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SYNTHESES BASED ON NORFLUOROCURARINE. 7. REDUCTION OF NORFLUOROCURARINE AND FLUOROCURARINE BY METALLIC SODIUM AND SODIUM BOROHYDRIDE

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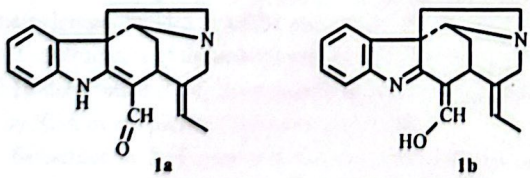
Reduction of norfluorocurarine by sodium in EtOH formed deoxytetrahydronorfluorocurarine and tetrahydronorfluorocurarine. The latter was identical to the Wieland–Humlich 18-deoxyglycol. Reduction of norfluorocurarine by sodium borohydride in alkaline solution occurred with opening of rings C and E and formation of the new indole base 16-decarbmethoxyepistemmadenine. Reduction of fluorocurarine chloride or iodide by sodium borohydride formed the corresponding de-acetylretuline salts. The structures of the products were established by x-ray crystal structure analyses. Norfluorocurarine and representatives of the α-methylenindolenine series formed indoline derivatives upon reduction in acidic and neutral solutions; indole derivatives, in alkaline solution.

Keywords: indole alkaloids, norfluorocurarine, deoxytetrahydronorfluorocurarine, tetrahydronorfluorocurarine, XSA.

We continued synthetic transformations of the available alkaloid norfluorocurarine (**1**) isolated from *Vinca erecta* in order to discover new physiologically active compounds based on it [1]. Norfluorocurarine was reduced in acidic and neutral solutions. Norfluorocurarine contains a reactive aldehyde conjugated to a double bond. IR spectroscopic data [2] and the x-ray molecular structure [3] revealed a strong intramolecular H-bond between the aldehyde and NH groups. This suggested that **1** could convert from the ketone (**1a**) to the enol (**1b**) depending on the reaction medium.

UV spectra of **1** in EtOH were characterized by a strong absorption band at 365 nm and weaker bands at 244 and 300 nm (Fig. 1, **a**). According to the semi-empirical CNDO/S method, the last of these was due to $n\rightarrow\pi^*$ electronic transitions of the carbonyl O atom and N4. Adding base to **1** in EtOH solution produced bathochromic shifts of the absorption bands at 244 and 365 nm and caused the absorption band at 300 nm to disappear (Fig. 1). These changes in the UV bands indicated that the enol tautomer formed in alkaline solution (Fig. 1, **b**). The enol form was energetically less favorable. The difference in the heats of formation (ΔH_f) of the ketone and enol tautomers according to quantum-chemical calculations (semi-empirical PM6 approximation method) was $\Delta H_f = 8.9$ kcal/mol. The transition barrier from the ketone to enol tautomer was 13.1 kcal/mol; the reverse transition barrier, 4.2 kcal/mol. The energetic similarity of the tautomers and the low barrier between them indicated that transitions were possible at room temperature, which was confirmed by the aforementioned assumption based on UV spectral data.



1a

1b

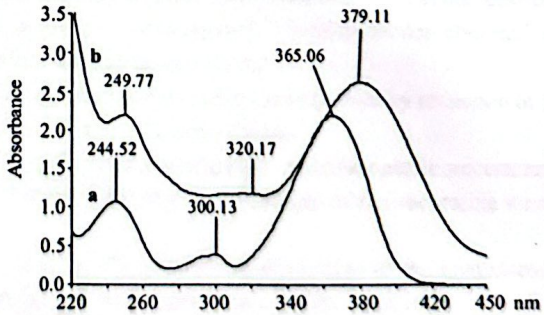


Fig. 1. UV spectra of norfluorocurarine in EtOH (a) and alkaline solution (b).

