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Indole alkaloids from *Vinca erecta* type of sarpagine and ajmaline

Shahobiddin Adizov [1,*] and Bakhodir Tashkhodjaev [2]

[1] Laboratory of High-Molecular Plant Substances and Physical Methods of Research, Institute of the Chemistry of Plant Substances, Academy of Sciences, 100170, Tashkent, Uzbekistan
adizovsh@gmail.com (S.A.)
[2] *Physical Methods of Research, Institute of the Chemistry of Plant Substances, Academy of Sciences of the Republic of Uzbekistan, Tashkent 100170, Uzbekistan*
tashkhodjaev@rambler.ru (B.T.)

* *Corresponding author at:* Laboratory of High-Molecular Plant Substances and Physical Methods of Research, Institute of the Chemistry of Plant Substances, Academy of Sciences, 100170, Tashkent, Uzbekistan.
Tel: +998.71.2625913 Fax: +998.71.2627348 e-mail: adizovsh@gmail.com (Sh. Adizov).

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ABSTRACT

The single crystal X-ray diffraction method established the absolute configuration of the *Vinca erecta* indole alkaloids of the akuammidine sarpagine type (3*S*, 5*S*, 15*R*, 16*R*) and its o-acyl derivative, as well as the type of ajmaline, quebrachidine (2*S*, 3*S*, 5*S*, 7*R*, 15*S*, 16*R*, 17*S*) and majoridine (2*R*, 3*S*, 5*S*, 7*R*, 15*R*, 16*S*, 17*R*). Crystal data for $C_{21}H_{24}N_2O_3$ (**1**): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 6.3949(5) Å, b = 13.5009(10) Å, c = 22.461(3) Å, Z = 4, 7694 reflections measured (7.64° ≤ 2Θ ≤ 152.294°), 3813 unique (R_{int} = 0.0798) which were used in all calculations. The final R_1 was 0.0680 (I > 2σ(I)) and wR_2 was 0.1650 (all data). Crystal data for $C_{23}H_{26}N_2O_4$ (**2**): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 9.9730(13) Å, b = 10.2090(10) Å, c = 20.409(3) Å, Z = 4, 7959 reflections measured (8.666° ≤ 2Θ ≤ 151.998°), 4212 unique (R_{int} = 0.0386) which were used in all calculations. The final R_1 was 0.0477 (I > 2σ(I)) and wR_2 was 0.1171 (all data). Crystal data for $C_{42}H_{48}N_4O_6$ (**3**): monoclinic, space group $P2_1$ (no. 4), a = 8.9320(10) Å, b = 21.515(5) Å, c = 9.5420(10) Å, β = 97.103(10)°, Z = 2, 16677 reflections measured (9.34° ≤ 2Θ ≤ 151.836°), 7393 unique (R_{int} = 0.0278) which were used in all calculations. The final R_1 was 0.0366 (I > 2σ(I)) and wR_2 was 0.1037 (all data). Crystal data for $C_{23}H_{28}N_2O_3$ (**4**): orthorhombic, space group $P2_12_12_1$ (no. 19), a = 10.636(2) Å, b = 11.208(12) Å, c = 16.725(13) Å, Z = 4, 1650 reflections measured (9.498° ≤ 2Θ ≤ 119.97°), 1650 unique (R_{int} = 0.0436) which were used in all calculations. The final R_1 was 0.0608 (I > 2σ(I)) and wR_2 was 0.1720 (all data). In alkaloids such as sarpagine and ajmaline exo, the substituents of alkaloids do not lead to conformational changes of a stable polycyclic framework. In the series of sarpagine, alkaloids form mono-salts in the tetrahedral nitrogen N4, and in indolines of the ajmaline type, the tetrahedral hybridization of the N1 and N4 atoms favors the formation of disols. In *V. erecta* alkaloids, the exomethylene fragment (C18-C19=C20-C21) of the polycyclic backbone always takes on the E-state.

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1. Introduction

Vinca erecta Rgl. et Schmalh. (сем. Apocynaceae)-Perennial herbaceous plant is common in the mountainous and foothill regions of Central Asia [1,2], and contains a large number of indole alkaloids [3-5]. Plant alkaloids are biologically active substances and have been used in medicine as important medicines [2,6].

The reference book [5] notes the isolation of five indole alkaloids of the sarpagine type from *V. erecta* (according to the systematics of Lee Men [7]): tombosine [8], 6-hydroxy-tombosine (ervincidine) [9], *o*-benzoyl-tombosine [10], 10-methoxy-alkyllosimine [11] and akuammidine [12], which differ in exo-substituents in the sarpagine skeleton (Figure 1). In tombosine, the carbon atom C22 is absent, but the polycyclic skeleton of sarpagin remains. Its structure was determined by X-ray diffraction method (XRD) in the form of an ethanol solvate called (+)-normacusine B [13].

V. erecta has been isolated four indolines with the ajmaline skeleton of a polycyclic skeleton [5]. The alkaloids vincamajine [14], vincamedine [15], quebrachidine [16] and majoridine (majdinine) [17] differ in substituents in the ajmaline skeleton, their structures are studied by various spectral methods [18,19].

The sarpagine and ajmaline groups have a 3D polycyclic framework and a two-dimensional representation of the structure, indicating the relative α- or β-orientation of the substituent is difficult. For example, due to the fuzzy reduction of the chemical structure of ervincidine [9], it was mistakenly accepted as 16-epi-6-hydroxy tombosine in the 2010 reference book [20], although later its structure was corrected for 6-hydroxy tombosine [5]. For this reason, in determining the absolute configuration, the values of the chirality descriptors *R*, *S* are the main addition in the description of the asymmetric center.

