Chemistry of Natural Compounds, Bioorganic, and Biomolecular Chemistry

Study of alkaloids of the Siberian and Altai flora 9.* Synthesis of amino derivatives of elatidine

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New secondary-tertiary diamines were prepared from elatidal imines with primary amino alcohols, derivatives of natural amino acids of the *S*-series. *N*-Methylation of the diamines yielded bi-tertiary diamines unable to undergo quaternization with MeI due to steric hindrance.

Key words: diterpene alkaloids, elatidine, elatidal, aldimines, diamines.

This study continues a series of works dealing with the synthesis of 18-amino-18-deoxy elatidine derivatives on the basis of elatidal (**1**).[2] The initial compounds used were elatidal imines with the *S*-alanine, *S*-valine, and *S*-tyrosine methyl esters and with *S*-valinol, *S*-tyrosinol, and *S*-methioninol (**2—7**), which are formed in high yields in the condensation of elatidal **1** with the appropriate amines (Scheme 1).

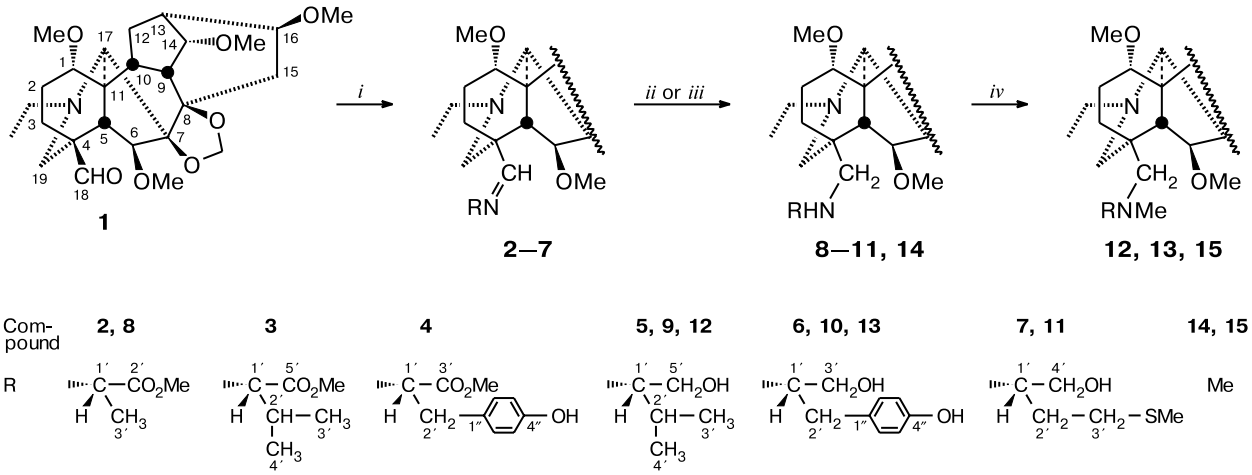
According to ^{1}H NMR spectroscopy, each imine **2—4** formed upon complete conversion of the initial elatidal **1** is a single geometric isomer, presumably, with the *E*-configured imino group, because the steric restrictions associated with the imine bond formation are less pronounced.[1] An attempt to reduce the C=N bond in imine **2** by $NaBH_4$ resulted in a complex mixture of products. Obviously, this is due to the side processes involving the ester group. A satisfactory yield of diamine **8** (71%) was attained in the catalytic hydrogenation (H_2, Pd/C) of imine **2**. The reduction of imines **5—7** on treatment with $NaBH_4$ gave rise to the corresponding diamines **9—11**, containing both secondary and tertiary amino groups in one molecule. *N*-Methylation of the secondary-tertiary

* For Part 8, see Ref. 1.

Published in Russian in *Izvestiya Akademii Nauk. Seriya Khimicheskaya,* No. 12, pp. 2127—2131, December, 2002.

