STEREOSELECTIVITY IN THE PREPARATION OF INDOLO[2,3-a]QUINOLIZIDINE N_b-METHO-SALTS

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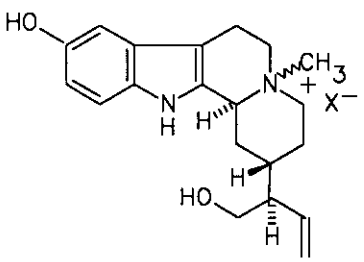
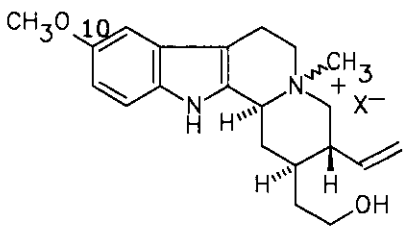
Abstract - Stereoselective preparation of indolo[2,3-a]quinolizidine N_b-metho-salts has been studied. Although the N_b-methylation is a kinetically controlled reaction (preferential methylation at the conformation where the N_b-atom is least hindered), isomeric mixtures were obtained in all cases where the trans-quinolizidine ring juncture (conformation a) of the starting compounds was strongly favoured. This indicates a partial conformational control of the reaction. BOC-protected compounds yielded C(12b)H-N_b-CH_3 cis-products only. Since this stereochemistry is maintained in deprotection, an attractive approach is offered for the stereoselective preparation of the cis-isomers.

Several indole alkaloid metho-salts have been isolated from nature. Both α- and β-N-methyl isomers [C(12b)H-N_b-CH_3 cis- and trans-products, respectively] have been found, e.g., hunterburnine metho-salts (1a) and (1b)[1] and 10-methoxycorynantheol metho-salts (2a) and (2b).[2,3]



1a α –N–CH_3
1b β –N–CH_3

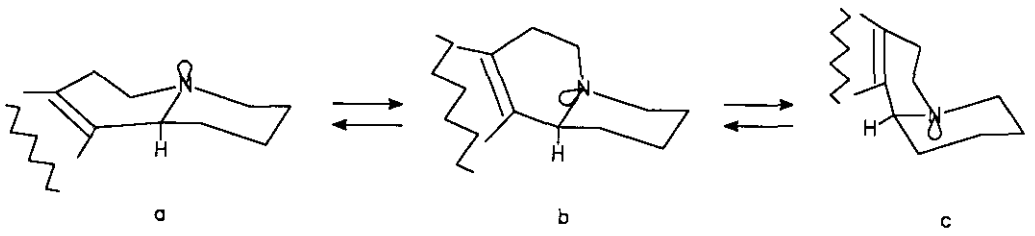


2a α –N–CH_3
2b β –N–CH_3

Although laboratory synthesis of indoloquinolizidine N_b-metho-salts from their corresponding tertiary bases is a straightforward procedure, the stereochemistry of the reaction is difficult to predict. It has long been recognized that the rate of methylation depends on sterical factors: for a given heteroyohimbine derivative, it is the conformer with the least hindered nitrogen atom (vide infra) that preferentially undergoes methylation.[4-6]

An interesting study has been performed by Fujii et al. concerning the stereoselectivity of methylation of quinolizidine derivatives.[7] Strong preference for the formation of cis-isomers was observed, although the conformational equilibrium of the starting amines also had an effect on the product ratio.

In the indoloquinolizidine series, the following conformational equilibrium (Scheme 1) has to be taken into account. The N_b-atom is less hindered in conformations b and c (cis-quinolizidine ring juncture) than in conformation a, thus favouring the formation of cis-isomers. However, when the proportion of conformer a (trans-quinolizidine ring juncture) in the equilibrium is dominant, the formation of isomeric mixtures can be expected.



a b c

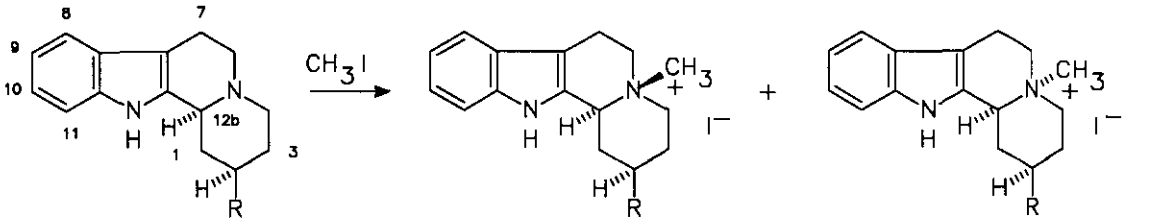
Scheme 1

We recently developed new methods for the stereoselective preparation of indoloquinolizidine N_b-oxides,[8] and in the present work we investigate the applicability of those methods for the preparation of indoloquinolizidine N_b-metho-salts.

