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STEREOREGULATION OF THE C(12b)H-C(2)H RELATIONSHIP IN THE PREPARATION OF 2-SUBSTITUTED 1,2,3,4,6,7,12,12b-OCTAHYDRO-INDOLO[2,3-a]QUINOLIZINES

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Abstract - Stereochemical control in the preparation of 2-substituted 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizines possessing at will the C(12b)H-C(2)H *cis* or *trans* configuration was achieved by catalytic reduction of the 2,3-dehydro analoques, which were either unsubstituted on the indole nitrogen or substituted with a BOC-group, respectively. The contribution of different conformations to the conformational equilibrium of the prepared compounds was estimated by ^{13}C NMR spectral analysis.

The preparation of 2-substituted 1,2,3,4,6,7,12,12b-octahydroindolo-[2,3-a]quinolizines possessing the desired C(12b)H-C(2)H relationship[1] (*cis* or *trans*) is not always straightforward and often necessitates epimerizations at C(12b) after the formation of the indoloquinolizidine skeleton. One frequently used method consists of transforming 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizines to the corresponding iminium species (C(12b)-N_b) and then reducing this species.[2-8] Another generally used method, when applicable, is acid-catalyzed C(12b) epimerization.[9-12] Unfortunately, all the methods involving epimerization in a later step reduce the yield of the final product, often in considerable amount.

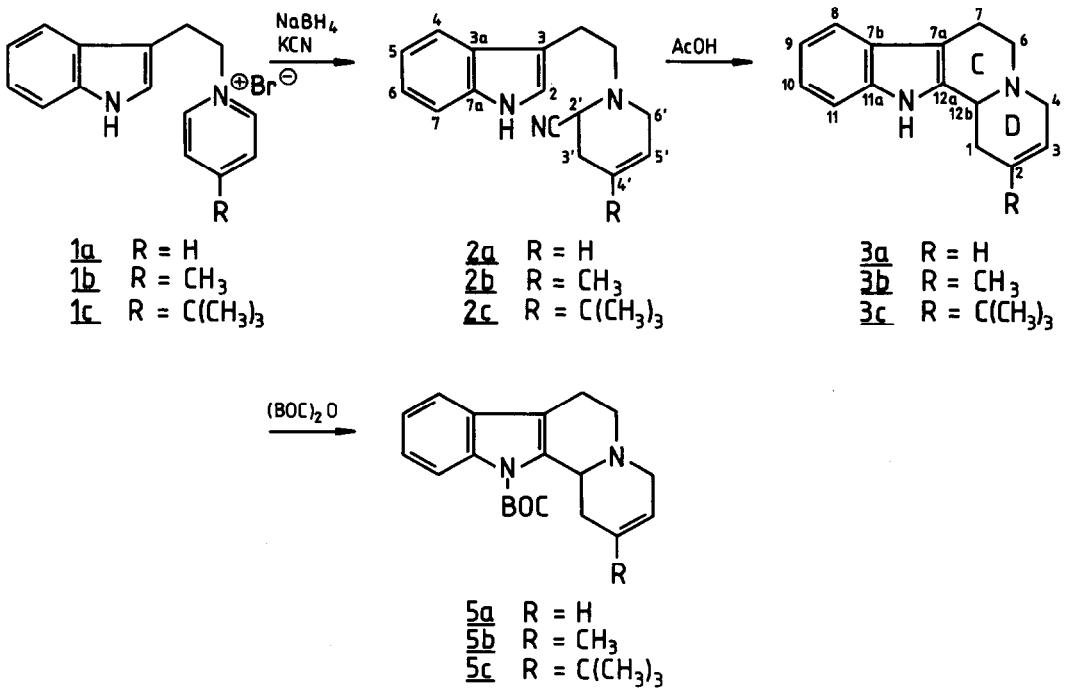
Stereoselective preparations of stereochemical pairs of 2-substituted 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizines have been described,[4,13,14] but only where different starting compounds and different reaction paths were used. Moreover, several methods are known[4,13,15] for

the simultaneous preparation of both stereoisomers [C(12b)H-C(2)H cis and trans], but separation procedures are required and yields often lowered.