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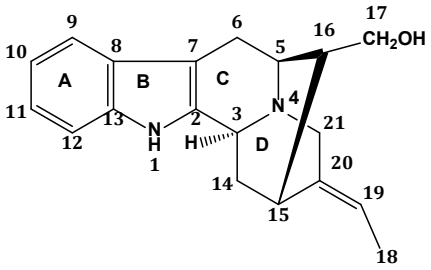
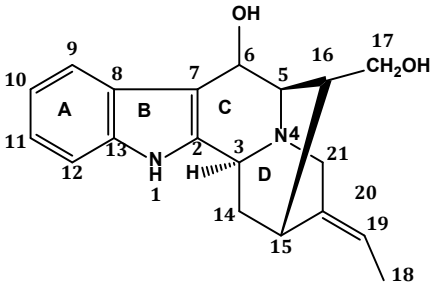
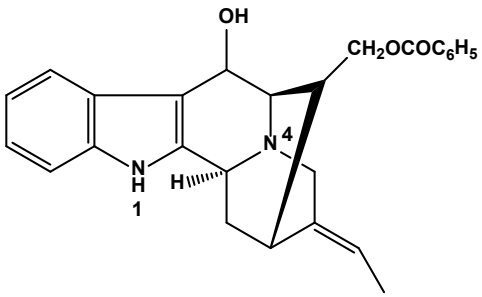
Sarpagines



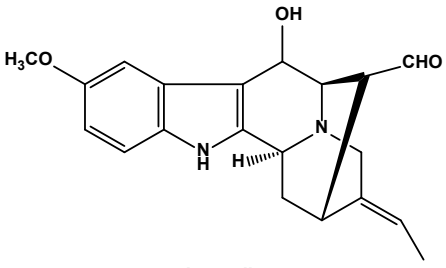
3S,5S,15R,16R Tombosine (Tombosine, Normacusine)



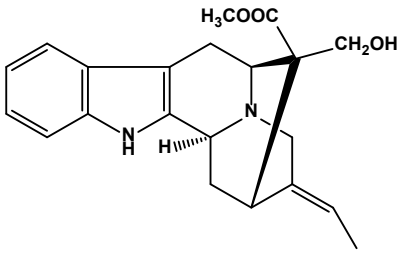
3S,5S,15R,16R 6-Hydoxytombosine (Ervincidine)



3S,5S,15R,16R o-Benzoyle-tombosine

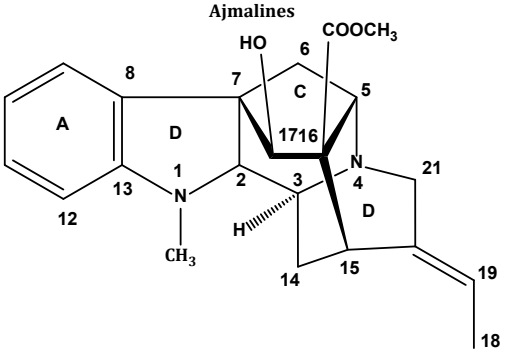


10-Methoxyvellosimine

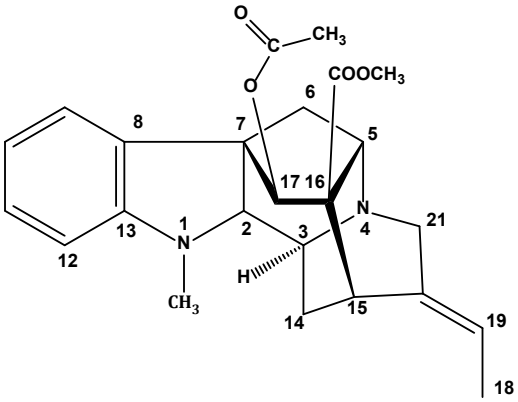


3S,5S,15S,16S, Akuammidine

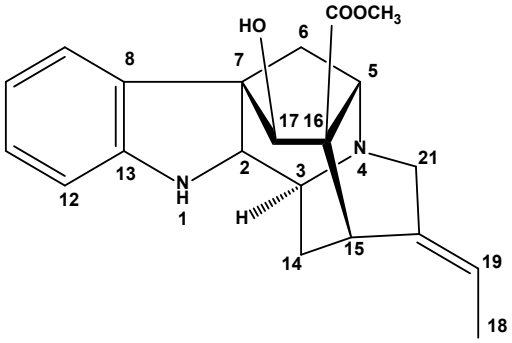
Ajmalines



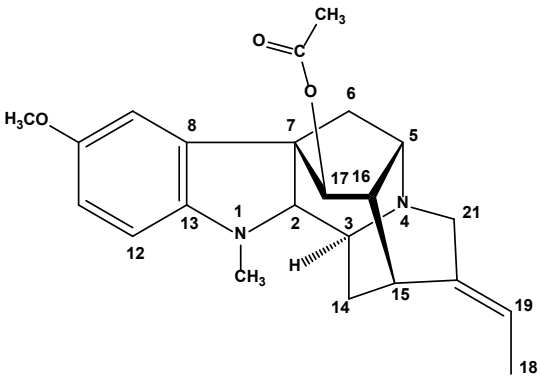
2S,3S,5S,7R,15S,16R,17S Vincamajine



2S,3S,5S,7R,15S,16R,17S Vincamedine



2S,3S,5S,7R,15S,16R,17S Quebrachidine (Vincarine)



2R,3S,5S,7R,15R,16S,17R Majoridine (Majdine)

Figure 1. The structure of sarpagines and ajmaline alkaloids from *Vinca erecta.*

Table 1. Crystal data and details of the structure refinement for compounds **1-4**.