1066-5285/02/5112-2290 $27.00

Scheme 1



Reagents, conditions, and product yields: *i*. RNH_2 ($-H_2O$): (a) *S*-alanine methyl ester, $CHCl_3$, **2** (95%); (b) *S*-valine methyl ester, $CHCl_3$, **3** (92%); (c) *S*-tyrosine methyl ester, $CHCl_3$, **4** (87%); (d) *S*-valinol, MeOH, **5** (90%); (e) *S*-tyrosinol, MeOH, **6** (92%); (f) *S*-methioninol, MeOH, **7** (94%); *ii*. (g) H_2, Pd/C, EtOH, **8**, (71%); *iii*. $NaBH_4$, MeOH: (h) **9** (80%); (i) **10** (82%); (j) **11** (81%); *iv*. MeI then NH_4OH ($-HI$): (k) **12** (90%); (l) **13** (91%); (m) **15** (85%).

diamines **9** and **10** yielded bi-tertiary diamines **12** and **13**, which are not quaternized on treatment with methyl iodide. It is known[3] that elatidine, containing a tertiary N atom in the ring, cannot be converted into iodomethylate. Apparently, this is due to steric hindrance to the formation of the tetracoordinated N atom. We showed that *N*-methylation of 18-methylamino-7,8-methylenedioxy-1α,6β,14α,16β-tetramethoxy-20-ethylaconitane (**14**) yields 18-dimethylamino derivative (**15**). Despite the fact that the exocyclic N atom in compound **15** bears substituents (methyl groups) that are less bulky than those in the similar fragment of compounds **12** and **13**, diamine **15** still does not undergo quaternization with methyl iodide. Apparently, the lack of coordination reactivity in the exocyclic tertiary N atom of compounds **12**, **13**, and **15** is also due to the above reasons.

Thus, we synthesized elatidal imines with *S*-alanine, *S*-valine, and *S*-tyrosine methyl esters and with *S*-valinol, *S*-tyrosinol, and *S*-methioninol. Catalytic hydrogenation of elatidal imine with the *S*-alanine methyl ester and the $NaBH_4$ reduction of elatidal imines with *S*-valinol, *S*-tyrosinol, and *S*-methioninol furnished the corresponding amino derivatives of elatidine containing both secondary and tertiary amino groups in one molecule. *N*-Methylation of these diamines yielded bi-tertiary diamines, which are not quaternized on treatment with methyl iodide due to steric hindrance.

Experimental

IR spectra were recorded on a Vector 22 spectrometer and UV spectra were measured on a Specord UV-VIS spectrophotometer. The molecular weights and the elemental compositions of new compounds were determined using a Finnigan MAT high-resolution mass spectrometer (version MS 8200, EI, 70 eV). Melting points were measured on a Koefler stage.

The optical rotation was measured on a Polamat A polarimeter (Carl Zeiss, λ = 578 nm). Specific rotation was expressed in (deg mL) $(g\ dm)^{-1}$, and the concentrations of solutions were expressed in g $(100\ mL)^{-1}$. The ^1H and ^{13}C NMR spectra of tyrosinol oxalate and compounds **9**, **10**, and **12** were recorded on a Bruker AC-400 instrument (^1H, 400.13 MHz; ^{13}C, 100.61 MHz) and the spectra of other compounds were measured on a Bruker AC-200 spectrometer (^1H, 200.13 MHz; ^{13}C, 50.32 MHz) for 10% solutions of compounds (in $CDCl_3$, unless indicated otherwise) at 25 °C using the deuterium signal of the solvent for resonance stabilization. The chemical shifts (δ) were referred to the signals of internal $CHCl_3$: δ_H 7.24 and δ_C 76.90. The signal multiplicity in the ^{13}C NMR spectra were determined by standard procedures[4] in the J-modulation mode (JMOD) and with off-resonance proton irradiation. The ^{13}C NMR chemical shifts for newly synthesized compounds are presented in Table 1. The ^1H and ^{13}C NMR signals were assigned using data for model compounds: elatidine[5] and the initial *S*-valinol, *S*-tyrosinol, and *S*-methioninol, and *S*-alanine, *S*-valine, and *S*-tyrosine methyl esters. Since the assignment of all ^1H NMR signals is a complicated task, only the data of characteristic signals are presented for the newly synthesized compounds.

Freshly distilled solvents and pure grade reagents were used in the work, together with the following initial compounds.

Elatidal (m.p. 146.5—148.0 °C (Et_2O), $[\alpha]_{578}^{20}$ −17.2 (*c* 5, $CHCl_3$)) was prepared by a previously described procedure.[6]

S-Alanine methyl ester synthesized by a known procedure[7] from *S*-alanine produced at the pilot plant of the Institute of Bioorganic Chemistry of the Ukrainian Republic had b.p. 38 °C (14 Torr) (*cf.* Ref. 8: b.p. 38 °C (14 Torr)). ^1H NMR, δ: 0.91 (d, 3 H, 3′-Me, *J* = 7 Hz); 3.12 (q, 1 H, C(2)H, *J* = 7 Hz); 3.31 (s,

