Study of alkaloids of the Siberian and Altai flora
11.* Synthesis of new lappaconitine derivatives

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A convenient procedure was developed for the preparation of *N*-deacetyllappaconitine by acid hydrolysis of lappaconitine. The crystal and molecular structures of by-products of acid hydrolysis of lappaconitine, *viz.*, 14- and 16-demethyl-*N*-deacetyllappaconitines, were established by X-ray diffraction analysis. Azocoupling of diazonium chlorides that were prepared from lappaconitine *N*-deacetylation products with β-naphthol afforded the corresponding 1,2-naphthoquinone 1-hydrazones.

Key words: alkaloids, lappaconitine, *N*-deacetyllappaconitines, X-ray diffraction analysis, azocoupling, β-naphthol.

As part of continuing screening for antiarrhythmics in the series of derivatives of diterpenoid alkaloid lappaconitine (**1**),[1,2] we attempted to prepare a diazo derivative of *N*-deacetyllappaconitine (**2**) containing a fragment of primary aromatic amine.

Amine **2** was first prepared[3] in 1922 under the name picrolappaconitine in 97% yield by hydrolysis of lappaconitine **1** with 1 *M* H_2SO_4. Later, compound **2** was isolated from *Aconitum septentrionale* Koelle[4] (synonym *A. lycoctonum* L., *cf.* lit.[5]) and from *Aconitum barbatum* Pers. *var. puberulum* Ledeb.[6] (under the name puberanidine). In the present study, we synthesized compound **2** by hydrolysis of lappaconitine **1** with concentrated HCl. As a result, we prepared the target product **2**, 16-demethyl-*N*-deacetyllappaconitine (**3**), and 14-demethyl-*N*-deacetyllappaconitine (**4**) in 46, 17, and 9% yields, respectively (Scheme 1).

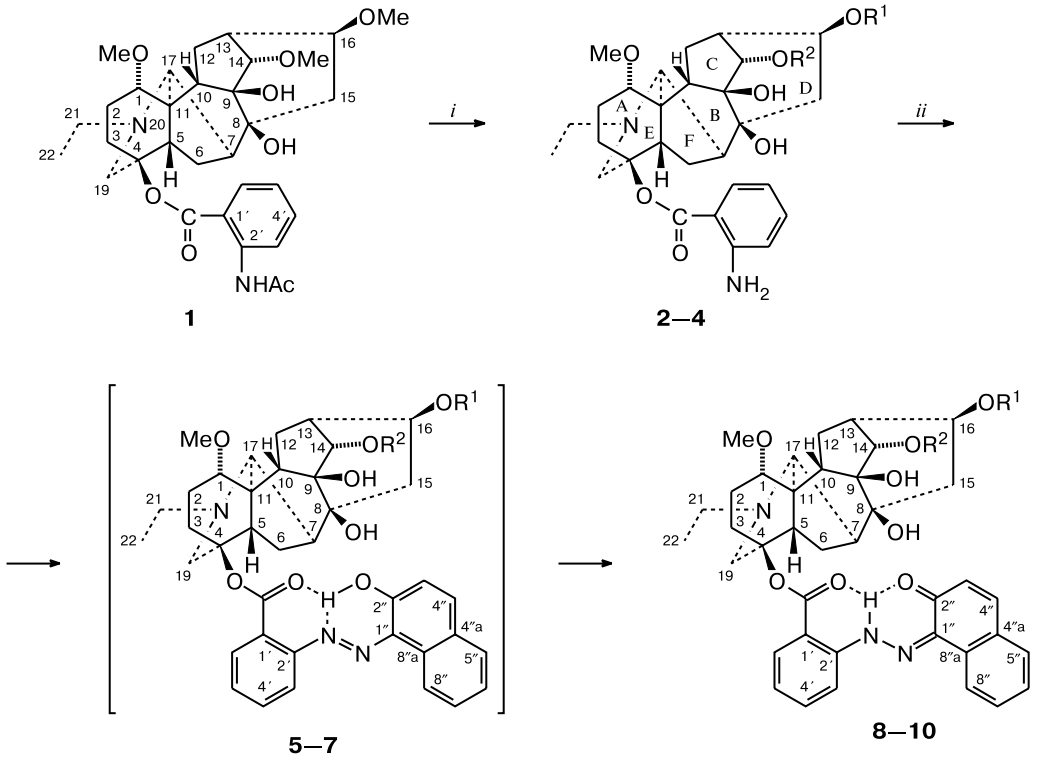
The crystal and molecular structures of compounds **3** and **4** were established by X-ray diffraction analysis (Fig. 1). The bond lengths and bond angles in molecules **3** and **4** are identical within 3σ and are close to the standard values.[7] Of 51 structures with the aconitane skeleton available in the Cambridge Structural Database,[8] only three compounds, *viz.*, lappaconine hydrobromide,[9] tatsinine perchlorate,[10] and excelsine hydroiodide,[11] contain a substituent OR at position 9. The conformations of the rings B (chair), C (envelope), and F (envelope) are determined by the character of junction and are identical in all aconitanes. The flattened boat conformation of the ring D and the chair conformation of the piperidine ring E in compounds **3** and **4** are also typical of most of aconitanes. The six-membered ring A in molecule **4** adopts a slightly distorted boat conformation. The same conformation is observed in lappaconine hydrobromide and tatsinine perchlorate. According to the data from the Cambridge Structural Database, the ring A in aconitanes adopts a boat conformation in 19 of 44 structures. The ring A in compound **3**, unlike that in compound **4**, assumes a chair conformation, which is indicative of its conformational lability. The orientation of the ethyl group at the N(20) atom in molecule **3** also differs from that in **4** (the C(17)—N(20)—C(21)—C(22) torsion angles are −157.4(4)° and −65.6(3)°, respectively). It should be noted that the orientation of the 2-aminobenzoate group in compound **3** is similar to that in **4** (see Fig. 1). The amino and hydroxy groups are involved in intra- and intermolecular hydrogen bonding (Table 1).