Structures	1	2	3	4
Empirical formula	$C_{21}H_{24}N_2O_3$	$C_{23}H_{26}N_2O_4$	$C_{46}H_{48}N_4O_6$	$C_{23}H_{28}N_2O_3$
Formula weight	352.42	394.46	704.84	380.47
Temperature (K)	290.15	293.15	293.15	293.15
Crystal system	Orthorhombic	Orthorhombic	Monoclinic	Orthorhombic
Space group	$P2_12_12_1$	$P2_12_12_1$	$P2_1$	$P2_12_12_1$
a (Å)	6.3949(5)	9.973(1)	8.932(1)	10.636(2)
b (Å)	13.5009(1)	10.209(1)	21.515(5)	11.208(12)
c (Å)	22.461(3)	20.409(3)	9.542(1)	16.725(13)
β (°)	90	90	97.103(10)	90
Volume (Å^3)	1939.2(3)	2078.0(4)	1819.6(5)	1994(3)
Z	4	4	2	4
ρ_{calc} (g/cm^3)	1.207	1.261	1.286	1.268
μ (mm^1)	0.652	0.702	0.695	0.671
F(000)	752	840	752	816
Crystal size (mm^3)	0.30 × 0.50 × 0.60	0.30 × 0.50 × 0.70	0.30 × 0.40 × 0.60	0.26 × 0.30 × 0.54
Radiation	CuKα (λ = 1.54184 Å)	CuKα (λ = 1.54184 Å)	CuKα (λ = 1.54184 Å)	CuKα (λ = 1.54184 Å)
2Θ range for data collection (°)	3.82 to 76.147	4.333 to 75.999	4.670 to 75.918	4.749 to 59.985
Index ranges	-7≤ *h* ≤ 4	-12≤ *h* ≤ 11	-9≤ *h* ≤ 11	0≤ *h* ≤ 11
	-16 ≤ *k* ≤ 15	-12 ≤ *k* ≤ 8	-26 ≤ *k* ≤ 27	0 ≤ *k* ≤ 12
	-26 ≤ *l* ≤ 28	-25 ≤ *l* ≤ 25	-11 ≤ *l* ≤ 11	0≤ *l* ≤ 18
Reflections collected	7694	7959	16677	1650
Independent reflections	3813	4212	7393	1202
	[R_{int} = 0.0798,	[R_{int} = 0.0386,	[R_{int} = 0.0278,	[R_{int} = 0.0436,
	R_{sigma} =0.1337]	R_{sigma} =0.0534]	R_{sigma} = 0.0291]	R_{sigma} = 0.0]
Data/restraints/parameters	3813/2/241	4212/0/267	7393/1/486	1650/0/258
Goodness-of-fit on F^2	0.998	0.940	0.980	1.243
Final R indexes [I≥2σ (I)]	R_1 = 0.068, wR_2 = 0.098	R_1 = 0.0477, wR_2 = 0.0999	R_1 = 0.0366, wR_2 = 0.1005	R_1 = 0.0608, wR_2 = 0.1326
Final R indexes [all data]	R_1 = 0.1969, wR_2 = 0.1650	R_1 = 0.0776, wR_2 = 0.1171	R_1 = 0.0417, wR_2 = 0.1037	R_1 = 0.1013, wR_2 = 0.1720
Largest diff. peak/hole (e.Å^{-3})	0.173/-0.148	0.182/-0.146	0.208/-0.168	0.206/-0.212
Flack parameter	0.1(4)	-0.1(2)	0.17(7)	1.6(1)
CCDC	1897669	1897666	1897662	978765

In order to unambiguously determine the absolute configuration (the values of the chirality descriptors *R*, *S*), X-ray structural analysis of the molecule of the indole alkaloid akuammidine (**1**) and its OAc-derivative (**2**), as well as the indolines of quebrachidine (**3**) and majoridine (**4**) was performed. The absolute configurations of alkaloids such as sarpagine and ajmaline *V. erecta* are clarified.

2. Experimental

2.1. Materials and apparatus

Plants of *V. erecta* were grown in natural conditions in the mountain of Alai, Fergana valley, Uzbekistan. Dried material was powdered and kept in a desiccator at room temperature, in the dark, until the analysis. Samples of alkaloids **1**-**4** were obtained from The Collection of the Laboratory of Chemistry of Alkaloids, Institute of the Chemistry of Plant Substances Academy of Sciences of Republic Uzbekistan.

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), or CCD Xcalibur Ruby diffractometer (Oxford Diffraction) diffractometer equipped with a graphite monochromatic CuKα radiation (λ = 1.54184 Å)

2.2. X-ray crystal structure determination of compounds 1-4

The unit cell parameters of the crystal of compounds **1**, **2**, and **3** were determined and refined on a CCD Xcalibur Ruby diffractometer (Oxford Diffraction) using CuKα radiation [21]. The X-ray diffraction experiment of the crystal of compound **4** was performed on a STOE Stadi-4 four-circle diffractometer using CuKα radiation. A three-dimensional set of reflections for crystals was obtained on these diffractometers, respectively. The absorption correction was introduced using the SADABS program [22]. Table 1 shows the main parameters of X-ray diffraction experiments and calculations of the refinement of the structures of crystals **1**-**4**.

