LACTONE FORMATION AS AN AID IN THE NMR CHARACTERIZATION OF TWO 3-(1'-HYDROXYETHYL)INDOLO[2,3-*a*]QUINOLIZIDINE-1-CARBOXYLATES: INTERMEDIATES FOR THE STEREOSELECTIVE SYNTHESIS OF TACAMINE-TYPE INDOLE ALKALOIDS

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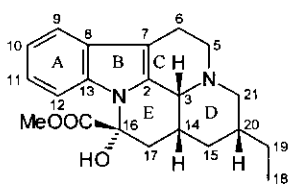
Abstract - NMR spectral characterization of methyl 3-(1'-hydroxyethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-1-carboxylates (**3**) and (**4**) is described. The configuration at the hydroxyethyl side chain was confirmed by NOE difference spectroscopy performed on 3-(1'-hydroxyethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-1-carboxylic acid lactones (**5**) and (**6**) obtained by epimerization of **3** and **4**. Base treatment of **3** and **4**, followed by esterification, led to methyl 3-(1'-hydroxyethyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-*a*]quinolizine-1-carboxylates (**7**) and (**8**), which are new intermediates for the preparation of tacamine-type indole alkaloids.

As part of our synthetic efforts towards tacamine-type indole alkaloids,[1] we have recently been working on the stereoselective synthesis of 1,3-disubstituted indolo[2,3-*a*]quinolizidines. The preparation of ester (**2**), the first potential intermediate for the synthesis of tacamine (**1**)[2a] and related compounds,[2b] has been reported in a preliminary communication.[3] Ester (**2**) was obtained in high stereoselectivity in three steps from the mixture of esters (**3**) and (**4**). In order to determine the stereochemistry of compounds (**3**) and (**4**), their ^{1}H- and ^{13}C-NMR spectra were first totally analyzed. The 2D H,H-COSY and H,C-COSY (HETCOR) spectra permitted the chemical shift assignments of all hydrogen and carbon atoms. This did not, however, allow the determination of the configuration at the hydroxyethyl side chain.



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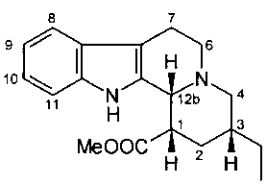

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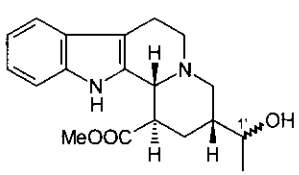
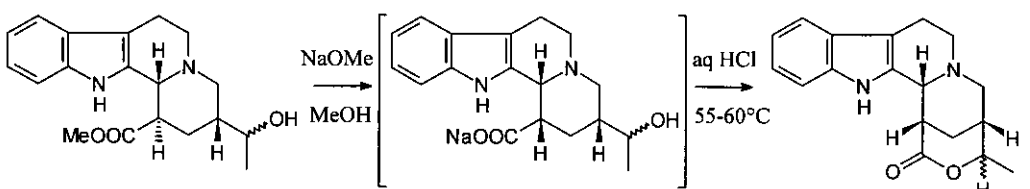


3 (α–OH)
4 (β–OH)

RESULTS AND DISCUSSION

A 1-hydroxyethyl side chain is a significant structural feature in many natural products, including several alkaloids.[4] Configuration at the chiral carbon of a side chain is often difficult to determine by NMR methods due to the rotation of the group.[5] A number of ways are available to slow down this motion, *e.g.* acylating the hydroxy group with a bulky reagent such as benzoyl chloride.[6] In certain cases the rotation of the 1-hydroxyethyl chain is sufficiently hindered by another large functional group in the molecule.[7] With the rotation of the side chain diminished, NOE difference spectroscopy can serve as a powerful tool for the determination of the configuration.

