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TOTAL SYNTHESIS OF (±)-DESMETHYLHEXAHYDROVALLESIACHOTAMINELACTONES

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Abstract—Total synthesis of (±)-desmethylhexahydrovallesiachotaminelactones **1a** and **1b**, and their isomers **2a** and **2b** is described. The formation of other epimeric pairs of lactones (**1a** and **3a**, and **1b** and **3b**) from vallesiachotamine **4** is also described.

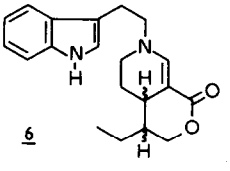
The sodium dithionite reduction of alkylpyridinium salts possessing an electron withdrawing group at the 3 position of the pyridinium ring, to the corresponding 1,4-dihydropyridine derivatives, followed by acid-induced cyclization of the appropriate derivatives to indoloquinolizine systems, has proven to be very useful in the preparation of several indole alkaloid models of the vallesiachotamine type.[1-6]

We have recently shown that the sodium dithionite reduction of the pyridinium salt **5** in aqueous MeOH yields tetrahydropyridine derivatives **6** and **7**.[7] The presence of the lactone ring in **5** apparently strongly hampers the formation of the corresponding 1,4-dihydropyridine derivative and "overreduction" to the tetrahydropyridine stage easily results. On the other hand, the formation of 1,2- and/or 1,6-dihydropyridine derivatives in connection with sodium dithionite treatment of several alkylpyridinium salts of the above type has been reported.[8]

With this information in mind we reasoned that if the "over-reduction" of **5** to the tetrahydropyridine stage could be avoided, the reduction might also yield the 1,2-dihydropyridine derivative **8**, which would be ideally suited for the preparation of (±)-desmethylhexahydrovallesiachotaminelactones **1a** and **1b**.

We found that when the dithionite reduction was effectuated in a two phase system the derivative **8** was indeed formed, and in the present report we describe the total synthesis of (±)-desmethylhexahydrovallesiachotaminelactones **1a** and **1b**. These were also prepared from vallesiachotamine **4** itself by successive reductions and lactonization (*vide infra*).

As far as we know, our work represents the first case where totally synthetic compounds have been proven identical with real vallesiachotamine derivatives.



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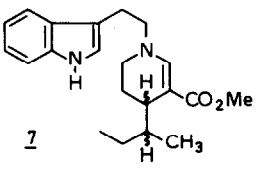

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RESULTS

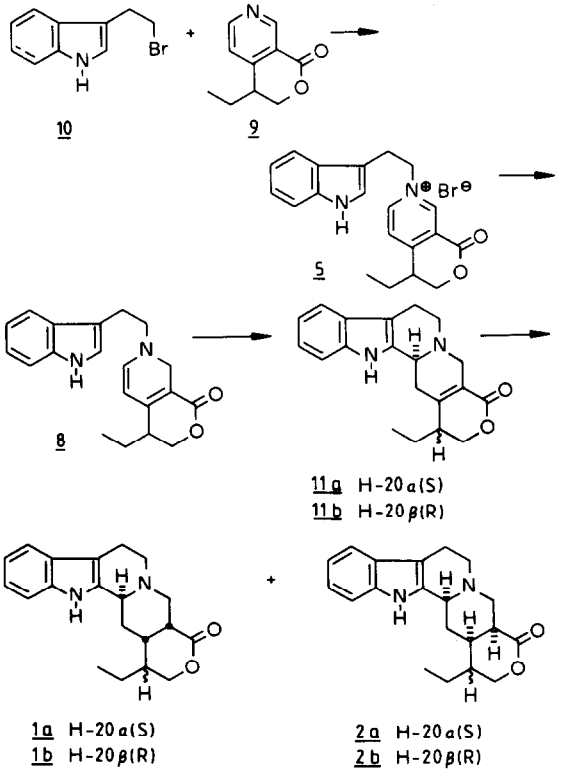
Alkylation of the lactone **9** with tryptophyl bromide **10** afforded the pyridinium salt **5**,[7] whose sodium dithionite reduction in a two phase system (CH_2Cl_2, H_2O) yielded the unstable 1,2-dihydropyridine derivative **8**. By acid-induced cyclization **8** was transformed to the indoloquinolizine lactones **11a** and **11b**, whereafter catalytic hydrogenation (H_2/PtO_2) of **11a** and **11b** afforded lactones **1a** and **2a**, and **1b** and **2b**, respectively.

