SYNTHESIS AND CONFORMATIONAL STUDY OF INDOLO[2,3-*a*]-QUINOLIZIDINE-3-ETHAN-1'-OLS: INTERMEDIATES FOR THE SYNTHESIS OF DEPLANCHEINE AND FLAVOPEREIRINE

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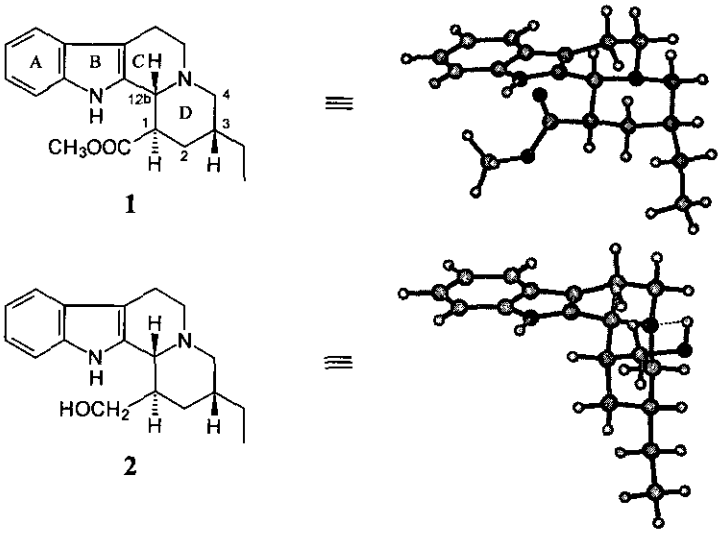
Abstract - The synthesis and stereostructures of all four indolo[2,3-*a*]-quinolizidine-3-ethan-1'-ols are described. The two alcohols with an axial side chain exist principally in the conformation where the C/D ring junction is *trans*, which is favoured by an intramolecular hydrogen bond between the hydroxyl group and the N_b-atom. Dehydration of the four alcohols with P_2O_5 in each case led to a mixture consisting of *E*-deplancheine and *Z*-deplancheine. The three side products were two 3-vinyl isomers, one of which can be converted to deplancheine *via* double bond isomerization, and 3-ethyl-1,4,6,7,12,12b-hexahydroindolo[2,3-*a*]quinolizine, which is a precursor of flavopereirine.

During our synthetic work on tacamine-type indole alkaloids,[1] we prepared indolo[2,3-*a*]quinolizidine derivatives possessing some interesting conformational features. Ester (**1**)[2] is the key intermediate for the synthesis of seven tacamine derivatives of the total of eight known alkaloids of this type.[3] Analysis of ^{1}H- and ^{13}C-NMR spectra ($CDCl_3$) showed that the ester (**1**) adopts a conformation where the rings C and D are *trans*-fused. Reduction of **1** with $LiAlH_4$ gives alcohol (**2**), which exists mainly in a conformation where the C/D ring junction is *cis*. This interesting conformational difference between two indolo[2,3-*a*]quinolizidines with seemingly identical stereostructures demanded closer scrutiny.



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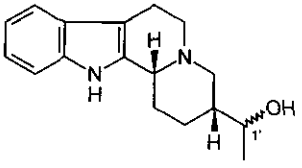
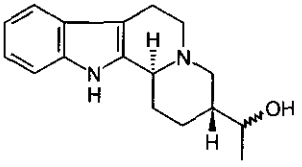
The conformational equilibrium in indolo[2,3-*a*]quinolizidines is possible *via* nitrogen inversion and *cis*-decalin type ring interconversion.[4] We tentatively attributed the different conformational behaviour of compounds (**1**) and (**2**) to the existence of intramolecular hydrogen bonding between the OH-group and the N_b-atom in alcohol (**2**). Furthermore, an interaction between the methoxycarbonyl group and the indole NH is presumable in ester (**1**). Interactions of this kind are often postulated but usually without any spectroscopic proof. To obtain more information about the interactions we sought model compounds where the conformational equilibrium would be more clearly affected by intramolecular hydrogen bonding. Analogues of ester (**1**) with a hydroxyl group in the ethyl side chain (compounds **3** and **4**)[5] were initially investigated, but no useful information was obtained. We then turned to the corresponding alcohols without the ester group. Four possible diastereomers (**5**-**8**) possess this carbon skeleton. Alcohols (**5**-**8**) are known[6-10] but have not been previously characterized in pure form.