NOE difference spectroscopy applied to compounds (**3**) and (**4**) did not allow the unambiguous determination of the stereochemistry at the side chain. On the basis of the results we nevertheless tentatively proposed that compound (**3**) was the (1'*S**)-isomer (*β*-OH in formula **3**).[1f,3] In order to verify this, a chemical modification seemed necessary, and conversion of the two compounds into lactones was the obvious choice. To effect both the necessary epimerization at C-1 and lactone ring formation, esters (**3**) and (**4**) were refluxed with NaOMe in methanol, which afforded lactones (**5**) and (**6**), respectively. As isolation of the lactones proved difficult, probably because of the easy opening of the lactone ring, the process was modified slightly. After the base treatment, gentle heating with 32% HCl furnished **5** and **6** in 10% yield each (Scheme 1). Proton NMR analysis was carried out on these two compounds, and the chemical shifts, together with those for compounds (**3**) and (**4**), are shown in Chart 1.

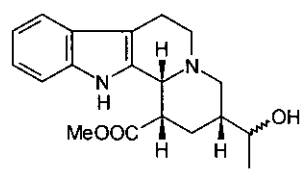


3 (α–OH)
4 (β–OH)

5 (α–H)
6 (β•H)

Scheme 1

When compounds (**3**) and (**4**) were treated first with NaOMe and then with methanol saturated with dry HCl gas, isomers (**7**) and (**8**) (H-1, H-3, H-12b all *cis*) were obtained in 50% and 60% isolated yields, respectively. The ^{13}C-NMR data for compounds (**3** - **8**) are shown in Chart 2.



7 (α–OH)
8 (β–OH)

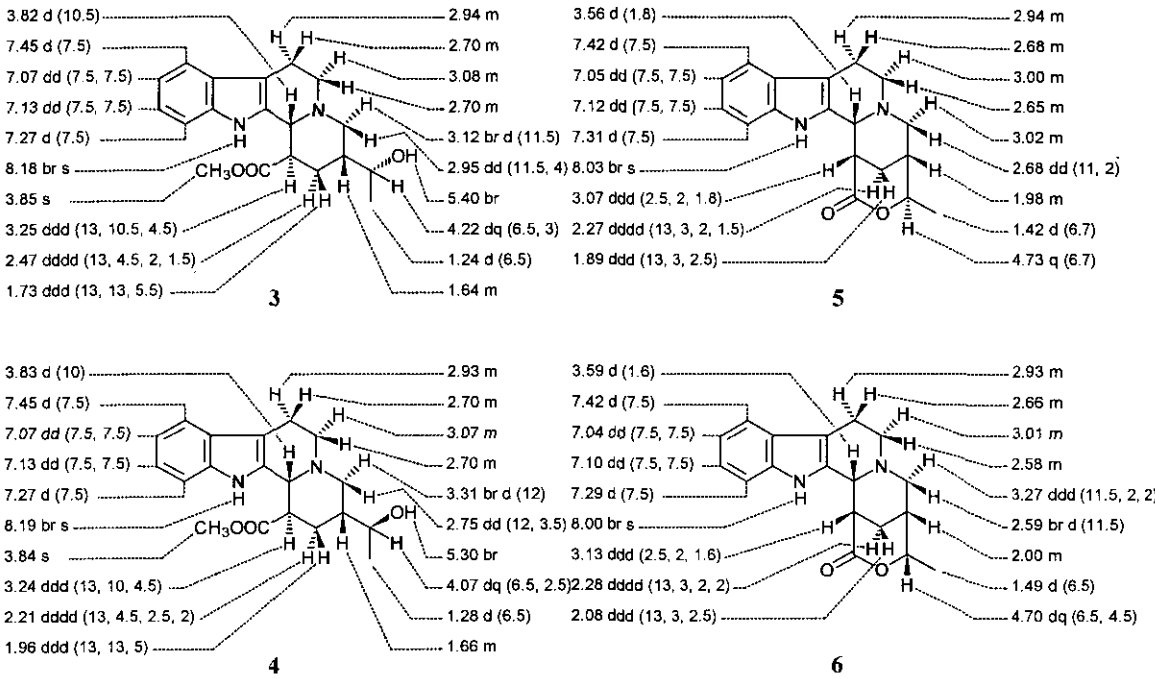
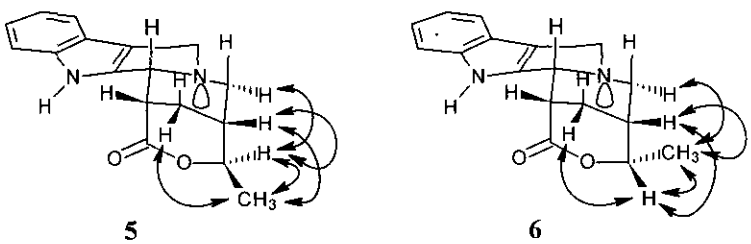


