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SYNTHETIC STUDIES IN THE ALKALOID FIELD—IX[a]

STEREOSPECIFIC TOTAL SYNTHESIS OF (±)-19,20-DIHYDRO-20-DESFORMYL-20-METHOXYCARBONYL-VALLESIACHOTAMINE AND ITS 20-DESETHYL ANALOGUE

MAURI LOUNASMAA,* PIRKKO JUUTINEN and PEKKA KAIRISALO
Laboratory for Chemistry of Natural Products, Biologinkuja 7, SF-02150 Espoo 15, Finland

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Abstract—The stereospecific total synthesis of (±) - 19,20 - dihydro - 20 - desformyl - 20 - methoxycarbonyl-vallesiachotamine and its 20-desethyl analogue has been carried out by sodium dithionite reduction of appropriate 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl pyridinium salts to the corresponding 1,4-dihydropyridine derivatives, followed by acid-induced cyclization.

During extensive studies on the constituents of the Peruvian plant *Vallesia dichotoma* Ruiz et Pav (Apocynaceae), Djerassi *et al.* isolated 28 alkaloids.[1] One of these, vallesiachotamine, was shown to possess the structure **1**, which is of unusual biogenetic interest containing the C(3)αH–C(15)βH configuration,[b] and C-17 attached to N_b. The only other known indole alkaloids possessing this configuration are antirhine **2**[3–6] with its metho salts[5,6] and hunterburnine α- and β-metho salts **3**.[7–10]

The interest in the vallesiachotamine structure **1** is increased by the fact that the stereochemistry of strictosidine (isovincoside) was established by chemical correlation with 18,19-dihydroantirhine via several vallesiachotamine derivatives[11] and strictosidine has just been shown to be the key intermediate in the biosynthetic formation of monoterpenoid indole alkaloids.[12]

In the present report we describe the stereospecific total synthesis of (±) - 19,20 - dihydro - 20 - desformyl - 20 - methoxycarbonylvallesiachotamine **4b** and its 20-desethyl analogue **4a**.[c] As far as we know, our work represents the first total synthesis of a true vallesiachotamine derivative. For earlier syntheses of simplified vallesiachotamine models see Refs. 14–18.

RESULTS

Treatment of 4-methylnicotinic acid **5a**[19,20] with oxalyl chloride and methanol yielded the ester lactone **6a**,[21] which by alkaline hydrolysis, alkaline hydrogen peroxide treatment, and esterification was transformed to methyl 4-methoxycarbonylmethylnicotinate **7a**.[21] Alkylation of the ester **7a** with tryptophyl bromide[22] afforded the pyridinium salt **8a**, whose sodium dithionite reduction led to the indoloquinolizine **4a** in low yield. However, buffering the sodium dithionite reaction medium with sodium bicarbonate permitted isolation of the intermediate 1,4-dihydro derivative **9a**, which produced through acid-induced cyclization, the indoloquinolizine **4a** in high yield (see Experimental).[d]

Our favourable experience in the preparation of **4a** (possessing the correct C(3)H–C(15)H *trans* configuration) via the 1,4-dihydro derivative **9a**, led us to attempt the synthesis of (±) - 19,20 - dihydro - 20 - desformyl - 20 - methoxycarbonylvallesiachotamine **4b** by a similar reaction sequence.

The transformation of 4-propylnicotinic acid **5b** via ester lactone **6b** to methyl 4 - (α - methoxycarbonylpropyl)nicotinate **7b**[21] was analogous to that described above. Alkylation of ester **7b** with tryptophyl bromide yielded the pyridinium salt **8b**. Sodium dithionite reduction of the latter, in the presence of sodium bicarbonate, led to the 1,4-dihydro derivative **9b**, which, by acid-induced cyclization was transformed to (±) - 19,20 - dihydro - 20 - desformyl - 20 - methoxycarbonylvallesiachotamine **4b**.