The structures were deciphered by direct methods within the SHELXS-97 program complex [23], calculations to refine the structures were performed using the SHELXL-2014/7 program [24]. All non-hydrogen atoms were refined by the least squares method 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 of displacement of the corresponding carbon atoms). The hydrogen atoms of the NH and OH groups were detected from difference syntheses of electron density (EP) and refined isotropically.

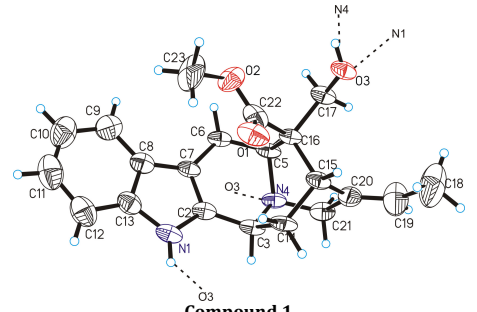
3. Results and discussion

The structure of alkaloids **1** and **2** of sarpagine type according to XRD data is shown in Figure 2, the Flack parameters for the two of them are -0.1(2) and 0.1(3), respectively, which allow determining the absolute configuration of four chiral centers as 3*S*, 5*S*, 15*S* and 16*S*. In the above example, tombosine in exo position 22 contains an H atom (unlike akuammidine), which leads to a change in the chirality of the 16 center-3*S*, 5*S*, 15*S*, 16*R*. Earlier, the spatial structure in the akuammidine crystal was established by XRD in the form of methyl iodide monohydrate [24]. However, the authors did not define the absolute configuration, and the optical antipode of alkaloid is given in the Cambridge Crystallographic Data Centre (CCDC) database. Figure 2 shows its inverted enantiomer, that is, the corrected structure. The structural parameters including bond distances and bond angles for compounds **1**-**4** are listed in Table 2-5, respectively.

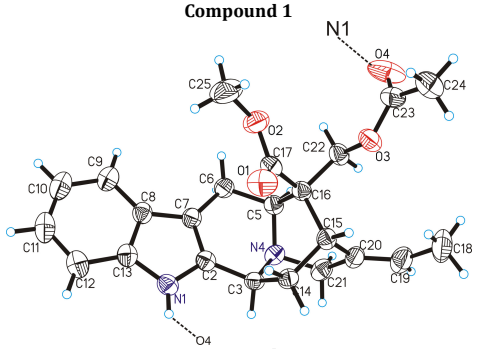
In sarpagines **1** and **2**, the nitrogen atoms N1 and N4 adopt the planar sp^2 and pyramidal-tetrahedral sp^3-configuration, respectively. In these molecules, the indole core is planar, cycle **C** (for compound **1** and **2**; C2, C3, N4, C5, C6, C7, Figure 2) takes a half-seat conformation with the release of N4 and C5 atoms in different directions, and the remaining six-membered cycles (atoms N4, C5, C16, C15, C20, C21) form a bicyclo [2.2.2]octane a heterosystem where the cycles take on the conformation of a slightly distorted bath.

Table 2. Selected bond lengths and angles for compound **1**.

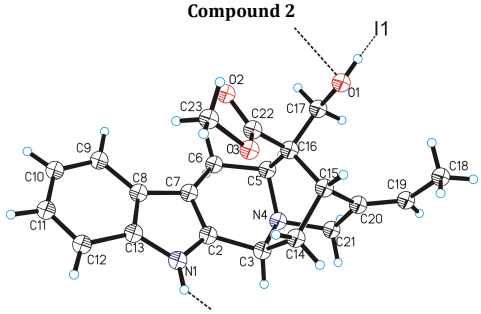
Atom-Atom	Bond length (Å)	Atom-Atom	Bond length (Å)
O3-C17	1.424(8)	C16-C15	1.539(10)
O2-C22	1.289(13)	C16-C17	1.542(9)
O2-C23	1.642(12)	C16-C5	1.585(9)
N1-C2	1.377(10)	C20-C19	1.305(13)
N1 C13	1.399(12)	C20-C15	1.469(12)
O1-C22	1.243(12)	C20-C21	1.508(12)
C22-C16	1.534(13)	C2-C7	1.370(11)
N4-C21	1.482(10)	C15-C14	1.553(9)
N4-C3	1.498(9)	C5-C6	1.514(10)
N4-C5	1.505(8)	C8-C7	1.415(12)
C3-C2	1.459(11)	C7-C6	1.489(10)
C3-C14	1.567(10)	C19-C18	1.539(15)
Atom-Atom-Atom	**Bond angles (°)**	**Atom-Atom-Atom**	**Bond angles (°)**
C22-O2-C23	99.0(9)	C15-C20-C21	111.0(9)
C2-N1-C13	107.3(8)	C7-C2-N1	110.4(9)
O1-C22-O2	123.8(12)	C7-C2-C3	125.0(9)
O1-C22-C16	120.5(12)	N1-C2-C3	124.1(9)
O2-C22-C16	115.5(11)	C20-C15-C14	105.0(7)
C21-N4-C3	109.5(7)	C16-C15-C14	110.7(7)
C21-N4-C5	109.6(7)	N4-C5-C6	108.2(7)
C3-N4-C5	108.2(7)	N4-C5-C16	109.5(6)
C2-C3-N4	108.8(8)	C6-C5-C16	117.3(7)
C2-C3-C14	113.4(7)	C12-C13-N1	126.5(13)
N4-C3-C14	109.2(7)	C12-C13-C8	125.7(13)
C22-C16-C15	110.0(8)	C15-C14-C3	108.3(6)
C22-C16-C17	105.1(7)	C2-C7-C8	107.2(9)
C15-C16-C17	112.2(7)	C2-C7-C6	121.0(10)
C22-C16-C5	116.3(8)	C8-C7-C6	131.6(9)
C15-C16-C5	108.3(6)	C7-C6-C5	109.1(7)
C17-C16-C5	104.9(6)	N4-C21-C20	111.2(8)
C19-C20-C15	127.9(12)	O3-C17-C16	112.4(6)
C19-C20-C21	127.9(12)	C20-C19-C18	126.8(14)