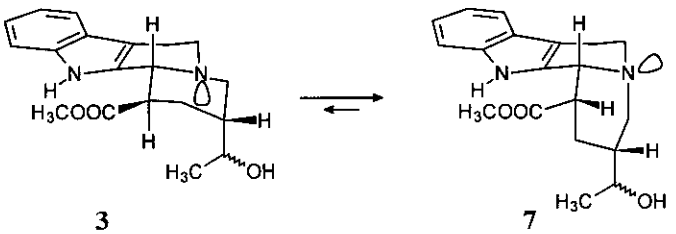
Chart 1

NOE difference spectroscopy applied to the two lactones provided conclusive evidence for the C-1' stereochemistry. In lactone (**5**), irradiating the methyl group (δ 1.42) resulted in NOEs only at protons H-2α (2%), H-3 (3%), and H-1' (6%), revealing that the configuration at C-1' of **5**, and also its precursor (**3**), was *R**, and not *S** as earlier proposed.[1f,3] Irradiation at H-1' (δ 4.73) resulted in NOEs at H-4α (5%), H-3 (3.5%), and the methyl group (6%). There is virtually no coupling between H-1' and H-3 (torsion angle about 90°), which provided additional evidence for the stereochemistry. As was expected, the *S** stereochemistry was confirmed at C-1' when the same measurements were carried out on lactone (**6**) [irradiation at H-1' (δ 4.70): NOEs at H-2α (3%), H-3 (8%), and the methyl group (4%); irradiation at the methyl group (δ 1.49): NOEs at H-3 (1%), H-4α (3%), and H-1' (5.5%)] (see figure below).