5 (β-OH)
6 (α-OH)

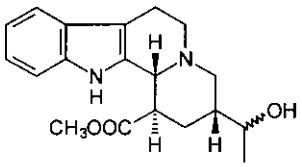


7 (β-OH)
8 (α-OH)

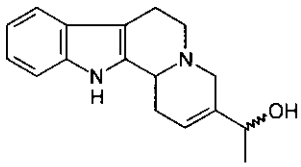
RESULTS AND DISCUSSION

Hydrolysis and decarboxylation of hydroxy esters (**3**) and (**4**) with H_3PO_4 was expected to lead to alcohols (**5**) and (**6**), respectively, but the reaction was accompanied by epimerization[11] and led mainly

to the more stable alcohols (**7**) and (**8**). Catalytic hydrogenation of alcohols (**9**) and (**10**), which are important intermediates for the synthesis of corynantheine-type alkaloids,[12] was expected to lead to all isomers (**5-8**), but in practice the main products of the hydrogenation were alcohols (**5**) and (**6**). Thus, after chromatography, all four compounds (**5-8**) were available in pure form. The formation of alcohols (**7**) and (**8**) from alcohols (**5**) and (**6**), respectively, was confirmed by acid-catalysed epimerization.



3 (β-OH)
4 (α-OH)



9 (β-OH)
10 (α-OH)

According to their ^{1}H-NMR and ^{13}C-NMR spectra, alcohols (**5**) and (**6**) both exist almost completely in a conformation where the C/D ring junction is *trans*. As this is not the case for the corresponding compounds without the hydroxyl group (3-ethylindolo[2,3-*a*]quinolizidines),[11,13] intramolecular hydrogen bonding must be keeping the hydroxyethyl side chain in axial orientation. In alcohols (**7**) and (**8**) this bulky group is equatorial and intramolecular hydrogen bonding is not possible.

Chemical shifts of the hydroxyl protons gave the best spectral indication of the postulated intramolecular hydrogen bonding. As expected,[14] the OH proton resonated at lower field in compounds (**5**) and (**6**) (δ 4-5 ppm) than in compounds (**7**) and (**8**) (δ 1.5-2.5 ppm). To exclude the effects of variable concentration and temperature, all the NMR samples were 0.04 molar and run at 22°C. Exchange with D_2O confirmed the chemical shift of the OH signal.

Finally, as alcohols (**5-8**) would appear to be like potential precursors of the indole alkaloid deplancheine,[15] their dehydration with P_2O_5 was attempted. Dehydration of alcohols (**5**) and (**6**) was slightly slower than that of alcohols (**7**) and (**8**). Alcohols (**5**) and (**6**) gave four double bond isomers in slightly different ratios (Table 1): *E*-deplancheine (**11**), *Z*-deplancheine (**12**), indoloquinolizideine (**13**), which results from the double bond migration in the deplancheines, and *cis*-3-vinylindoloquinolizidine (**14**). Alcohols (**7**) and (**8**) similarly afforded isomers (**11-13**) and *trans*-3-vinylindoloquinolizidine (**15**). Isomer (**13**) has recently been converted to the simple quaternary indole alkaloid flavopereirine (**16**)[16] and the vinyl compound (**15**) is a precursor of *E*-deplancheine (**11**).[17]

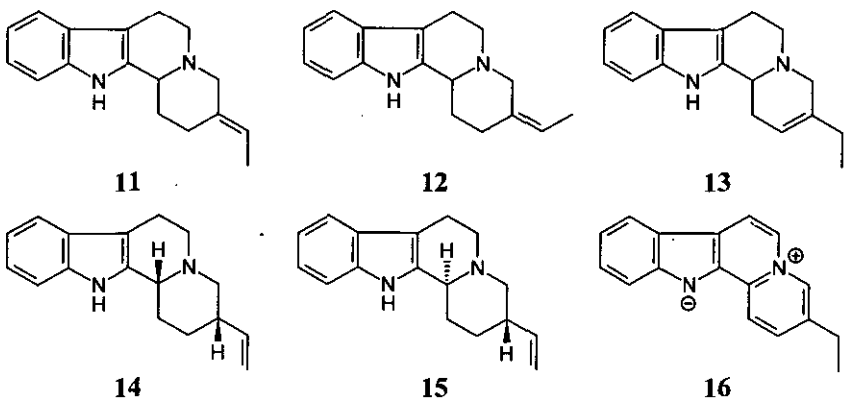
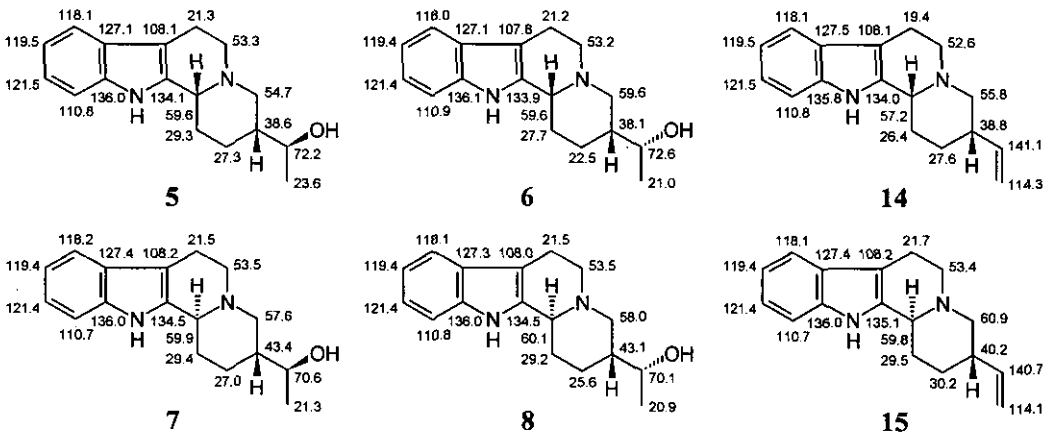


