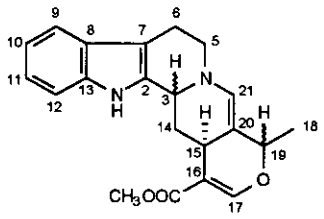
FORMATION OF 3-ISO-19-EPICATHENAMINE, ISOLATED AS ITS CYANO ADDUCT 21α-CYANO-3-ISORAUNITICINE

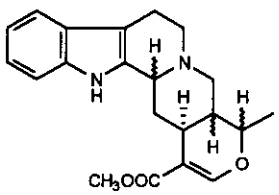
Mauri Lounasmaa* and Pirjo Hanhinen

Laboratory for Organic and Bioorganic Chemistry,
Technical University of Helsinki,
FIN-02150 Espoo, Finland

Abstract - Formation of 3-iso-19-epicathenamine (**8**), which is a plausible intermediate in the biogenetic formation of heteroyohimbine alkaloids 3-isorauniticine (**11**) and 3-iso-19-epiajmalicine (**12**), is described. Compound (**8**) was isolated as its cyano adduct, 21α-cyano-3-isorauniticine (**17**). The Brown and Leonards' 21-cyano adduct, isolated after a biomimetic conversion process of a mixture of strictosidine (**18**) and vincoside (**19**), and for which the 21α-cyanoakuammigine structure (**21**) was claimed, is shown to be in reality identical with compound (**17**).

Cathenamine (**1**) and 19-epicathenamine (**2**) are important, naturally occurring, biogenetic intermediates for the heteroyohimbine alkaloids tetrahydroalstonine (**3**), ajmalicine (**4**), rauniticine (**5**) (not detected in cell-free systems), and 19-epiajmalicine (**6**).[1-5]





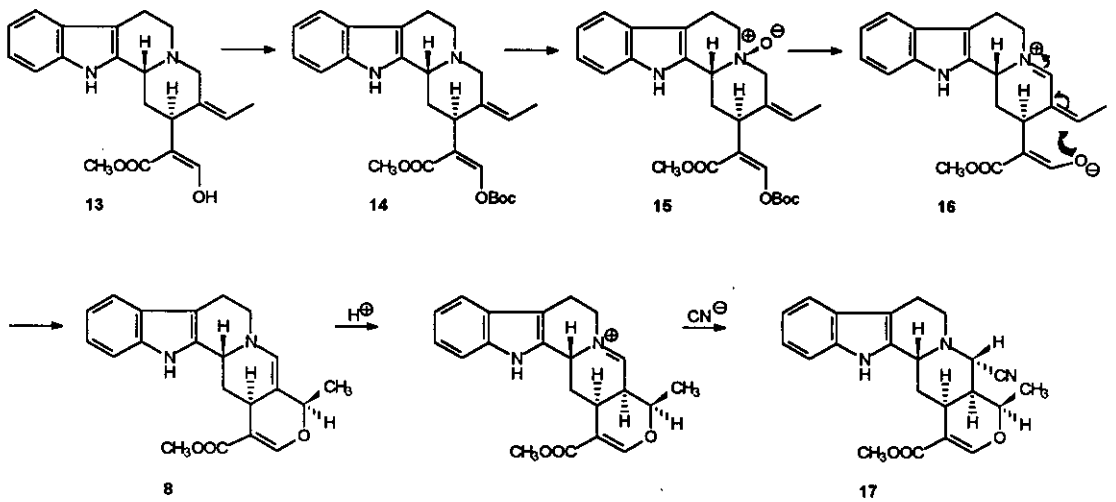
1 H-3 α ; H-19 β
2 H-3 α ; H-19 α
7 H-3 β ; H-19 β
8 H-3 β ; H-19 α

3 H-3 α ; H-19 β ; H-20 α
5 H-3 α ; H-19 α ; H-20 α
9 H-3 β ; H-19 β ; H-20 α
11 H-3 β ; H-19 α ; H-20 α

4 H-3 α ; H-19 β ; H-20 β
6 H-3 α ; H-19 α ; H-20 β
10 H-3 β ; H-19 β ; H-20 β
12 H-3 β ; H-19 α ; H-20 β

By analogy, 3-isocathenamine (**7**) and 3-iso-19-epicathenamine (**8**), which are not yet naturally found, can be expected to be biogenetic intermediates for the remaining four basic heteroyohimbine alkaloids akuammigine (**9**), 3-isoajmalicine (**10**), 3-isorauniticine (**11**), and 3-iso-19-epiajmalicine (**12**).