The structures of compounds **3** and **4** were confirmed also by comparing the data from their ^{13}C NMR spectra with the ^{13}C NMR spectroscopic data for compound **2**. It should be noted that the chemical shifts of the signals for the C(2), C(6), C(10), C(12), and C(13) atoms in the ^{13}C NMR spectrum of *N*-deacetyllappaconitine **2** reported earlier[6] were assigned incorrectly. Taking into account the ^{13}C NMR spectroscopic data for the model compound, *viz.*, lappaconitine **1**, which were obtained using the ^{13}C—^{13}C 2D-INADEQUATE NMR spectroscopy,[1] we assigned the signals for the carbon atoms in compound **2** by interchanging the chemical shifts for the carbon atoms with the respective multiplicities (Table 2). The assignments of the signals of the aconitane fragment in the ^{13}C NMR spectra of compounds **3** and **4** were made by

* For Part 10, see Ref. 1.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 11, pp. 2363—2369, November, 2003.

Scheme 1



2, 5, 8: $R^1 = R^2 = Me$
3, 6, 9: $R^1 = H$, $R^2 = Me$
4, 7, 10: $R^1 = Me$, $R^2 = H$

Reagents and conditions: *i.* HCl (conc.), 90—95 °C, 1 h; *ii.* 1) HCl; 2) $NaNO_2$, 0—5 °C; 3) β-naphthol, NaOH, NaOAc.

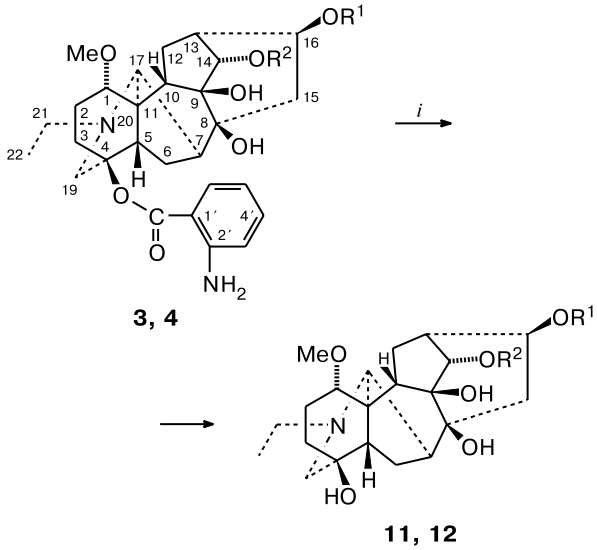
comparing these spectra with the ^{13}C NMR spectra of compound **2** taking into account the upfield shifts of the signals for the carbon atoms bearing the OH groups by δ ~9.4—9.8 compared to the signals for the carbon atoms bearing the OMe groups.

Alkaline hydrolysis of compounds **3** and **4** afforded 16- and 14-demethyllappaconines (**11** and **12**, respectively) (Scheme 2). 1-Demethyllappaconine known under the name lappaconidine was isolated from *Aconitum septentrionale* Koelle.[12]

N-Deacetyllappaconitine **2** was subjected to diazotization. To prove the formation of the diazonium salt, we carried out azocoupling with β-naphthol in an alkaline buffer (NaOH, NaOAc), which gave rise to hydrazone (see Scheme 1). Apparently, the latter was derived from intermediate azo compound **5** due to the electron density redistribution in the conjugated polyunsaturated system.

