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NITROGEN ASSISTED ACETAL RING CLEAVAGE. PART III[#]. SYNTHESIS AND REACTIONS OF 1-FORMYL-3,4,6,7,12,12b-HEXAHYDROINDOLO[2,3-a]QUINOLIZINE

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Abstract: The synthesis of 1-formyl-3,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine 4 and its use as an intermediate for desethyl eburnamine-vincamine alkaloids are described.

Synthetic routes to 1-formylindolo[2,3-a]quinolizidines, useful intermediates in the synthesis of eburnamine-vincamine type indole alkaloids, have recently been reported[2-5]. The reactivity of the aldehyde group has been successfully utilised in creating the fifth ring (ring E)[6]. The behaviour of cyclic 3-substituted tetrahydropyridine acetals[7] under the modified Polonovski reaction conditions was reported in our earlier paper[1]. Here we describe an application of the reaction towards the construction of the pentacyclic eburnamine-vincamine skeleton[8].

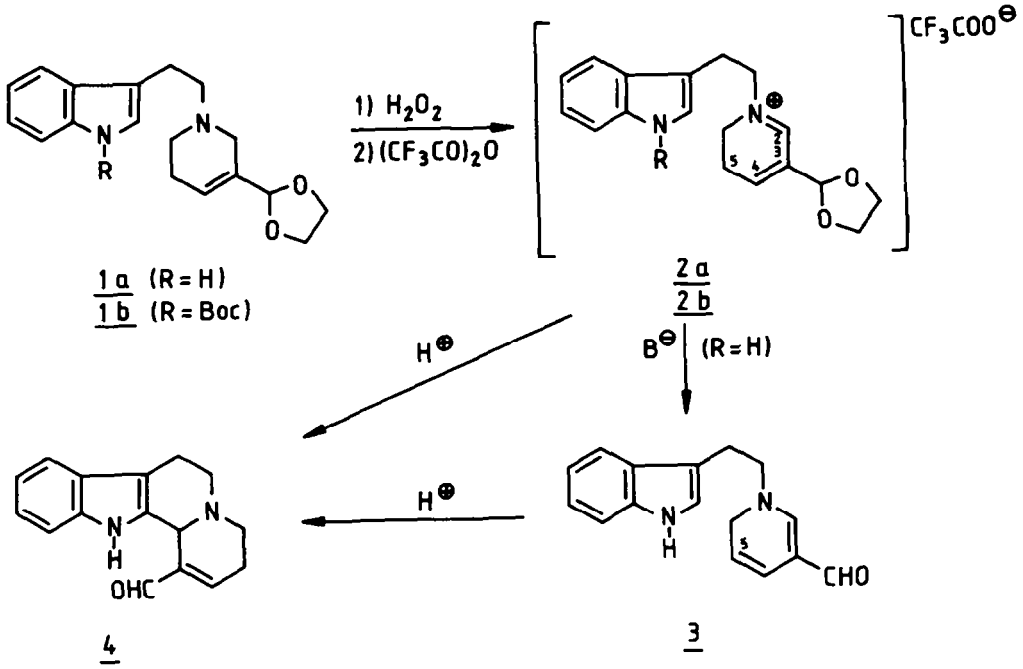
RESULTS AND DISCUSSION

The acid-induced cyclisation of the iminium intermediate 2b (derived from the tetrahydropyridine 1b (R=Boc)) in methanol (acting as a nucleophile) gives methoxy group containing products[1]. In the present synthesis of the tetracyclic aldehyde 4 (Scheme 1), it was desirable to prevent external nucleophilic attacks and the cyclisation of 2 was carried out with hydrogen chloride in ether solvent under carefully controlled conditions.

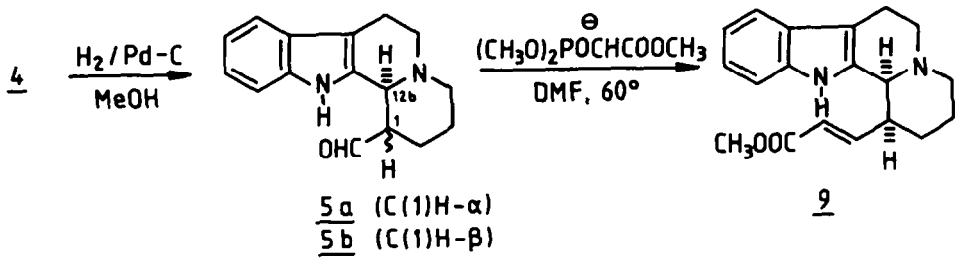
Another route to the aldehyde 4 was available as well. The proton at the 5-position of the piperidine ring of 2a (R=H) was abstracted with a base (e.g. NaH), after which the nitrogen assisted acetal ring cleavage was induced by way of our earlier proposed mechanism[1,9], giving the carbonyl group stabilized dihydropyridine 3 (=vinylogous amide, Scheme 1). This relatively stable dihydropyridine product was subsequently cyclised with acid to 4, since, as expected, the protonation occurred at the 5-position of the dihydropyridine ring.