RESULTS AND DISCUSSION

The stereoselectivity of the N_b-metho-salt formation was studied for indolo[2,3-a]quinolizidine derivatives (3), (4) and (5). The same experiments were performed with the BOC-protected counterparts (6), (7) and (8).

Mixtures of the C(12b)H-N_b-CH_3 cis- and trans-isomers were obtained when compounds (3) and (4) were treated with CH_3I (Scheme 2).



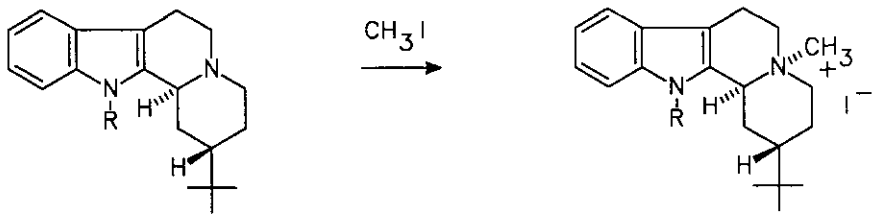
3 R=H
4 R=C(CH$_3$)$_3$

3a R=H
4a R=C(CH$_3$)$_3$

3b R=H
4b R=C(CH$_3$)$_3$

Scheme 2

Separation of the isomeric mixtures (3a,b) and (4a,b) was attempted by crystallisation in various solvents. The less soluble trans-isomers (3a) and (4a) could be obtained in pure form (cf. Experimental), but the cis-isomers (3b) and (4b) were in some degree contaminated with the other isomer.



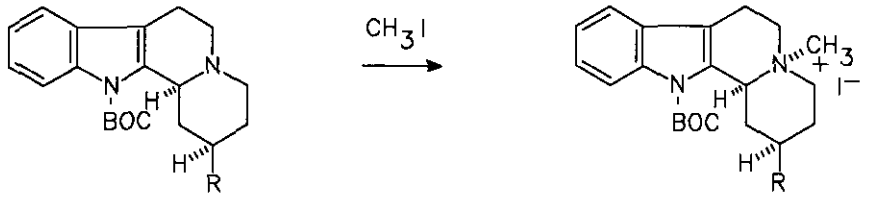
5 R=H
8 R=BOC

5b R=H
8b R=BOC

Scheme 3

The configurations of compounds (5) and (8) favour the formation of cis-isomers (compounds 5b and 8b) (Scheme 3).

The CH_3I-treatment of the BOC-protected compounds (6) and (7) yielded only cis-isomers (6b) and (7b) (Scheme 4). We earlier found similar stereoselectivity in N_b-oxide formation and explained it by conformational differences between the BOC-protected and unprotected compounds.[8]

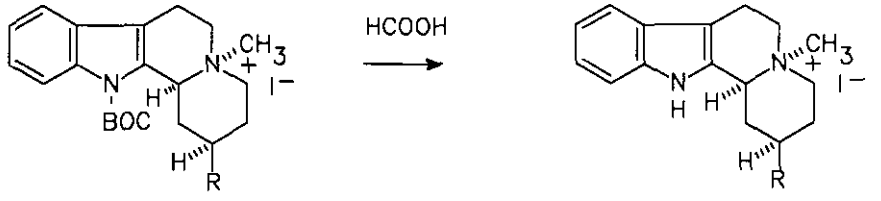


6 R=H
7 R=C(CH3)3

6b R=H
7b R=C(CH3)3

Scheme 4

The stereoselective formation of cis-isomers in the BOC-protected series offers an attractive choice for the preparation of the corresponding unprotected compounds (3b) and (4b). Deprotection of compounds (6b) and (7b) with formic acid yielded compounds (3b) and (4b), respectively, in pure state (Scheme 5).

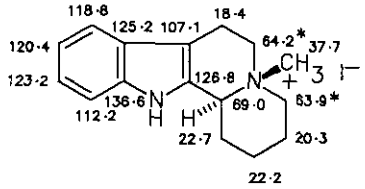


6b R=H
7b R=C(CH3)3

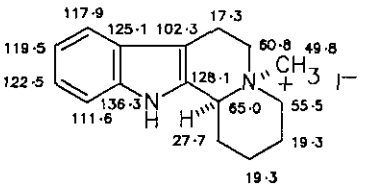
3b R=H
4b R=C(CH3)3

Scheme 5

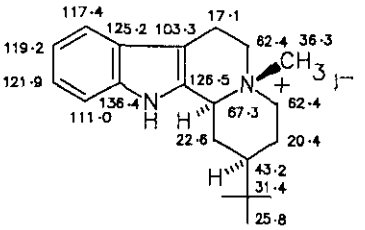
The ^{13}C nmr values depicted in Figure 1 are in good agreement with the proposed configurations. Signals marked in any formula with an asterisk may be interchanged.