We have developed a new method which permits choice of the C(12b)H-C(2)H relationship (cis or trans) in 2-substituted 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizines with a high degree of stereoselectivity, starting from the same compound. In the present paper we describe the application of our method to the preparation of the 2-methyl- and 2-t-butylindolo[2,3-a]quinolizidines 4b, 7b, 4c and 7c.

RESULTS AND DISCUSSION

Alkylation of appropriate pyridines with tryptophyl bromide[16] yielded pyridinium salts 1a, 1b and 1c, which, by $NaBH_4$-reduction and cyanide trapping,[17-20] were transformed to α-aminonitriles 2a, 2b and 2c, respectively. Treatment of 2a, 2b and 2c with AcOH yielded indolo[2,3-a]-quinolizidines 3a, 3b and 3c[21-23]. A part of the compounds 3a, 3b and 3c was treated with di-t-butyl dicarbonate [$(BOC)_2O$][20,24,25] leading to the corresponding BOC-protected indolo[2,3-a]quinolizidines 5a, 5b and 5c (Scheme 1)[20].



1a R = H
1b R = CH_3
1c R = $C(CH_3)_3$

2a R = H
2b R = CH_3
2c R = $C(CH_3)_3$

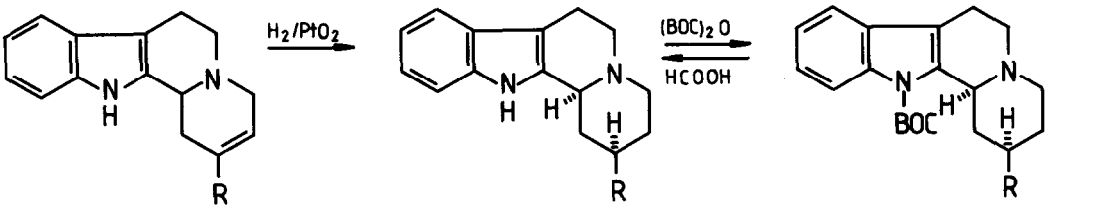
3a R = H
3b R = CH_3
3c R = $C(CH_3)_3$

5a R = H
5b R = CH_3
5c R = $C(CH_3)_3$

Scheme 1

Catalytic hydrogenation of compounds like 3b and 3c, possessing a $\Delta^{2(3)}$ double bond is reported to lead in about 95% yield to compounds 4b and 4c, which possess the C(12b)H-C(2)H cis configuration.[4] We fully confirm these results completed by the reduction of compound 3a to compound 4a (Scheme 2).

Compounds 4a, 4b and 4c were transformed to the corresponding BOC-protected compounds 8a, 8b and 8c by $(BOC)_2O$ treatment. We also verified that acid-induced cleavage (HCOOH) of the protective BOC-group leads back to the initial non-protected compounds 4a, 4b and 4c (Scheme 2).



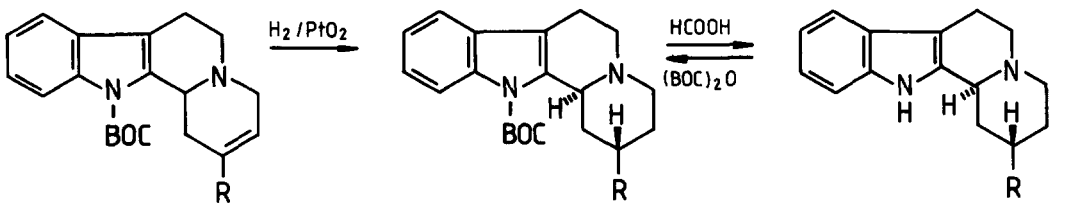
3a R = H
3b R = CH_3
3c R = $C(CH_3)_3$

4a = 7a R = H
4b R = CH_3
4c R = $C(CH_3)_3$

8a = 6a R = H
8b R = CH_3
8c R = $C(CH_3)_3$

Scheme 2

In contrast to these results, we have found catalytic hydrogenation of the corresponding BOC-protected compounds 5a, 5b and 5c to lead in about 80% yield to compounds 6a (=8a), 6b and 6c, respectively, of which the 2-substituted compounds 6b and 6c possess the C(12b)H-C(2)H trans