Further transformations of the tetracyclic unsaturated aldehyde 4 (1-formyl-3,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine) were performed as depicted in Scheme 2. The aldehyde 4 was hydrogenated in the usual manner (Pd-C, MeOH) to a mixture of epimers 5a (major) and 5b (minor) in nearly quantitative yield. The relative configuration at C(1) was deduced as follows. The known 1-carbomethoxy derivative 6, which has the C(12b)H - C(1)H *trans* configuration[10], was reduced with $LiAlH_4$ and the formed alcohol acetylated (to ensure solubility in $CDCl_3$) to yield acetate 7 as shown in Scheme 3. When the same procedure was performed with the mixture of isomers 5a and 5b, the acetate ester 8 with the C(12b)H - C(1)H *cis* configuration was obtained as the major product, in addition to 7 as the minor product. Thus, the C(12b)H - C(1)H configuration of the aldehyde isomer 5a was determined to be *cis*.

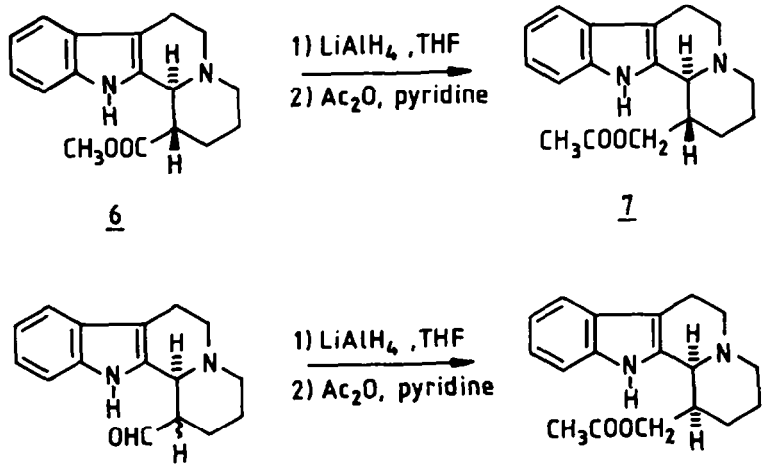
[#]For Part II, see Ref. 1.



Scheme 1



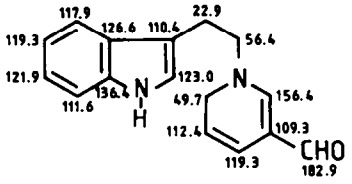
Scheme 2



Scheme 3

The Wittig-Horner reaction[2] of aldehyde 5a with the anion derived from trimethyl phosphonoacetate gave the methyl acrylate 9 as the only isomer. The unsaturated aldehyde 4 was not reactive under these conditions, probably due to an interaction between the formyl group and the indole NH group. Several methods to convert compounds possessing the structure 9 (or its dihydro derivative) to the pentacyclic skeleton present in eburnamine-vincamine alkaloids are available in the literature[2,6].

The present method provides a convenient alternative to the synthesis of 1-formylindolo[2,3-a]-quinolizidines, which are important synthetic intermediates but rather difficult to prepare.



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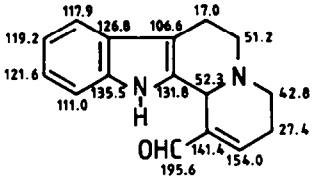

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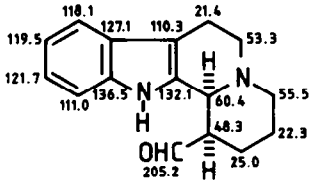
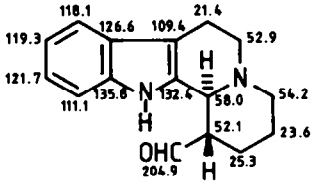


5a



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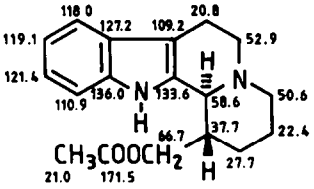

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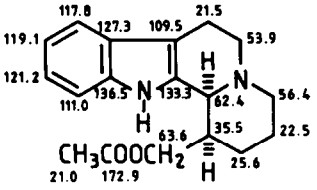

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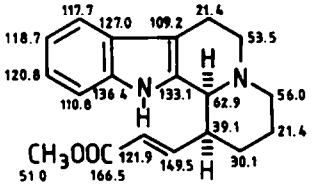

9

Fig. 1.