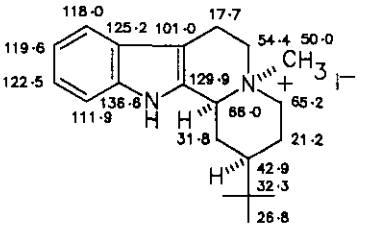
3a



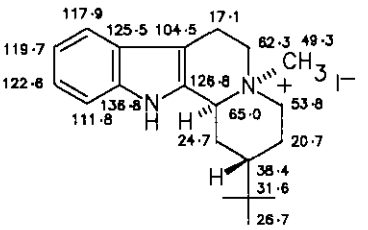
3b



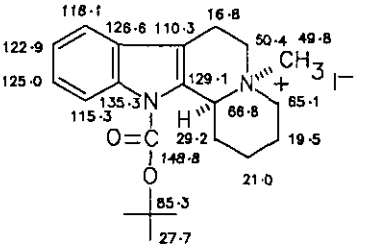
4a



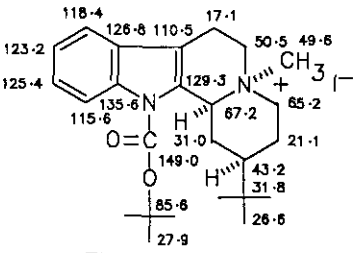
4b



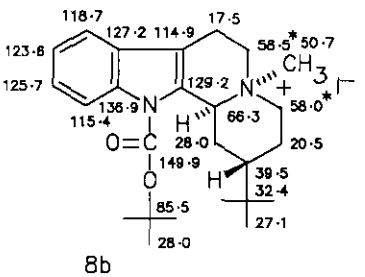
5b



6b



7b



8b

Figure 1

CONCLUSIONS

Although the N_b-methylation of indolo[2,3-a]quinolizidine derivatives is a kinetically controlled reaction (preferential methylation at the

conformation where the N_b-atom is least hindered), isomeric mixtures were obtained in all cases where conformation a (trans-quinolizidine ring juncture) was strongly favoured in the conformational equilibrium (vide supra) of the starting compounds. This points to partial conformational control of the reaction.

BOC-protected compounds yielded C(12b)H-N_b-CH_3 cis-products only. Since the stereochemistry was maintained in deprotection, starting from these compounds offers an attractive approach for the stereoselective preparation of cis-products.

EXPERIMENTAL

Ir spectra were recorded with a Perkin-Elmer 700 spectrophotometer using liquid film between NaCl crystals or KBr tablets. Ir absorption bands are expressed in reciprocal centimetres (cm^{-1}). ^1H and ^{13}C Nmr spectra were measured with a JEOL JNM-FX 60 spectrometer working at 58.80 MHz (^1H Nmr) and 15.04 MHz (^{13}C Nmr). Chemical shift data are given in ppm downfield from TMS. Abbreviations s, d, t, m, and br are used to designate singlet, doublet, triplet, multiplet and broad, respectively. For the ^{13}C Nmr data, see Figure 1.

Preparation of compounds 3a, 3b, 4a, 4b, 5b, 6b, 7b, and 8b

General procedure: 0.5 mmol of the corresponding indoloquinolizidine (compound 3, 4, 5, 6, 7, or 8; for the preparation, see ref. 9) was dissolved in 6 ml of CH_3CN. CH_3I (0.6 ml) was added and the mixture was stirred overnight at room temperature. Evaporation yielded either mixtures of isomeric metho-salts (compounds 3a and 3b, and 4a, and 4b) or pure cis-isomers (compounds 5b, 6b, 7b, and 8b).

Compounds 3a and 3b
Yield: 98% (3a:3b = 1:1).
The components (3a) and (3b) were separated by crystallisation with EtOH, compound (3a) being obtained as a white precipitate and (3b) as the more soluble isomer.
Compound 3a
mp 231°C (EtOH) (partial melting and resolidification at 155-165°C).

^{1}H Nmr (MeOH-d_4): 2.95 (3H, s, NCH_3), 6.80 - 7.60 (4H, m, H-8, 9, 10, 11) (cf. Note 10). Anal. Calcd for $C_{16}H_{21}N_2I$: C, 52.18; H, 5.75; N, 7.61. Found: C, 52.32; H, 5.76; N, 7.58.

Compound 3b (slightly contaminated with 3a)

mp 198-201°C (EtOH).

For the analytical data of pure compound 3b, see below.

Compounds 4a and 4b

Yield: 92% (4a:4b = 1:1).

The components (4a) and (4b) were separated by crystallisation with EtOH, compound (4a) being obtained as a white precipitate and (4b) as the more soluble isomer.

Compound 4a

mp 277°C (EtOH).