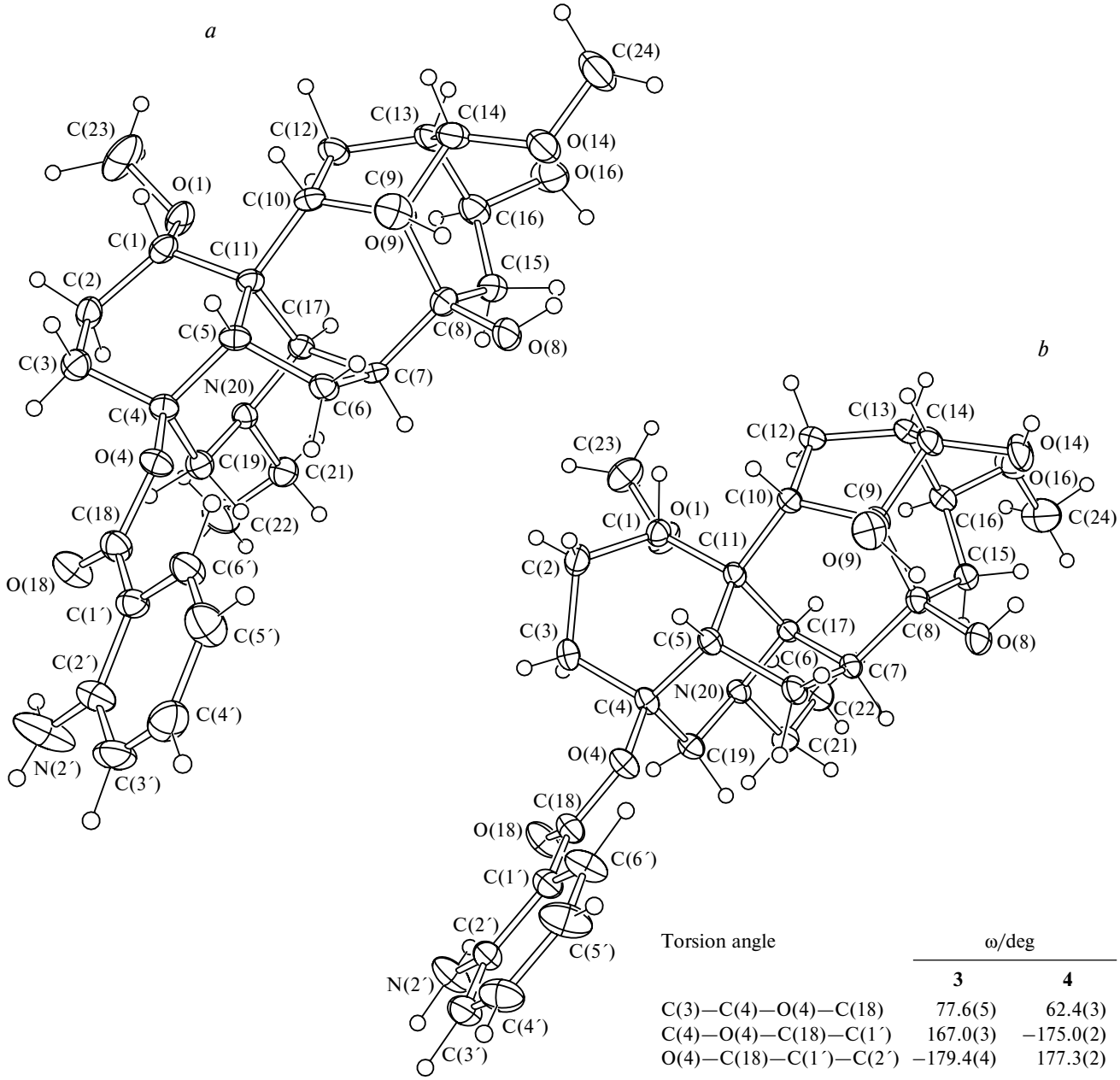
Diazotization of a mixture of compounds **2—4**, which was prepared by hydrolysis of lappaconitine **1**, followed by azocoupling with β-naphthol under analogous conditions afforded a mixture of the corresponding hydrazones **8—10** derived apparently from intermediate azo compounds **5—7**. Individual hydrazones **8—10** were isolated

Scheme 2



3, 11: $R^1 = H$, $R^2 = Me$
4, 12: $R^1 = Me$, $R^2 = H$

i. NaOH, EtOH, 95 °C, 2 h.



Torsion angle	ω/deg	
	3	**4**
C(3)—C(4)—O(4)—C(18)	77.6(5)	62.4(3)
C(4)—O(4)—C(18)—C(1′)	167.0(3)	−175.0(2)
O(4)—C(18)—C(1′)—C(2′)	−179.4(4)	177.3(2)

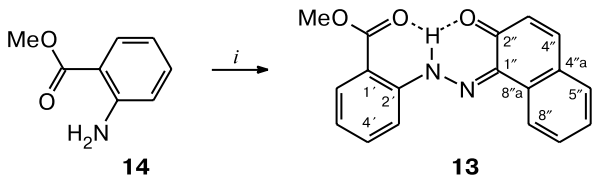
Fig. 1. Three-dimensional structures of molecules **3** (*a*) and **4** (*b*) determined by X-ray diffraction analysis.

by chromatography, their bright red color allowing one to visually follow the course of chromatography.

To assign the signals for the hydrogen and carbon atoms of the polyunsaturated fragments in the ^{1}H and ^{13}C NMR spectra of hydrazones **8—10**, we synthesized a model compound, *viz.*, hydrazone **13**, by azocoupling of diazonium chloride prepared from methyl anthranilate **14** with β-naphthol (Scheme 3).

The conclusion about the formation of 1,2-naphthoquinone derivatives (compounds **8—10** and **13**) was made based on the chemical shifts of the C atoms of the naphthyl fragments in the ^{13}C NMR spectra. For azo compounds of the type **5**, the expected chemical shifts of the C(2″) atom bound to the phenolic hydroxy group should

Scheme 3



14 **13**

i. 1) HCl; 2) $NaNO_2$, 0—5 °C; 3) β-naphthol, NaOH, NaOAc.