Sodium borohydride reduction of vallesiachotamine **4** afforded dihydrovallesiachotamine **12**,[9] which by catalytic hydrogenation (H_2/PtO_2) yielded tetrahydrovallesiachotamines **13a** and **13b**. A small amount of hydrogenolysis product **14** was also obtained. Reduction of tetrahydrovallesiachotamines **13a** and **13b** with sodium borohydride in acetic acid[10] afforded lactones **1a** and **3a**, and **1b** and **3b**, respectively.

The lactones **1a** and **1b** synthesized from vallesiachotamine **4** proved to be identical (IR, ^{1}H NMR, MS, TLC) with the lactones **1a** and **1b** synthesized via compound **8**, thereby confirming the total synthesis of (±)-desmethylhexahydrovallesiachotaminelactones **1a** and **1b**.

The reaction producing lactones **3a** and **3b** must proceed through the *cis* C/D ring juncture conformation[11] and leads to *trans* diequatorial D/E ring juncture.

The choice of C-20 stereochemistry for **11a** and **11b** was made on the basis of ^{1}H NMR results (Table 1). The



10 9

5

8

11a H-20α(S)
11b H-20β(R)

1a H-20α(S)
1b H-20β(R)

2a H-20α(S)
2b H-20β(R)

Table 1. ^{1}H NMR data of lactones 11a, 11b, 2a, 2b, 3a and 3b. Spectra were run in $CDCl_3$ at 400 MHz. Values are in δ (TMS=0), s, singlet, d, doublet, t, triplet, q, quartet, m, multiplet, br, broad. The coupling constants between the aromatic protons are not included

Chemical shifts

	11a	11b	2a	2b	3a	3b
H-3	3.58 br	3.58 br	3.32 br	3.34 br	4.56 br s	4.62 br s
H-5α	2.7 ddd	2.7 br dd	2.6 m	2.6 m	3.30 ddd	3.26 ddd
H-5β	3.28 dd	3.27 dd	3.10 dd	3.20 br d	3.40 dd	3.38 dd
H-6α	2.6 m	2.5 m	2.7 m	2.8 m	3.10 m	3.05 m
H-6β	3.00 m	3.02 m	2.95 m	2.95 m	2.62 dd	2.62 dd
H-9	7.48	7.48	7.46	7.44	7.52	7.48
H-10	7.08	7.06	7.07	7.06	7.14	7.14
H-11	7.15	7.14	7.12	7.12	7.19	7.18
H-12	7.30	7.30	7.30	7.30	7.37	7.36
H-14α	2.65^{a}m	2.73^{b}m	2.23 br d	2.22 m	2.40 d	2.25 br d
H-14β	2.78^{a}m	2.78^{b}m	1.49 q	1.50 q	1.94 ddd	2.18 ddd
H-15			2.08 m	2.05 m	1.22 m	1.25 m
H-16			2.34 m	2.34 m	2.54 ddd	2.66 ddd
H-17α	3.18 br d	3.32 br d	2.52 dd	2.56 br d	3.20 dd	3.30 dd
H-17β	3.90 d	3.73 d	3.78 dd	3.70 dd	2.82 dd	2.82 dd
H-18	1.00 t	1.04 t	1.03 t	1.03 t	0.97 t	0.99 t
H-19	1.48 m	1.68 m	1.6 m	1.6 m	1.45 m	1.40 m
H-19'	1.72 m	1.68 m	1.6 m	1.6 m	1.60 m	1.63 m
H-20	2.27 br	1.98 br	2.00 m	2.00 m	1.65 m	1.76 m
H-21α	4.43 dd	4.37 dd	4.29 dd	4.28 dd	4.38 dd	4.25 dd
H-21β	4.23 dd	4.31 dd	4.07 dd	4.05 dd	4.02 dd	4.18 dd
NH	7.8 br	7.8 br	7.7 br	7.8 br	7.8 br	8.3 br

