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Acid-Catalysed Epimerization of 1-Substituted Indolo[2,3-*a*]quinolizidines: Stereoselective Routes to *cis*- and *trans*-Deethyleburnamonine Starting from the Same Ester Intermediate

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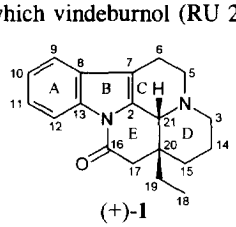
Abstract: Efficient syntheses of the pharmacologically interesting deethyleburnamonines **2** and **3** are described. Independent routes to **2** and **3** start from the same, easily accessible ester **5**. The choice between the routes requires an acid-catalysed epimerization of **5**. Conformations of some intermediate indolo[2,3-*a*]quinolizidines are discussed. Copyright © 1996 Elsevier Science Ltd

Eburnamonine, as both its optically active forms (+)-**1** and (-)-**1**, is a highly valued drug of natural origin used in the treatment of cerebral disorders. In view of its wide use, this indole alkaloid of eburnamine-vincamine type is now a popular synthetic target.[1] Interesting pharmacological properties are also possessed by several derivatives of eburnamonine, including the two ethyl group lacking compounds *cis*-deethyleburnamonine (**2**) and *trans*-deethyleburnamonine (**3**).[2] These compounds are precursors of other important derivatives, of which vindeburnol (RU 24722) (**4**)[3] is one of the most studied.



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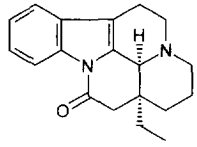

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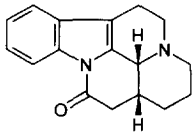

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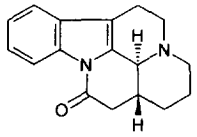

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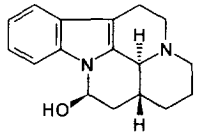

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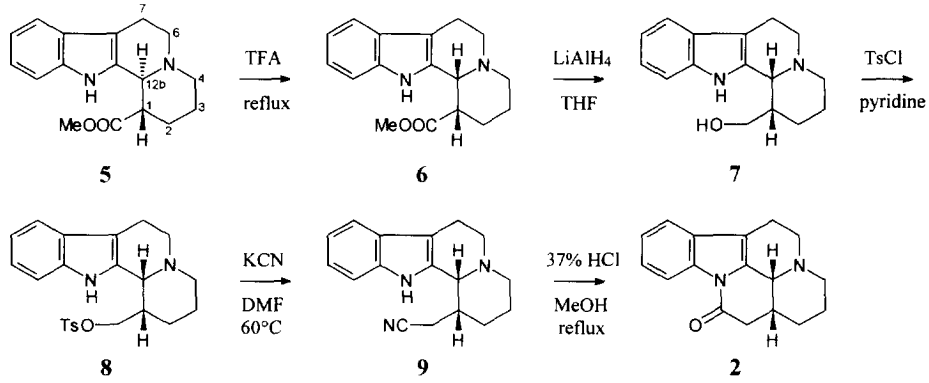
Much of the recent synthetic work carried out in our laboratory has been directed to alkaloids of eburnamine-vincamine type and their structurally close *Iboga* analogues, the tacamines.[4] The interesting

epimerization behaviour of certain 1,3-disubstituted indolo[2,3-*a*]quinolizidines required in the synthesis of tacamine-type compounds[4d,4e,4g] prompted us to examine some 1-substituted analogues. Instead of relying on the tedious oxidation/reduction procedures normally used with 1-substituted indolo[2,3-*a*]quinolizidines, we controlled the configurational relationship between H-1 and H-12b by a simple acid-catalysed epimerization, which led mainly to the isomer where the 1-substituent is axial (H-1 and H-12b *cis*). By choosing the proper starting compound, stereoselective routes to *cis*- and *trans*-deethyleburnamonine can be devised.