5a R = H
5b R = CH_3
5c R = $C(CH_3)_3$

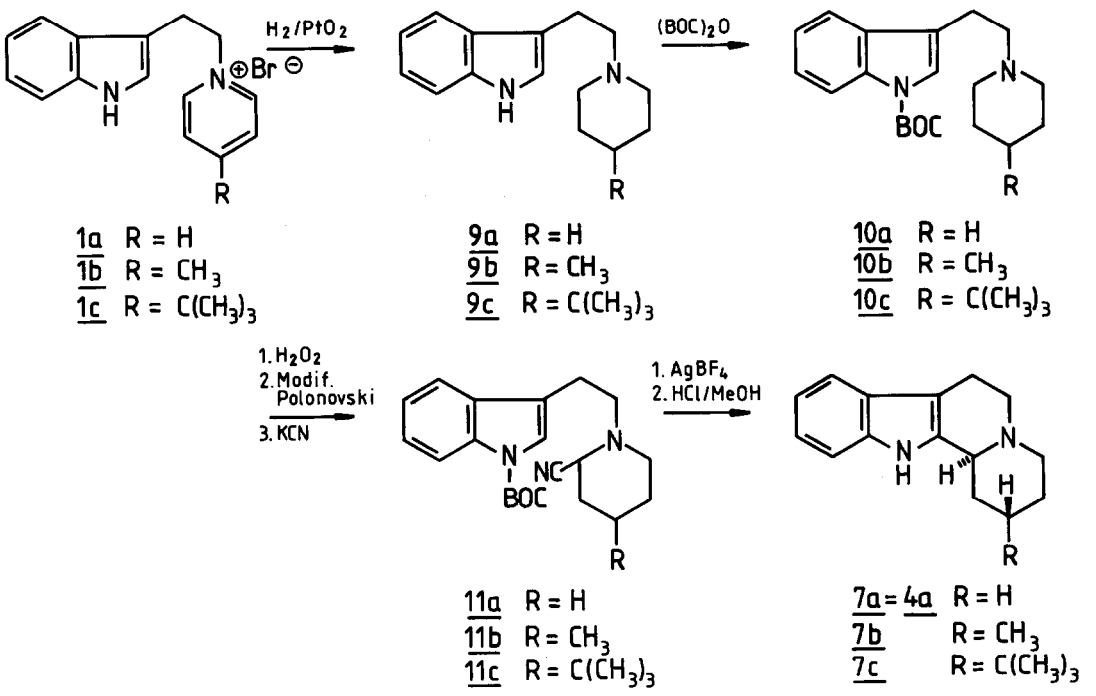
6a = 8a R = H
6b R = CH_3
6c R = $C(CH_3)_3$

7a = 4a R = H
7b R = CH_3
7c R = $C(CH_3)_3$

Scheme 3

configuration. Acid-induced cleavage (HCOOH) of the protective BOC-group afforded in practically quantitative yield the corresponding non-protected compounds 7a (=4a), 7b and 7c. To be sure that a C(12b) epimerization had not taken place during the acid induced cleavage (HCOOH) of the protective BOC-group (vide supra), compounds 7b and 7c were retransformed to compounds 6b and 6c by $(BOC)_2O$ treatment (Scheme 3).