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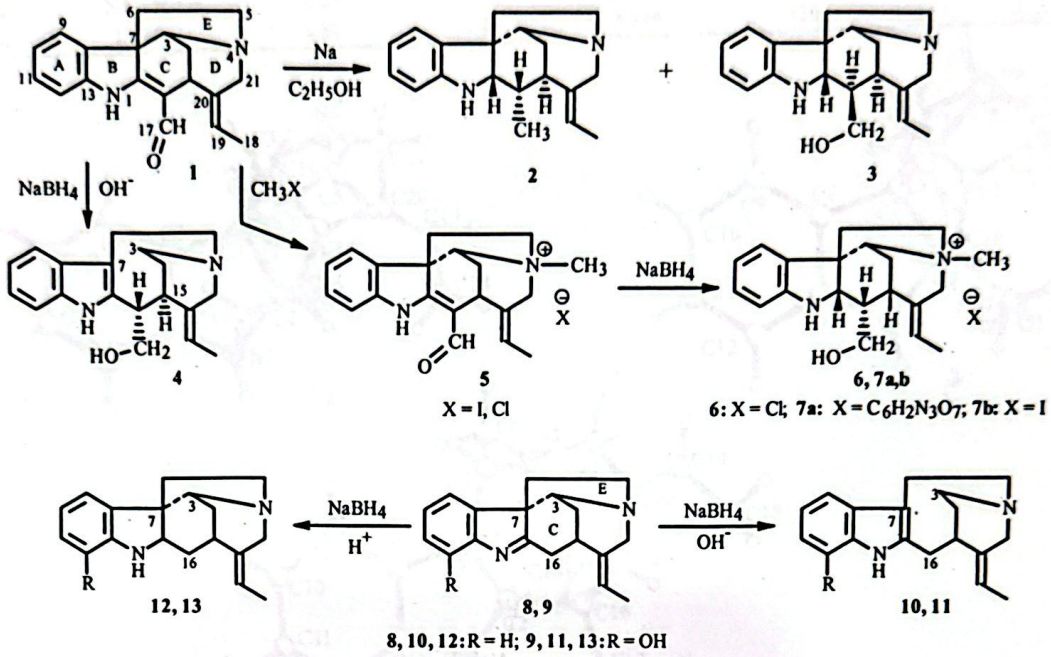
Further studies of the structures of the reaction products showed that the medium determining the tautomeric state of the alkaloid in the reductions played an important role.

The absolute configurations of the asymmetric centers in **1** are considered established [1]. Centers 3*S*, 7*R*, and 15*S* were not affected in all reductions. Atoms C2 and C16 became asymmetric centers and could adopt various configurations after reduction of the C2=C16 double bond. Stereochemical issues in the present work were solved by x-ray crystal structure analyses (XSA) of the reduction products.

Reduction of **1** by metallic sodium in anhydrous EtOH formed two products, deoxytetrahydronorfluorocurarine (**2**) and tetrahydronorfluorocurarine (**3**) [4]. Our structural studies showed that the latter was identical to the Wieland–Humlich 18-deoxyglycol that was synthesized earlier from the natural alkaloid strychnine [5].



Reduction of **1** by $NaBH_4$ in alkaline medium formed the indole base 16-decarbmethoxyepistemmadenine (**4**) with opening of rings C and E (cleavage of the C3–C7 bond) but with retention of the C16 hydroxymethyl group. A similar reaction with cleavage of the C3–C7 bond was observed after reduction of indolenine bases (without the C16 hydroxymethyl) decarbmethoxyakuammicine (**8**) [6] and decarbmethoxyvinervine (**9**) [7], which converted into indole derivatives **10** and **11** in alkaline solution. However, they formed indoline derivatives **12** and **13** upon reduction in acidic solution [7, 8], retaining the norfluorocurarine cyclic framework.

Reduction of fluorocurarine (*N*-β-methylnorfluorocurarine) chloride (**5**) was described earlier. It produced tetrahydrofluorocurarine chloride (**6**) [9]. We repeated this experiment. The resulting structural study showed that the reduced alkaloid was a stereoisomer at C16 of the quaternary salt of **3** (Wieland–Humlich 18-deoxyglycol). The alkaloid deacetylretuline is known in the literature [10]. Its quaternary salt was identical to **6** that was synthesized by us.

In summarizing the aforementioned reactions, it can be noted that indoline derivatives were formed by reduction of **1** and α-methylenindolenines in acidic and neutral solutions; indole derivatives, in alkaline solution.

The structures of the reduction products of **1**, i.e., deoxytetrahydronorfluorocurarine (**2**), tetrahydronorfluorocurarine (**3**), and 16-decarbmethoxyepistemmadenine (**4**), were established by XSA. The reduction products of fluorocurarine were studied by XSA as the picrate (**7a**) and iodide (**7b**).