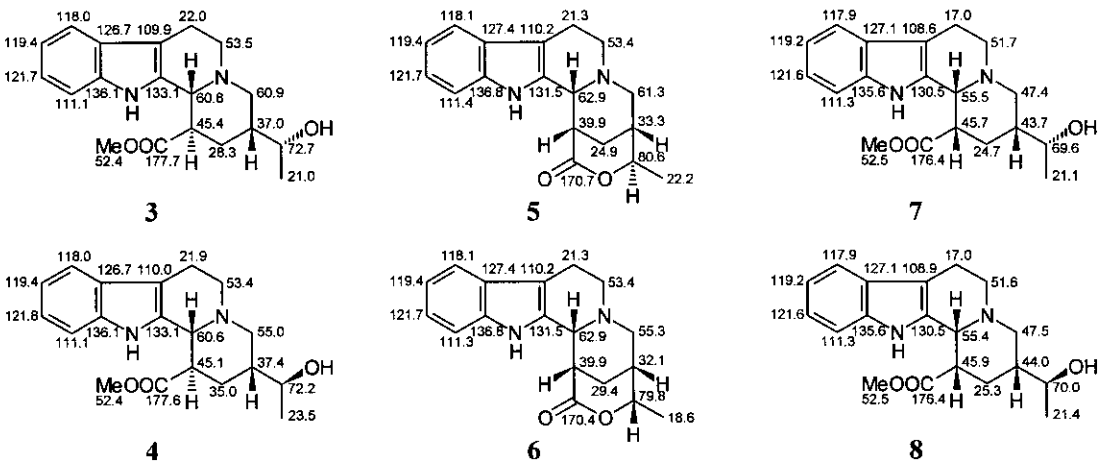


CONCLUSIONS

The stereochemistry of the hydroxyethyl side chain of compounds (**3**) and (**4**) was verified by converting them to the corresponding lactones (**5**) and (**6**), which proved ideally suited for solving this problem. NOE difference spectroscopy performed on **5** and **6** unambiguously settled the stereochemistry at C-1'. Base-catalysed equilibration of **3** and **4** led to hydroxyethyl esters (**7**) and (**8**), respectively. As these new compounds possess the desired relative configurational relationship at centres C-1, C-3 and C-12b (see figure below), they constitute new interesting intermediates for the synthesis of tacamine-type indole alkaloids.



3 **7**
4 **8**



3 **5** **7**
4 **6** **8**

Chart 2

EXPERIMENTAL

All reactions were carried out under argon. 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) and ^{13}C-NMR (100 MHz) spectra were recorded on a Varian Unity 400 spectrometer using $CDCl_3$ as solvent. Chemical shifts are given in ppm downfield from TMS (δ_H = 0) and $CDCl_3$ (δ_C = 77.0 ppm). Coupling constants (J) are given in Hz. Signal assignments are based on standard APT, COSY and HETCOR experiments. For the ^{1}H-NMR data

of compounds (**3** - **6**), see Chart 1. For the ^{13}C-NMR data of compounds (**3** - **8**), see Chart 2. LR and HR mass spectra (EI, 70 eV) were measured with a Jeol DX 303/DA 5000 mass spectrometer. Merck Kieselgel 60 (230-400 mesh) was used in chromatography. The relative notations α and β refer to the formulas drawn for compounds (**3** - **8**).

Esters (3) and (4). The preparation of compounds (**3**) and (**4**) has been described earlier.[1f] The two compounds were separated by column chromatography. Elution with CH_2Cl_2/MeOH (99:1) gave ester (**3**) (methyl 3α-(1'α-hydroxyethyl)-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine-1β-carboxylate); mp 175-176°C (MeOH) IR: 1720 (C=O); ^{1}H-NMR: see Chart 1; MS: 328 (M^+, 100), 327 (78), 283 (67), 184 (55), 170 (98), 169 (79); HRMS: calcd for $C_{19}H_{24}N_2O_3$: 328.1787, found: 328.1796. Elution with CH_2Cl_2/MeOH (98:2) gave ester (**4**) (methyl 3α-(1'β-hydroxyethyl)-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine-1β-carboxylate); mp 171-172°C (MeOH); IR: 1715 (C=O); ^{1}H-NMR: see Chart 1; MS: 328 (M^+, 100), 327 (85), 283 (63), 184 (98), 170 (90), 169 (74); HRMS: calcd for $C_{19}H_{24}N_2O_3$: 328.1787, found: 328.1786.

Lactone (5). A solution of sodium methoxide in MeOH was prepared from sodium (13.2 mg, 0.57 mmol) and methanol (6 mL). Ester (**3**) (30.2 mg, 0.09 mmol) was added and the mixture was refluxed for 19 h. After evaporation of the solvent the residue was dissolved in 32% aq HCl (5 mL) and the mixture was heated at 55-60°C for 3 h. The cooled mixture was basified with sat. aq $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4) and evaporated and the residue was subjected to column chromatography (CH_2Cl_2/MeOH, 99:1) to give 2.7 mg (10%) of amorphous lactone (**5**) (3α-(1'α-hydroxyethyl)-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine-1α-carboxylic acid lactone); IR: 1720 (C=O); ^{1}H-NMR: see Chart 1; MS: 296 (M^+, 76), 295 (100), 223 (13), 184 (22), 169 (26); HRMS: calcd for $C_{18}H_{20}N_2O_2$: 296.1525, found: 296.1520.