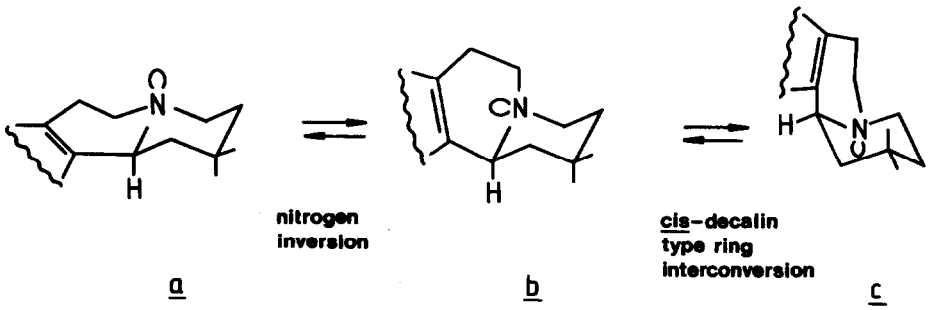
For purposes of comparison and in order to get new and useful ^{13}C NMR data for the intermediates 9a,b,c - 11a,b,c (vide infra), compounds 7a (=4a), 7b and 7c were also prepared by an independent route. Catalytic reduction of compounds 1a, 1b and 1c afforded compounds 9a, 9b and 9c, which were treated with $(BOC)_2O$ to yield the corresponding BOC-protected compounds 10a, 10b and 10c. Using successively H_2O_2 oxidation, modified Polonovski reaction and cyanide trapping, compounds 10a, 10b and 10c were transformed to compounds 11a, 11b and 11c. Finally, treatment of compounds 11a, 11b and 11c first with $AgBF_4$ and then with HCl/MeOH afforded compounds which were in all aspects identical with compounds 7a (=4a), 7b and 7c prepared by our method (vide supra) (Scheme 4).



Scheme 4

Conformational considerations

The 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine system can exist in three conformations with equilibration by nitrogen inversion and cis-decalin type ring interconversion (Scheme 5).[26-28]



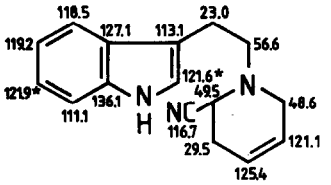
Scheme 5

1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-a]quinolizine itself (compound 4a) exists predominantly in conformation a.[4,5,29-31] The predominance of conformation a should be even more pronounced for compounds 4b and 4c, where the C(2) substituent occupies an axial position in conformation c (equatorial in conformation a). Similarly, for compound 3a, and for compounds 3b and 3c, where the bond between C(2) and C(3) is unsaturated, the predominance of conformation a can be assumed.

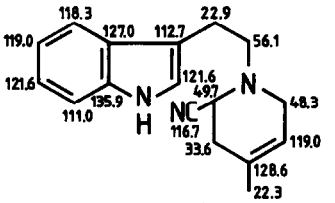
On the other hand, for compounds 7b and 7c, where the C(2) substituent occupies an equatorial position in conformation c (axial in conformation a), the contribution of conformation c to the conformational equilibrium should be more pronounced and might even be totally predominant (cf. compound 7c).

It can be predicted for the BOC-protected compounds 5a, 5b, 5c, 6a (=8a), 6b, 6c, 8b and 8c, that the strong interaction in conformation c between the BOC-group and the D-ring moves the equilibrium in favour of conformation a (vide infra).[20]

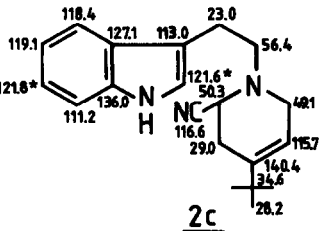
The ^{13}C NMR data of all the compounds formed are given in Fig. 1. The proper shift assignment was confirmed by recording single frequency, off-resonance decoupled (sford) spectra and through reference to the earlier shift assignment.