Structure of 2. Figure 2 shows the XSA molecular structure of **2**. The absolute configuration of the asymmetric centers in **2** that arose as a result of reducing the C2=C16 bond corresponded with those shown in Fig. 2 (2*S*,16*S*).

The five-membered heterocycle B in the indole core adopted the 2α-envelope conformation; ring E, close to the 7α-envelope conformation. Ring C was a distorted chair; ring D, a boat with C14 and C21 deviating from the plane of the other four atoms. A weak intermolecular H-bond between tertiary N4 of the starting molecule and an NH group translated along the *a* axis was noted in the crystal. Table 1 presents the parameters of this H-bond.

TABLE 1. Intermolecular H-bonds in Crystal Structures of **2**, **3**, **4**, **7a**, **7b**

Compound	A...H-D	D (D-H), Å	D (H...A), Å	D (D...A), Å	< (DHA), deg	Symmetry
2	N4...H-N1	0.86	2.50	3.120	130	$-1+x, y, z$
3	O1...H-N1	0.86	2.27	3.012	145	x, y, z
	O1...H-O_w	0.85	1.91	2.697	153	$-2-x+y, -2-x, 1/3+z$
	N4...H-O1	0.88	1.83	2.712	178	$-1-y, -1+x-y, -1/3+z$
4	N4...H-O1	1.03	1.72	2.704	158	$x, -1+y, z$
	O1...H-O_e	0.82	1.96	2.740	157	x, y, z
	N1...H-O_e	0.86	2.06	2.842	157	$-1-x, y, -z$
7a	N1...H-O1	1.25	2.05	3.045	132	$-x, -1/2+y, 2-z$
7b	I...H-N1	0.86	3.16	3.734	126	x, y, z

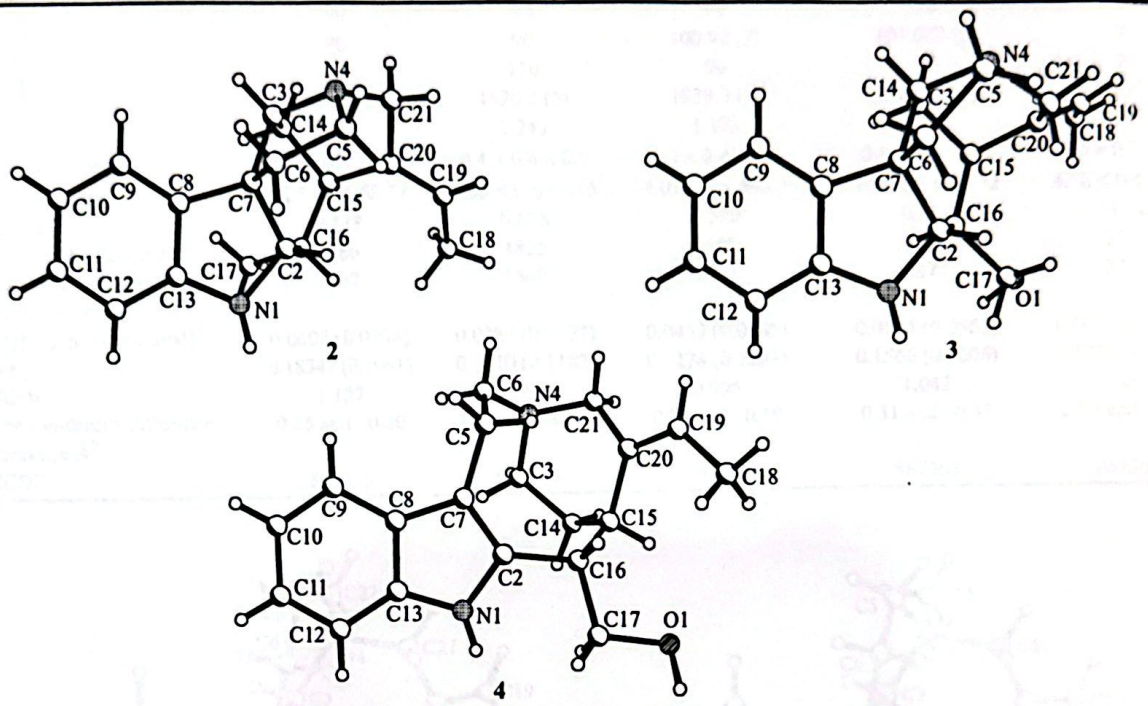


Fig. 2. Molecular structures of **2**, **3**, and **4**.