EXPERIMENTAL

All reactions were carried out under argon. DME, DMF, THF and CH_2Cl_2 were distilled from CaH_2, diethyl ether was sodium-dried. In preparative column chromatography Silica Woelm TSC (act III) or Alumina Woelm TSC (act III) was used.

High performance liquid chromatography was performed with a Waters PrepLC/System 500 A apparatus and PrepPAK-500/silica columns.

The IR spectra ($CHCl_3$, 1/cm) were recorded with a Perkin-Elmer 700 spectrometer, and the NMR spectra were measured with a JEOL JNM-FX 60 spectrometer working at 59.8 MHz (^1H) or 15.04 MHz

(^{13}C) in $CDCl_3$ (δ ppm downfield from TMS). The EI mass spectra (70 eV, m/z) and high resolution mass measurements were obtained with a JEOL JMS-DX303/DA 5000 spectrometer.

1-[2-(3-Indolyl)ethyl]-3-[2-(1,3-dioxolanyl)]-1,2,5,6-tetrahydropyridine 1a: 1-[2-(3-Indolyl)-ethyl]-3-[2-(1,3-dioxolanyl)]-pyridinium bromide (2.6 g) (prepared in the usual manner from pyridine-3-carbaldehyde acetal[11] and tryptophyl bromide: yield 97%, mp. 178-9°C) was dissolved in EtOH (30 ml) and cooled on an ice bath, after which excess $NaBH_4$ (0.6 g) was added portionwise over a period of 15 min. Stirring was continued at rt for 1 h. Most of the solvent was evaporated, water was added and the solution was extracted with CH_2Cl_2. After drying and evaporation compound 1a was separated from the more polar side product (see Ref. 9, compound 4b) by HPLC (eluent: petroleum ether/EtOAc/EtOH/Et_3N, 4.5:4.5:1:0.05) to yield 0.90 g (44%) of a white foam (for spectral data, see Ref. 9, compound 9).

1-(2-(3-(1-t-Butoxycarbonyl)indolyl)ethyl)-3-[2-(1,3-dioxolanyl)]-1,2,5,6-tetrahydropyridine 1b: Tetrahydropyridine 1a (R=H) (0.79 g, 2.7 mmol) was dissolved in CH_2Cl_2 (30 ml), and di-tert-butyl dicarbonate (0.64 g, 2.9 mmol) and dimethylaminopyridine (0.04 g, 0.3 mmol) were added. After 1 h stirring at rt TLC showed that the reaction was complete. The solvent was evaporated and the product was purified by chromatography on silica (eluent: CH_2Cl_2/MeOH, 99:1) to furnish 1.00 g (95%) of tetrahydropyridine 1b (R=Boc) as a pale yellow viscous oil.
IR: 2950, 1720.
^1H NMR: 8.10 (1H, m), 7.5-7.1 (4H, m), 5.97 (1H, br s), 5.17 (1H, s), 3.90 (4H, s), 1.64 (9H, s).
^{13}C NMR: 149.5 (s), 135.2 (s), 133.4 (s), 130.4 (s), 125.4 (d), 124.0 (d), 122.4 (d), 122.1 (d), 118.7 (s), 118.7 (d), 114.9 (d), 104.6 (d), 83.0 (s), 64.9 (t, 2C), 57.8 (t), 49.7 (t, 2C), 28.0 (q, 3C), 25.5 (t), 22.8 (t).
MS: 398 (M^+, 5), 169 (11), 168 (100); exact mass: 398.2210 (calc. for $C_{23}H_{30}N_2O_4$: 398.2206).

N-oxide: N-Boc tetrahydropyridine 1b (0.94 g, 2.36 mmol) was treated with aq H_2O_2 (1.5 ml) in $CHCl_3$/EtOH (1:1, 20 ml) at 60°C for 16 h. Excess peroxide was destroyed by the addition of 10% Pd/C (50 mg) and stirring was continued at 60°C for 2 h. After filtration and normal drying procedures 0.89 g (91%) of a white hygroscopic solid was obtained. This was immediately used for the next step.