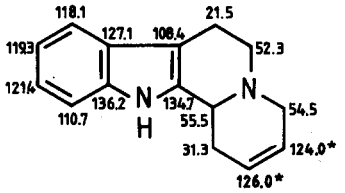
2a



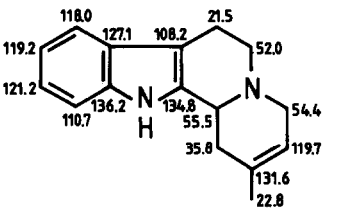
2b



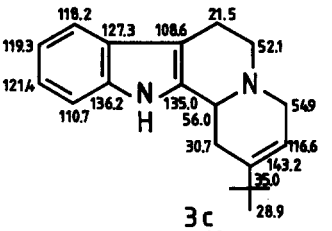
2c



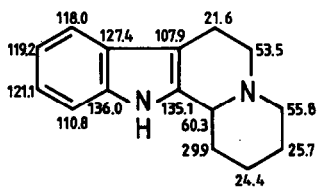
3a



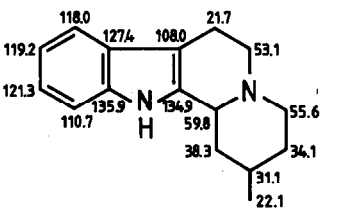
3b



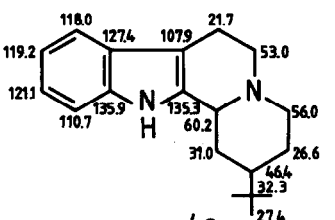
3c



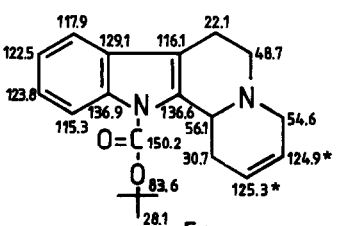
4a = 7a



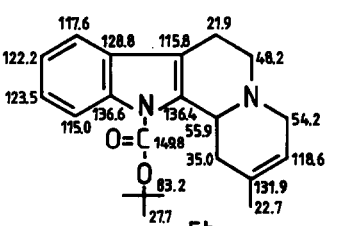
4b



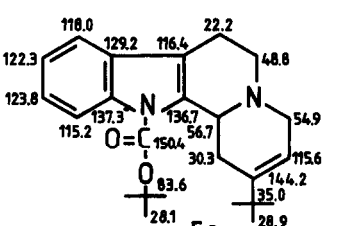
4c



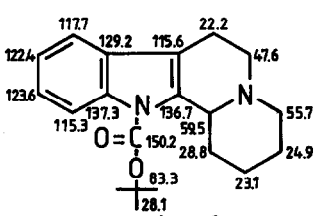
5a



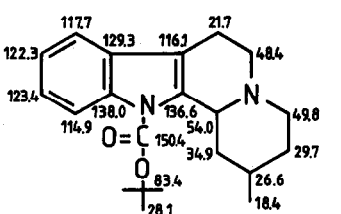
5b



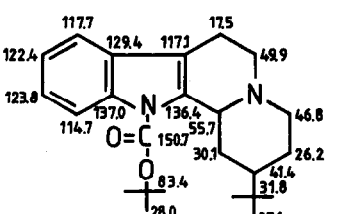
5c



6a = 8a

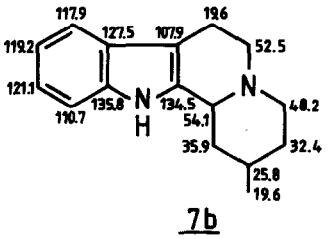


6b

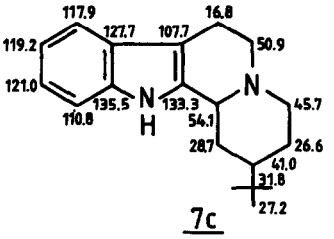


6c

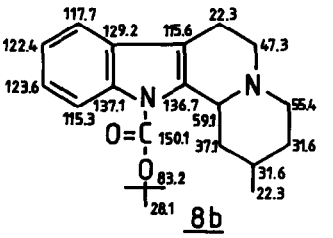
Fig. 1



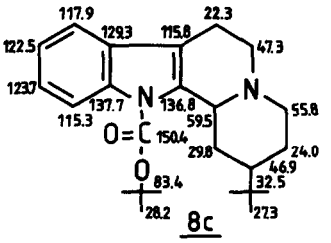
7b



7c



8b



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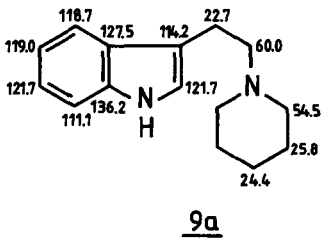
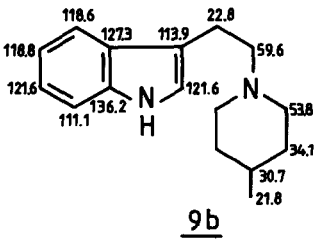