Compound 1



Compound 2



Akuammidine [20]

Figure 2. Spatial structure of compounds **1** and **2**; and quaternary salt of akuammidine [20] (The corrected enantiomer and directions of intermolecular H-bonds are shown).

Table 3. Selected bond lengths and angles for compounds **2**.

Atom-Atom	Bond length (Å)	Atom-Atom	Bond length (Å)
O3-C23	1.310(6)	C16-C15	1.561(6)
O3-C22	1.459(5)	C16-C5	1.596(6)
N1-C13	1.378(6)	C13-C8	1.407(6)
N1-C2	1.379(6)	O4-C23	1.193(6)
N4-C21	1.463(6)	C7-C8	1.434(6)
N4-C5	1.470(5)	C7-C6	1.494(6)
N4-C3	1.477(5)	C14-C15	1.526(6)
O2-C17	1.344(5)	C14-C3	1.557(5)
O2-C25	1.441(7)	C21-C20	1.513(7)
O1-C17	1.199(5)	C15-C20	1.517(6)
C2-C7	1.356(6)	C5-C6	1.540(6)
C2-C3	1.490(5)	C23-C24	1.472(7)
C16-C17	1.524(6)	C20-C19	1.322(7)
C16-C22	1.530(6)	C19-C18	1.491(9)
Atom-Atom-Atom	**Bond angles (°)**	**Atom-Atom-Atom**	**Bond angles (°)**
C23-O3-C22	117.8(4)	N4-C3-C2	106.8(3)
C13-N1-C2	108.3(4)	N4-C3-C14	110.7(3)
C21-N4-C5	109.9(4)	C2-C3-C14	113.5(3)
C21-N4-C3	109.1(3)	O3-C22-C16	107.7(3)
C5-N4-C3	109.1(3)	O1-C17-O2	122.0(4)
C17-O2-C25	117.4(4)	O1-C17-C16	126.5(4)
C7-C2-N1	110.3(4)	O2-C17-C16	111.4(4)
C7-C2-C3	125.3(4)	N4-C21-C20	111.6(4)
N1-C2-C3	124.4(4)	C20-C15-C14	107.0(4)
C17-C16-C22	106.7(4)	C20-C15-C16	107.0(3)
C17-C16-C15	110.3(3)	C14-C15-C16	111.8(3)
C22-C16-C15	111.5(3)	N4-C5-C6	108.9(3)
C17-C16-C5	115.4(3)	N4-C5-C16	111.2(3)
C22-C16-C5	106.7(3)	C6-C5-C16	117.4(3)
C15-C16-C5	106.3(3)	C7-C6-C5	108.4(3)
N1-C13-C12	129.9(5)	O4-C23-O3	122.6(5)
N1-C13-C8	107.7(4)	O4-C23-C24	124.2(5)
C12-C13-C8	122.4(4)	O3-C23-C24	113.2(4)
C2-C7-C8	106.7(4)	C19-C20-C15	126.6(5)
C2-C7-C6	121.4(4)	C19-C20-C21	123.8(5)
C8-C7-C6	131.9(4)	C15-C20-C21	109.6(3)
C15-C14-C3	108.1(3)	C20-C19-C18	129.0(6)

Table 4. Selected bond lengths and angles for compounds **3**.