The C(3)–C(15) stereochemical relationships proposed for **4a** and **4b** were determined by ^{13}C NMR.[e] The fully proton-decoupled spectra of **4a** and **4b**, taken in $CDCl_3$, showed the chemical shifts depicted on the formulas. The proper shift assignment was confirmed by single-frequency, off-resonance decoupled (sford) spectra and by comparison with the earlier shift assignment.[17,18,23–27] The chemical shifts found for C(3) and C(14) reflect the influence of the *endo*cyclic homoallyl effect.[23] Most interestingly, the ^{13}C NMR results also indicate that compound **4b** practically consists of just one C(20) epimer.[f]

Sodium dithionite reduction of 1 - [2 - (3 - indolyl)-ethyl] - 3 - methoxycarbonyl pyridinium salts **8a** and **8b** to the corresponding 1,4-dihydropyridine derivatives **9a** and **9b**, respectively, followed by acid-induced cyclization to tetracyclic compounds, represents a convenient method for the preparation of the indoloquinolizine derivatives **4a**

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[a] Part VIII. M. Lounasmaa and M. Puhakka, *Acta Chem. Scand.* **B32**, 216 (1978).

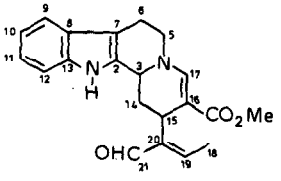
[b] Corresponding to the C(12b)αH–C(2)βH configuration when the Ring Index[2] nomenclature is utilized.

[c] To simplify the nomenclature, the biogenetic numbering of indole alkaloids[13] is utilized for the indoloquinolizines **4a** and **4b**, even though they are not naturally occurring compounds.

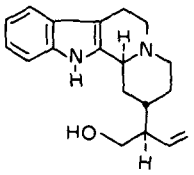
[d] Thus the acid-induced cyclization of **9a** leads to the C(3)H–C(15)H *trans* configuration, in contrast to earlier analogous cyclizations.[17] The size of the C(15) substituent may be critical in determining the C(3)–C(15)-stereochemical relationship.

[e] Compounds **4a** and **4b** can exist in conformational equilibrium by nitrogen inversion and half-chair ring interconversion. See Ref. 17 for a more detailed discussion concerning the different conformations of similar compounds.

[f] The small "supplementary" ^{13}C NMR signals due to the other C(20) epimer of **4b** are not marked on the formula.



1



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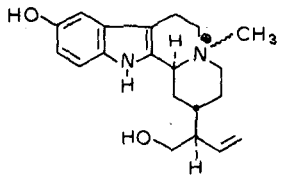

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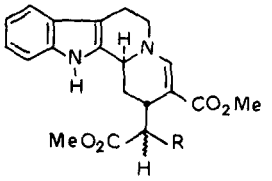
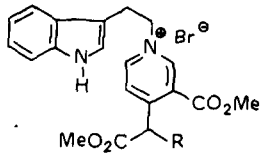
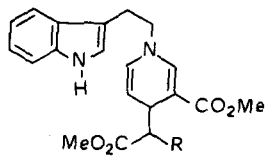


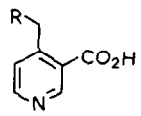
4a R = H
4b R = Et



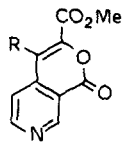
8a R = H
8b R = Et



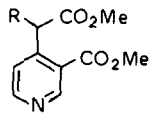
9a R = H
9b R = Et



5a R = H
5b R = Et



6a R = H
6b R = Et



7a R = H
7b R = Et

and **4b**. Compound **4b** is the first totally synthetic, true vallesiachotamine derivative. The method described, which permits the preparation of compounds of type **4b** with a high stereoselectivity at C(20), can be expected to find useful applications in other stereoselective syntheses of similar nature.

EXPERIMENTAL

The IR spectra were measured on a Perkin–Elmer 237 apparatus and the UV spectra on a Perkin–Elmer 137 UV apparatus. The ^{1}H NMR spectra were taken with a Jeol JNM-PMX-60 instrument and the ^{13}C NMR spectra with a Jeol JNM-FX-100 instrument operating at 25.20 MHz in the Fourier transform mode. TMS was used as internal standard. The mass spectra were recorded either on a Jeol JMS-D-100 Mass Spectrometer or a Hitachi Perkin–Elmer RMU 6E Mass Spectrometer at 70 eV using direct sample insertion into the ion source, whose temp. was 100–120°. The elemental compositions when given for the molecular ions were confirmed by high-resolution mass measurements. The m.ps were determined in a Büchi capillary m.p. apparatus and are uncorrected.