Structure of 3. Figure 2 shows the molecular structure of **3** from an XSA. The absolute configuration of the asymmetric centers (2*S*,16*R*) arising as a result of reducing the C2=C16 bond corresponded to those shown in Fig. 2. Whereas H2 and H16 in **2** were *syn*-positioned and had the α-orientation, they were *trans*-positioned in **3** and H16 changed configuration to the β-orientation.

Five-membered heterocycle B in the indole core also adopted the 2α-envelope conformation. Ring E was close to a 6β-envelope conformation. Rings C and D in **3**, in contrast with **2**, had identical slightly distorted chair conformations.

The crystal cell of **3** contained a water of crystallization that formed a H-bond between N1H of the starting molecule and a hydroxyl translated by 3_1 symmetry along the *a* axis. Table 1 shows other H-bonds formed in the crystal.

Structure of 4 (indole base with C3–C7 bond cleavage). Figure 2 shows the XSA molecular structure. The asymmetric center arising as a result of the reaction at C16 adopted the *S*-configuration. The C15 center retained the *S*-configuration.

An analysis of the bond lengths confirmed that the arbitrary double bond (initial C2=C16) shifted to C2=C7. Atoms C2 and C7 became sp^2-hybridized. The N1–C2 [1.387(3) Å], C2=C7 [1.363(4) Å], and C7–C8 [1.423(4) Å] bonds became closer to those observed in the aromatic pyrrole ring [11]. The indole core was planar within ±0.011 Å. Ring D had a slightly distorted boat conformation with C14 and C21 deviating from the plane of the other four atoms.

Base **4** crystallized as a solvate with an EtOH molecule in a 1:1 ratio. The H atom of the EtOH hydroxyl approached the hydroxyl O atom of **4** in the crystal. An unshared pair of the EtOH oxygen atom was bonded to an NH proton of a translated molecule of **4**. Table 1 presents the parameters of the intermolecular H-bonds.

Table 2. Principal Crystallographic Parameters and Characteristics of X-ray Experiments for **2**, **3**, **4**, **7a**, **7b**

Parameters	2	3	4	7a	7b
Molecular Formula	$C_{19}H_{24}N_2$	$C_{19}H_{26}N_2O{\cdot}H_2O$	$C_{19}H_{24}N_2O{\cdot}C_2H_5OH$	$C_{20}H_{27}N_2O{\cdot}C_6H_2N_3O_7$	$C_{20}H_{27}N_2O{\cdot}I$
MW, g/mol	280.40	314.42	342.47	388.92	438.34
System	Orthorhombic	Trigonal	Monoclinic	Monoclinic	Orthorhombic
Space group	$P2_12_12_1$	$P3_2$	C2	$P2_1$	$P2_12_12_1$
Z	4	6	4	2	4
a, Å	7.081 (1)	9.587 (1)	22.116 (4)	11.7270 (3)	9.8503 (3)
b, Å	13.947 (1)	9.587 (1)	8.200 (2)	7.1498 (2)	10.7390 (2)
c, Å	15.589 (3)	15.825 (2)	10.891 (2)	15.5200 (4)	18.2014 (3)
α, deg	90	90	90	90	90
β, deg	90	90	100.92 (3)	101.022 (2)	90
γ, deg	90	120	90	90	90
V, Å^3	1539.5 (3)	1820.2 (5)	1939.3 (7)	1277.29 (5)	1925.39 (7)
ρ, g/cm^3	1.210	1.243	1.173	1.403	1.512
Crystal size, mm	0.2 × 0.3 × 0.5	0.4 × 0.8 × 0.5	0.3 × 0.4 × 0.7	0.6 × 0.4 × 0.4	0.5 × 0.7 × 0.9
Scan range θ°	4.25 ≤ θ ≤ 68.37	5.33 ≤ θ ≤ 67.16	4.07 ≤ θ ≤ 60.03	3.84 ≤ θ ≤ 75.72	4.78 ≤ θ ≤ 75.96
μ_{calc}, cm^{-1}	0.538	0.638	0.590	0.885	13.123
Number of reflections	1786	1825	1550	3553	3742
Number of reflections with $I > 2\sigma(I)$	1497	1569	1502	3273	3324
R_1 [$I > 2\sigma(I)$ and total]	0.0608 (0.0708)	0.0388 (0.0477)	0.0453 (0.0465)	0.0534 (0.0563)	0.0663 (0.0723)
WR_2	0.18347 (0.1961)	0.1110 (0.1182)	0.1274 (0.1297)	0.1566 (0.1606)	0.1771 (0.1802)
GOOF	1.127	0.926	0.996	1.042	1.299
Electron-density difference peaks,, e Å^{-3}	0.25 and –0.20	0.18 and –0.13	0.24 and –0.19	0.31 and –0.43	2.03 and –2.01
CCDC	867365	867366	867367	867368	867369