Table 1. Distances and hydrogen bond angles in the crystals of **3** and **4**

Distance	*d*/Å		Distance	*d*/Å		Angle	ω/deg	
	3	**4**		**3**	**4**		**3**	**4**
N(2′)—H(2′A)	0.88(6)	0.80(3)	H(2′A)...O(18)	2.06(6)	2.08(4)	N(2′)—H(2′A)...O(18)	126(5)	137(3)
N(2′)—H(2′B)	—	0.91(4)	H(8A)...O(14)	2.46(6)	2.38(6)	N(2′)—H(2′B)...O(16)$^{\#1}$	—	162(4)
O(8)—H(8A)	0.82(6)	0.77(7)	H(8A)...O(16)	2.35(7)	—	O(8)—H(8A)...O(14)	118(6)	134(6)
O(9)—H(9A)	0.83(6)	1.02(4)	H(9A)...O(8)	2.13(6)	2.03(4)	O(8)—H(8A)...O(16)$^{\#2}$	146(6)	—
O(14)—H(14B)	—	0.89(7)	H(2′B)...O(16)	—	2.35(4)	O(9)—H(9A)...O(8)	122(5)	116(3)
O(16)—H(16B)	0.98(7)	—	H(14B)...O(1)	—	2.14(7)	O(14)—H(14B)...O(1)$^{\#3}$	—	150(5)
			H(16B)...O(9)	2.15(7)	—	O(16)—H(16B)...O(9)$^{\#4}$	157(5)	—

Note. Symmetry transformations: $^{\#1}$ $x, y-1, z-1$; $^{\#2}$ $-x-1, y-1/2, -z+3/2$; $^{\#3}$ $x, y+1, z$; $^{\#4}$ $x-1, y, z$.

Table 2. ^{13}C NMR spectra of compounds **2—4** and **8—13**

Atom	δ								
	2	**3**	**4**	**8**	**9**	**10**	**11**	**12**	**13**
C(1)	83.1	84.4	84.7	84.2	84.3	84.5	85.0	85.2	—
C(2)	26.9	26.5	26.4	26.8	26.6	26.4	26.5	26.6	—
C(3)	32.1	31.8	31.9	31.8	31.7	31.7	37.1	37.1	—
C(4)	84.6	84.4	83.0	84.1	84.2	84.2	71.0	70.8	—
C(5)	48.6	48.5	49.7	49.8	49.4	49.8	50.5	50.4	—
C(6)	24.2	24.0	24.0	24.0	24.0	23.9	23.5	23.5	—
C(7)	47.7	47.9	48.6	47.7	48.0	48.5	48.0	48.7	—
C(8)	75.7	75.4	75.1	75.6	75.4	75.0	75.4	74.9	—
C(9)	78.6	78.4	78.9	78.5	78.4	78.7	78.4	78.8	—
C(10)	49.0	49.3	48.6	48.7	48.5	48.6	49.2	49.9	—
C(11)	51.0	50.6	50.7	50.9	50.8	50.8	50.7	50.8	—
C(12)	26.4	25.5	25.3	26.2	25.6	25.4	25.7	25.9	—
C(13)	36.9	40.1	38.0	36.4	40.2	38.1	40.0	38.3	—
C(14)	90.3	91. 0	80.9	90.1	91.0	80.6	91.1	80.2	—
C(15)	44.9	47.3	42.5	44.7	47.3	42.4	47.2	42.2	—
C(16)	83.0	73.2	82.5	82.9	73.3	82.5	73.2	82.8	—
C(17)	61.6	61.5	61.9	61.1	61.2	61.5	61.6	61.8	—
C(19)	55.7	55.6	55.8	55.3	55.4	55.4	57.8	57.8	—
NCH_2	50.1	48.8	48.9	48.7	48.8	48.8	48.8	48.9	—
Me	13.6	13.4	13.5	13.4	13.5	13.5	13.4	13.4	—
1-OMe	56.3	56.4	56.3	56.2	56.3	56.3	56.3	56.3	—
14-OMe	57.9	58.9	—	57.7	58.8	—	59.0	—	—
16-OMe	56.1	—	56.2	55.9	—	56.2	—	56.3	—
OC=O	167.7	167.2	167.3	165.2	165.2	165.1	—	—	166.3
C(1′)	112.2	111.8	112.0	117.4	117.3	117.2	—	—	115.9
C(2′)	150.6	150.3	150.3	144.7	144.7	144.6	—	—	144.2
C(3′)	116.8	116.5	116.6	131.3	131.3	131.2	—	—	131.1
C(4′)	134.1	133.7	133.7	133.7	133.7	133.7	—	—	133.9
C(5′)	116.4	116.1	116.2	123.8	123.7	123.7	—	—	123.6
C(6′)	131.6	131.4	131.5	116.3	116.3	116.2	—	—	116.1
C(1″)	—	—	—	133.9	133.8	133.8	—	—	133.6
C(2″)	—	—	—	179.8	179.9	179.8	—	—	179.8
C(3″)	—	—	—	127.2	127.2	127.1	—	—	128.0
C(4″)	—	—	—	142.1	142.1	142.1	—	—	142.0
C(4a″)	—	—	—	128.4	128.4	128.3	—	—	128.3
C(5″)	—	—	—	122.3	122.3	122.2	—	—	122.2
C(6″)	—	—	—	129.0	129.1	129.0	—	—	128.9
C(7″)	—	—	—	126.6	126.6	126.5	—	—	126.5
C(8″)	—	—	—	128.7	128.7	128.6	—	—	128.5
C(8a″)	—	—	—	131.2	131.3	131.1	—	—	131.1
OCOMe	—	—	—	—	—	—	—	—	52.2

appear at δ ~ 150±10. The observed chemical shifts of the C(2″) atoms for compounds **8—10** and **13** are in the range δ 179.75—179.86, *i.e.*, are close to the expected chemical shifts for the carbon atoms of the carbonyl groups in conjugated systems (*cf.* lit.[13]).