Table 1. Chemical shifts (δ) of signals in the ^{13}C NMR spectra of compounds **2—4**, **8—13**, and **15**

Atom	δ									
	2	**3**	**4***	**8**	**9**	**10**	**11**	**12**	**13**	**15**
C(1)	83.1	83.2	84.5	83.0	83.2	83.2	83.1	83.4	83.1	82.5
C(2)	25.8	25.6	26.7	26.1	26.4	26.3	26.2	26.4	26.4	25.6
C(3)	32.5	32.6	33.0	31.6	32.2	32.0	32.0	32.5	32.6	31.7
C(4)	42.4	42.7	43.6	36.6	37.0	36.9	36.8	39.0	38.5	39.3
C(5)	53.1	53.3	53.2	52.5	53.8	53.5	54.8**	48.4	48.2	54.2
C(6)	89.6	89.4	90.3	89.0	89.6	89.4	89.6	91.8	89.9	89.1
C(7)	91.8	91.6	93.3	91.7	91.8	91.9	91.7	91.8	91.7	90.9
C(8)	83.3	83.4	84.7	82.9	83.2	83.2	83.0	83.2	83.3	82.8
C(9)	39.7	39.8	41.1	39.4	39.6	39.6	39.4	38.3	38.2	39.0
C(10)	48.0	48.1	49.2	48.0	48.4	48.2	48.2	39.5	39.5	47.6
C(11)	49.3	49.3	50.6	49.5	49.4	49.5	49.4	49.6	49.4	48.8
C(12)	27.7	27.6	28.9	27.4	27.6	27.6	27.5	27.7	27.6	27.1
C(13)	38.3	38.4	39.6	38.2	38.3	38.2	38.2	36.3	36.6	37.5
C(14)	81.4	81.5	83.1	81.2	81.4	81.4	81.2	81.4	81.3	80.7
C(15)	34.6	34.7	36.3	34.4	34.1	34.2	34.1	34.1	34.0	33.4
C(16)	81.1	81.2	82.5	81.2	83.3	81.4	81.2	81.3	81.3	79.0
C(17)	64.1	64.1	65.1	63.9	64.5	64.3	64.2	64.3	64.3	62.8
C(18)	170.6	171.1	174.1	54.2	54.9	54.7	54.7	60.6	61.1	72.4
C(19)	52.3	52.2	53.3	54.2	54.6	54.1	53.7	54.9	54.9	54.4
N—$\underline{C}H_2CH_3$	50.2	50.1	51.3	50.0	50.3	50.3	50.1	50.3	50.3	49.6
N—$CH_2\underline{C}H_3$	13.6	13.7	14.2	13.5	13.7	13.7	13.6	13.7	13.7	13.0
OCH_2O	93.2	93.3	94.4	93.0	93.0	93.0	92.9	92.9	92.9	92.6
1-OMe	55.0	55.1	55.6	54.7	54.9	54.9	55.8	54.9**	54.3	54.5
6-OMe	57.4	57.5	57.7	57.0	57.6	57.5	58.5	57.6	57.5	57.1
14-OMe	59.1	59.1	59.5	58.1	59.0	58.7	58.8	59.2	59.2	59.2
16-OMe	55.8	55.9	56.3	55.7	56.0	55.9	57.4	55.9	55.9	55.5
C(1′)	172.2	171.9	173.4	175.8	65.2	60.9	53.5**	72.6	68.8	—
C(2′)	67.7	80.4	76.1	57.3	28.8	37.2	30.9	28.1	31.0	—
C(3′)	19.0	31.0	39.3	18.7	18.3	62.2	30.7	19.7	63.6	—
C(4′)	—	16.3	—	—	19.3	—	62.6	22.0	—	—
C(5′)	—	19.2	—	—	60.2	—	—	66.3	—	—
C(1″)	—	—	128.9	—	—	129.3	—	—	129.8	—
C(2″)	—	—	131.8	—	—	115.4	—	—	115.4	—
C(3″)	—	—	116.1	—	—	129.9	—	—	129.6	—
C(4″)	—	—	157.2	—	—	155.0	—	—	154.7	—
C(5″)	—	—	116.1	—	—	129.9	—	—	129.6	—
C(6″)	—	—	131.8	—	—	115.4	—	—	115.4	—
$CO_2\underline{C}H_3$	51.7	51.5	52.5	51.2	—	—	—	—	—	—
NMe	—	—	—	—	—	—	—	54.6**	54.3	—
NMe_2	—	—	—	—	—	—	—	—	—	56.4
SMe	—	—	—	—	—	—	15.2	—	—	—

* Solution in CD_3OD.