Coupling constants 11a

$J_{3,14\alpha} \sim 4$ Hz; $J_{3,14\beta} \sim 9$ Hz; $J_{5\alpha,5\beta} = 13$ Hz; $J_{5\alpha,6\alpha} = 3$ Hz;
$J_{5\alpha,6\beta} = 9$ Hz; $J_{5\beta,6\alpha} < 1$ Hz; $J_{5\beta,6\beta} = 5$ Hz; $J_{6\alpha,6\beta} = 15$ Hz;
$J_{14\alpha,14\beta} = 16$ Hz; $J_{17\alpha,17\beta} = 16$ Hz; $J_{18,19} = 7$ Hz; $J_{18,19'} = 7$ Hz;
$J_{20,21\alpha} = 4$ Hz; $J_{20,21\beta} = 6$ Hz; $J_{21\alpha,21\beta} = 12$ Hz.

Coupling constants 11b

$J_{3,14\alpha} \sim 4$ Hz; $J_{3,14\beta} \sim 9$ Hz; $J_{5\alpha,5\beta} = 13$ Hz; $J_{5\alpha,6\alpha} = 3$ Hz;
$J_{5\alpha,6\beta} = 9$ Hz; $J_{5\beta,6\alpha} < 1$ Hz; $J_{5\beta,6\beta} = 5$ Hz; $J_{6\alpha,6\beta} \sim 15$ Hz;
$J_{14\alpha,14\beta} \sim 16$ Hz; $J_{17\alpha,17\beta} = 16$ Hz; $J_{18,19} = 7$ Hz; $J_{18,19'} = 7$ Hz;
$J_{20,21\alpha} = 3$ Hz; $J_{20,21\beta} \sim 1$ Hz; $J_{21\alpha,21\beta} = 12$ Hz.

Coupling constants 2a

$J_{3,14\alpha} \sim 3$ Hz; $J_{3,14\beta} \sim 12$ Hz; $J_{5\alpha,5\beta} = 12$ Hz; $J_{5\beta,6\alpha} < 1$ Hz;
$J_{5\beta,6\beta} = 6$ Hz; $J_{14\alpha,14\beta} = 12$ Hz; $J_{14\beta,15} = 12$ Hz; $J_{16,17\alpha} = 5$ Hz;
$J_{16,17\beta} \sim 2$ Hz; $J_{17\alpha,17\beta} = 12$ Hz; $J_{18,19} = 7$ Hz; $J_{18,19'} = 7$ Hz;
$J_{20,21\alpha} \sim 5$ Hz; $J_{20,21\beta} \sim 3$ Hz; $J_{21\alpha,21\beta} = 12.5$ Hz.

Table 1. (*Contd*)

Coupling constants 2b

$J_{3,14\alpha} \sim 3$ Hz; $J_{3,14\beta} \sim 12$ Hz; $J_{14\alpha,14\beta} \sim 12$ Hz; $J_{17\alpha,17\beta} = 12.5$ Hz; $J_{18,19} = 7$ Hz; $J_{18,19'} = 7$ Hz; $J_{21\alpha,21\beta} = 12.5$ Hz.

Coupling constants 3a

$J_{3,14\alpha} \sim 2$ Hz; $J_{3,14\beta} = 4$ Hz; $J_{5\alpha,5\beta} = 12.5$ Hz; $J_{5\alpha,6\alpha} = 5$ Hz; $J_{5\alpha,6\beta} = 12.5$ Hz; $J_{5\beta,6\alpha} < 1$ Hz; $J_{5\beta,6\beta} = 6$ Hz; $J_{6\alpha,6\beta} = 16$ Hz; $J_{14\alpha,14\beta} = 12$ Hz; $J_{14\alpha,15} = 12$ Hz; $J_{14\beta,15} \sim 2$ Hz; $J_{16,17\alpha} = 3$ Hz; $J_{16,17\beta} = 12$ Hz; $J_{17\alpha,17\beta} = 12$ Hz; $J_{18,19} = 7$ Hz; $J_{18,19'} = 7$ Hz; $J_{20,21\alpha} = 5$ Hz; $J_{20,21\beta} = 6$ Hz; $J_{21\alpha,21\beta} = 12$ Hz.