To summarize, a convenient procedure was developed for the synthesis of *N*-deacetyllappaconitine by acid hydrolysis of lappaconitine. It was established that this resulted in the cleavage of both the amide and ether bonds to form the target product and by-products, *viz.*, demethylated *N*-deacetyllappaconitines. The crystal and molecular structures of the by-products were established by X-ray diffraction analysis, which unambiguously demonstrated that these compounds are 14- and 16-demethyl-*N*-deacetyllappaconitines. Azocoupling of diazonium chlorides prepared from *N*-deacetylation products of lappaconitines with β-naphthol afforded the corresponding 1,2-naphthoquinone 1-hydrazones.

Experimental

The IR spectra were recorded on a Vector 22 spectrometer. The UV spectra were measured on a Specord UV-VIS spectrophotometer. The ^{1}H and ^{13}C NMR spectra of compounds **3**, **4**, and **8—12** were recorded for 10% solutions in $CDCl_3$ on a Bruker AC-200 instrument (200.13 MHz for ^{1}H and 50.32 MHz for ^{13}C) and the ^{1}H and ^{13}C NMR spectra of compound **13** were measured on a Bruker DRX 500 instrument (500.13 MHz for ^{1}H and 125.76 MHz for ^{13}C) at 25 °C with resonance stabilization based on the signal for deuterium of the solvent. The 2D ^{1}H—^{1}H COSY and 2D ^{13}C—^{1}H NMR spectra (125 Hz for HC-COSY and 10 Hz for COLOC) were measured on a Bruker DRX 500 instrument. The spectra were recorded using the standard Bruker software. The chemical shifts (δ) were measured with respect to the signals of $CHCl_3$ as the internal standard (δ_H 7.24 and δ_C 76.90). The multiplicities of signals in the ^{13}C NMR spectra were determined according to standard procedures using J modulation (JMOD) and off-resonance irradiation of protons. Due to the difficulties of assigning all signals in the ^{1}H NMR spectra of the compounds described for the first time, only the characteristic signals are given. The ^{13}C NMR spectroscopic data are presented in Table 2. The assignments of the signals in the ^{1}H and ^{13}C NMR spectra of compound **13** were made using the correlation 2D ^{1}H—^{1}H COSY and 2D ^{13}C—^{1}H (125 Hz for HC-COSY and 10 Hz for COLOC) experiments.

The optical rotation was measured on a Polamat A polarimeter (Carl Zeiss, λ = 578 nm). The specific rotation is given in (deg mL) (g dm)$^{-1}$. The concentrations of solutions are given in g (100 mL)$^{-1}$.

The melting points were measured on a Kofler hot-stage apparatus.

Freshly distilled solvents and reagents of "pure" grade were used.

Preparative TLC was carried out on Al_2O_3 (50—250 μm, Russia), which was activated at 250 °C for 6 h and then deactivated to the Brockmann activity II by adding 3% of water. This sorbent was mixed with luminophore K-35 (1 wt.%, Russia) to enhance the sensitivity of visual control over the process of separation in the UV light. Plates (30×30 cm) with thickness of a sorbent layer of 2 mm and the Pr^iOH—Et_2O solvent system (1 : 9, v/v) were used.

Analytical TLC was performed using glass plates of dimensions 7.5×7.5 cm with a sorbent layer (0.04 g cm^{-2}) of neutral Al_2O_3, 5/40 μm (Chemapol, Czech Republic) containing 1 wt.% of luminophore K-35 (Russia) and 1% of Na_2CO_3, which were prepared according to a procedure described earlier.[2] Chromatographic bands of alkaloids were detected by irradiation of a dried plate with UV light and were also visualized with iodine vapor.

Lappaconitine **1** used in the study had physicochemical and spectroscopic characteristics described earlier.[1]

The molecular weights and elemental compositions of the new compounds were determined on a Finnigan MAT (MS 8200 model) high-resolution mass spectrometer (EI, 70 eV).

X-ray diffraction study was performed on a Syntex $P2_1$ diffractometer (Cu-Kα radiation, graphite monochromator, 2θ/θ scanning technique in the range 2θ < 140°). The empirical absorption corrections were applied based on Psi scans. The structures were solved by direct methods using the SHELXS-97 program package. The coordinates of the hydrogen atoms were revealed from difference electron density syntheses. The structures were refined based on all F^2 by the full-matrix least-squares method with anisotropic and isotropic thermal parameters for nonhydrogen and hydrogen atoms, respectively, using the SHELXL-97 program package.[14]

The atomic coordinates and thermal parameters were deposited with the Cambridge Structural Database (refcodes CCDC 214892 and CCDC 214893 for compounds **3** and **4**, respectively).

Crystals of compound **3** are orthorhombic: at T = 296 K, a = 7.830(2), b = 9.252(2), c = 35.530(7) Å, V = 2573.9(9) Å^3, space group $P2_12_12_1$, Z = 4. $C_{29}H_{40}N_2O_7$. M = 528.63, d_{calc} = 1.364 g cm^{-3}, λ = 1.54178 Å, μ = 0.794 mm^{-1}, transmission 0.57—0.92, 2834 independent reflections with 2θ < 140°, wR_2 = 0.1160, S = 1.039, 504 parameters were refined (R = 0.0470 for 2112 $F > 4\sigma$).