** The chemical shifts of the signals may have to be interchanged.

3 H, OMe). ^{13}C NMR, δ: 175.5 (C(1)); 48.5 (C(2)); 19.1 (C(3)); 50.2 (OMe). *S*-Alanine methyl ester hydrochloride synthesized by the same procedure[7] had $[\alpha]_{578}^{20}$ +7 (*c* 2, MeOH) (*cf.* Ref. 9: $[\alpha]_D^{20}$ +9.0 (*c* 2, MeOH)).

S-Valine methyl ester synthesized[7] from *S*-valine had b.p. 80 °C (40 Torr), $[\alpha]_{578}^{20}$ +42.1 (*c* 8.6, anhydrous MeOH) (*cf.* Ref. 7: b.p. 80 °C (40 Torr)). ^1H NMR, δ: 0.72 and 0.78 (both d, each 3 H, C(3)$\underline{Me}_2$, J = 7 Hz); 1.84 (septet d, 1 H, C(3)H, J = 7 and J = 5 Hz); 3.12 (d, 1 H, C(2)H, J = 5 Hz); 3.54 (s, 3 H, OMe). ^{13}C NMR, δ: 175.0 (C(1)); 59.0 (C(2)); 31.3 (C(3)); 18.2 and 16.3 (2 Me). *S*-Valine methyl ester hydrochloride synthesized by the same procedure[7] had $[\alpha]_{578}^{20}$ +14 (*c* 3.9, H_2O) (*cf.* Ref. 7: $[\alpha]_D^{23}$ +16 (*c* 4.12, H_2O)).

S-Tyrosine methyl ester synthesized[7] from *S*-tyrosine (Kiev plant of Medical Preparations) had m.p. 135—136 °C (EtOAc), $[\alpha]_{578}^{20}$ +30.5 (*c* 3.1, MeOH) (*cf.* Ref. 10: m.p. 135—136 °C (EtOAc), $[\alpha]_D^{20}$ +25.75 (*c* 3.1, MeOH)). ^1H NMR, δ: 2.84 (dd, 1 H, J = 12.5 and J = 7 Hz) and 2.93 (dd, 1 H, J = 12.5 and J = 6.5 Hz) (C(3)H_2); 3.63 (m, 1 H, C(2)H); 6.74 (dm, 2 H, J = 8 Hz) and 7.01 (dm, 2 H, J = 8 Hz) (AA′BB′ system, H(3′),

H(5′) and H(2′), H(6′)). ^{13}C NMR, δ: 176.4 (C(1)); 56.8 (C(2)); 40.8 (C(3)); 52.3 (OMe); 128.8 (C(1′)); 116.4 (C(2′), C(6′)); 131.3 (C(2′), C(5′)); 157.4 (C(4′)).

S-Methionine methyl ester,[11] b.p. 124—125 °C (11 Torr) (*cf.* Ref:[11] b.p. 124—125 °C (11 Torr)). ^{1}H NMR, δ: 1.48 (br.s, 2 H, NH_2); 1.70—2.00 (m, 2 H, C(3)H_2); 2.08 (s, 3 H, SMe); 2.60 (t, 2 H, C(4′)H_2, J = 7.3 Hz); 3.56 (dd, 1 H, C(2′)H, J = 8 and J = 5 Hz); 3.71 (s, 3 H, OMe). ^{13}C NMR, δ: 175.24 (C(1)); 52.30 (C(2)); 29.45 (C(3)); 33.05 (C(4)); 51.0 (OMe) and 14.29 (SMe). The hydrochloride with the composition $C_6H_{13}NO_2S \cdot HCl$, prepared by a previously described procedure,[11] had $[\alpha]_{578}^{20}$ +27 (*c* 5, H_2O) (*cf.* Ref. 11: $[\alpha]_D^{19}$ +26.8 (*c* 5, H_2O)).

S-Valinol prepared by a known procedure[12] from *S*-valine (Reanal) had m.p. 31—32 °C, b.p. 75 °C (6 Torr), $[\alpha]_{578}^{33}$ +17 (*c* 11, EtOH) (*cf.* Ref. 13: m.p. 31—32 °C, b.p. 75 °C (6 Torr), Ref.:[7] $[\alpha]_{578}^{33}$ +17.0 (*c* 11, EtOH)). ^{1}H NMR, δ: 0.416 and 0.424 (both d, each 3 H, C(3)$\underline{Me}_2$, J = 6.8 Hz); 1.12 (m, 1 H, C(3′)H); 2.05 (m, 1 H, C(2)H); 2.79 (dd, 1 H, J = 10.5 and J = 8.3 Hz), 3.11 (dd, 1 H, J = 10.5 and J = 3.7 Hz) (CH_2OH). ^{13}C NMR, δ: 63.7 (C(1)); 57.6 (C(2)); 30.0 (C(3)); 17.3 and 18.4 (2 Me).