Table 1. Results of the Dehydration of Alcohols (**5-8**) (^{1}H-NMR integration).

Compound	**11** (%)	**12** (%)	**13** (%)	**14** (%)	**15** (%)
5	27	26	25	22	
6	42	16	25	17	
7	29	20	35		16
8	33	15	40		12

CONCLUSIONS

The diastereomeric alcohols (**5-8**) were prepared and characterized for the first time in pure form. Although alcohols (**7**) and (**8**) are more stable than alcohols (**5**) and (**6**), only the configuration at the hydroxyethyl side chain had a significant effect on the product ratio in the dehydration. Alcohol (**6**) gave the best yield of *E*-deplancheine (**11**).



Chart

EXPERIMENTAL

All reactions were carried out under argon. Alkaline work-up: addition of sat. 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. ^{1}H-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 with $CDCl_3$ used 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 the compounds (**5-8** and **14-15**), see Chart. 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 and Merck Kieselgel 60 $PF_{254+366}$ in preparative layer chromatography (PLC).

Alcohol (5). A mixture of alcohol (**9**) (32.3 mg, 0.12 mmol) and PtO_2 (3.2 mg) in MeOH (10 mL) was hydrogenated for 3 h. After filtration and evaporation of solvent, the residue was purified by PLC (CH_2Cl_2/MeOH, 85:15) to give 22.1 mg (68%) of alcohol (**5**), mp 212-213°C (MeOH/CH_2Cl_2); lit.,[9] mp 164°C (for mixture of alcohols **5** and **6**); IR: 3460 (NH), 3250 (OH), 2860-2770 (Bohlmann bands); ^{1}H-NMR: 7.84 (1H, br s, NH), 7.47-7.07 (m, 4H, arom.), 4.97 (1H, br s, -OH), 3.98 (dq, 1H, *J* = 3 and 6.5, -C*H*(OH)Me), 3.46 (br d, 1H, *J* = 11.5, H-12b), 1.26 (3H, d, *J* = 6.5, -CH(OH)*Me*); MS: 270 (M^+, 86), 269 (100), 225 (25), 170 (19), 169 (18); HRMS: Calcd for $C_{17}H_{22}N_2O$: 270.1732, found: 270.1725.

Alcohol (6). Hydrogenation of a mixture of alcohol (**10**) (29.6 mg, 0.11 mmol) and PtO_2 (3.0 mg) in MeOH (10 mL) for 2 h and further treatment as described for alcohol (**5**) gave 19.8 mg (66%) of alcohol **6**, mp 207-208°C (EtOH); lit.,[8] mp 200-201°C; lit.,[9] mp 164°C (for mixture of alcohols **5** and **6**); IR: 3470 (NH), 3230 (OH), 2860-2770 (Bohlmann bands); ^{1}H-NMR: 7.77 (1H, br s, NH), 7.45-7.05 (m, 4H, arom.), 5.00 (br s, 1H, -OH), 4.20 (dq, 1H, *J* = 3 and 6.5, -C*H*(OH)Me), 3.41 (br d, 1H, *J* = 10.5, H-12b), 1.20 (d, 3H, *J* = 6.5, -CH(OH)*Me*); MS: 270 (M^+, 91), 269 (100), 225 (27), 171 (24), 170 (18), 169 (18); HRMS: Calcd for $C_{17}H_{22}N_2O$: 270.1732, found: 270.1722.