Preparation of 4-alkylnicotinic acids **5a** *and* **5b**

A mixture of methyl 4-alkylnicotinate and KOH in aqueous MeOH was left standing for 12 hr. Dry ether was added and the resultant precipitate separated, dried and dissolved in a minimum quantity of water. The solution was brought to pH 4 with HCl. The resultant precipitate was separated and dried.

4 - *Methylnicotinic acid* **5a**. Hydrolysis of 6.5 g of methyl 4-methylnicotinate[17] yielded 4.8 g (81%) of **5a**. M.p. 215–217° (EtOH) (lit. 215–216°,[19] 213.5–215.5°[20]). IR (KBr): C=O 1705 (s) cm^{-1}. MS M$^+$ at *m/e* 137.

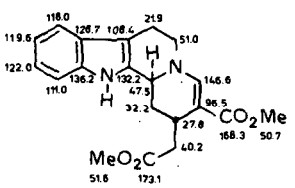
4-*Propylnicotinic acid* **5b**. Hydrolysis of 6.9 g of methyl 4-propylnicotinate[17] yielded 3.8 g (60%) of **5b**. M.p. 94–96° (subl.). IR (KBr): C=O 1710 (s) cm^{-1}. MS M$^+$ at *m/e* 165.

Preparation of ester lactones **6a** *and* **6b**

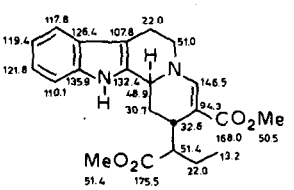
A solution of freshly distilled oxalyl chloride in dry chloroform was dropped during 1 hr into an ice-cold mixture of nicotinic acid derivative and triethylamine in dry chloroform. The solution was allowed to reach room temp. and stirred for an additional hour. Methanol and chloroform were added and the solution was stirred overnight. The solution was washed with a solution of an excess of sodium bicarbonate. Evaporation of the solvent and crystallization of the residue yielded the ester lactone.

Ester lactone **6a**. Reaction between 3.3 g of 4-methylnicotinic acid **5a**, 5 ml of oxalyl chloride and 7.5 ml of triethylamine yielded 3.1 g (63%) of **6a**. M.p. 185–187° (MeOH) (lit.[21] 187–188°). MS M$^+$ at *m/e* 205. IR and ^{1}H NMR were identical with those of a sample prepared by a different method.[21]

Ester lactone **6b**. Reaction between 3.7 g of 4-propylnicotinic acid **5b**, 5 ml of oxalyl chloride and 7.5 ml of triethylamine yielded 1.7 g (32%) of **6b**. M.p. 145–146° (MeOH). IR (KBr): C=O 1740 (s), 1720 (s), C=C 1595 (m) cm^{-1}. ^{1}H NMR ($CDCl_3$): δ 1.28 (3 H, t, *J* 7 Hz, $-CH_2-CH_3$), 3.07 (2 H, q, *J* 7 Hz, $-CH_2-CH_3$), 3.95 (3 H, s, $-COOCH_3$), 7.77 (1 H, d, *J* 5 Hz, C-5-H), 8.94 (1 H, d, *J* 5 Hz, C-6-H), 9.50 (1 H, s, C-2-H). MS M$^+$ at *m/e* 233.



4a



4b

Preparation of methyl 4-methoxycarbonylalkylnicotinates **7a** *and* **7b**

A mixture of ester lactone and KOH dissolved in water was stirred at room temp. for 1 hr and the resulting soln cooled to 5°. Hydrogen peroxide (30%) was added in 0.1 ml portions at 3 hr intervals. After a total reaction time of 45 hr the soln was concentrated to dryness under vacuum at 30°. The residue was dried in a vacuum desiccator, cooled to −70°, and treated with methanol saturated with dry HCl gas and precooled to −40°. The mixture was allowed to reach room temp. slowly. After standing for a further 72 hr the mixture was slowly poured onto a suspension of excess of sodium bicarbonate in dichloromethane. The mixture was filtered and the filtrate evaporated under vacuum. The residue was chromatographed on alumina (act. IV).