S-Tyrosinol was prepared by reduction of the *S*-tyrosine methyl ester with $LiAlH_4$ in ether by a previously described procedure[14] (*cf.* Ref. 15), which we modified in the following way. Excess CO_2 was passed through a methanolic solution of crude tyrosinol to precipitate Li_2CO_3 and $Al_2(CO_3)_3$. The precipitated carbonates were separated by centrifugation, the supernatant was concentrated *in vacuo*, and the residue was dried at 50 °C (3 Torr) to give pure *S*-tyrosinol as a thick oil. ^{1}H NMR (CD_3OD), δ: 2.48 (dd, 1 H, C(3)H_a, J = 14 and J = 8 Hz); 2.72 (dd, 1 H, C(3)H_b, J = 14 and J = 6 Hz); 3.00 (m, 1 H, C(2)H); 3.38 (m, 1 H, C(1)H_a); 3.57 (dd, 1 H, C(1)H_b, J = 11 and J = 4 Hz); 6.77 (m, 2 H, C(2′)H and C(6′)H) and 7.03 (m, 2 H, C(3′)H and C(5′)H). ^{13}C NMR, δ: 66.6 (C(1)); 55.5 (C(2)); 39.8 (C(3)); 130.1 (C(1′)), 131.2 (C(2′), C(6′)); 116.7 (C(3′), C(5′)); 157.5 (C(4′)). *S*-Tyrosinol oxalate $(C_9H_{13}NO_2)_2 \cdot H_2C_2O_4$, prepared by a known method,[14] had $[\alpha]_{578}^{20}$ −20 (*c* 1, H_2O) (*cf.* Ref. 14: $[\alpha]_D^{17}$ −20 (*c* 1, H_2O)). The ^{1}H NMR spectrum of the oxalate (D_2O), δ: 3.10 (dd, 1 H, J = 14.0 and J = 7.5 Hz) and 3.14 (dd, 1 H, J = 14.0 and J = 7.0 Hz) (C(3)H_2); 3.80 (m, 1 H, C(2)H); 3.85 (dd, 1 H, J = 12.0 and J = 6.7 Hz) and 4.03 (dd, 1 H, J = 12.0 and J = 3.4 Hz) (C(1)H_2); 7.13, 7.42 (both dm, each 2 H, AA′BB′ system, H(3′), H(5′) and H(2′), H(6′), J = 8 Hz). ^{13}C NMR, δ: 61.45 (C(1)); 55.30 (C(2)); 34.61 (C(3)); 128.18(C(1′)); 131.60 (C(2′), C(6′)); 116.76 (C(3′), C(5′)); 155.66 (C(4′)) and 174.05 (2 CO_2^-).

S-Methioninol synthezised[16] from *S*-methionine methyl ester had b.p. 120 °C (3 Torr), $[\alpha]_{578}^{20}$ −10 (*c* 1.5, EtOH) (*cf.* Ref. 16: b.p. 104—108 °C (0.05 Torr), Ref. 17: b.p. 110—132 °C (5 Torr), $[\alpha]_D^{21}$ −9.7 (*c* 1.5, EtOH)). ^{1}H NMR, δ: 1.40 (m, 2 H, C(3)H_2); 1.87 (s, 3 H, SMe); 2.34 (m, 2 H, C(4)H_2); 2.71 (m, 1 H, C(2)H); 3.08 (dd, 1 H, C(1)H_a, J = 10 and J = 7 Hz); 3.42 (dd, 1 H, C(1)H_b, J = 10 and J = 4 Hz). ^{13}C NMR, δ: 66.0 (C(1)); 51.8 (C(2)); 33.0 (C(3)); 30.8 (C(4)) and 15.2 (SMe).

18-Methylamino-7,8-methylenedioxy-1α,6β,14α,16β-tetramethoxy-20-ethylaconitane (**14**) was prepared by a known method.[2]

Imines **2—7** were synthesized by a general procedure.[2] The spectral or analytical characteristics of imines **5—7** were not determined.