We have now prepared one of these two plausible biogenetic intermediates, 3-iso-19-epicathenamine (**8**).



Scheme 1.

RESULTS AND DISCUSSION

Our earlier described 3-epi-*Z*-geissoschizine (**13**)[6] was transformed by controlled $(Boc)_2O$ treatment to *O*-Boc-3-epi-*Z*-geissoschizine (**14**). Oxidation of compound (**14**) with *m*-chloroperbenzoic acid (*m*CPBA) yielded the corresponding *cis*-N_b-oxide (**15**). The Polonovski-Potier reaction [trifluoroacetic anhydride (TFAA)][7-9] led, *via* compound (**16**), to 3-iso-19-epicathenamine (**8**),[10] which was isolated as its 21-cyano adduct,[11-14] (±)-21α-cyano-3-isorauniticine (**17**) (Scheme 1).

The spectral data of compounds (**14**, **15**, and **17**) support the presented structures. Especially, the ^{13}C-NMR spectra (Figure 1), compared with earlier results,[15-19] are in good agreement with the proposed structures. The coupling constant (11 Hz; *vide infra*), found between C-20-H and C-21-H, in the ^{1}H-NMR spectrum of compound (**17**), confirms the α-stereochemistry for the 21-cyano group.

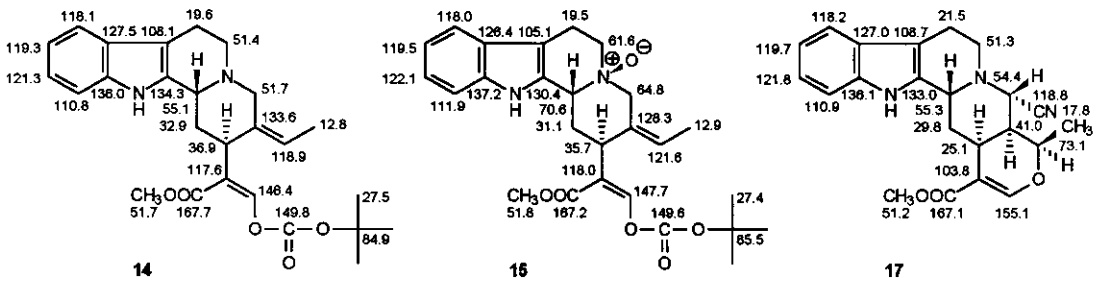
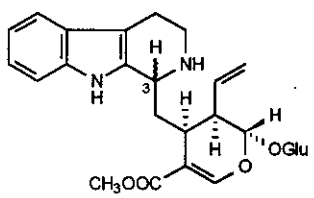
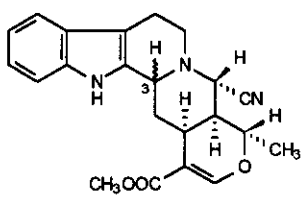


Figure 1.

Brown and Leonard studied biomimetic conversion processes carried out on a mixture of strictosidine (**18**) and vincoside (**19**).[20,21] The 21-cyano adduct [compound (**7b**) in Ref. 20], which was isolated together with 21α-cyanotetrahydroalstonine (**20**) [compound (**7a**) in Ref. 20; see also, Ref. 16], and for which the 21α-cyanoakuammigine structure (**21**) was claimed,[22] is in reality 21α-cyano-3-isorauniticine (**17**) as shown by the ^{1}H-NMR values in Table 1.



18 H-3 α
19 H-3 β



20 H-3 α
21 H-3 β

Table 1. Comparison of the ^{1}H-NMR data of compounds (**9**, **11**, and **17**) with those of compound (**A**) [= the "21α-cyanoakuammigine" of Brown and Leonard[20-22] [compound (**7b**) in Ref. 20 and compound (**5b**) in Ref. 21]].

	Compd **11**[a]	Compd **17**	Compd **A**[b]	Compd **9**[a]
H-3	3.12 br d	3.30 br d	3.30 d	3.78 br d
H-5α	3.1 m	3.67 dd	3.66 q	3.13 dd
H-5β	2.62 td	2.61 ddd[c]	2.60 td	2.94 m
H-6α	3.0 m	3.02 m	3.00 m	3.05 m
H-6β	2.73 br d	2.78 br d	2.76 d	2.66 br d
H-14α	1.74 td	1.75 ddd[c]	1.74 td	2.13 br
H-14β	3.10 br d	3.25 ddd[c]	3.25 td	3.04 br t
H-15	3.06 br s	3.09 m	3.09 br s	2.74 br
H-17	7.63 d	7.60 d	7.62 s	7.55 d
H-18	1.36 d	1.35 d	1.35 d	1.36 d
H-19	4.14 br q	4.76 dq	4.77 q	4.46 qd
H-20	2.29 br	2.29 ddd	2.28 q	1.86 br t
H-21α	3.00 dd	-	-	2.98 dd
H-21β	2.36 t	3.37 d	3.37 d	2.62 dd
MeO	3.75 s	3.76 s	3.73 s	3.76 s
NH	7.90 br s	7.89 br s	7.87 s	7.89 s

[a]Values taken from Ref. 15.
[b]Values taken from Ref. 20.
[c]Looks like a td.