Methyl 4-methoxycarbonylmethylnicotinate **7a**. Reaction between 850 mg of ester lactone **6a**, 900 mg of KOH and 1.30 ml of hydrogen peroxide yielded 360 mg (42%) of **7a**. M.p. 50–52° (hexane) (lit.[21] 51.5–52°). MS M^+ at *m/e* 209. IR and ^1H NMR were identical with those of the sample described in the literature.[21]

Methyl 4 - (α - methoxycarbonylpropyl)nicotinate **7b**. Reaction between 800 mg of ester lactone **6b**, 800 mg of KOH and 1.10 ml of hydrogen peroxide yielded 350 mg (43%) of **7b** as an oil. MS M^+ at *m/e* 237. IR and ^1H NMR were identical with those of a sample prepared by a different method.[21]

Preparation of 1 - [2 - (3 - indolyl)ethyl] - 3 - methoxycarbonyl pyridinium bromides **8a** *and* **8b**. A mixture of nicotinic acid derivative and tryptophyl bromide[22] was heated under N_2 at 100° for 1 hr. The mixture was allowed to cool, crushed to grains, and stirred in ether for 1 hr. The mixture was filtered.

1 - [2 - (3 - Indolyl)ethyl] - 3 - methoxycarbonyl - 4 - methoxycarbonylmethyl pyridinium bromide **8a**. Reaction between 215 mg of **7a** and 240 mg of tryptophyl bromide yielded 389 mg (90%) of **8a**. Amorphous mass. IR (KBr) C=O 1735 (s), 1725 (s) cm^{-1}.

1 - [2 - (3 - Indolyl)ethyl] - 3 - methoxycarbonyl - 4 - (α - methoxycarbonylpropyl) pyridinium bromide **8b**. Reaction between 287 mg of **7b** and 277 mg of tryptophyl bromide yielded 520 mg (93%) of **8b**. Amorphous mass. IR (KBr) C=O 1735 (s), 1725 (s) cm^{-1}.

Preparation of 1 - [2 - (3 - indolyl)ethyl] - 3 - methoxycarbonyl-1,4 - dihydropyridines **9a** *and* **9b**. Sodium dithionite was added in small portions during 1 hr to a magnetically stirred soln of pyridinium bromide derivative and $NaHCO_3$ in aqueous MeOH (1:2, H_2O:MeOH) under N_2. The mixture was stirred for 20 hr, filtered and the filtrate evaporated under vacuum. The residue was extracted with dichloromethane and the extract washed with water, dried over Na_2SO_4, and evaporated under vacuum. The final residue was chromatographed on alumina (act. IV).

1 - [2 - (3 - Indolyl)ethyl] - 3 - methoxycarbonyl - 4 - methoxycarbonylmethyl - 1,4 - dihydropyridine **9a**. Reaction between 230 mg of **8a**, 900 mg of $NaHCO_3$, and 600 mg of sodium dithionite in 45 ml of aqueous MeOH yielded 94 mg (50%) of **9a** as an oil. IR (film) NH 3480 (m), C=O 1730 (s), 1680 (s), C=C 1595 (m) cm^{-1}. UV [EtOH 94% (log ε)] λ_{max} 223 (4.52), 284 (3.86), 292 (3.84) and 347 (3.80) nm. λ_{min} 212, 257, 289 and 310 nm. ^1H NMR ($CDCl_3$), δ 2.48 (2 H, d, *J* 5 Hz, $-\underline{CH_2}-COOCH_3$), 3.64 (3 H, s, $-COOCH_3$), 3.75 (3H, s, $-\overline{COOCH_3}$), 4.85 (1 H, dd, J_1 8 Hz, J_2 5 Hz, C–5–H), 5.78 (1 H, dd, J_1 8 Hz, J_2 2 Hz, C–6–H), 6.95 (1 H, d, *J* 2 Hz, indolyl α-H), 7.08 (1 H, d, *J* 2 Hz, C–2–H) and 8.50 (1 H, s, N–H). MS M^+ at *m/e* 354 corresponding to $C_{20}H_{22}N_2O_4$. Other noteworthy peaks at *m/e* 295, 281, 221, 144 and 130.