^{1}H Nmr ($CDCl_3$ + MeOH-d_4; 4:1): 1.03 [9H, s, $-C(CH_3)_3$], 2.87 (3H, s, NCH_3), 4.56 (1H, br s, H-12b), 7.05 - 7.60 (4H, m, H-8, 9, 10, 11). Anal. Calcd for $C_{20}H_{29}N_2I$: C, 56.61; H, 6.89; N, 6.60. Found: C, 57.16; H, 7.22; N, 6.63.

Compound 4b (slightly contaminated with 4a)

Amorphous material.

For the analytica data of pure compound 4b, see below.

Compound 5b

Yield: 100%. mp 212-214°C (EtOH/hexane).

^{1}H Nmr ($CDCl_3$ + 4 drops of MeOH-d_4): 0.90 [9H, s, $-C(CH_3)_3$], 3.50 (3H, s, NCH_3), 4.86 (1H, br s, H-12b), 7.00 - 7.75 (4H, m, H-8, 9, 10, 11), 10.46 (1H, br s, NH). Anal. Calcd for $C_{20}H_{29}N_2I$: C, 56.61; H, 6.89; N, 6.60. Found: C, 56.03; H, 6.94; N, 6.30.

Compound 6b

Yield: 100%. mp 182-183°C (EtOH/hexane).

Ir: 1730 (C=O). ^{1}H Nmr ($CDCl_3$): 1.73 [9H, s, $-OC(CH_3)_3$], 3.47 (3H, s, NCH_3), 5.14 (1H, br d, J=8.4 Hz, H-12b), 7.15 - 7.65 (3H, m, H-8, 9, 10), 8.08-8.18 (1H, m, H-11). Anal. Calcd for $C_{21}H_{29}N_2O_2I$: C, 53.85; H, 6.24; N, 5.98. Found: C, 53.83; H, 6.23; N, 5.98.

Compound 7b

Yield: 100%. Amorphous material.

Ir: 1730 (C=O). ^{1}H Nmr ($CDCl_3$): 0.92 [9H, s, $-C(CH_3)_3$], 1.73 [9H, s,-$OC(CH_3)_3$], 3.56 (3H, s, NCH_3), 5.08 (1H, br d, J=10.2 Hz, H-12b), 7.20-7.55 (3H, m, H-8, 9, 10), 7.96 - 8.20 (1H, m, H-11). Anal. Calcd for

$C_{25}H_{37}N_2O_2I$: C, 57.25; H, 7.11; N, 5.34. Found: C, 56.76; H, 7.01; N, 5.31.

Compound 8b
Yield: 98%. Amorphous material.
Ir: 1730 (C=O). ^1H Nmr ($CDCl_3$): 0.93 [9H, s, $-C(CH_3)_3$], 1.69 [9H, s,-$OC(CH_3)_3$], 3.65 (3H, s, NCH_3), 5.29 (1H, br s, H-12b), 7.15 - 7.60 (3H, m, H-8, 9, 10), 7,87 - 8.16 (1H, m, H-11). Anal. Calcd for $C_{25}H_{37}N_2O_2I$: C, 57.25; H, 7.11; N, 5.34. Found: C, 57.00; H, 7.40; N, 5.06.

Preparation of compounds 3b and 4b

General procedure: 0.1 mmol of the corresponding BOC-protected metho-salt (compound 7b or 6b) was stirred with 5 ml of HCOOH for 1 day and the solution was evaporated to dryness.

Compound 3b (prepared from compound 7b)
Yield. 100%. mp 218-219°C (EtOH/hexane).
^1H Nmr ($CDCl_3$ + 4 drops of MeOH-d_4): 3.22 (3H, s, NCH_3), 4.83 (1H, br s, H-12b), 7.05 - 7.75 (4H, m, H-8, 9, 10, 11), 10.37 (1H, br s, NH). Anal. Calcd for $C_{16}H_{21}N_2I$: C, 52.18; H, 5.75; N, 7.61. Found: C, 51.94; H, 5.55; N, 7.51.

Compound 4b (prepared from compound 6b)
Yield. 100%. mp 243-245°C (EtOH/hexane).
^1H Nmr ($CDCl_3$ + 4 drops of MeOH-d_4): 0.92 [9H, s, $-C(CH_3)_3$], 3.32 (3H, s, NCH_3), 5.16 (1H, br d, J=8.4 Hz, H-12b), 6.90 - 7.60 (4H, m, H-8, 9, 10, 11). Anal. Calcd for $C_{20}H_{29}N_2I$: C, 56.61; H, 6.89; N, 6.60. Found: C, 56.02; H, 6.77; N, 6.45.

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10. The mixture of isomers (3a) and (3b) can be analysed in $CDCl_3$ (containing a small amount of MeOH-d_4) in spite of the poor solubility of pure (3a) in $CDCl_3$.

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