CONCLUSIONS

An easy method is now available for the preparation of the not yet naturally found, relatively unstable compound (±)-3-iso-19-epicathenamine (**8**), isolable as its synthetic equivalent, (±)-21α-cyano-3-isorauniticine (**17**).

Our results, which show that the "21α-cyanoakuammigine" of Brown and

Leonard[20,21] [compound (**7b**) in Ref. 20] in reality is (±)-21α-cyano-3-isorauniticine (**17**), are important, because they demonstrate that in the biomimetic conversion described in Ref. 20 the process partly passes through an intermediate possessing a *Z*-ethylidene side chain (*Cf.* Scheme 1).

EXPERIMENTAL

IR spectra were recorded with a Perkin-Elmer 700 IR spectrophotometer using $CHCl_3$ as solvent. IR absorption bands are expressed in reciprocal centimetres (cm^{-1}). ^1H- and ^{13}C-NMR spectra were measured either with a Varian Gemini-200 spectrometer working at 199.975 MHz (^1H-NMR) and 50.289 MHz (^{13}C-NMR) or with a Varian Unity-400 NMR spectrometer working at 399.952 MHz (^1H-NMR) and 100.577 MHz (^{13}C-NMR). $CDCl_3$ was used as solvent. Chemical shifts are given in ppm by reference to TMS (^1H-NMR; δ_H=0.00 ppm) and $CDCl_3$ (^{13}C-NMR; δ_C=77.00 ppm). Signal assignments were confirmed by APT and COSY experiments. Abbreviations s, d, t, q, m, def, and br are used to designate singlet, doublet, triplet, quartet, multiplet, deformed, and broad, respectively. Mass spectrometry (EIMS and HRMS) was done on a Jeol DX 303/DA 5000 instrument.

Preparation of *O*-Boc-3-epi-*Z*-geissoschizine (14).

Reaction of compound (**13**)[6] (1158.7 mg, 3.29 mmol) with DMAP (40.2 mg, 0.10 equiv.) and $(Boc)_2O$ (752.8 mg, 3.45 mmol, 1.05 equiv.) in CH_2Cl_2 (70 mL) for 2 h at rt (Ar atm) led, after purification by flash chromatography (silica gel, CH_2Cl_2:CH_3OH; 99.5:0.5), to compound (**14**).

Compound (**14**). Y. 1148.5 mg (77%). Amorphous. IR: 1760, 1720 (C=O). ^1H-NMR: 1.51 [9H, s, $-C(CH_3)_3$], 1.63 (3H, d, J=7 Hz, H-18), 3.34 (1H, br d, J=13.5 Hz, H-21), 3.55 (1H, br d, J=13.5 Hz, H-21), 3.73 (3H, s, $-COOCH_3$),

4.0 (1H, br, H-3), 5.20 (1H, q, J=7 Hz, H-19), 7.05-7.17 (2H, m, H-10, H-11), 7.29 (1H, d, J=7.5 Hz, H-9), 7.51 (1H, d, J=7.5 Hz, H-12), 7.89 (1H, br s, NH), 8.12 (1H, s, H-17). For the ^{13}C-NMR data, see Figure 1. MS: 452 (M^+), 352, 251 (100%), 169. HRMS: Calcd for $C_{26}H_{32}N_2O_5$: 452.2311. Found: 452.2331.

Preparation of *O*-Boc-3-epi-*Z*-geissoschizine *cis*-N_b-oxide (15).

Compound (**14**) (100.8 mg, 0.22 mmol) and *m*CPBA (57.7 mg, 0.33 mmol, 1.50 equiv.) in CH_2Cl_2 (30 mL) were stirred for 3 h at rt (Ar atm). The crude product was purified by column chromatography (alumina, CH_2Cl_2:CH_3OH; 99.5:0.5) to give compound (**15**).

