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17,18-DIDEHYDROLOESENERINE AND 16,17-DIDEHYDROLOESENERIN-18-OL, ALKALOIDS FROM *MAYTENUS LOESENERI*

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Key Word Index—*Maytenus loeseneri*; Celastraceae; spermidine alkaloids; 17,18-didehydroloesenerine; 16,17-didehydroloesenerin-18-ol.

Abstract—17,18-Didehydroloesenerine and 16,17-didehydroloesenerin-18-ol have been isolated from *Maytenus loeseneri* and their structures have been elucidated as (*R*)-1-acetyl-8-[(1*Z*,4*Z*)-1,4-heptadienyl]-1,5,9-triazacyclotridecan-6-one and (8*R*)-1-acetyl-8-[(1*Z*,3*E*)-5ξ-hydroxy-1-3-heptadienyl]-1,5,9-triazacyclotridecan-6-one, respectively.

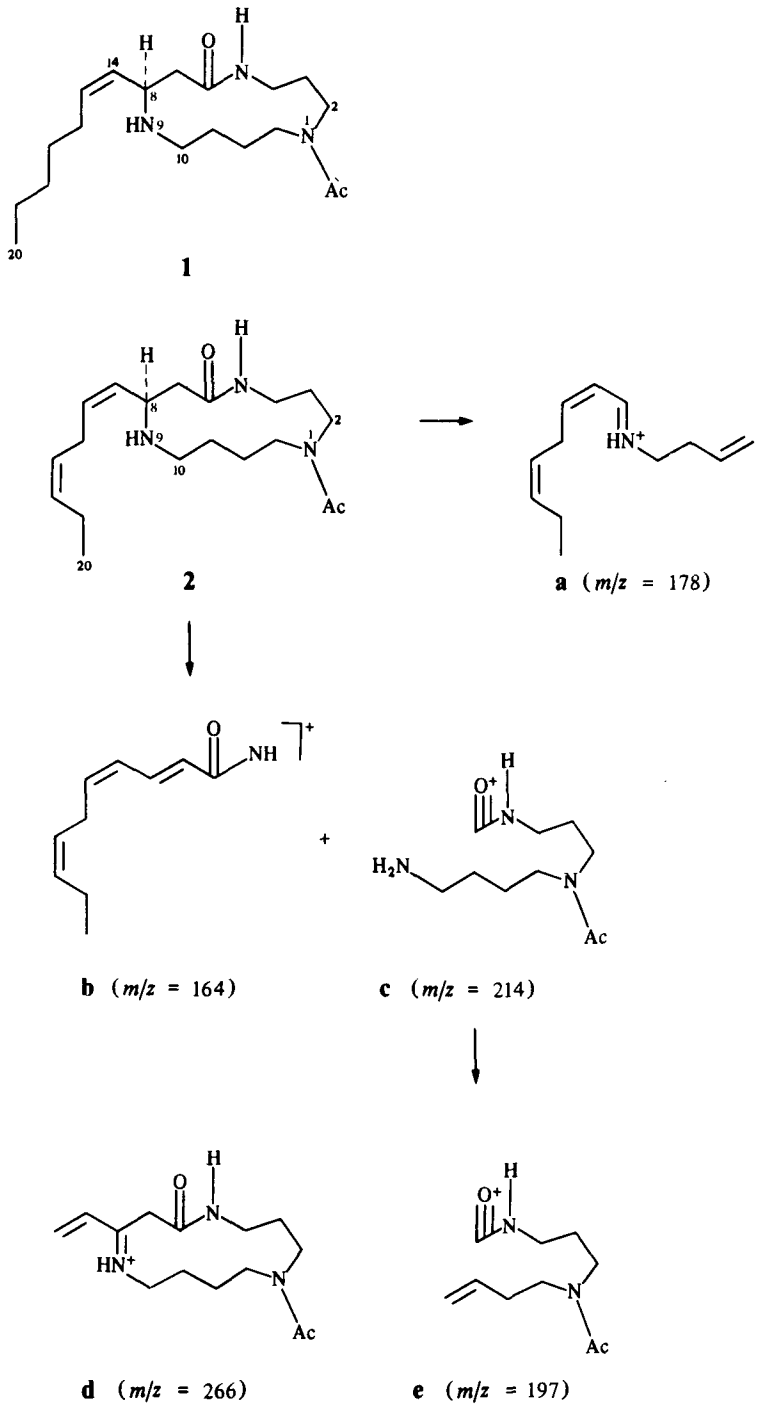
From leaves of *Maytenus loeseneri* Urb. the alkaloid loesenerine (**1**) had been isolated [1]. Two further spermidine alkaloids, 17,18-didehydroloesenerine and 16,17-didehydroloesenerin-18-ol, have been obtained from this plant material. Their structures of (*R*)-1-acetyl-8-[(1*Z*,4*Z*)-1,4-heptadienyl]-1,5,9-triazacyclotridecan-6-one (**2**) and (8*R*)-1-acetyl-8-[(1*Z*,3*E*)-5ξ-hydroxy-1,3-heptadienyl]-1,5,9-triazacyclotridecan-6-one (**3**), respectively, are in accordance with spectroscopic data as outlined below. Similar macrocyclic spermidine alkaloids, especially with regard to the type of spermidine incorporation, also occur in other *Maytenus* species and further members of the Celastraceae [2–5].