Crystals of compound **4** are monoclinic: at T = 296 K, a = 11.344(3), b = 8.821(2), c = 12.995(2) Å, β = 98.83(2)°, V = 1284.9(5) Å^3, space group $P2_1$, Z = 2. $C_{29}H_{40}N_2O_7$. M = 528.63, d_{calc} = 1.366 g cm^{-3}, λ = 1.54178 Å, μ = 0.795 mm^{-1}, transmission 0.64—0.92, 2588 independent reflections with 2θ < 140°, wR_2 = 0.0976, S = 1.032, 509 parameters were refined (R = 0.0368 for 2447 $F > 4\sigma$). The C(2) atom is disordered over two positions, which are denoted as C(2) and C(2A), in a ratio of 0.81(1) : 0.19(1), respectively. The presence of C(2A) is indicative of a small contribution of the chair conformation of the ring A.

Hydrolysis of lappaconitine (1). A solution of lappaconitine **1** (4.38 g, 7.5 mmol) in concentrated HCl (d = 1.19) (7.5 mL) was heated with stirring at 95—100 °C for 1 h and then cooled to 20 °C. The solution was diluted with water (15 mL) and filtered. A 25% aqueous NH_3 was added to the filtrate to pH 8. The reaction mixture was extracted with $CHCl_3$ (4×10 mL), the extract was concentrated *in vacuo*, and the residue was dried at 50 °C (3 Torr). A mixture of compounds was obtained as an amorphous powder in a yield of 4.00 g. The mixture was subjected to preparative TLC. Three zones of the sorbent, which showed blue fluorescence under UV light, with R_f 0.86, 0.45, and 0.05 were collected; these zones correspond to individual

compounds **2**, **3**, and **4**, respectively. The target compounds were eluted with methanol and the eluates were concentrated. The yields of crystalline compounds **2**, **3**, and **4** were 1.86, 0.67, and 0.36 g (46, 17, and 9%), respectively.

***N*-Deacetyllappaconitine (2).** Rectangular platelet-like crystals (*cf.* lit.[3]), m.p. 218—220 °C (MeOH) (*cf.* lit.[4]: m.p. 209—214 °C (acetone—hexane)), $[\alpha]_{578}^{20}$ +20.8 (*c* 4.9, $CHCl_3$) (*cf.* lit.[6]: $[\alpha]_D^{20}$ +23.2 (*c* 0.9, $CHCl_3$)). The ^1H and ^{13}C NMR spectra are identical with those published in the literature.[4,6]

4-*O*-(2-Aminobenzoyl)-20-ethyl-1α,14α-dimethoxyaconitane-4,8,9,16β-tetrol, 16-demethyl-*N*-deacetyllappaconitine (3), m.p. 256—258 °C (with decomp., from MeOH), $[\alpha]_{578}^{20}$ +20.4 (*c* 1.5, $CHCl_3$). ^1H NMR, δ: 1.08 (t, 3 H, $NCH_2\underline{Me}$, J = 7 Hz); 3.25 and 3.49 (both s, 3 H each, 1- and 14-OMe); 5.61 (br.s, 2 H, NH_2); 6.57 (m, 2 H, H(4′), H(6′)); 7.19 (t, 1 H, H(5′), J = 8 Hz); 7.73 (d, 1 H, H(3′), J = 8 Hz). IR (KBr), ν/cm^{-1}: 753, 995, 1041, 1098, 1147, 1210, 1244, 1298, 1321, 1363, 1381, 1454, 1488, 1560, 1586, 1617, 1684 (C=O), 2822, 2864, 2917, 2935, 2970, 3383 (NH), 3499 (OH). UV (EtOH), λ_{max}/nm (log ε): 219 (4.45), 248 (3.90), 338 (3.74).

4-*O*-(2-Aminobenzoyl)-20-ethyl-1α,16β-dimethoxyaconitane-4,8,9,14α-tetrol, 14-demethyl-*N*-deacetyllappaconitine (4), m.p. 236—238 °C (with decomp., from MeOH), $[\alpha]_{578}^{20}$ +22.0 (*c* 1.3, $CHCl_3$). ^1H NMR, δ: 1.08 (t, 3 H, $NCH_2\underline{Me}$, J = 7 Hz); 3.24 and 3.30 (both s, 3 H each, 1- and 16-OMe); 5.61 (s, 2 H, NH_2); 6.57 (m, 2 H, H(4′), H(6′)); 7.19 (t, 1 H, H(5′), J = 8 Hz); 7.73 (d, 1 H, H(3′), J = 8 Hz). IR (KBr), ν/cm^{-1}: 756, 1077, 1111, 1145, 1178, 1232, 1254, 1300, 1322, 1377, 1455, 1490, 1585, 1614, 1679 (C=O), 2874, 2902, 2924, 2957, 3361 (NH), 3471 (OH). UV (EtOH), λ_{max}/nm (log ε): 219 (4.41), 248 (3.86), 338 (3.70).