1-Formyl-3,4,6,7,12,12b-hexahydroindolo[2,3-a]quinolizine 4: The N-oxide described above (0.65 g, 1.57 mol) was dissolved in dry CH_2Cl_2, cooled below 0°C and trifluoroacetic anhydride (0.55 ml, 3.9 mmol) was added dropwise over a period of 15 min. Stirring was continued at 0°C for 1 h and at rt for 15 min. After evaporation of the solvent in vacuo (bath temp 15°C) the dark red iminium intermediate was immediately subjected to acid treatment. The iminium salt was suspended in dry diethyl ether (60 ml) that was presaturated with dry HCl gas (a small amount of CH_2Cl_2 was used to dissolve the formed precipitate). After 1 h stirring at rt a complete conversion to the dihydropyridine 3 was observed (TLC-MS analysis). Because the cyclisation of 3 to the desired aldehyde 4 was not fast enough in this medium, the solvent was changed to 1,2-dimethoxyethane (DME), likewise presaturated with dry HCl gas. Stirring was continued at 60°C for 16 h. Work-up was achieved by neutralisation with solid $NaHCO_3$, evaporation and filtration through a short alumina column (CH_2Cl_2/MeOH, 95:5). Aldehyde 4 (0.19 g, 48%) was obtained as a brown solid. Direct heating of the acidic iminium intermediate solution led to unwanted side products[12] and lowered the yield. Prolonged heating also yielded unidentified polar material as a consequence of the instability of the aldehyde product.
IR: 3350, 2950, 1670, 1590.
^1H NMR: 9.57 (1H, s), 8.48 (1H, br s), 7.5-7.0 (4H, m), 5.83 (1H, m), 5.07 (1H, br s).
^{13}C NMR: see Fig. 1.
MS: 252 (M^+, 100), 251 (42), 223 (38); exact mass: 252.1279 (calc. for $C_{16}H_{16}N_2O$: 252.1263).

Formation of 1-[2-(3-indolyl)ethyl]-5,6-dihydropyridine-3-carbaldehyde 3 under alkaline conditions: The N-oxide derived from tetrahydropyridine 1a (R=H) (0.25 g, 0.80 mmol) was treated with trifluoroacetic anhydride as above, the solvent was evaporated and the residue was dissolved in dry DME. An excess of NaH (50 mg) was added portionwise to the solution and the mixture was stirred at 40°C overnight. Water was added and the aqueous solution was extracted with CH_2Cl_2. The residue obtained after drying and evaporation of the solvent was chromatographed on silica (eluent: CH_2Cl_2/MeOH, 95:5) to yield 48 mg (24%) of product 3 as a red-yellow amorphous solid.
IR: 3350, 2950, 1625, 1580.
^1H NMR: 9.07 (1H, br s), 8.37 (1H, br s), 7.5-7.0 (4H, m), 6.94 (1H, d), 6.35 (1H, br s), 6.34 (1H, d, J = 10 Hz), 5.11 (1H, d, J = 10 Hz).
^{13}C NMR: see Fig. 1.
MS: 252 (M^+, 100), 144 (55), 143 (20), 130 (52), 122 (20); exact mass: 252.1258 (calc. for $C_{16}H_{16}N_2O$: 252.1263).

Cyclisation of 3: Dihydropyridine 3 (48 mg, 0.19 mmol) was cyclised in DME/HCl as described above to afford 22 mg (46%) of aldehyde 4.

1-Formyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizines 5a and 5b: The unsaturated aldehyde 4 (70 mg, 0.28 mmol) was hydrogenated in MeOH with Pd/C (20 mg) as catalyst for 3 h. After usual work-up a mixture (70 mg, 99%) of two isomers 5a (major) and 5b (minor) (ca. 3:1) was obtained. The isomers were separated by preparative TLC on silica [CH_2Cl_2/MeOH, 90:10; 5a, R_f 0.35; 5b, R_f 0.25].
Compound 5a:
IR: 3300, 2960, 2890, 2790, 1715.
^1H NMR: 9.42 (1H, s), 8.63 (1H, br s), 7.5-7.0 (4H, m).
^{13}C NMR: see Fig. 1.
MS: 254 (M^+, 92), 253 (100), 225 (21), 197 (48), 170 (43), 169 (45); exact mass: 254.1415 (calc. for $C_{16}H_{18}N_2O$: 254.1419).

Compound 5b:
IR: 3300, 2960, 2875, 2830, 2770, 1710.
^{1}H NMR: 9.69 (1H, s), 8.28 (1H, br s), 7.5-7.0 (4H, m).
^{13}C NMR: see Fig. 1.
MS: 254 (M^+, 96), 253 (100), 225 (29), 197 (57), 170 (80), 169 (74), 168 (68); exact mass: 254.1423 (calc. for $C_{16}H_{18}N_2O$: 254.1419).