Coupling constants 3b

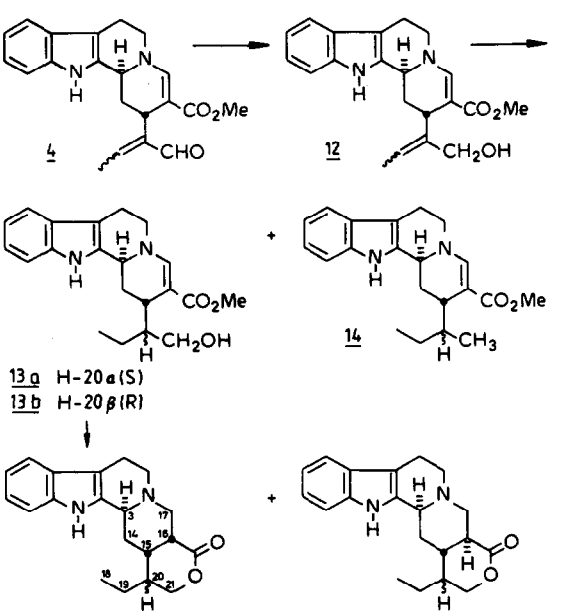
$J_{3,14\alpha} \sim 2$ Hz; $J_{3,14\beta} \sim 4$ Hz; $J_{5\alpha,5\beta} = 12.5$ Hz; $J_{5\alpha,6\alpha} = 5$ Hz; $J_{5\alpha,6\beta} = 12.5$ Hz; $J_{5\beta,5\alpha} < 1$ Hz; $J_{5\beta,6\beta} = 6$ Hz; $J_{6\alpha,6\beta} \sim 16$ Hz; $J_{14\alpha,14\beta} \sim 12$ Hz; $J_{14\alpha,15} \sim 12$ Hz; $J_{14\beta,15} \sim 2$ Hz; $J_{16,17\alpha} = 3$ Hz; $J_{16,17\beta} = 12$ Hz; $J_{17\alpha,17\beta} = 12$ Hz; $J_{18,19} = 7$ Hz; $J_{18,19'} = 7$ Hz; $J_{20,21\alpha} = 2.5$ Hz; $J_{20,21\beta} = 3$ Hz; $J_{21\alpha,21\beta} = 12$ Hz.

[a,b] Assignments may be interchanged.

transformation of **11a** to **1a** and **2a**, and of **11b** to **1b** and **2b** determines the C-20 stereochemistry of these four compounds. Moreover, it can be supposed that the catalytic hydrogenation of **11a** and **11b** proceeds in a *cis* manner.

The C-15 stereochemistry of vallesiachotamine **4** is known,[12] and it is reasonable to suppose that the C-15 stereochemistry in tetrahydrovallesiachotamine **13a** and **13b** is the same as in **4**. Since then the transformation of **13a** to **1a** and **3a**, and of **13b** to **1b** and **3b** determines a like C-15 stereochemistry for these four compounds, the difference between **1a** and **3a** and between **1b** and **3b** must be at C-16. The identicalness of fully synthetic and vallesiachotamine derived **1a** and **1b** indicates that both C-15-H and C-16-H must be β.[13] As a consequence, the stereochemistries of **1a** and **1b**, and as a corollary those of **2a**, **2b**, **3a**, **3b**, **13a** and **13b** are completely determined.

A similar reasoning concerning the stereochemistry of the compounds can equally well start from several other pairs of epimeric lactones. The conformationally "rigid" lactones **3a** and **3b** are particularly favourable for that purpose.



EXPERIMENTAL

The IR spectra were measured on a Perkin–Elmer 700 apparatus. The ^{1}H NMR spectra were taken with the I.E.F. 400

(400 MHz) spectrometer[14] using the sample temperature of 52°. The mass spectra were recorded on a Jeol JMS-D-100 Mass Spectrometer at 70 eV using direct sample insertion into the ion source, whose temp. was 140°. The m.ps were determined on a Kofler micro hot stage and are uncorrected.