Atom-Atom	Bond length (Å)	Atom-Atom	Bond length (Å)
O1-C17	1.422(3)	C3-C2	1.517(4)
O1-C17	1.418(3)	C3-C14	1.536(4)
O3-C22	1.330(3)	C17-C7	1.558(3)
O3-C23	1.439(3)	C17-C7	1.556(3)
O3-C22	1.334(3)	C22-C16	1.516(3)
O3-C23	1.444(3)	C6-C7	1.522(3)
O2-C22	1.200(3)	C15-C20	1.511(4)
N4-C21	1.477(4)	C15-C14	1.539(3)
N4-C5	1.493(3)	C15-C16	1.560(3)
N4-C3	1.496(3)	C6-C7	1.526(3)
N4-C21	1.477(4)	C6-C5	1.529(4)
N4-C5	1.493(3)	C16-C5	1.563(3)
N4-C3	1.497(3)	C7-C8	1.508(4)
O2-C22	1.194(3)	C7-C2	1.548(3)
C16-C22	1.519(3)	C9-C8	1.379(4)
C16-C15	1.556(3)	C13-C12	1.390(4)
C16-C17	1.567(3)	C3-C14	1.539(4)
C16-C5	1.575(3)	C21-C20	1.530(4)
N1-C13	1.406(4)	C21-C20	1.523(4)
N1-C2	1.470(4)	C20-C19	1.326(4)
C15-C20	1.514(4)	C20-C19	1.323(4)
C15-C14	1.537(3)	C19-C18	1.498(5)
C2-N1	1.460(3)	C9-C10	1.387(5)
C2-C3	1.525(4)	C19-C18	1.494(6)
C2-C7	1.549(3)	C10-C11	1.374(5)
N1-C13	1.395(4)	C12-C11	1.393(5)
C5-C6	1.532(4)	C11-C10	1.381(5)
Atom-Atom-Atom	**Bond angles (°)**	**Atom-Atom-Atom**	**Bond angles (°)**
C22-O3-C23	117.0(2)	C15-C16-C17	112.52(18)
C22-O3-C23	116.3(2)	C5-C16-C17	104.0(2)
C21-N4-C5	107.3(2)	C8-C7-C6	124.8(2)
C21-N4-C3	108.6(2)	C8-C7-C2	99.02(19)
C5-N4-C3	109.38(19)	C6-C7-C2	106.3(2)
C21-N4-C5	107.0(2)	C8-C7-C17	112.79(19)
C21-N4-C3	108.7(2)	C6-C7-C17	100.14(18)
C5-N4-C3	109.86(19)	C2-C7-C17	114.2(2)
C22-C16-C15	111.1(2)	C12-C13-N1	128.4(2)
C22-C16-C17	108.77(19)	C12-C13-C8	120.9(3)
C15-C16-C17	113.30(19)	N1-C13-C8	110.7(2)

Table 4. Continued.

Atom-Atom-Atom	Bond angles (°)	Atom-Atom-Atom	Bond angles (°)
C22-C16-C5	111.3(2)	O2-C22-O3	123.5(2)
C15-C16-C5	108.39(19)	O2-C22-C16	125.7(2)
C17-C16-C5	103.79(19)	O3-C22-C16	110.8(2)
C13-N1-C2	104.3(2)	N4-C3-C2	106.7(2)
C20-C15-C14	106.4(2)	N4-C3-C14	110.4(2)
C20-C15-C16	107.4(2)	C2-C3-C14	115.1(2)
C14-C15-C16	109.1(2)	N1-C2-C3	116.6(2)
N1-C2-C3	116.9(2)	N1-C2-C7	102.2(2)
N1-C2-C7	102.15(19)	C3-C2-C7	115.1(2)
C3-C2-C7	114.77(19)	C8-C7-C6	126.4(2)
C13-N1-C2	105.2(2)	C8-C7-C2	99.51(18)
N4-C5-C6	111.6(2)	C6-C7-C2	107.20(19)
N4-C5-C16	108.76(19)	C8-C7-C17	111.01(19)
C6-C5-C16	103.69(19)	C6-C7-C17	101.57(19)
N4-C3-C2	106.4(2)	C2-C7-C17	110.92(19)
N4-C3-C14	111.1(2)	C9-C8-C13	120.0(3)
C2-C3-C14	113.9(2)	C9-C8-C7	132.8(2)
O1-C17-C7	110.93(19)	C13-C8-C7	107.1(2)
O1-C17-C16	111.84(19)	N4-C21-C20	110.9(2)
C7-C17-C16	103.61(18)	N4-C21-C20	110.9(2)
O1-C17-C7	108.06(19)	N4-C5-C6	111.6(2)
O1-C17-C16	110.24(18)	N4-C5-C16	109.09(19)
C7-C17-C16	103.36(18)	C6-C5-C16	104.5(2)
O2-C22-O3	123.8(2)	C19-C20-C15	126.6(3)
O2-C22-C16	124.0(2)	C19-C20-C21	124.0(3)
O3-C22-C16	112.2(2)	C15-C20-C21	109.4(2)
C7-C6-C5	99.70(19)	C19-C20-C15	126.7(3)
C20-C15-C14	106.4(2)	C19-C20-C21	123.7(3)
C20-C15-C16	107.4(2)	C15-C20-C21	109.5(2)
C14-C15-C16	108.4(2)	C3-C14-C15	107.90(19)
C7-C6-C5	99.19(19)	C12-C13-N1	128.4(3)
C22-C16-C15	112.2(2)	C8-C13-N1	110.7(2)
C22-C16-C5	110.04(19)	C3-C14-C15	107.7(2)
C15-C16-C5	108.12(19)	C20-C19-C18	127.1(3)
C22-C16-C17	109.6(2)	C20-C19-C18	127.3(4)

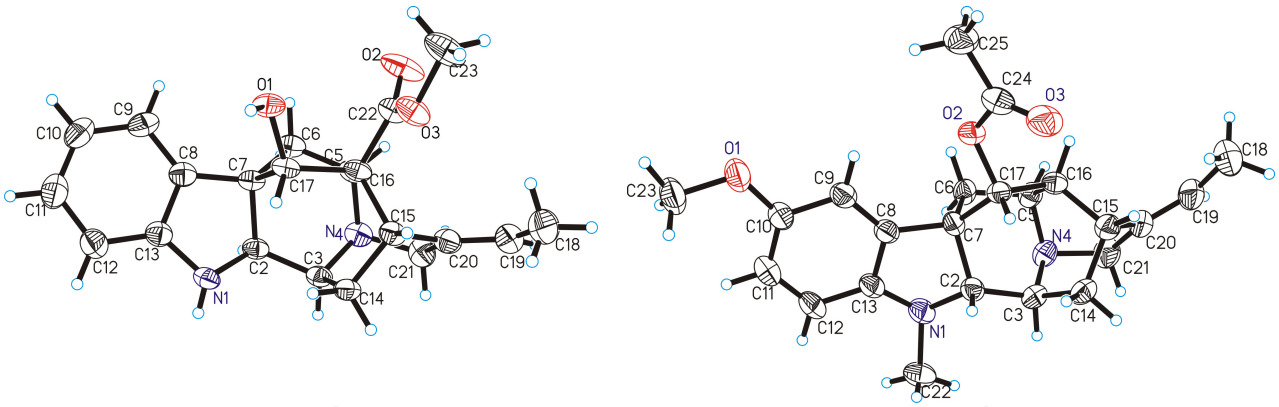
Table 5. Selected bond lengths and angles for compounds **4**.