9a



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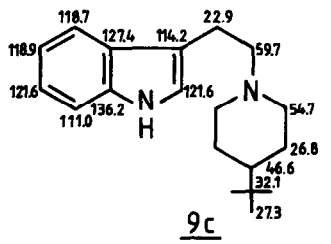

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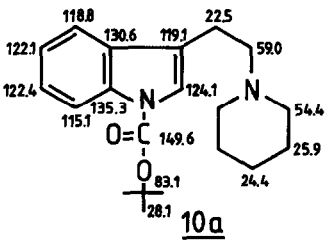
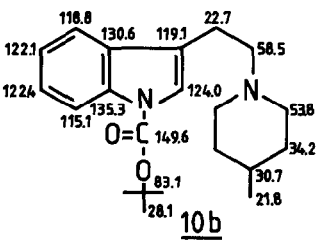


10a



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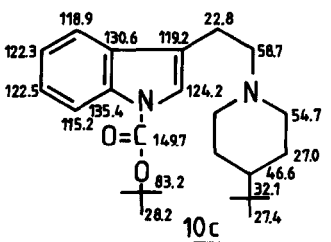

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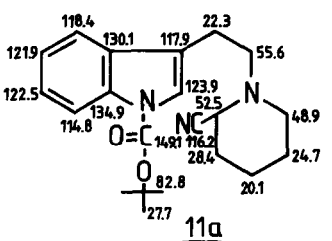
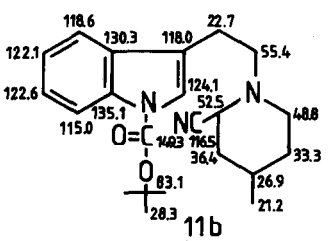


11a



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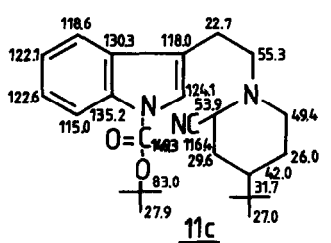

11c

Fig. 1 (continued)

A general comparison of the chemical shifts found for compounds 3b, 3c, 4b, 4c, 5b, 5c, 6b, 6c, 7b, 7c, 8b and 8c with those of their unsubstituted counterparts 4a, 8a, 3a and 5a, taking into account the conformational considerations (vide supra), the shielding effects of the C(2) substituents, and the changes in the shift values especially for C(6), C(7a), C(11) and C(12a) in the BOC-protected compounds compared with the non-protected compounds,[20] provides clear evidence for the stereostructures depicted in the formulae.

The chemical shift of C(7) reflects the contribution of the different conformations to the conformational equilibrium.[6,29,31,32] Taking as a basis the shift values 21.8 and 16.8 ppm, and 22.3 and 16.8 ppm for the non-protected and for the BOC-protected indolo[2,3-a]quinolizidines, respectively, the conformational equilibrium between conformations a and c (the contribution of conformation b is considered negligible) can be estimated with a relatively high degree of accuracy.

The values 21.8 and 16.8 ppm are found for the signals of C(7) in the two possible 2-t-butyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizines (compounds 4c and 7c) where the C(2) t-butyl group, with its overwhelming equatorial preference is used to force the compounds to exist essentially in just one conformation (conformation a or c). The value 22.3 ppm is taken from the spectrum of the BOC-protected counterpart (compound 8c) of the 2-t-butyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine 4c. Since the BOC-protected counterpart (compound 6c) of the 2-t-butyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine 7c does not exist totally in conformation c (vide infra), we were forced to use the hypothetical value 16.8 ppm, taken from the spectrum of compound 7c. It is assumed that the values 21.8 and 16.8 ppm, and 22.3 and 16.8 ppm, represent relatively well the chemical shifts of C(7) for the pure conformations a and c of the indolo[2,3-a]quinolizidines 3a, 3b, 3c, 4a, 4b, 4c, 7b and 7c, and their BOC-protected counterparts 5a, 5b, 5c, 8a, 8b, 8c, 6b and 6c, respectively.