Preparation of lactones **11a** *and* **11b**

To a stirred mixture of **5**[7] (550 mg), $KHCO_3$ (1000 mg), H_2O (40 ml) and CH_2Cl_2 (40 ml) under N_2 was rapidly added 780 mg of sodium dithionite. The mixture was stirred for 1 hr. The CH_2Cl_2 layer was separated, a new lot of CH_2Cl_2 was added and the mixture stirred for a further hr. This procedure was repeated twice. The combined CH_2Cl_2 layers were washed with water and dried over Na_2SO_4. Filtration and careful evaporation of the solvent yielded **8** (MS: *m/e* 322 (M^+ calc. for $C_{20}H_{22}N_2O_4$), 144, 130). Owing to the instability of **8**, it was cyclized, without purification, in anhyd MeOH presaturated with dry HCl gas. After purification by PLC (toluene/EtOH/AcOEt; 2/1/2) two isomers were obtained.

Lactone **11a**, yield 22 mg, m.p. 160–163° (MeOH). IR ($CHCl_3$) NH 3340 (m), Bohlmann bands 2830, 2770, C=O 1690 (s) cm^{-1}. UV (EtOH 94%) λ_{max} 247 nm. ^1H NMR ($CDCl_3$). See Table 1. MS M^+ at *m/e* 322 corresponding to $C_{20}H_{22}N_2O_2$. Other noteworthy peaks at *m/e* 321, 170, 169.

Lactone **11b**, yield 22 mg, m.p. 172–175° (MeOH). IR ($CHCl_3$) NH 3340 (m), Bohlmann bands 2830, 2770, C=O 1690 (s) cm^{-1}. UV (EtOH 94%) λ_{max} 247 nm. ^1H NMR ($CDCl_3$). See Table 1. MS M^+ at *m/e* 322 corresponding to $C_{20}H_{22}N_2O_2$. Other noteworthy peaks at *m/e* 321, 170, 169.

Preparation of lactones **1a** *and* **2a**

The lactone **11a** (20 mg) in 10 ml MeOH was catalytically hydrogenated in the presence of 30 mg PtO_2. Reaction time 25 hr. After purification by PLC (toluene/EtOH/AcOEt; 2/1/2) two isomers were obtained.

Lactone **1a**, yield 3 mg, amorphous. IR ($CHCl_3$) NH 3380 (m), C=O 1720 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 1.00 (3 H, t, J = 7 Hz, H-18), 4.10 (1 H, m, H-21), 4.28 (1 H, m, H-21), 7.08 (1 H, t, J = 8 Hz, H-10), 7.17 (1H, t, J = 8 Hz, H-11), 7.32 (1 H, d, J = 8 Hz, H-12), 7.44 (1 H, d, J = 8 Hz, H-9). MS M^+ at *m/e* 324 corresponding to $C_{20}H_{24}N_2O_2$. Other noteworthy peaks at *m/e* 323, 170, 169.

Lactone **2a**, yield 6 mg, m.p. 224–227° (MeOH). IR (KBr) NH 3400 (m), C=O 1725 (s) cm^{-1}. ^1H NMR ($CDCl_3$). See Table 1. MS M^+ at *m/e* 324 corresponding to $C_{20}H_{24}N_2O_2$. Other noteworthy peaks at *m/e* 323, 170, 169.

Preparation of lactones **1b** *and* **2b**

The lactone **11b** (20 mg) in 10 ml of MeOH was catalytically hydrogenated in the presence of 30 mg of PtO_2. Reaction time 30 hr. After purification by PLC (toluene/EtOH/AcOEt; 2/1/2) two isomers were obtained.

Lactone **1b**, yield 3 mg, amorphous. IR ($CHCl_3$) NH 3380 (m), C=O 1720 (s) cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.96 (3 H, t, J = 7 Hz, H-18), 4.08 (1 H, m, H-21), 4.26 (1 H, m, H-21), 7.08 (1 H, t, J = 8 Hz, H-10) 7.14 (1 H, t, J = 8 Hz, H-11), 7.34 (1 H, d, J = 8 Hz, H-12), 7.45 (1 H, d, J = 8 Hz, H-9). MS M^+ at *m/e* 324 corresponding to $C_{20}H_{24}N_2O_2$. Other noteworthy peaks at *m/e* 323, 170, 169.