The IR spectra of **2** and **3** indicated secondary amide groups, the UV spectrum of **3** conjugated double bonds. The elemental composition of **2** was shown to be $C_{19}H_{33}N_3O_2$ by high resolution MS. The MS fragmentation is very similar to that of loesenerine (**1**) (cf. [1]). Thus, the appearance of the ion **a**, the low intensity of the cleavage of the side chain ($m/z=240$) and of the ion at $m/z=152$ are in accordance with a 13-membered ring, four unsubstituted CH_2 groups between N-1 and N-9 and a 14,15-position of one of the double bonds (cf. [1]). The fragments **b**–**e** are analogous to loesenerine ions [1]. High resolution MS indicated an empirical formula of $C_{19}H_{33}N_3O_3$ for the alkaloid **3**. The ion **a'** revealed the same ring structure as in **1** and **2**. The intensity of the fragment at $m/z=266$ (possibly a loss of a C_5-side chain) is weak, however the intensity of the ion at $m/z=240$, corresponding to the cleavage of the C_7-side chain, is relatively strong, so that a 15-membered ring had not to be considered in this case (cf. the discussion in [1]). The co-occurrence of the fragment ions $[M-H_2O-Et]^+$ and $[M-C_3H_7O]^+$ indicated the 18-position of the hydroxy group. The ion **b'** corresponds to **b**.

^{1}H NMR investigations were especially useful for the structure elucidation of the side chains of **2** and **3**. The position of the side chains was proved by decoupling of H-8 of **2** and **3**, the signals of which appear as in **1** at the low-field end of the methylene proton region (**2**: 3.70 ppm, **3**: 3.88 ppm). The (14*Z*,16*E*)-diene partial structure and the 18-position of the hydroxy group in **3** was recognized from the chemical shifts and coupling constants of the corresponding protons, when their coupling connectivities had been determined by spin decoupling (Table 1). In the more complicated case of **2** the olefinic region (four protons) was analysed, in addition to decoupling experiments, by a 2D *J*-resolved spectrum (Fig. 1b, c). The methylene protons at C-16 and C-19 were identified by a spin decoupling difference spectrum (Fig. 1d). Because of the strong coupling between H-17 and H-18 the chemical shifts and coupling constants of the olefinic protons had to be determined by iterative simulation (Table 1). The extracted coupling constants indicated the *cis*-configuration of both double bonds.

Two signals were observed in the ^{13}C NMR spectrum of **2** and **3** for most of the ring carbon atoms (Table 2). This is in agreement with the fact, that larger ring lactams exist at room temperature as an equilibrium mixture of *cis* and *trans* conformers [6]. The signals of the ring carbons were assigned as in the case of loesenerine (**1**) [1], the signals of the side chains mainly by selective $^{13}C\{^1H\}$ decoupling experiments, when the corresponding ^{1}H signals had been unambiguously identified. The assignment of the side chain carbons of **2** is supported by the ^{13}C data of (3*Z*,6*Z*,9*Z*)-3,6,9-octadecatriene [7]. Identical NMR chemical shifts of the ring carbons of **1**, **2** and **3** (Table 2) are in accordance with the same ring structure and side chain attachment of these alkaloids.