4-*O*-{2-[2-(2-Oxo-1,2-dihydronaphthalen-1-ylidene)hydrazino]benzoyl}-20-ethyl-1α,14α,16β-trimethoxyaconitane-4,8,9-triol (8). A solution of $NaNO_2$ (0.103 g, 1.49 mmol) in water (2 mL) cooled to 5 °C was gradually added to a solution of compound **2** (0.543 g, 1 mmol) in 16% HCl (4.73 mmol, 1 mL) cooled to 5 °C. After 5 min, an iodide-starch paper test for the presence of HNO_2 in the solution was positive. β-Naphthol (0.144 g, 1 mmol) was suspended in a solution of NaOH (0.194 g, 4.85 mmol) in water (0.5 mL) and then mixed with a solution of AcONa (0.9 g, 11 mmol) in water (3.6 mL). The resulting mixture was heated to 40 °C until the β-naphthol dissolved and then cooled to 5 °C. Then a diazo solution cooled to 5 °C was added dropwise with stirring. The red reaction mixture was kept at 20 °C for 0.5 h. The red precipitate that formed was extracted with $CHCl_3$ (4×4 mL). The extract was concentrated *in vacuo* to 2 mL and subjected to preparative TLC on Al_2O_3. The red zone of the sorbent with R_f 0.85 corresponding to compound **8** was collected. The target product was eluted with methanol. The methanolic solution was concentrated and the crystals that formed were separated and dried. The yield was 0.672 g (95%), m.p. 190—192 °C (with decomp.). Found (%): C, 68.10; H, 6.88; N, 5.88. $C_{40}H_{47}N_3O_8 \cdot 0.5\ H_2O$. Calculated (%): C, 67.96; H, 6.86; N, 5.95. ^1H NMR, δ: 1.09 (t, 3 H, $NCH_2\underline{Me}$, J = 7 Hz); 3.26, 3.28, and 3.38 (all s, 3 H each, 1-, 14-, and 16-OMe); 6.68 (d, 1 H, H(3″), J = 10 Hz); 7.11 (t, 1 H, H(4′), J = 8 Hz); 7.32 (t, 1 H, H(7″), J = 8 Hz); 7.43 (m, 2 H, H(8″), H(6″)), 7.55 (m, 2 H, H(4″), H(5′)); 7.94 (d, 1 H, H(3′), J = 7.5 Hz); 8.26 (d, 1 H, H(6′), J = 8 Hz); 8.38 (d, 1 H, H(5″), J = 8 Hz). IR (KBr), ν/cm^{-1}: 754, 843, 1081, 1094, 1134, 1155, 1197, 1267, 1318, 1383, 1399, 1447, 1480, 1492, 1572, 1601, 1623, 1702 (C=O), 2819, 2927, 2965. UV (EtOH), λ_{max}/nm (log ε): 225 (4.54), 289 (3.92), 300 (3.89), 482(4.22).

Synthesis of hydrazones 8—10. Diazotization was carried out using an amorphous powder of a mixture of hydrolysis products of lappaconitine **1**. A mixture of compounds **2**, **3**, and **4** in a ratio of ~5 : 2 : 1 (0.543 g) was subjected to diazotization followed by azocoupling with β-naphthol under the above-described conditions. The chloroform extract containing a mixture of compounds **8—10** was subjected to preparative TLC on Al_2O_3. Three red zones of the sorbent with R_f 0.85, 0.45, and 0.05 corresponding to individual compounds **8**, **9**, and **10**, respectively, were collected. The target compounds were eluted with methanol. The methanolic solutions were concentrated and then crystals of compounds **8—10** were separated and dried. The yield were 0.208, 0.104, and 0.056 g, respectively.

4-*O*-{2-[2-(2-Oxo-1,2-dihydronaphthalen-1-ylidene)hydrazino]benzoyl}-20-ethyl-1α,14α-dimethoxyaconitane-4,8,9,16β-tetrol (9), red crystals, m.p. 198—200 °C (with decomp.). Found (%): C, 65.46; H, 6.66; N, 5.77. $C_{39}H_{45}N_3O_8 \cdot 1.5\ H_2O$. Calculated (%): C, 65.89; H, 6.82; N, 5.91. ^1H NMR, δ: 1.09 (t, 3 H, $NCH_2\underline{Me}$, J = 7 Hz); 3.25 and 3.48 (both s, 3 H each, 1- and 14-OMe); 6.68 (d, 1 H, H(3″), J = 10 Hz); 7.12 (t, 1 H, H(4′), J = 8 Hz); 7.32 (t, 1 H, H(7″), J = 8 Hz); 7.44 (m, 2 H, H(8″), H(6″)); 7.57 (m, 2 H, H(4″), H(5′)); 7.94 (d, 1 H, H(3′), J = 7.5 Hz); 8.27 (d, 1 H, H(6′), J = 8 Hz); 8.38 (d, 1 H, H(5″), J = 8 Hz). IR (KBr), ν/cm^{-1}: 754, 840, 1045, 1081, 1096, 1134, 1155, 1197, 1267, 1319, 1380, 1399, 1447, 1480, 1492, 1571, 1622, 1701 (C=O), 2820, 2927, 2965. UV (EtOH), λ_{max}/nm (log ε): 225 (4.58 sh), 289 (3.97), 300 (3.95), 485 (4.23).