Atom-Atom	Bond length (Å)	Atom-Atom	Bond length (Å)
O1-C10	1.369(9)	C3-C14	1.540(10)
O1-C23	1.409(9)	C5-C6	1.517(9)
O2-C24	1.359(9)	C5-C16	1.548(9)
O2-C17	1.439(7)	C7-C8	1.509(9)
O3-C24	1.175(9)	C7-C17	1.526(9)
N1-C13	1.404(9)	C14-C15	1.515(10)
N1-C22	1.469(9)	C15-C20	1.492(10)
N1-C2	1.469(8)	C15-C16	1.526(9)
N4-C3	1.465(9)	C16-C17	1.549(9)
N4-C5	1.475(9)	C18-C19	1.496(13)
N4-C21	1.481(9)	C19-C20	1.340(11)
C2-C3	1.523(10)	C20-C21	1.521(11)
C2-C7	1.538(9)	C24-C25	1.480(10)
Atom-Atom-Atom	**Bond angles (°)**	**Atom-Atom-Atom**	**Bond angles (°)**
C10-O1-C23	116.8(6)	C6-C7-C2	107.5(6)
C24-O2-C17	116.2(6)	C17-C7-C2	109.2(5)
C13-N1-C22	116.7(7)	C12-C13-N1	130.0(7)
C13-N1-C2	103.1(6)	N1-C13-C8	111.6(7)
C22-N1-C2	116.0(6)	C15-C14-C3	108.1(5)
C3-N4-C5	109.7(5)	C20-C15-C14	106.0(6)
C3-N4-C21	108.2(6)	C20-C15-C16	105.2(6)
C5-N4-C21	106.1(6)	C14-C15-C16	109.6(6)
N1-C2-C3	119.4(6)	C15-C16-C5	107.7(6)
N1-C2-C7	101.3(5)	C15-C16-C17	114.0(5)
C3-C2-C7	114.6(6)	C5-C16-C17	105.8(5)
N4-C3-C2	111.9(6)	O2-C17-C7	106.7(5)
N4-C3-C14	109.9(6)	O2-C17-C16	111.4(5)
C2-C3-C14	108.9(6)	C7-C17-C16	103.0(5)
N4-C5-C6	107.5(6)	C20-C19-C18	125.2(9)
N4-C5-C16	110.2(5)	C19-C20-C15	126.7(8)
C6-C5-C16	104.1(5)	C19-C20-C21	122.4(8)
C5-C6-C7	100.9(5)	C15-C20-C21	110.5(7)
C8-C7-C6	112.4(5)	N4-C21-C20	108.8(6)
C8-C7-C17	123.8(6)	O3-C24-O2	122.3(8)
C6-C7-C17	102.7(5)	O3-C24-C25	127.4(8)
C8-C7-C2	100.5(5)	O2-C24-C25	110.3(8)

The realized conformations of the cycles do not differ from those observed in the akuammidine cation [25], as well as in the bases of 19(*Z*)-akuammidine isolated from *Gelsemium elegans* [26] and normacusine B [13]. Thus, the conformation of the sarpagine polycyclic framework in various natural derivatives is preserved.In the indoles of *V. erecta* with sarpagine skeletons, the *E*-states of the exomethylene group (C18-C19=C20-C21 atoms) are observed in the C20 position, in contrast to the 19(*Z*)-akuammidine.

Table 6. Intermolecular H-bonds in structures of compounds **1**-**4** (*d*: distance, D: donor, A: acceptor).

Compound	Structure	*d*(N1···O3), Å	*d*(H···A), Å	∠(DHA), °	Symmetry
1	N1-H···O3	2.825(10)	1.98	165	-1/2+*x*, -1/2-*y*, -1-*z*
	O3-H···N4	2.768(9)	1.98	161	1/2+*x*, -1/2-*y*, -1-*z*
2	N1-H···O4	2.917(6)	2.19(4)	145(4)	1+*x*, *y*, *z*
3	O1-H···N4'	2.938 (3)	2.12(6)	167(4)	*x*, *y*, *z*
	O1'-H···N4	2.788(3)	1.99(4)	162(5)	*x*, *y*, -1+*z*
	N1-H···O2	2.953(3)	2.17(4)	166(3)	*x*, *y*, *z*
	N1'-H···O2'	3.156(3)	2.32(4)	165(3)	1+*x*, *y*, *z*



Compound 3 **Compound 4**

Figure 3. Spatial structure of ajmaline **3** (one of two asymmetric molecules is shown) and **4**.