An (8*R*)-configuration had been assigned to loesenerine (**1**) [1]. The positive *n*-π* Cotton effect of the *N*(9)-nitroso derivatives of **1**–**3** (**1**: $a_{382}=+21.2°$, **2**: $a_{382}=+23.0°$, **3**: $a_{378}=+10.5°$) proved the same configuration of loesenerine (**1**), 17,18-didehydroloesenerine (**2**) and 16,17-didehydroloesenerin-18-ol (**3**) at C-8. (*S*)-*N*-Nitrosoconiine with the same stereochemistry has the same sign of the corresponding Cotton effect [8]. The π–π* Cotton effect of the *N*(9)-nitroso derivatives of **1**–**3** is also positive. Only the long wavelength extremum could be measured.



EXPERIMENTAL

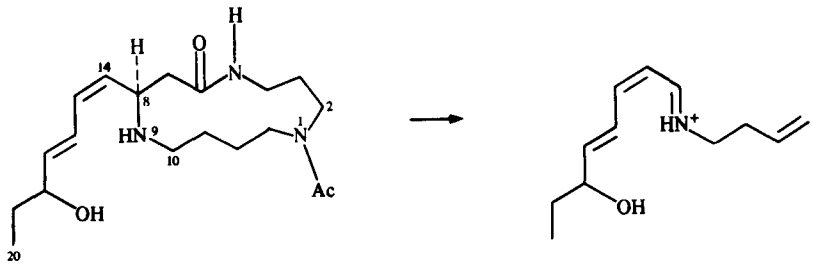
The ^1H and ^{13}C NMR spectra were recorded in general in $CDCl_3$ at 200.13 and 50.33 MHz, respectively, using TMS as the internal standard. Because of the low solubility of **3** in $CDCl_3$, the ^{13}C spectrum was measured in $CDCl_3$–C_5D_5N (4:1). The proton decoupling difference spectrum of **2** was obtained using the DISNMRP program (version 820601, microprogram DIFF). The decoupler power was 7 dB below 0.2 W, and the off-resonance frequency was spaced 100 Hz to lower field from the primary decoupler frequency. For the 2D *J*-resolved spectrum of **2** the sample concn was *ca* 0.2 M in $CDCl_3$. The F_2 spectral width was 1082.25 Hz, while F_1 was $\pm$33.83 Hz.The number of data points was 1024 in t_2 and 128 in t_1 direction, providing a digital resolution of 1.057Hz per point in F_2 and, after zero filling, 0.264 Hz per point in the F_1 direction. Both time domains were multiplied with a sine-bell function, and 64 scans were collected for each t_1 increment. The simulation of the olefinic region of the ^1H NMR spectrum of **2** was performed by the program PANIC, version 820601. Because two signals for H-14 were observed as a consequence of a dynamic process in the lactam ring (see also Fig. 1c), the spectrum simulation was carried out two times with different shift values for H-14. The calculated spectra were then written in DISNMR file format and added. The RMS error of the

Table 1. ^{1}H NMR chemical shifts δ and coupling constants J (Hz) of the side chain protons in **2** and **3**