1 - [2 - (3 - Indolyl)ethyl] - 3 - methoxycarbonyl - 4 - (α - methoxycarbonylpropyl) - 1,4 - dihydropyridine **9b**. Reaction between 243 mg of **8b**, 900 mg of $NaHCO_3$ and 600 mg of sodium dithionite in 45 ml of aqueous MeOH yielded 171 mg (85%) of **9b** as an oil. IR ($CHCl_3$) C=O 1725 (s), 1680 (s), C=C 1590 (s) cm^{-1}. UV [EtOH 94% (log ε)] λ_{max} 223 (4.50), 284 (3.90), 292 (3.86) and 3.47 (3.78) nm. λ_{min} 259, 290 and 312 nm. ^1H NMR ($CDCl_3$) δ 0.85 (3 H, t, *J* 7 Hz, $-CH-CH_2-\underline{CH_3}$), 3.66 (6 H, s, both $-COOCH_3$), 4.66 (1 H, dd, J_1 8 Hz, J_2 5 Hz, C–5–H), 5.86 (1 H, dd, J_1 8 Hz, J_2 2 Hz, C–6–H), 6.92 (1 H, d, *J* 2 Hz, indolyl α-H), 7.10 (1 H, d, *J* 2 Hz, C–2–H) and 8.60 (1 H, s, N–H). MS M^+ at *m/e* 382 corresponding to $C_{22}H_{26}N_2O_4$. Other noteworthy peaks at *m/e* 281, 252, 144 and 130.

Indoloquinolizine **4a**. Reaction between 100 mg of **8b** and 200 mg of sodium dithionite in 30 ml of aqueous MeOH (1:2, H_2O:MeOH) under N_2 yielded after normal work-up 14 mg (17%) of **4a**. M.p. 211–212° (MeOH). IR (KBr): NH 3300 (m), C=O 1735 (s), 1670 (s), C=C 1600 (s), 1585 (s) cm^{-1}. UV [EtOH 94% (log ε)] λ_{max} 207 (infl.) (4.30), 224 (4.50), 292 (4.48) nm. λ_{min} 251 nm. ^1H NMR ($CDCl_3$): δ 2.36 (2 H, d, *J* 10 Hz, $-\underline{CH_2}-COOCH_3$), 3.70 (3 H, s, $-COOCH_3$), 3.75 (3 H, s, $-\overline{COOCH_3}$), 4.52 (1 H, br d, *J* 10 Hz, C–3–H), 7.56 (1 H, s, C–17–H) and 8.10 (1 H, s, N–H). MS M^+ at *m/e* 354 corresponding to $C_{20}H_{22}N_2O_4$. Other noteworthy peaks at *m/e* 295 and 281.

Cyclization of dihydropyridines **9a** *and* **9b**

A soln of the dihydropyridine in anhydrous MeOH was saturated with dry HCl gas during a 2 hr period. The soln was left standing at room temp. for 16 hr and then poured slowly into a suspension of $NaHCO_3$ in dichloromethane. The inorganic salts were filtered off and the dried filtrate evaporated under vacuum. The residue was chromatographed on alumina (act. IV).

Indoloquinolizine **4a**. Cyclization of 210 mg of **9a** yielded 190 mg (90%) of **4a**. M.p. 211–212° (MeOH). IR, UV, ^1H NMR, MS and TLC were identical with those of the sample above.

(±) - 19,20 - Dihydro - 20 - desformyl - 20 - methoxycarbonyl-vallesiachotamine **4b**. Cyclization of 122 mg of **9b** yielded 109 mg (90%) of **4b**. M.p. 203–205° (MeOH). IR (KBr): NH 3270 (m), C=O 1740 (s), 1665 (s), C=C 1600 (m), 1585 (s) cm^{-1}. UV [EtOH 94% (log ε)] λ_{max} 207 (infl.) (4.29), 225 (4.49), 293 (4.48) nm. λ_{min} 252 nm. ^1H NMR ($CDCl_3$): δ 0.90 (3 H, t, *J* 7 Hz, $-CH-CH_2-\underline{CH_3}$), 3.70 (6 H, s, both $-COOCH_3$), 4.52 (1 H, br d, *J* 10 Hz, C–3–H), 7.60 (1 H, s, C–17–H) and 8.66 (1 H, s, N–H). MS M^+ at *m/e* 382 corresponding to $C_{22}H_{26}N_2O_4$. Other noteworthy peaks at *m/e* 351, 323, 282, 281, 221.

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