18-(*E*)-[1*S*-Methoxycarbonyl)ethylimino]-7,8-methylenedioxy-1α,6β,14α,16β-tetramethoxy-20-ethylaconitane (2). Thick oil, $[\alpha]_{578}^{20}$ −55.5 (*c* 3.1, MeOH). Found, *m/z*: 562.3256 $[M]^+$. $C_{30}H_{46}N_2O_8$. Calculated: M 562.3254. ^{1}H NMR, δ: 0.98 (t, 3 H, $NCH_2C\underline{H}_3$); 1.31 (d, 3 H, C(3′)H_3, J = 7 Hz); 3.13, 3.18, 3.25 and 3.33 (all s, each 3 H, 1-, 6-, 14- and 16-OMe); 3.61 (s, 3 H, CO_2Me); 4.93 and 4.96 (both s, each 1 H, OCH_2O); 7.40 (s, 1 H, C(18)H). IR (KBr), ν/cm^{-1}: 731, 940, 962, 1007, 1051, 1090, 1123, 1379, 1450, 1662 (C=N), 1743 (C=O), 2822, 2878, 2933 and 2973.

18-(*E*)-(2-Methyl-1*S*-methoxycarbonylpropylimino)-7,8-methylenedioxy-1α,6β,14α,16β-tetramethoxy-20-ethylaconitane (3). Amorphous powder, $[\alpha]_{578}^{20}$ −60.5 (*c* 3.7, MeOH). High-resolution MS, *m/z*: 590.3568 $[M]^+$. $C_{32}H_{50}N_2O_8$. Calculated: M 590.3567. ^{1}H NMR, δ: 0.77 and 0.82 (both d, each 3 H, C(2′)$\underline{Me}_2$ J = 7 Hz); 1.00 (t, 3 H, $NCH_2C\underline{H}_3$); 3.10, 3.20, 3.27 and 3.35 (all s, each 3 H, 1-, 6-, 14-, and 16-OMe); 3.63 (s, 3 H, CO_2Me); 4.94 and 4.97 (both s, each 1 H, OCH_2O); 7.35 (s, 1 H, C(18)H). IR (KBr), ν/cm^{-1}: 960, 982, 1015, 1037, 1081, 1122, 1140, 1207, 1309, 1463, 1672 (C=N), 1743 (C=O), 2822, 2882, 2918 and 2974.

18-(*E*)-[2-(4-Hydroxyphenyl)-1*S*-methoxycarbonylethylimino]-7,8-methylenedioxy-1α,6β,14α,16β-tetramethoxy-20-ethylaconitane (4). Amorphous powder, $[\alpha]_{578}^{20}$ −72.5 (*c* 3.8, MeOH). Found (%): C, 65.27, 65.43; H, 8.07, 8.23; N, 4.18, 4.08. $C_{36}H_{50}N_2O_9$. Calculated (%): C, 66.02; H, 7.71; N, 4.28. ^{1}H NMR (CD_3OD), δ: 1.09 (t, 3 H, $NCH_2C\underline{H}_3$, J = 7 Hz); 3.13, 3.26, 3.30 and 3.36 (all s, each 3 H, 1-, 6-, 14- and 16-OMe); 3.73 (s, 3 H, CO_2Me); 4.98 and 5.00 (both s, each 1 H, OCH_2O); 6.71 (dm, 2 H, J = 8 Hz) and 6.94 (dm, 2 H, J = 8 Hz) (AA′BB′ system, H(3″), H(5″) and H(2″), H(6″), respectively); 7.06 (s, 1 H, C(18)H). IR (KBr), ν/cm^{-1}: 935, 961, 980, 1038, 1089, 1129, 1171, 1201, 1270, 1333, 1380, 1446, 1517, 1615, 1660 (C=N), 1742 (C=O), 2821, 2878, 2931, 2973. UV (EtOH), λ_{max}/nm (logε): 226 (3.83) and 279 (3.08).