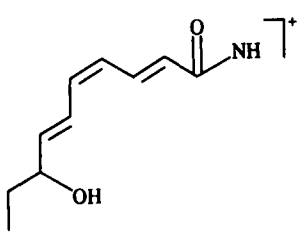
Proton	2*	3
H-14	5.11; 5.12	5.15
	$J_{H-14,H-8}=9.5$	$J_{H-14,H-8}=10.5$
	$J_{H-14,H-15}=10.8$	$J_{H-14,H-15}=10.5$
	$J_{H-14,H_2-16}=-1.3$	
H-15	5.49	6.12
	$J_{H-15,H-8}=-0.8$†	$J_{H-15,H-14}=10.5$
	$J_{H-15,H-14}=10.8$	$J_{H-15,H-16}=11.5$
	$J_{H-15,H_2-16}=7.3$	
H_2-16; H-16	2.80	6.50
	$J_{H_2-16,H-14}=-1.3$	$J_{H-16,H-15}=11.5$
	$J_{H_2-16,H-15}=7.3$	$J_{H-16,H-17}=15.0$
	$J_{H_2-16,H-17}=7.3$	
	$J_{H_2-16,H-18}=-1.6$	
H-17	5.24	5.77
	$J_{H-17,H_2-16}=7.3$	$J_{H-17,H-16}=15.0$
	$J_{H-17,H-18}=10.6$	$J_{H-17,H-18}=6.2$
	$J_{H-17,H_2-19}=-1.5$	
H-18	5.39	4.13
	$J_{H-18,H_2-16}=-1.6$	$J_{H-18,H-17}=6.2$
	$J_{H-18,H-17}=10.6$	$J_{H-18,H_2-19}=6.3$
	$J_{H-18,H_2-19}=7.3$	
H_2-19	2.04	1.60
	$J_{H_2-19,H-17}=-1.5$	$J_{H_2-19,H-18}=6.3$
	$J_{H_2-19,H-18}=7.3$	$J_{H_2-19,H_3-20}=7.5$
	$J_{H_2-19,H_3-20}=7.5$	
H_3-20	0.93	0.95
	$J_{H_3-20,H_2-19}=7.5$	$J_{H_3-20,H_2-19}=7.5$

*Values obtained by iterative simulation.

†A negative sign was used in the spectrum calculation, but it may be reversed.



3 **a'** (*m/z* = 194)



b' (*m/z* = 180)