Results and Discussion

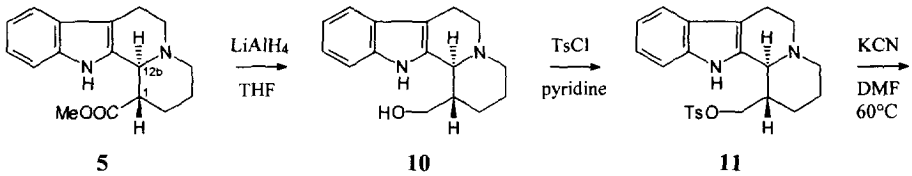
Ester **5**, which can be prepared in three steps from tryptophyl bromide and methyl nicotinate[5,6], was chosen as the starting compound for the synthesis of the deethyleburnamonines. Treatment of ester **5** with trifluoroacetic acid (TFA)[7] under reflux for 16 h led to a mixture consisting of the starting compound and its isomer **6**, the latter of which was isolated from this mixture in 78% yield. The two esters were then converted to the two deethyleburnamonines *via* essentially identical homologation processes (Schemes 1 and 2). Reduction of **6** and **5** with $LiAlH_4$ gave in high yields the corresponding alcohols (**7** and **10**), which were converted to nitriles **9** and **12** *via* tosylates **8** and **11**, respectively. Cyclization of nitrile **9**[8] in aq HCl/MeOH furnished (±)-*cis*-deethyleburnamonine (**2**) in 82% yield. Treatment of tosylate **11** with potassium cyanide in DMF yielded nitrile **12**, which exists partly in its tautomeric imine form **13** (Scheme 2). The ratio of **12** and **13** seems to be dependent on the pH, but the two compounds can be separated and characterized without difficulty. Mild acid treatment of a crude mixture of **12** and **13** afforded (±)-*trans*-deethyleburnamonine (**3**) from **11** in 55% yield (two steps).



Scheme 1

The complete spectral data of ester **6** have not been published, although this compound has been mentioned in the literature.[9] The ^{13}C NMR data of **6** indicate that, in $CDCl_3$ solution, it does not exist purely as a C/D *trans*-fused indoloquinolizidine (conformation a), but there is also a considerable contribution of conformer c (C/D-*cis*) to the equilibrium.[10] The same applies to nitrile **12**, which spectrally resembles the

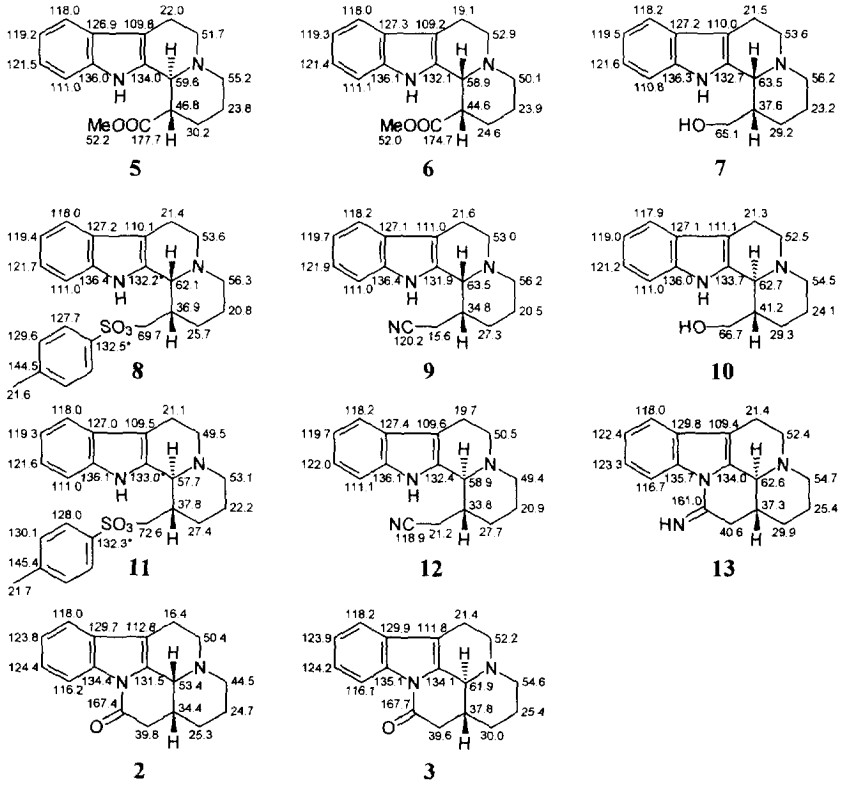
corresponding 1-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine.[11] Surprisingly, the ^{13}C NMR analysis of alcohol **10** gave a different result. As Stoit and Pandit[12] have pointed out, in DMSO-d_6 there is an equilibrium between the two conformations as described above. However, we were able to run a spectrum also in $CDCl_3$, which showed that in this solvent (in very low concentration) alcohol **10** exists predominantly in conformation a (C/D-*trans*).