18-[(1*S*-Methoxycarbonyl)ethylamino]-7,8-methylenedioxy-1α,6β,14α,16β-tetramethoxy-20-ethylaconitane (8). A solution of compound **2** (0.75 g, 1.34 mmol) in 7 mL of EtOH was hydrogenated over Pd supported on activated carbon (0.90 g of the IKT-3-25 catalyst, Pd content 0.25%)[18] at 20 °C (760 Torr) until a theoretical amount of hydrogen has been absorbed. The catalyst was filtered off and washed with EtOH (2×7 mL). The solvent was removed from the filtrate *in vacuo* (bath temperature 50 °C) and the residue was dissolved in 2 mL of $CHCl_3$ and subjected to preparative TLC on Al_2O_3 (5/40 μm Chemapol, Czechia) containing 1% luminophore K-35 and 3% Na_2CO_3 in the $Bu^tOMe—CHCl_3$ solvent system (9 : 1, v/v). The UV-absorbing band of the sorbent with R_f 0.87 was collected. The target product was eluted with the same solvent system. Removal of the solvent from the eluate and drying of the residue at 50 °C (3 Torr) gave 0.54 g (71%) of compound **8** as an amorphous powder, $[\alpha]_{578}^{20}$ +4.5 (*c* 4.4, $CHCl_3$). Found, *m/z*: 564.3417 $[M]^+$. $C_{30}H_{48}N_2O_8$. Calculated: M 564.3410. ^{1}H NMR, δ: 0.90 (t, 3 H, $NCH_2C\underline{H}_3$, J = 7 Hz); 1.12 (d, 3 H, C(2′)H_3, J = 7 Hz); 3.10, 3.13, 3.21 and 3.27 (all s, each 3 H, 1-, 6-, 14-, and 16-OMe); 4.91 (s, 2 H, OCH_2O). IR (KBr), ν/cm^{-1}: 728, 753, 964, 1010, 1089, 1126, 1171, 1200, 1298, 1385, 1446, 1738 (C=O), 2752, 2822, 2930 and 3337 (NH).

Diamines **9—11** were prepared by reducing imines **5—7** with $NaBH_4$ according to the general procedure of imine reduction.[2]

18-(1*S*-Hydroxymethyl-2-methylpropylamino)-7,8-methylenedioxy-1α,6β,14α,16β-tetramethoxy-20-ethylaconitane (9). Thick oil, $[\alpha]_{578}^{20}$ +10 (*c* 2.0, $CHCl_3$). Found, *m/z*: 564.3788 $[M]^+$. $C_{31}H_{52}N_2O_7$. Calculated: M 564.3774. ^{1}H NMR, δ: 0.83 and 0.90 (both d, each 3 H, C(2′)$\underline{Me}_2$, *J* = 6.8 Hz); 0.98 (t, 3 H, $NCH_2C\underline{H}_3$, *J* = 7.1 Hz); 3.19, 3.28, 3.31 and 3.37 (all s, each 3 H, 1-, 6-, 14-, and 16-OMe); 4.98 and 5.01 (both s, each 1 H, OCH_2O). IR (KBr), ν/cm^{-1}: 963, 1090, 1123, 1159, 1197, 1386, 1453, 1467, 2818, 2875, 2932, 2959.

18-[1*S*-Hydroxymethyl-2-(4-hydroxyphenyl)ethylamino]-7,8-methylenedioxy-1α,6β,14α,16β-tetramethoxy-20-ethylaconitane (10). Amorphous powder. Found, *m/z*: 627.3646 $[M]^+$. $C_{35}H_{51}N_2O_8$. Calculated: M 627.3645. ^{1}H NMR, δ: 0.98 (t, 3 H, $NCH_2C\underline{H}_3$, *J* = 7.1 Hz); 3.20 (6 H), 3.29 (3 H) and 3.37 (3 H) (all s, 1-, 6-, 14-, and 16-OMe); 4.99 and 5.00 (both s, each 1 H, OCH_2O); 6.72 (dm, 2 H, *J* = 8.2 Hz) and 6.94 (dm, 2 H, *J* = 8.2 Hz) (AA′BB′ system, H(3″), H(5″) and H(2″), H(6″), respectively). IR (KBr), ν/cm^{-1}: 1089, 1120, 1199, 1227, 1265, 1449, 1516, 2819, 2881, 2930, 2965. UV (EtOH), λ_{max}/nm (logε): 225 (3.92) and 280 (3.20).

18-[1*S*-Hydroxymethyl-3-(methylthio)propylamino]-7,8-methylenedioxy-1α,6β,14α,16β-tetramethoxy-20-ethylaconitane (11). Thick oil. Found, *m/z*: 596.4 $[M]^+$. $C_{31}H_{52}N_2O_7S$. Calculated: M = 596.4. For a fragment ion, found, *m/z*: 565.3312. $C_{31}H_{52}N_2O_7S - OCH_3 = C_{30}H_{49}N_2O_6S$. Calculated: M = 565.3311. ^{1}H NMR, δ: 0.95 (t, 3 H, $NCH_2C\underline{H}_3$, *J* = 7 Hz); 2.01 (s, 3 H, SMe); 3.15, 3.24, 3.27, 3.32 (all s, each 3 H, 1-, 6-, 14-, and 16-OMe); 4.94 and 4.96 (both s, each 1 H, OCH_2O). IR (KBr), ν/cm^{-1}: 732, 911, 963, 1046, 1090, 1120, 1160, 1197, 1446, 1464, 2820, 2881, 2921. UV (EtOH), λ_{max}/nm (logε): 219 (3.95).