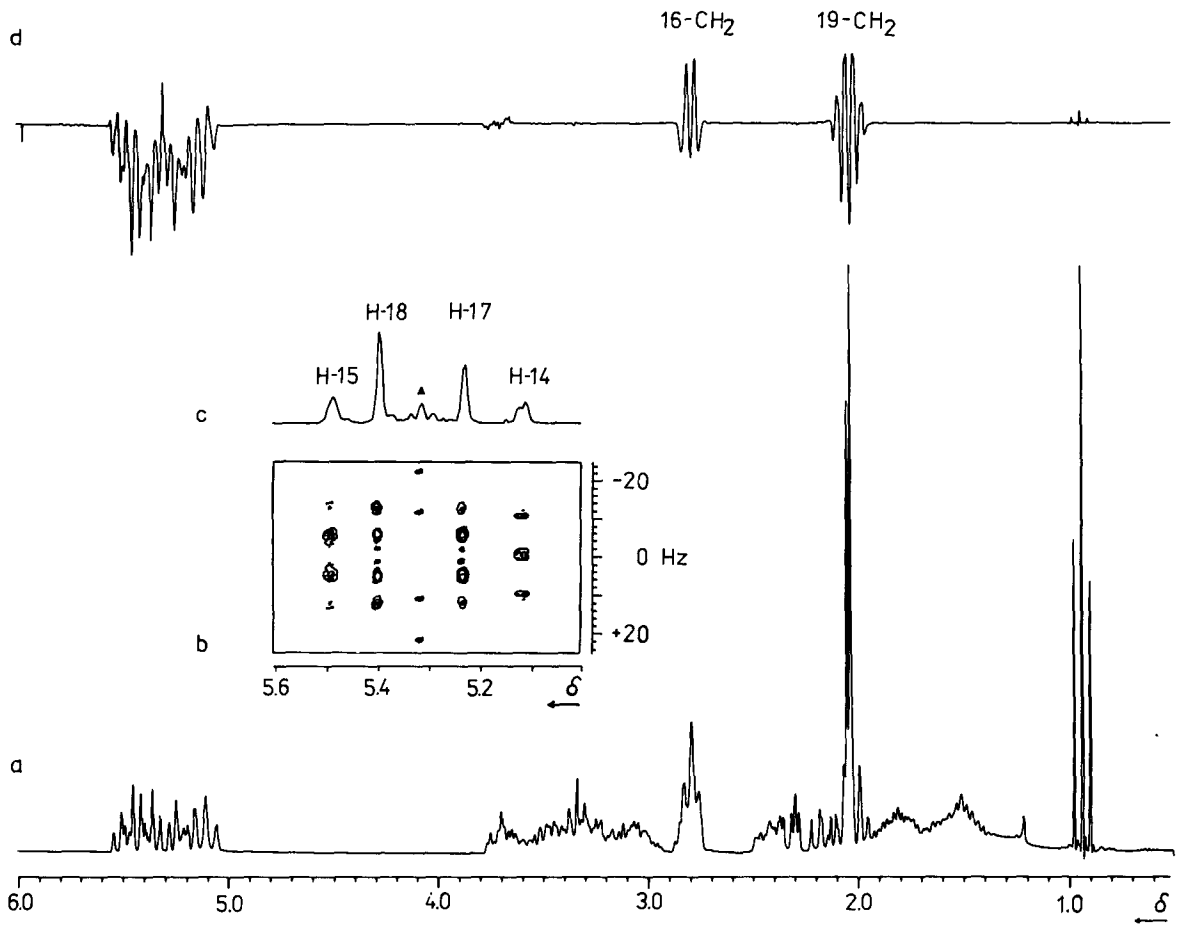


Fig. 1. Partial 200.13 MHz ^{1}H NMR spectra of 17,18-didehydroloesenerine (**2**) in $CDCl_3$. (a) Conventional 1D spectrum without the low-field NH signals. (b) Contour plot (olefinic region) of the 2D *J*-resolved spectrum. (c) Projection of the 2D *J*-resolved spectrum on the chemical shift axis. (The peak indicated by ▲ and the corresponding cross peaks in the contour plot appear from strong coupling between H-17 and H-18.) (d) Spin-decoupling difference spectrum after irradiation on the centre of the olefinic protons.

calculated versus experimental spectrum was found to be ±0.08 Hz. The selective $^{13}C\{^1H\}$ decoupling experiments were carried out with a power level of 12 dB below 0.2 W, after the exact proton frequencies had been determined via the decoupler channel.

Plant material. Leaves of *M. loeseneri* Urb. were collected, determined, dried and extracted as described [1].

17,18-*Didehydroloesenerine* (**2**). The crude alkaloid fraction was chromatographed over Si gel G using $CHCl_3$–MeOH (19:1), over Si gel G containing 9% $AgNO_3$ using $CHCl_3$–MeOH (9:1) and again over Si gel G. From Me_2CO crystals; yield 0.12%; mp 106°, $[\alpha]_D^{22}$ +51.3° ($CHCl_3$; *c* 0.52). ν_{max}^{KBr} cm^{-1}: 3327, 3272 (NHCO), 1632 (N-CO), 1561 (NHCO); EIMS 70 eV, *m/z* (rel. int.): 335.2556 $[M]^+$, calc. for $C_{19}H_{33}N_3O_2$ 335.2573 (100), 320.2359 $[M-Me]^+$, calc. for $C_{18}H_{30}N_3O_2$ 320.2338 (5), 306.2188 $[M-Et]^+$, calc. for $C_{17}H_{28}N_3O_2$ 306.2181 (7), 292.2399 $[M-Ac]^+$, calc. for $C_{17}H_{30}N_3O$ 292.2389 (9), 292.2029 $[M-C_3H_7]^+$, calc. for $C_{16}H_{26}N_3O_2$ 292.2025 (4), 266.1851 **d**, calc. for $C_{14}H_{24}N_3O_2$ 266.1868 (87), 240.1703 $[M-C_7H_{11}]^+$, calc. for $C_{12}H_{22}N_3O_2$ 240.1712 (9), 214.1546 **c**, calc. for $C_{10}H_{20}N_3O_2$ 214.1555 (27), 197.1265 **e**, calc. for $C_{10}H_{17}N_2O_2$ 197.1290 (27), 178.1584 **a**, calc. for $C_{12}H_{20}N$ 178.1596 (11), 164.1066 **b**, calc. for $C_{10}H_{14}NO$ 164.1075 (11).