Comparison of the molecular structure of the quaternary salt and the base of akuammidine shows the difference in the position of the flat $COOCH_3$-group at position 22 relative to the sarpagine skeleton. The value of the torsion angle C15-C16-C22-O1 is an indicator of this difference.

In compounds **1** and **2**, it is equal to 2.9 and 5.1°, respectively, in 19(*Z*)-akuammidine, this angle is 5.4° [26], and in the quaternary alkaloid salt, the similar angle takes (opposite) 171.2°. Although the -$COOCH_3$- group in these compounds does not participate in intra- and inter-molecular weak interactions (H-bonds), which indicates the possibility of two (alternative) energetically close conditions.

The spatial structure of alkaloids of the type of ajmaline, quebrachidine (**3**) and majoridine (**4**) according to XRD data is shown in Figure 3. The Flack parameter (0.17(7)) allows determining the absolute configuration of the seven chiral centers of molecule **3** as *2S, 3S, 5S, 7R, 15S, 16R, 17S*. The absolute configuration of *V. erecta* alkaloids of vincamajine and vincamedine is identical with that observed in compound 3. Although earlier their spatial structure was established by PCA [27,28], but the absolute configuration is not determined, optical antipodes are given in the CCDC database. In alkaloid **4**, the H atom of the chiral center C2 is *β*-directed, unlike other ajmalines *V. erecta*. For compound **4**, the chiral centers have the following meanings *2R, 3S, 5S, 7R, 15R, 16S, 17R.*

In alkaloids **3** and **4**, the nitrogen atoms N1 and N4 are in the tetrahedral sp^3-hybridization. The H atom at N1 in 3*α*-is similar to that observed in vincamajine and vincamedine [29], but in compound **4**, nitrogen N1 is inverted and the methyl group has β-direction. In the molecular structures of the ajmalines, the atoms N4, C5, C16, C15, C20, C21 also form a rigid bicycle[2.2.2]octane system, in which six-membered cycles are in the form of a slightly distorted bath (Figure 3). A visual comparison of compounds **3** and **4** shows that the ajmaline skeleton is rigid and there are no differences in exo-substituents for conformational changes. In addition to the ring B (for compound **3** and **4**; N1, C2, C7, C8, C13; Figure 3), which in compound **3** takes the 2*α*-envelope form, and in the compound **4** 2*β*-envelope.

In molecule **3**, there is a difference (rotational) in the location of the flat $COOCH_3$-group (at position 16) relative to the ajmaline skeleton compared to that realized in vincamajine and vincamedine [29]. The C15-C16-C22-O1 torsion angle in compound **3** for two independently found molecules is 134.3 and 130.2°, and in vincamajine and vincamedine the similar angle is -42.8 and -51.1° [29], respectively. Such a difference in torsion angles is probably due to the nature of the intermolecular H-bonds and the packing factor.

In the indoles and *V. erecta* indolines with the skeletons of sarpagine and ajmaline, the E-condition of the exomethylene group (C18-C19=C20-C21) are observed in position C20. However, in the 19(*Z*)-akummidine, the *Z*-condition of this exomethylene group is realized [28]. In this case, the conformation of the polycyclic frame is the same, that is, different exo skeleton substituents and their location do not affect the conformation of the polycyclic frame.

In crystal of compound **1**, the OH group of the initial and N1H groups transformed along the *a* and *b* axes of the molecules form an H-bond of the type N1-H···O3 and O3-H···N4 (Table 6). In crystal of compound **1**, weak H-bonds like C5-H···O1 can be observed. These H-bonds form a two-dimensional grid in the plane of the axes *a* and *b*. In crystal of compound **2**, due to the intermolecular H-bond of type N1-H···O4, between the translated molecules along the *a* axis, a chain is formed. In crystal of compound **2**, there are also weak H-bonds of the type C6-H···O4 and C25-H···O1. In crystal cell of compound **3,** there are two asymmetric alkaloid molecules that are linked by the O1-H···N1 H-bond. This pair, transformed by the symmetry element 2_1 along the *b* axis, forms a chain along the helical axis. Other intermolecular H-bonds of the N1-H···O2 type are formed due to the translation element along the *a* axis (Table 6). As a result, a network is formed in the crystal in the *ab* plane. In crystal of compound **4**, the molecules are located at van der Waals interactions.

Until present time usually do not always noted the obtaining of mono- and disols from isolated alkaloids. However, an analysis of the literature [4,19] shows that disols of alkaloids were obtained only for indoline alkaloids. It is possible that in indolines the tetrahedral hybridization of the N1 and N4 atom favors the formation of disol (disalt). That is, under normal conditions, salt formation depends on the coordination of the nitrogen atoms N1 and N4, and they, due to

the absence of the neighboring double bond, accept the sp^3 hybridization.

4. Conclusion

In alkaloids such as sarpagine and ajmaline exo, the substituents of alkaloids do not lead to conformational changes of a stable polycyclic framework. In the series of sarpagine, alkaloids form mono-salts in the tetrahedral nitrogen N4, and in indolines of the ajmaline type, tetrahedral hybridization of the N1 and N4 atoms favors the formation of disols. 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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Supporting information

CCDC-1897669 (Akuammidine), CCDC-1897666 (OAc-Akuammidine), CCDC-1897662 (Quebrachidine) and CCDC-978765 (Majoridine) contain 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

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ORCID

Shahobiddin Adizov
http://orcid.org/0000-0002-8902-7466

Bakhodir Tashkhodjaev
http://orcid.org/0000-0003-3027-9893

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