***N*-Methylation of compounds 9, 10 and 14.** A solution of the substrate (1 mmol) in 1.2 mL of MeI was sealed and kept at 20 °C for 72 h. Excess MeI was removed, and the residue was dissolved in 2.5 mL of $CHCl_3$ and washed with 0.15 mL of 25% NH_4OH. The organic layer was separated, the solvent was removed, and the residue was dried *in vacuo* at 50 °C (3 Torr).

18-[*N*-(1*S*-Hydroxymethyl-2-methylpropyl)-*N*-methylamino]-7,8-methylenedioxy-1α,6β,14α,16β-tetramethoxy-20-ethylaconitane (12). Thick oil, $[\alpha]_{578}^{20}$ −34 (*c* 1.5, $CHCl_3$). For the fragment ion, found *m/z*: 547.3743. $C_{32}H_{54}N_2O_7 - OCH_3 = C_{31}H_{51}N_2O_6$. Calculated: M 547.3747. ^{1}H NMR, δ: 0.77 and 0.95 (both d, each 3 H, C(2′)$\underline{Me}_2$, *J* = 6.5 Hz); 0.98 (t, 3 H, $NCH_2\underline{Me}$, *J* = 7.0 Hz); 2.27 (s, 3 H, NMe); 3.19, 3.28, 3.32, 3.37 (all s, each 3 H, 1-, 6-, 14-, and 16-OMe); 4.99 and 5.03 (both s, each 1 H, OCH_2O). IR (KBr), ν/cm^{-1}: 731, 962, 1010, 1121, 1161, 1198, 1386, 1449, 1469, 2817, 2883 and 2933.

18-{*N*-[1*S*-Hydroxymethyl-2-(4-hydroxyphenyl)ethyl]-*N*-methylamino}-7,8-methylenedioxy-1α,6β,14α,16β-tetramethoxy-20-ethylaconitane (13). Amorphous powder, $[\alpha]_{578}^{20}$ −33 (*c* 4.2, $CHCl_3$). For the fragment ion, found *m/z*: 611.3662. $C_{36}H_{53}N_2O_8 - CH_2O = C_{35}H_{51}N_2O_8$. Calculated: M 611.3696. ^{1}H NMR, δ: 0.98 (t, 3 H, NCH_2Me, *J* = 7.1 Hz); 2.31 (s, 3 H, NMe); 3.22, 3.29, 3.30 and 3.38 (all s, each 3 H, 1-, 6-, 14-, and 16-OMe); 4.99 and 5.03 (both s, each 1 H, OCH_2O); 6.69 (dm, 2 H, *J* = 8.2 Hz) and 6.89 (dm, 2 H, *J* = 8.2 Hz) (AA′BB′ system, H(3″), H(5″) and H(2″), H(6″), respectively). IR (KBr), ν/cm^{-1}: 732, 962, 1033, 1090, 1116, 1162, 1199, 1450, 1516, 2819, 2883 and 2932. UV (EtOH), λ_{max}/nm (logε): 224 (3.80) and 280 (3.04).

18-Dimethylamino-7,8-methylenedioxy-1α,6β,14α,16β-tetramethoxy-20-ethylaconitane (15). Thick oil. Found, *m/z*: 506.3345 $[M]^+$. $C_{28}H_{46}N_2O_6$. Calculated: M 506.3366. ^{1}H NMR, δ: 0.86 (t, 3 H, NCH_2Me, *J* = 7.1 Hz); 3.05, 3.14, 3.22, 3.28 (all s, each 3 H, 1-, 6-, 14-, and 16-OMe); 3.43 (s, 6 H, NMe_2); 4.83 and 4.88 (both s, each 1 H, OCH_2O). IR (KBr), ν/cm^{-1}: 731, 753, 920, 950, 964, 1007, 1088, 1117, 1161, 1199, 1227, 1386, 1450, 1469, 2821, 1881, 2933, 2971. UV (EtOH), λ_{max}/nm (logε): 219 (3.95).

This work was financially supported by the Russian Foundation for Basic Research (Project No. 01-03-32431).

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Received June 14, 2002