5 **10** **11**

12 **13** **3**

Scheme 2



5 **6** **7**

8 **9** **10**

11 **12** **13**

2 **3**

Chart 1

Conclusions

The method described above represents the first selective routes to both deethyleburnamonines at will. Previous reports in the literature include the preparation of deethyleburnamonines from deethylvincamine[13a], from methyl (3-pyridyl)acetate[13b], from a deethyl derivative of Wenkert's enamine[13c], from 3,4-dihydro-β-carboline[13d], and from methyl (3-pyridyl)acetate *via* an α-aminonitrile[14] and *via* regioselective cyclization.[15] Recently Stoit and Pandit described a route where two lactam ester intermediates (4-oxo derivatives of **5** and **6**) were prepared *via* folate models.[12]

Experimental

All reactions were carried out under argon. Solvents were distilled over appropriate drying materials before use. Alkaline work-up: addition of aq $NaHCO_3$, extraction with CH_2Cl_2 (3x), drying of the combined organic layers with Na_2SO_4, and evaporation of the solvent under vacuum. Melting points were determined with a Gallenkamp melting point apparatus and are uncorrected. IR spectra (cm^{-1}, in $CHCl_3$ unless otherwise noted) were recorded on a Perkin-Elmer 700 spectrophotometer. ^1H NMR (400 MHz, reference: TMS, δ_H = 0.0 ppm) and ^{13}C NMR (100 MHz, reference: $CDCl_3$, δ_C = 77.0 ppm) spectra were recorded on a Varian Unity 400 spectrometer using $CDCl_3$ as solvent. Coupling constants (J) are given in Hz. Signal assignments are based on standard APT, COSY and HETCOR experiments. For the ^{13}C NMR data of compounds **2**, **3**, and **5** - **13**, see Chart 1. EI and HR mass spectra (70 eV, *m/z*) were measured with a Jeol DX 303/DA 5000 mass spectrometer. Merck Kieselgel 60 (230-400 mesh) was used in column chromatography.

Ester 5. Prepared according to a literature procedure[5,6] from tryptophyl bromide and methyl nicotinate in three steps. Yield 67% overall; mp. 144-146°C (Et_2O), lit.[6] mp. 143-145°C (Et_2O); IR: 2830-2750 (Wenkert-Bohlmann bands), 1715 (C=O); ^1H NMR: 8.15 (1H, br s, NH), 7.48-7.04 (4H, m, arom.), 3.82 (1H, d, J = 10, H-12b), 3.80 (3H, s, -$COOCH_3$); MS: 284 (M^+, 100), 283 (68), 225 (10), 197 (43), 170 (40), 169 (44); HR-MS: calcd for $C_{17}H_{20}N_2O_2$: 284.1525, found: 284.1506.

Acid-catalyzed Epimerization of Ester 5 to Ester 6. Ester **5** (197 mg, 0.69 mmol) was dissolved in trifluoroacetic acid (5 ml) and the solution was refluxed overnight (16 h). After evaporation of TFA, alkaline work-up of the residue gave 197 mg of a mixture of esters **5** and **6**. Column chromatography (CH_2Cl_2/MeOH, 99:1) gave 44 mg (22%) of starting ester **5** and 153 mg (78%) of ester **6**; mp. 159-161°C (CH_2Cl_2/hexane); IR: 1715 (C=O); ^1H NMR: 8.41 (1H, br s, NH), 7.48-7.06 (4H, m, arom.), 4.14 (1H, br s, H-12b), 3.65 (3H, s, -$COOCH_3$); MS: 284 (M^+, 83), 283 (100), 225 (9), 197 (47), 170 (30), 169 (26); HR-MS: calcd for $C_{17}H_{20}N_2O_2$; 284.1525, found: 284.1524.