4-*O*-{2-[2-(2-Oxo-1,2-dihydronaphthalen-1-ylidene)hydrazino]benzoyl}-20-ethyl-1α,16β-dimethoxyaconitane-4,8,9,14α-tetrol (10), red crystals, m.p. 192—194 °C (with decomp.). Found (%): C, 64.47; H, 6.38; N, 5.70. $C_{39}H_{45}N_3O_8 \cdot 2.5H_2O$. Calculated (%): C, 64.26; H, 6.93; N, 5.77. ^1H NMR, δ: 1.09 (t, 3 H, $NCH_2\underline{Me}$, J = 7 Hz); 3.23 and 3.29 (both s, 3 H each, 1- and 16-OMe); 6.67 (d, 1 H, H(3″), J = 10 Hz); 7.10 (t, 1 H, H(4′), J = 8 Hz); 7.29 (t, 1 H, H(7″), J = 8 Hz), 7.42 (m, 2 H, H(8″), H(6″)); 7.55 (m, 2 H, H(4″), H(5′)); 7.92 (d, 1 H, H(3′), J = 7.5 Hz); 8.23 (d, 1 H, H(6′), J = 8 Hz); 8.34 (d, 1 H, H(5″), J = 8 Hz). IR (KBr), ν/cm^{-1}: 755, 841, 987, 1045, 1081, 1095, 1135, 1155, 1196, 1267, 1318, 1382, 1399, 1447, 1480, 1491, 1571, 1621, 1700 (C=O), 2820, 2928. UV (EtOH), λ_{max}/nm (log ε): 225 (4.49), 289 (3.87), 300 (3.84), 482 (4.16).

20-Ethyl-1α,14α-dimethoxyaconitane-4,8,9,16β-tetrol, 16-demethyllappaconine (11). A solution of NaOH (0.056 g, 1.4 mmol) in water (0.2 mL) was added dropwise with stirring to a solution of compound **3** (0.212 g, 0.4 mmol) in EtOH (2.8 mL) and the reaction mixture was heated at 95—100 °C for 2 h. The solvent was distilled off, the residue was extracted with chloroform, and the extract was concentrated. The residue was extracted with water (4×0.6 mL) and the extract was centrifuged (5 min, 5000 rpm). Water was removed from the supernatant to yield 0.120 g (74%) of product **11** as an amorphous powder. High-resolution mass spectrum. Found: m/z 409.2464. $C_{22}H_{35}NO_6$. Calculated: M = 409.2464. ^1H NMR, δ: 1.03 (t, 3 H, $NCH_2\underline{Me}$, J = 7 Hz); 3.22 and 3.47 (both s, 3 H each, 1- and 14-OMe). IR (KBr), ν/cm^{-1}: 961, 1052, 1077, 1118, 1152, 1197, 1363, 1382, 1451, 2820, 2925, 3427 (OH).

20-Ethyl-1α,16β-dimethoxyaconitane-4,8,9,16α-tetrol, 14-demethyllappaconine (12). Compound **12** was prepared analogously by refluxing compound **4** in an aqueous-methanolic solu-

tion of NaOH for 6 h. An amorphous powder, yield 75%. High-resolution mass spectrum. Found: *m/z* 409.2473. $C_{22}H_{35}NO_6$. Calculated: M = 409.2464. ^{1}H NMR, δ: 1.02 (t, 3 H, $NCH_2\underline{Me}$, J = 7 Hz); 3.21 and 3.27 (both s, 3 H each, 1- and 16-OMe). IR (KBr), ν/cm^{-1}: 924, 958, 986, 1087, 1120, 1154, 1197, 1298, 1378, 1451, 1494, 1612, 2534, 2818, 2928, 3424 (OH).

Methyl 2-[2-(2-oxo-1,2-dihydronaphthalen-1-ylidene)hydrazino]benzoate (13). Methyl anthranilate **14** (0.453 g, 3 mmol) was subjected to diazotization followed by azocoupling with β-naphthol (0.432 g, 3 mmol) under the conditions of the synthesis of hydrazone **8**. The target product was extracted from the reaction mixture with chloroform (6×15 mL). After removal of the solvent, the extract was filtered and compound **13** was obtained in a yield of 0.402 g (44%) as red crystals, m.p. 176—178 °C (with decomp., from $CHCl_3$). High-resolution mass spectrum. Found: *m/z* 306.1004. $C_{18}H_{14}N_2O_3$. Calculated: M = 306.1004. ^{1}H NMR, δ: 3.99 (s, 3 H, OMe); 6.58 (d, 1 H, H(3″), J = 10 Hz, $\Delta\nu_{1/2}$ 1.0 Hz); 7.07 (td, 1 H, H(4′), J = 8 Hz, J = 1.5 Hz); 7.24 (td, 1 H, H(7″), J = 8 Hz, J = 1.5 Hz); 7.33 (dd, 1 H, H(8″), J = 8 Hz, J = 1.5 Hz); 7.38 (td, 1 H, H(6″), J = 8 Hz, J = 1.5 Hz); 7.47 (d, 1 H, H(4″), J = 10 Hz, $\Delta\nu_{1/2}$ 1.5 Hz); 7.51 (tdd, 1 H, H(5′) J = 8 Hz, J = 2 Hz); 7.96 (dd, 1 H, H(3′), J = 7.5 Hz, J = 2 Hz); 8.16 (d, 1 H, H(6′), J = 8 Hz); 8.25 (d, 1 H, H(5″), J = 8 Hz). IR (KBr), ν/cm^{-1}: 505, 694, 753, 779, 840, 871, 986, 1081, 1093, 1132, 1151, 1196, 1217, 1262, 1321, 1401, 1446, 1481, 1492, 1572, 1600, 1624, 1706 (C=O), 2852, 2945, 3028. UV (EtOH), λ_{max}/nm (log ε): 225 (4.68), 253 (4.10), 288 (4.09), 301 (4.07), 484 (4.41).

We thank the Russian Foundation for Basic Research for paying for the license for the Cambridge Structural Database (Project No. 02-07-90322). This study was financially supported by the Russian Foundation for Basic Research (Project Nos. 01-03-32431 and 02-07-90322).

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Received April 28, 2003