Lactone **2b**, yield 6 mg, m.p. 230–232° (MeOH). IR (KBr) NH 3400 (m), C=O 1725 (s) cm^{-1}. ^1H NMR ($CDCl_3$). See Table 1.MS M^+ at *m/e* 324 corresponding to $C_{20}H_{24}N_2O_2$. Other noteworthy peaks at *m/e* 323, 170, 169.

Dihydrovallesiachotamine **12**

$NaBH_4$ (500 mg) was added to a soln of 146 mg of **4**[9] in 25 ml abs EtOH. The stirring was continued for 3 hr. Water was added and the mixture extracted several times with CH_2Cl_2. Purification by PLC (toluene/EtOH/AcOEt; 2/1/2) afforded 110 mg of **12**,[9] m.p. 171–173° (MeOH) (lit.[6] 172–174°). MS M^+ at *m/e* 352 corresponding to $C_{21}H_{24}N_2O_3$. Other noteworthy peaks at *m/e* 334, 321, 293, 281, 280, 279, 251.

Preparation of tetrahydrovallesiachotamines **13a** *and* **13b**

Compound **12**[9] (107 mg) in 15 ml abs EtOH was catalytically hydrogenated in the presence of 75 mg PtO_2. Reaction time 12 hr. After purification by PTC (toluene/EtOH/AcOEt; 2/1/2) two isomers were obtained.

Tetrahydrovallesiachotamine **13a**, yield 32 mg, m.p. 136–138° (MeOH). MS M^+at *m/e* 354 corresponding to $C_{21}H_{26}N_2O_3$. Other noteworthy peaks at *m/e* 322, 282, 281 (100%), 156.

Tetrahydrovallesiachotamine **13b**, yield 28 mg, m.p. 146–149° (MeOH). MS M^+ at *m/e* 354 corresponding to $C_{21}H_{26}N_2O_3$. Other noteworthy peaks at *m/e* 322, 282, 281 (100%), 156.

Preparation of lactones **1a** *and* **3a**

Compound **13a** (30 mg) was dissolved in 10 ml of glacial AcOH. $NaBH_4$ (600 mg) was added and the mixture stirred for 2 hr. Water was then added, the soln neutralized with $NaHCO_3$, and the products extracted with CH_2Cl_2. After purification by PLC (toluene/EtOH/AcOEt; 2/1/2) two isomers were obtained.

Lactone **1a**, yield 3 mg, amorphous. IR, ^1H NMR, MS, TLC identical with those of the synthetic **1a** described above.

Lactone **3a**, yield 20 mg, m.p. 232–235° (MeOH). IR (KBr) NH 3375 (m), C = O 1725 (s) cm^{-1}. ^1H NMR ($CDCl_3$). See Table 1. MS M^+ at *m/e* 324 corresponding to $C_{20}H_{24}N_2O_2$. Other noteworthy peaks at *m/e* 323, 170, 169.

Preparation of lactones **1b** *and* **3b**

Compound **13b** (25 mg) was dissolved in 10 ml glacial AcOH. $NaBH_4$ (500 mg) was added and the mixture stirred for 2 hr. Water was added, the soln neutralized with $NaHCO_3$, and the products extracted with CH_2Cl_2. After purification by PLC (toluene/EtOH/AcOEt; 2/1/2) two isomers were obtained.

Lactone **1b**, yield 2 mg, amorphous. IR, ^1H NMR, MS, TLC, identical with those of the synthetic **1b** described above.

Lactone **3b**, yield 16 mg, m.p. 216–219° ($MeOH/H_2O$; 1/1). IR (KBr) NH 3375 (m), C=O 1725 (s) cm^{-1}. ^1H NMR ($CDCl_3$). See Table 1. MS M^+ at *m/e* 324 corresponding to $C_{20}H_{24}N_2O_2$. Other noteworthy peaks at *m/e* 323, 170, 169.

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