Alcohol 7. Ester **6** (224 mg, 0.79 mmol) in dry THF (20 ml) was added to a suspension of $LiAlH_4$ (150 mg, 3.95 mmol) in dry THF (20 ml). After 1h stirring, alkaline work-up (aq NaOH) gave 190 mg (94%) of pure alcohol **7**; mp. 195-197°C (MeOH); IR: 3300 (OH), 2830-2750 (Wenkert-Bohlmann bands); ^1H NMR: 7.78 (1H, br s, NH), 7.50-7.07 (4H, m, arom.), 3.85-3.62 (2H, m, -$C\underline{H}_2OH$), 3.66 (1H, br s, H-12b); MS: 256 (M^+, 88), 255 (100), 239 (42), 225 (22), 197 (28), 170 (23), 169 (25); HR-MS: calcd for $C_{16}H_{20}N_2O$: 256.1576, found: 256.1565.

Tosylate 8. Alcohol **7** (170 mg, 0.66 mmol) was dissolved in dry pyridine (4 ml) and freshly recrystallized *p*-TsCl (253 mg, 1.33 mmol) was added. The mixture was kept at -20°C for 30 h, after which the solvent was evaporated. Alkaline work-up of the residue in the usual manner, followed by column chromatography (CH_2Cl_2/MeOH, 98:2), yielded 177 mg (65%) of amorphous **8**; IR: 3400 (NH); ^1H NMR:

7.91 (1H, br s, NH), 7.49 (2H, d, J = 8.5, H-3' and H-5' of Ts), 7.07 (2H, d, J = 8.5, H-2' and H-6' of Ts), 7.45-7.05 (4H, m, arom.), 4.21 (1H, dd, J = 10.5 and 9, -C<u>H</u>$_2$OTs), 3.79 (1H, dd, J = 10.5 and 4, -C<u>H</u>$_2$OTs), 3.43 (1H, br s, H-12b), 2.34 (3H, s, -CH_3 of Ts); MS: 410 (M^+, 5), 239 (75), 238 (100), 237 (48); HR-MS: calcd for $C_{16}H_{19}N_2$ (M-OTs)$^+$: 239.1548, found: 239.1546.

Nitrile 9. Tosylate **8** (151 mg, 0.37 mmol) and KCN (133 mg, 2.0 mmol) were heated in DMF (5 ml) at 60°C for 16 h. DMF was evaporated and alkaline work-up of the residue gave the crude product, which was purified by column chromatography (CH_2Cl_2/MeOH, 98:2) to give 99 mg (100%) of nitrile **9**; mp. 182-183°C (CH_2Cl_2/hexane), lit.[8] mp. 185-186°C (EtOH); IR: 2830-2750 (Wenkert-Bohlmann bands), 2250 (CN); ^{1}H NMR: 7.77 (1H, br s, NH), 7.49-7.07 (4H, m, arom.), 3.50 (1H, br d, J = 2, H-12b); MS: 265 (M^+, 76), 264 (100), 239 (9), 225 (11), 197 (62), 170 (74), 169 (58); HR-MS: calcd for $C_{17}H_{19}N_3$: 265.1579, found: 265.1570.

(±)-*cis*-Deethyleburnamonine (20-Deethyleburnamonine) (2). Nitrile **9** (26 mg, 0.096 mmol) was refluxed in a 2:1 mixture of 37% HCl and MeOH (3 ml) for 16 h. Alkaline work-up and column chromatography (CH_2Cl_2/MeOH, 96:4) gave 21 mg (82%) of (±)-*cis*-deethyleburnamonine (**2**); mp. 152-154°C (CH_2Cl_2/hexane), lit.[13c] mp. 156°C (hexane); IR: 1695 (C=O); ^{1}H NMR: 8.38 (1H, m, H-12), 7.46-7.25 (3H, m, arom.), 4.35 (1H, dt, J = 5 and 2.5, H-21); MS: 266 (M^+, 100), 265 (93), 222 (40), 209 (81), 180 (21), 168 (29), 167 (29); HR-MS: calcd for $C_{17}H_{18}N_2O$: 266.1419, found: 266.1437.