Compound (**15**). Y. 64.4 mg (62%). Amorphous. IR: 1760, 1710 (C=O). ^{1}H-NMR: 1.52 [9H, s, $-C(CH_3)_3$], 1.67 (3H, d, J=7 Hz, H-18), 3.66 (3H, s, $-COOCH_3$), 5.46 (1H, q, J=7 Hz, H-19), 7.06-7.18 (2H, m, H-10, H-11), 7.28 (1H, d, J=7 Hz, H-9), 7.44 (1H, d, J=7 Hz, H-12), 8.10 (1H, s, NH), 8.21 (1H, br s, H-17). For the ^{13}C-NMR data, see Figure 1. MS: 352 [$C_{21}H_{23}N_2O_3$ = $C_{26}H_{32}N_2O_6$ - ($C_5H_9O_2$ + O)] (thermolabile compound).

Preparation of (±)-21α-cyano-3-isorauniticine (17) from *O*-Boc-3-epi-Z-geissoschizine *cis*-N_b-oxide (15).

TFAA (90 μL, 0.64 mmol, 1.87 equiv.) was added with a syringe during 10 min to a solution of compound (**15**) (159.2 mg, 0.34 mmol) and CH_2Cl_2 (5 mL). The solution was stirred for 2 h at rt (Ar atm). KCN (66.5 mg, 1.02 mmol, 3.00 equiv.) in H_2O (3 mL) was added, pH was adjusted to 4-5 with NaOAc and the solution was stirred at rt for 30 min, after which it was basified with saturated $NaHCO_3$ solution, extracted with CH_2Cl_2 and dried with Na_2SO_4. The crude product was purified several times by TLC (silica gel, CH_2Cl_2:MeOH; 99:1) to give compound (**17**).

Compound (**17**). Y. 26.0 mg (20%). Amorphous. IR: 2250 (CN), 1700 (C=O).

^{1}H-NMR: 1.35 (3H, d, $J_{18,19}$=6.5 Hz, H-18), 1.75 (1H, ddd, $J_{3,14\alpha}$=12 Hz, $J_{14\alpha,14\beta}$=13.5 Hz, $J_{14\alpha,15}$=4.5 Hz, H-14α), 2.29 (1H, ddd, $J_{15,20}$=5.5 Hz, $J_{19,20}$=1.5 Hz, $J_{20,21\beta}$=11 Hz, H-20), 2.61 (1H, ddd, $J_{5\alpha,5\beta}$=11.5 Hz, $J_{5\alpha,6\alpha}$=11.5 Hz, $J_{5\alpha,6\beta}$=4 Hz, H-5α), 2.78 (1H, br d, $J_{6\alpha,6\beta}$=15.5 Hz, H-6β), 3.02 (1H, m, H-6α), 3.09 (1H, m, H-15), 3.25 (1H, ddd, $J_{3,14\beta}$=2.5 Hz, $J_{14\alpha,14\beta}$=13.5 Hz, $J_{14\beta,15}$=2.5 Hz, H-14β), 3.30 (1H, br d, $J_{3,14\alpha}$=11 Hz, H-3), 3.37 (1H, d, $J_{20,21\beta}$=11 Hz, H-21β), 3.67 (1H, ddd, $J_{5\alpha,5\beta}$=11 Hz, $J_{5\beta,6\alpha}$=1 Hz, $J_{5\beta,6\beta}$=5 Hz, H-5β), 3.76 (3H, s, -$COOCH_3$), 4.76 (1H, dq, $J_{18,19}$=6.5 Hz, $J_{19,20}$=1.5 Hz, H-19), 7.09 (1H, dd, $J_{9,10}$=7.5 Hz, $J_{10,11}$=7.5 Hz, H-10), 7.15 (1H, dd, $J_{10,11}$=7.5 Hz, $J_{11,12}$=7.5 Hz, H-11), 7.31 (1H, d, $J_{11,12}$=7.5 Hz, H-12), 7.47 (1H, d, $J_{9,10}$=7.5 Hz, H-9), 7.60 (1H, d, $J_{15,17}$=2 Hz, H-17), 7.89 (1H, br s, NH). For the ^{13}C-NMR data, see Figure 1. MS: 377 (M^+, 100%), 362, 350, 335, 323, 249, 224, 209, 184, 170, 169, 156. HRMS: Calcd for $C_{22}H_{23}N_3O_3$: 377.1739. Found: 377.1733. Anal. Calcd for $C_{22}H_{23}N_3O_3$: C, 70.01; H, 6.14; N, 11.13. Found: C, 69.84; H, 6.22; N, 10.92.

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