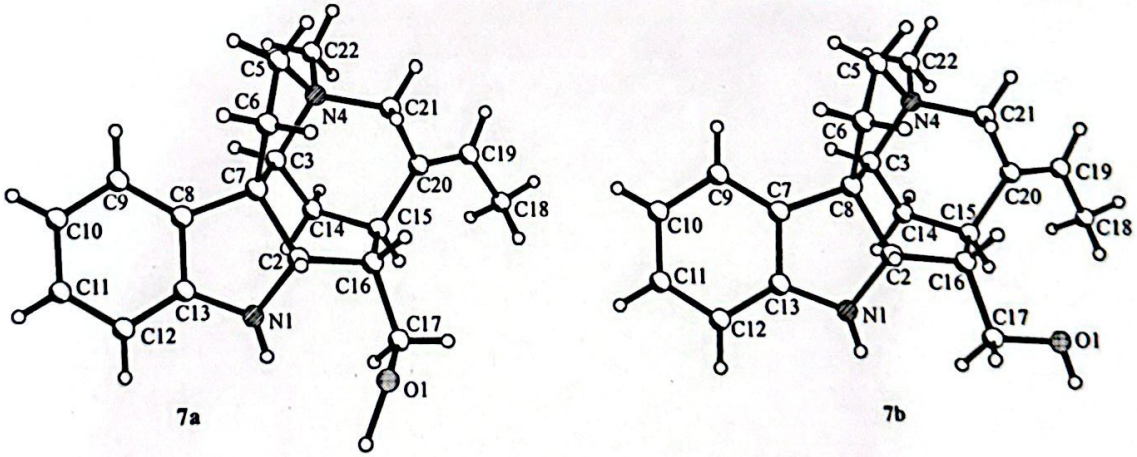


Fig. 3. Molecular structures of cations **7a** and **7b**.

Structure of 16-Decarbmethoxyepistemmadenine. This was studied as the picrate (**7a**) and iodide (**7b**) salts, the cations of which are shown in Fig. 3 in approximately the same projection. The absolute configurations of the asymmetric centers of the cations coincided with those observed in **2**, i.e., formed centers with 2*S*,16*S*-configurations.

It could be seen visually that both cations had the same framework conformation. However, the positions of the fluxional hydroxyl were different. The crystal of **7a** had a weak intramolecular H-bond between an unshared pair of the hydroxyl O atom and the NH group with distance O1…N1 2.967 Å, O1…H 2.69 Å, and angle O1…N1–H 101°. The observed difference in the position of the fluxional OH group relative to the NH group in **7a** and **7b** was apparently related to the aforementioned H-bond. However, the NH group of the starting molecule was simultaneously involved in an intermolecular H-bond with an OH group of a translated molecule (Table 1). An intermolecular H-bond between the iodide anion and the NH proton was observed in the crystal of **7b**, in contrast with **7a**.

Heterocycle B in the indole core adopted the 2α-envelope conformation. Ring E was close to a 4β-envelope conformation. Ring C had a boat conformation with C2 and C14 deviating from the plane of the other four atoms. Ring D was a distorted chair.

The picrate in **7a** was planar. However, the NO_2 group of the anion was slightly twisted (up to 17°) relative to the aromatic plane (±0.012 Å). The picrate did not participate in intermolecular H-bonds. However, the π-electron systems of two aromatic rings of picrate and the alkaloid did approach each other (3.30 Å).

EXPERIMENTAL

UV spectra were measured on a Lambda-16 spectrophotometer (Perkin—Elmer). UV spectra were calculated using the CNDO/S method in the Winmostar program package [12]. The geometries of the compounds were optimized by the PM6 semi-empirical method [13] in the MOPAC2009 program set [14] using XSA data for (–)-norfluorocurarine [15].

