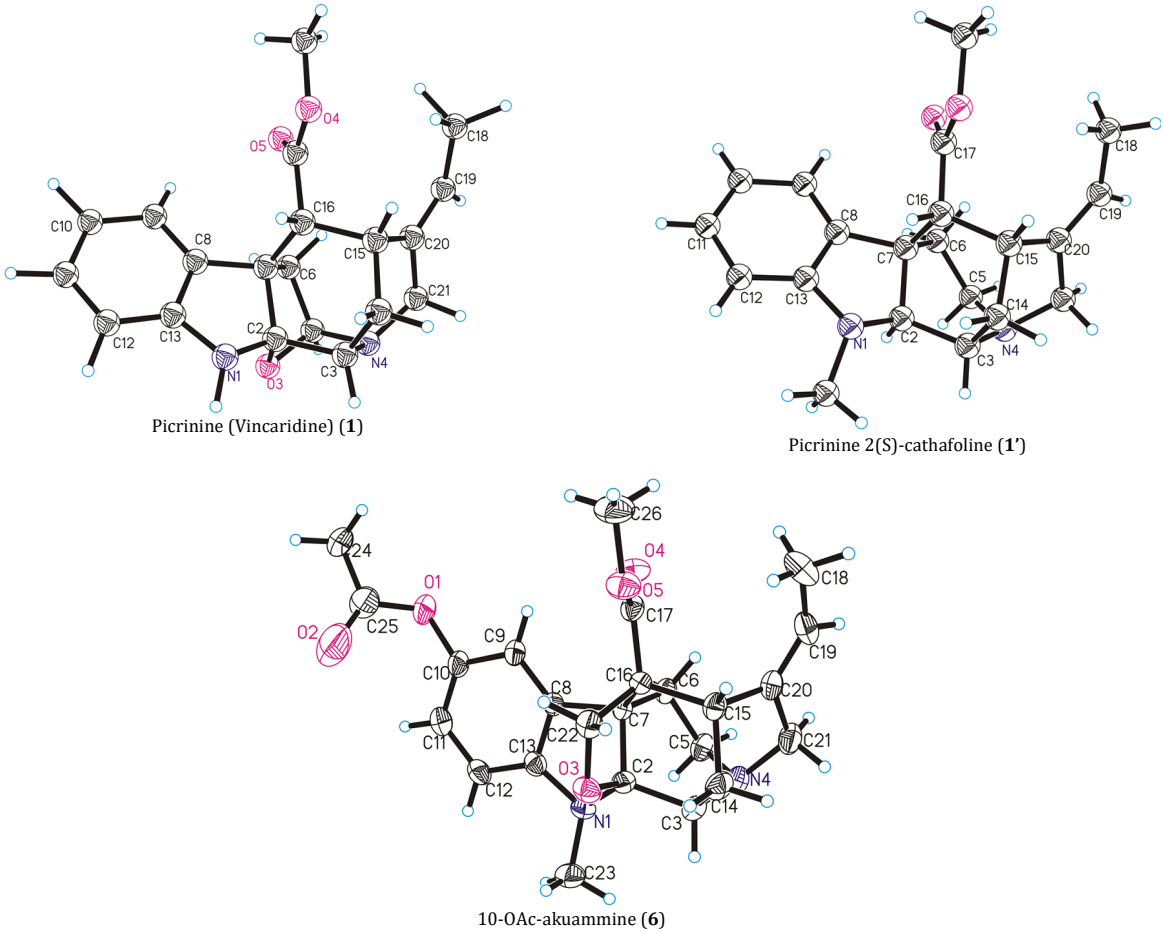

Figure 2. The crystal structure of compounds **1**, **1'** and **6**.

4. Conclusion

The ether bridges located in different positions and forming five-membered cycles do not change the conformation of the polycyclic akuammiline framework. In indolines of *V. erecta*, skeletons of the akuammiline type are observed in the ***Z***-states of the exomethylene group.

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Supporting information

CCDC-1038564 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via https://www.ccdc.cam.ac.uk/structures/, or by e-mailing data request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0)1223-336033.

Disclosure statement

Conflict of interests: The authors declare that they have no conflict of interest.
Author contributions: All authors contributed equally to this work.
Ethical approval: All ethical guidelines have been adhered.

Sample availability: Samples of the compounds are available from the author.

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