Lactone (6). As described for lactone (**5**), ester (**4**) (33.2 mg, 0.10 mmol) was reacted with sodium (13 mg, 0.57 mmol) in MeOH (6 mL) and then treated with 32% HCl (5 mL) to give 3.0 mg (10%) of amorphous lactone (**6**) (3α-(1'β-hydroxyethyl)-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine-1β-carboxylic acid lactone); IR: 1720 (C=O); ^{1}H-NMR: see Chart 1; MS: 296 (M^+, 75), 295 (100), 223 (13), 184 (15), 182 (17), 169 (27); HRMS: calcd for $C_{18}H_{20}N_2O_2$: 296.1525, found: 296.1530.

Ester (7). A solution of sodium methoxide in MeOH was prepared from sodium (13.2 mg, 0.57 mmol) and methanol (6 mL). Ester (**3**) (30.2 mg, 0.09 mmol) was added and the mixture was refluxed for 19 h. After evaporation of the solvent, MeOH saturated with dry HCl (6 mL) was added and this mixture was stirred for 16 h. MeOH was evaporated, sat. aq $NaHCO_3$ was added to the residue and the mixture was extracted with CH_2Cl_2. Drying (Na_2SO_4) and evaporation gave the crude product, which was purified by column chromatography. Elution with CH_2Cl_2/MeOH (98:2) gave 5.4 mg (18%) of the starting ester (**3**). Further elution with CH_2Cl_2/MeOH (97:3) furnished 15.2 mg (50%) of ester (**7**) (methyl 3α-(1'α-hydroxyethyl)-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine-1α-carboxylate); mp 147-148°C (MeOH) (obtained after predrying at 70°C for 4 h); IR: 1715 (C=O); ^{1}H-NMR: 8.89 (br s, 1H, N-H), 7.48-7.06 (m, 4H, arom.), 4.67 (br s, 1H, H-12b), 3.83 (s, 3H, COOMe), 3.42 (dq, 1H, J = 6.5 and

6.5, -C*H*(OH)Me), 1.11 (d, 3H, J = 6.5, -CH(OH)*Me*); MS: 328 (M^+, 100), 327 (92), 283 (67), 184 (60), 170 (95), 169 (68); HRMS: calcd for $C_{19}H_{24}N_2O_3$: 328.1787, found: 328.1774. Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.32; H, 7.25; N 8.37.

Ester (8). As described for compound (**7**), ester (**4**) (30.4 mg, 0.09 mmol) was reacted with sodium (12.4 mg, 0.54 mmol) in MeOH (6 mL) and then treated with sat. HCl_g/MeOH (6 mL) to give 3.9 mg (13%) of the starting ester (**4**) and 18.4 mg (60%) of ester (**8**) (methyl 3α-(1'β-hydroxyethyl)-1,2,3,4,6,7,12,12bβ-octahydroindolo[2,3-*a*]quinolizine-1α-carboxylate); mp 165-166°C (MeOH); IR: 1710 (C=O); ^{1}H-NMR: 8.82 (br s, 1H, N-H), 7.49-7.06 (m, 4H, arom.), 4.68 (br s, 1H, H-12b), 3.85 (s, 3H, COOMe), 3.38 (dq, 1H, J = 7 and 6.5, -C*H*(OH)Me), 1.13 (d, 3H, J = 6.5, -CH(OH)*Me*); MS: 328 (M^+, 100), 327 (96), 283 (63), 184 (66), 170 (93), 169 (65); HRMS: calcd for $C_{19}H_{24}N_2O_3$: 328.1787, found: 328.1796. Anal. Calcd for $C_{19}H_{24}N_2O_3$: C, 69.49; H, 7.37; N, 8.53. Found: C, 69.35; H, 7.31; N 8.40.

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