Deoxytetrahydronorfluorocurarine (2) was prepared by the literature method [1, 4], mp 185–186°C (acetone), $[\alpha]_D^{20}$ –61.1° (*c* 2.43, MeOH). $C_{19}H_{24}N_2$. UV spectrum (λ_{max}, nm, log ε): 250(3.84), 300 (3.50).

Tetrahydronorfluorocurarine (3) (Wieland–Gumlich 18-deoxyglycol) was prepared by the literature method [1, 4], mp 174–175°C (acetone, $[\alpha]_D^{20}$ –28.5° (*c* 1.51, MeOH). $C_{19}H_{26}ON_2$. UV spectrum (λ_{max}, nm, log ε): 245 (3.80), 298 (3.40).

16-Decarbmethoxyepistemmadenine (4). Norfluorocurarine (6 g) was dissolved in MeOH (100 mL), treated with NaOH solution (10 mL, 5%), stirred vigorously, and treated in portions with $NaBH_4$ (6 g) over 2 h. Fine crystals started to precipitate during the reduction. The reaction mixture was left in a refrigerator for 1 d. White crystals formed. Yield 3.54 g, mp 109–110°C (dec., aq. MeOH), $[\alpha]_D^{17}$ –41.13° (*c* 1.00, MeOH). $C_{19}H_{24}ON_2$. UV spectrum (λ_{max}, nm): 234, 283.

16-Decarbmethoxyepistemmadenine chloride (6) was prepared as before [9], mp 238–240°C (MeOH, dec.), $[\alpha]_D^{17}$ +40° (*c* 1.00, MeOH). $C_{20}H_{27}ON_2Cl$. UV spectrum (λ_{max}, nm): 244, 300.

16-Decarbmethoxyepistemmadenine picrate (7a) was prepared from fluorocurarine chloride by the literature method [9], orange crystals, mp 153°C (aq. acetone). $C_{20}H_{27}ON_2 \cdot C_6H_2O_7N_3$.

16-Decarbmethoxyepistemmadenine iodide (7b). Fluorocurarine iodide (**5**, 6 g) was dissolved with heating in a mixture of NaOH (100 mL, 0.2 N) and MeOH (50 mL), treated in portions with $NaBH_4$ (6 g) over 2 h, and cooled in a refrigerator. The resulting finely crystalline precipitate was separated (yield 4.01 g), mp 242–243°C (aq. EtOH, dec.), $[\alpha]_D^{17}$ +46.5° (*c* 1.00, MeOH). $C_{20}H_{27}ON_2I$. UV spectrum (λ_{max}, nm): 242, 300.

X-ray Structure Analysis. Single crystals of **2**, **3**, **4**, **7a**, and **7b** were obtained by slow evaporation from mixtures of MeOH and acetone at room temperature. Unit-cell constants of crystals of **2**, **3**, **7a**, and **7b** were determined and refined on an Xcalibur Ruby CCD diffractometer (Oxford Diffraction) using Cu Kα-radiation (300 K, graphite monochromator) [16]. A three-dimensional dataset of reflections was obtained on the same diffractometer. The XSA of **4** was performed on a STOE Stadi-4 four-circle diffractometer using Cu Kα-radiation (300 K, graphite monochromator, θ/2θ-scanning). Absorption corrections in all instances were applied semi-empirically using the SADABS program [17]. Table 2 presents the principal parameters of the XSA and refinement calculations for the structures of **2**, **3**, **4**, **7a**, and **7b**.

The structures were solved by direct methods using the SHELXS-97 programs. Refinement calculations were carried out using the SHELXL-97 program [18]. All nonhydrogen atoms were refined by anisotropic full-matrix least-squares method (over F^2). Positions of H atoms were found geometrically and refined with fixed isotropic thermal factors $U_{iso} = nU_{eq}$, where n = 1.5 for methyls and 1.2 for others and U_{eq} is the equivalent isotropic thermal factor of the corresponding C atoms. Atomic coordinates of H atoms of water and hydroxyls of EtOH and alkaloids were determined experimentally from difference electron-density syntheses and refined isotropically.

CIF files containing complete information for the studied structures were deposited in the CCDC under the numbers given in Table 2 (http://www.ccdc.cam.ac.uk/deposit).

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