1α-Acetoxymethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine 7: $LiAlH_4$ (25 mg, 0.66 mmol) was refluxed in dry THF (10 ml) for 30 min. Ester 6 (54 mg, 0.19 mmol) in dry THF (5 ml) was added dropwise (15 min) to the cooled solution and refluxing was continued for 3 h. Water (10 ml) was added and the solution was extracted with CH_2Cl_2 (5x10 ml). After drying and evaporation 43.0 mg of a white solid alcohol product, homogeneous to TLC, was obtained. The alcohol was dissolved in Ac_2O (5 ml), a drop of pyridine was added and the solution was stirred at rt overnight. Usual work-up yielded 45.5 mg (80% from 6) of the acetate ester 7 as a white amorphous solid.
IR: 3340, 2950, 2870, 2820, 2770, 1720.
^{1}H NMR: 8.70 (1H, br s), 7.5-7.0 (4H, m), 4.58 (1H, dd, J = 12 and 4 Hz), 4.27 (1H, dd, J = 12 and 4 Hz), 3.65 (1H, d, J = 8 Hz), 2.14 (3H, s).
^{13}C NMR: see Fig. 1.
MS: 298 (M^+, 42), 297 (23), 240 (18), 239 (100); exact mass: 298.1685 (calc. for $C_{18}H_{22}N_2O_2$: 298.1681.

1β-Acetoxymethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine 8: The aldehyde mixture of 5a and 5b (34 mg, 0.13 mmol) was reduced with $LiAlH_4$ and the formed alcohols were acetylated as above. A mixture (37 mg, 92%) of 8 and 7 (ca. 3:1) was obtained. Product 8 was separated by column chromatography (silica, CH_2Cl_2/MeOH, 95:5).
IR: 3350, 2950, 2860, 2820, 2760, 1670.
^{1}H NMR: 8.57 (1H, br s), 7.5-7.0 (4H, m), 4.12 (2H, m), 3.47 (1H, d, J = 3 Hz), 1.98 (3H, s).
^{13}C NMR: see Fig. 1.
MS: 298 (M^+, 85), 297 (42), 240 (20), 239 (100); exact mass: 298.1672 (calc. for $C_{18}H_{22}N_2O_2$: 298.1681.

1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-a]quinolizine-1-acrylic acid methyl ester 9: Trimethylphosphonoacetate (0.10 ml, 0.7 mmol) was added to a suspension of NaH (21 mg, 0.7 mmol, washed with dry ether) in 2 ml of DMF at 0°C. After hydrogen evolution had stopped, the aldehyde isomer 5a (88 mg, 0.35 mmol) in 2 ml of DMF was added and the mixture was heated at 60°C for 4 h. The solvent was evaporated under vacuum, water was added and the mixture was extracted with CH_2Cl_2 (4x15 ml). The brown oil obtained after drying and evaporation of the solvent was passed through a short column of silica (eluent CH_2Cl_2) to yield 53 mg (49%) of the methyl acrylate 9.
IR: 3350, 2970, 2870, 2820, 2770, 1730.
^{1}H NMR: 8.84 (1H, br s), 7.45-6.90 (5H, m), 5.86 (1H, d, J = 16 Hz), 3.56 (3H, s).
^{13}C NMR: see Fig. 1.
MS: 310 (M^+, 88), 309 (100), 295 (21), 197 (58), 170 (57), 169 (62); exact mass: 310.1691 (calc. for $C_{19}H_{22}N_2O_2$: 310.1681).

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7. Throughout this work, the term "acetal" refers to the 1,3-dioxolane system (ethylene glycol acetal).
8. Results presented at the 15th IUPAC International Symposium on the Chemistry of Natural Products, 17-22 August 1986, the Hague, the Netherlands.
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10. M. Lounasmaa and C.-J. Johansson, Acta Chem. Scand., Ser. B, 1975, 29, 655.
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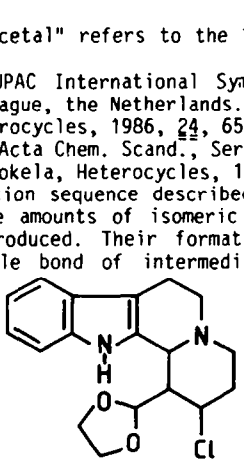
12. The stepwise deprotection/cyclisation sequence described in the Experimental Part was found preferable. Otherwise considerable amounts of isomeric side products 10 (MS, m/z: 334 (8), 332 (M^+, 18), 297 (100) were produced. Their formation can be explained by the direct addition of HCl to the 3,4-double bond of intermediate 2b, either before or after the cyclisation.



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