Alcohol (7). Hydroxy ester (**3**) (80.6 mg, 0.25 mmol) was dissolved in 85% aq H_3PO_4 (4 mL) and the mixture was heated at 120°C for 3 h. Alkaline work-up gave the crude product, which was purified by

PLC (CH_2Cl_2/MeOH, 85:15) to give 9.5 mg (14%) of alcohol (**7**), mp 160-161°C (MeOH/EtOAc); lit.,[7] mp 199-200°C (acetone); lit.,[8] mp 159-160°C (for mixture of alcohols **7** and **8**); lit.,[10] mp 180-185°C (for mixture of alcohols **7** and **8**); IR: 3400 (br, NH and OH), 2870-2790 (Bohlmann bands); ^{1}H-NMR: 7.79 (br s, 1H, NH), 7.48-7.09 (m, 4H, arom.), 3.63 (dq, 1H, J = 6 and 7, -C*H*(OH)Me), 3.23 (br d, 1H, J = 11.5, H-12b), 2.00 (br s, 1H, -OH), 1.25 (d, 3H, J = 6, -CH(OH)*Me*); MS: 270 (M^+, 78), 269 (100), 225 (24), 170 (17), 169 (19); HRMS: Calcd for $C_{17}H_{22}N_2O$: 270.1732, found: 270.1724.

Alcohol (8). Dissolving of hydroxy ester (**4**) (50.4 mg, 0.15 mmol) in 85% aq H_3PO_4 (2.5 mL) and further treatment as described for alcohol (**7**) gave 11 mg (27%) of alcohol (**8**), mp 208-209°C ($MeOH/CH_2Cl_2$); lit.,[8] mp 159-160°C (for mixture of alcohols **7** and **8**); lit.,[9] mp 192-194°C; lit.,[10] mp 202-204°C (EtOH); IR: 3300 (br, NH and OH), 2870-2770 (Bohlmann bands); ^{1}H-NMR: 7.97 (br s, 1H, NH), 7.47-7.06 (m, 4H, arom.), 3.66 (dq, 1H, J = 6 and 6.5, -C*H*(OH)Me), 3.18 (br d, 1H, J = 10, H-12b), 2.02 (br s, 1H, -OH), 1.21 (d, 3H, J = 6.5, -CH(OH)*Me*); MS: 270 (M^+, 88), 269 (100), 225 (31), 170 (28), 169 (26); HRMS: Calcd for $C_{17}H_{22}N_2O$: 270.1732, found: 270.1726.

Acid-catalysed Epimerization of Alcohol (5). Alcohol (**5**) (10.3 mg, 0.04 mmol) was dissolved in 85% aq H_3PO_4 (3 mL) and the mixture was heated at 120°C for 3 h. After alkaline work-up the residue was purified by PLC (CH_2Cl_2/MeOH 85:15) to give 4.4 mg (60%) of alcohol (**7**) and 1.7 mg (17%) of the starting alcohol (**5**).

Acid-catalysed Epimerization of Alcohol (6). Epimerized as described for alcohol (**5**), alcohol (**6**) (30.8 mg, 0.11 mmol) in 85% aq H_3PO_4 (3 mL) gave 18.3 mg (59%) of alcohol (**8**) and 4.9 mg (16%) of the starting alcohol (**6**).

Dehydration of alcohol (5). A mixture of alcohol (**5**) (22.2 mg, 0.08 mmol) and P_2O_5 (35 mg, 0.25 mmol) in dry toluene (10 mL) was refluxed for 6 h. Alkaline work-up and column chromatography (CH_2Cl_2/MeOH, 99:1 and 97:3) gave 2.1 mg (10%) of indoloquinolizideine (**13**), 4.4 mg of a mixture of deplancheines (**11**) and (**12**) (51:49), and 1.9 mg (9%) of *cis*-3-vinylindoloquinolizidine (**14**). The mixture was purified by PLC (CH_2Cl_2/MeOH, 90:10) to give 2.3 mg (11%) of *E*-deplancheine (**11**) and 2.1 mg (10%) of *Z*-deplancheine (**12**).

E-Deplancheine (**11**). IR: 3460 (NH), 2810-2750 (Bohlmann bands), 1650 (C=C); ^{1}H-NMR: 7.86 (br s, 1H, NH), 7.47-7.06 (m, 4H, arom.), 5.43 (q, 1H, J = 7, =C*H*Me), 1.62 (d, 3H, J = 7,

=CH*Me*); For ^{13}C-NMR see Ref. 18; MS: 252 (M^+, 100), 251 (95), 169 (47), 156 (24); HRMS: Calcd for $C_{17}H_{20}N_2$: 252.1626, found: 252.1636.