Alcohol 10. Prepared from ester **5** as described above (see alcohol **7**). Yield 100%; mp. 242-245°C (dec.) (MeOH), lit.[12] mp. 244-245°C (dec.) (MeOH); IR (KBr): 3400 (OH); ^{1}H NMR: 9.48 (1H, br s, NH), 7.49-7.04 (4H, m, arom.), 4.00 (1H, dd, J = 11.5 and 3.5, -C<u>H</u>$_2$OH), 3.81 (1H, dd, J = 11.5 and 4.5, -C<u>H</u>$_2$OH), 3.55 (1H, d, J = 8.5, H-12b); MS: 256 (M^+, 89), 255 (100), 239 (44), 225 (22), 197 (27), 170 (22), 169 (25); HR-MS: calcd for $C_{16}H_{20}N_2O$: 256.1576, found: 256.1578.

Tosylate 11. Prepared from alcohol **10** as described above (see tosylate **8**). Yield 80%; amorphous; IR: 3400 (NH); ^{1}H NMR: 8.36 (1H, br s, NH), 7.86 (2H, d, J = 8.5, H-3' and H-5' of Ts), 7.39 (2H, d, J = 8.5, H-2' and H-6' of Ts), 7.48-7.05 (4H, m, arom.), 4.64 (1H, dd, J = 10 and 4, -C<u>H</u>$_2$OTs), 4.04 (1H, dd, J = 10 and 3, -C<u>H</u>$_2$OTs), 3.82 (1H, d, J = 8, H-12b), 2.48 (3H, s, -CH_3 of Ts); MS: 410 (M^+, 23), 239 (87), 238 (100); HR-MS: calcd for $C_{23}H_{26}N_2O_3S$: 410.1664, found: 410.1664.

(±)-*trans*-Deethyleburnamonine (21-Epi-20-deethyleburnamonine) (3) *via* Nitrile 12 and Imine 13. Tosylate **11** (82 mg, 0.20 mmol) was treated with KCN (65 mg, 1.0 mmol) in DMF (3 ml) as above (60°C, 20h). The crude mixture, containing mainly nitrile **12** and imine **13** was then refluxed with 1M HCl for 1h. After alkaline work-up of the cooled solution, the crude product was purified by column chromatography (CH_2Cl_2/MeOH, 98.5:1.5) to give 30 mg (55% from **11**) of (±)-*trans*-deethyleburnamonine (**3**). For obtaining their analytical data, intermediates **12** and **13** were isolated from another experiment.

Nitrile **12**: mp. 169-170°C (CH_2Cl_2/hexane); IR: 2250 (CN); ^{1}H NMR: 7.86 (1H, br s, NH), 7.50-7.09 (4H, m, arom.), 3.95 (1H, d, J = 6, H-12b); MS: 265 (M^+, 79), 264 (100), 197 (60), 170 (66), 169 (50); HR-MS: calcd for $C_{17}H_{19}N_3$: 265.1579, found: 265.1564.

Imine **13**: amorphous; IR: 2830-2750 (Wenkert-Bohlmann bands), 1630 (C=N); ^{1}H NMR: 8.57 (1H, d, J = 8, H-12), 7.45-7.19 (3H, m, arom.); MS: 265 (M^+, 86), 264 (100), 221 (19); HR-MS: calcd for $C_{17}H_{19}N_3$: 265.1579, found: 265.1571.

(±)-*trans*-Deethyleburnamonine (**3**): mp. 145-146°C (CH_2Cl_2/hexane), lit.[13b] mp. 146°C (acetone/hexane); IR: 2830-2750 (Wenkert-Bohlmann bands), 1705 (C=O); ^{1}H NMR: 8.34 (1H, m, H-12), 7.43-7.22 (3H,

m, arom.); MS: 266 (M^+, 94), 265 (100), 209 (17), 180 (17), 169 (15), 168 (22), 167 (24); HR-MS: calcd for $C_{17}H_{18}N_2O$: 266.1419, found: 266.1436.

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