16,17-*Didehydroloesenerin-18-ol* (**3**). When the crude alkaloid fraction was chromatographed over Si gel G using $CHCl_3$–MeOH (9:1), **3** was eluted. From MeOH–Me_2CO crystals; yield 0.003%; mp 203–207°, $[\alpha]_D^{22}$ +176.8° [$CHCl_3$–EtOH (19:1); *c* 0.39]. ν_{max}^{KBr} cm^{-1}: 3312 (OH, NHCO), 1625 (N-CO), 1563 (NHCO); λ_{max}^{MeOH} nm (log ε): 229 (4.39); EIMS 70 eV, *m/z* (rel. int.): 351.2536 $[M]^+$, calc. for $C_{19}H_{33}N_3O_3$ 351.2522 (9), 333.2409 $[M-H_2O]^+$, calc. for $C_{19}H_{31}N_3O_2$ 333.2416 (82), 308.2326 $[M-Ac]^+$, calc. for $C_{17}H_{30}N_3O_2$ 308.2338 (9), 304.2002 $[M-H_2O-Et]^+$, calc. for $C_{17}H_{26}N_3O_2$ 304.2025 (25), 292.2020 $[M-C_3H_7O]^+$, calc. for $C_{16}H_{26}N_3O_2$ 292.2025 (100), 240 $[M-C_7H_{11}O]^+$ (50), 194.1524 **a'**, calc. for $C_{12}H_{20}NO$ 194.1545 (12), 180.1015 **b'**, calc. for $C_{10}H_{14}NO_2$ 180.1024 (6), 176.1426 [**a'**$-H_2O$], calc. for $C_{12}H_{18}N$ 176.1439 (8), 162.0905 [**b'**$-H_2O$], calc. for $C_{10}H_{12}NO$ 162.0919 (18).

N-*Nitroso derivatives.* A soln of 170 mg of $NaNO_2$ in 0.3 ml of H_2O was added to 10 mg of the alkaloid in 0.3 ml of HOAc. After 15 hr at room temp. aq. Na_2CO_3 was added and the product was extracted with $CHCl_3$.

N(9)-*Nitrosoloesenerine.* λ_{max}^{EtOH} nm (log ε): 236 (3.72); ORD (EtOH): $[\phi]_{404}$ +2000° (peak), $[\phi]_{360}$ −120° (trough), $[\phi]_{253}$ +2600° (peak).

N(9)-*Nitroso*-17,18-*didehydroloesenerine.* λ_{max}^{EtOH} nm (log ε): 235

Table 2. ^{13}C NMR chemical shifts* of **1–3**

Carbon	**1**† $CDCl_3$	**2** $CDCl_3$	**3** $CDCl_3$–C_5D_5N (4:1)
C-CH_2 C	23.0, 24.7	23.0, 24.7	23.2, 24.5[c]
	24.1, 24.9	24.1, 24.9	24.3[c], 24.7
	27.7, 28.6	27.7, 28.7	27.6, 28.8
C-CH_2 N	36.6, 36.9	36.7, 37.0	36.3, 36.7
	42.2	42.1, 42.2	42.2, 42.7[d]
	42.9, 45.1	42.8, 45.1	43.1[d], 45.0
	44.7	44.7	44.8
C-6	171.9, 172.1	171.9, 172.1	171.7
C-7	43.4, 47.2	43.4, 47.2	43.4, 47.2
C-8	52.9	53.0	53.1
C-14	130.7, 130.9	130.7[b], 130.9[b]	132.3
C-15	132.5, 132.7	130.3[b], 131.2[b]	129.7
C-16	27.7	25.9	124.1
C-17	29.4[a]	126.2	139.1
C-18	31.5[a]	132.7	72.8, 72.9
C-19	22.5	20.6	30.2
C-20	14.0	14.2	9.6
Ac (Me)	21.3, 21.4	21.2, 21.3	21.0
Ac (CO)	169.9	169.9	169.8

*In ppm downfield from internal TMS.
†Assignment is discussed in [1].
[a–d]Assignment may be interchanged.

(3.74). ORD (EtOH): $[\phi]_{404}+2100°$ (peak), $[\phi]_{360}-200°$ (trough), $[\phi]_{254}+2800°$ (peak).

N(9)-*Nitroso*-16-17-*didehydroloesenerin*-18-*ol*. ORD (EtOH): $[\phi]_{403}+950°$ (peak), $[\phi]_{353}-100°$ (trough), $[\phi]_{264}+2200°$ (peak).

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