Z-Deplancheine (**12**). IR: 3450 (NH), 2810-2760 (Bohlmann bands), 1650 (C=C); ^{1}H-NMR: 7.75 (br s, 1H, NH), 7.48-7.06 (m, 4H, arom.), 5.34 (q, 1H, J = 7, =C*H*Me), 1.66 (d, 3H, J = 7, =CH*Me*); For ^{13}C-NMR see Ref. 19; MS: 252 (M^+, 97), 251 (100), 169 (43), 156 (25); HRMS: Calcd for $C_{17}H_{20}N_2$: 252.1626, found: 252.1629.

Indoloquinolizideine (**13**). IR: 3470 (NH), 2810-2770 (Bohlmann bands), 1620 (C=C); ^{1}H-NMR: 7.71 (br s, 1H, NH), 7.51-7.08 (m, 4H, arom.), 5.54 (br m, 1H, H-2), 2.04 (br q, 2H, J = 7.5, -CH_2Me), 1.07 (t, 3H, J = 7.5, -CH$_2$*Me*); For ^{13}C-NMR see Ref. 18; MS: 252 (M^+, 66), 251 (25), 170 (100), 169 (67); HRMS: Calcd for $C_{17}H_{20}N_2$: 252.1626, found: 252.1619.

cis-3-Vinylindoloquinolizidine (**14**). IR: 3450 (NH), 1680 (C=C); ^{1}H-NMR: 7.77 (br s, 1H, NH), 7.49-7.08 (m, 4H, arom.), 5.97 (br m, 1H, -C*H*=CH$_2$), 5.06 (dd, 1H, J = 1.5 and 17.5, -CH=CH_2), 4.99 (dd, 1H, J = 1.5 and 10.5, -CH=CH_2); For ^{13}C-NMR see Chart; MS: 252 (M^+, 100), 251 (89), 223 (26), 170 (64), 169 (39), 156 (33); HRMS: Calcd for $C_{17}H_{20}N_2$: 252.1626, found: 252.1623.

Dehydration of alcohol (6). Dehydration was carried out as described for alcohol (**5**). Yield 17% of *E*-deplancheine (**11**), 6% of *Z*-deplancheine (**12**), 10% of indoloquinolizideine (**13**), and 7% of *cis*-3-vinylindoloquinolizidine (**14**).

Dehydration of alcohol (7). A mixture of alcohol (**7**) (32.6 mg, 0.12 mmol) and P_2O_5 (52 mg, 0.36 mmol) in dry toluene (10 mL) was refluxed for 4 h. Alkaline work-up and column chromatography (CH_2Cl_2/MeOH, 99:1 and 97:3) afforded 6.4 mg of a mixture of compounds (**13**) and (**15**) (31:69), and 6.1 mg of a mixture of deplancheines (**11**) and (**12**) (59:41). Both mixtures were purified by PLC (the mixture of **11** and **12** with CH_2Cl_2/MeOH, 90:10 and the mixture of **13** and **15** with EtOAc/acetone, 95:5) to give 3.7 mg (12%) of *E*-deplancheine (**11**), 2.4 mg (8%) of *Z*-deplancheine (**12**), 4.3 mg (14%) of indoloquinolizideine (**13**), and 2.1 mg (7%) of *trans*-3-vinylindoloquinolizidine (**15**).

trans-3-Vinylindoloquinolizidine (**15**). IR: 3450 (NH), 2810-2770 (Bohlmann bands), 1630 (C=C); ^{1}H-NMR: 7.73 (br s, 1H, NH), 7.48-7.07 (m, 4H, arom.), 5.76 (ddd, 1H, J = 6.5, 10.5 and 17, -C*H*=CH$_2$), 5.09 (dd, 1H, J = 1.5 and 17, -CH=CH_2), 5.02 (dd, 1H, J = 1.5 and 10.5, -CH=CH_2); For ^{13}C-NMR see Chart; MS: 252 (M^+, 100), 251 (79), 223 (23), 170 (50), 169 (27), 156 (25); HRMS: Calcd for $C_{17}H_{20}N_2$: 252.1626, found: 252.1631.

Dehydration of alcohol (8). Alcohol (**8**) was dehydrated as described for alcohol (**7**). Yield 13% of *E*-deplancheine (**11**), 6% of *Z*-deplancheine (**12**), 16% of indoloquinolizideine (**13**), and 5% of *trans*-3-vinylindoloquinolizidine (**15**).

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Received, 31st March, 1997