Calculating the proportional relation of the shift value 19.6 ppm, found for the signal of C(7) in compound 7b, to the values 21.8 and 16.8 ppm indicates the contribution of conformation c to the conformational equilibrium to be about 44%. In the corresponding BOC-protected compound 6b the contribution of conformation c is reduced to about 11%, as indicated by the C(7) shift value 21.7 ppm [proportional to the values 22.3 and 16.8 ppm (vide supra)].

Compound 7c is known to exist > 99.9% in conformation c owing to the overwhelming equatorial preference of its t-butyl group.[29] Its C(7) shift value 16.8 ppm could therefore be used as basis for the conformation c (vide supra). In the corresponding BOC-protected compound (compound 6c) the contribution of conformation c to the conformational equilibrium is still preponderant, but the interaction between the BOC-group and the D-ring moves the equilibrium toward conformation a (vide supra). The proportional relation of the shift value 17.5 ppm to the values 22.3 and 16.8 ppm indicates the contribution of conformation c to the conformational equilibrium to be about 87%. The shift values between 22.3 and 21.5 ppm found for C(7) of compounds 3a, 3b, 4a, 4b, 5a, 5b, 8a, 8b, 9a and 9b indicate a strong preponderance of conformation a.

CONCLUSIONS

The developed method permits the stereoselective preparation of 2-substituted 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizines with the desired C(12b)H-C(2)H relationship (cis or trans).
Application of the method in the preparation of dihydroantirhine[33] and 3-epi-dihydroantirhine[34] is in progress.

EXPERIMENTAL

IR spectra were recorded on a Perkin-Elmer 700 spectrophotometer, using liquid film between NaCl crystals. IR absorption bands are expressed in reciprocal centimetres (cm^{-1}) using polystyrene calibration. ^{1}H and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Jeol JNM-FX 60 spectrometer working at 59.80 MHz (^{1}H NMR) and 15.04 MHz (^{13}C NMR). Chemical shift data are given in ppm downfield from TMS. Abbreviations d, t, m, n, br and def are used to designate singlet, doublet, triplet, multiplet, narrow, broad and deformed, respectively. For ^{13}C NMR data see Fig. 1. Mass spectrometry was done on a Jeol DX 303/DA 5000 instrument.

Preparation of compounds 2a, 2b and 2c
Hydrochloric acid (6N, 2.5 ml) was added dropwise to a stirred, cooled solution (0°C) of KCN (1.68 g, 25.85 mmol) in H_2O (2.5 ml) and layered with Et_2O (15 ml). MeOH (4 ml) and the corresponding pyridinium salt 1a, 1b or 1c (5.00 mmol) was added, after which $NaBH_4$ (0.20 g, 5.29 mmol) was added during 0.5 h (0°C). Stirring was continued for 4h at rt. The ethereal layer was separated and the aqueous layer was extracted several

times with Et_2O. The combined organic layers were dried (Na_2SO_4) and evaporated to yield compounds 2a, 2b and 2c, respectively.

Compound 2a:

Y. 92%. Amorphous material.

IR: 3430 (NH), 2260 (CN).

^1H NMR: 3.94 (1H, m, H-2'), 5.73 (2H, n m, H-4', 5'), 6.97 (1H, d, J=2.4 Hz, H-2), 7.21 - 7.68 (4H, m, H-4, 5, 6, 7) 8.15 (1H, br s, NH).

MS: 251 (M^+), 224, 144, 130, 121 (100%); exact mass: 251.1382 (calc. for $C_{16}H_{17}N_3$: 251.1423).

Compound 2b:

Y. 93%. Amorphous material.

IR: 3430 (NH), 2260 (CN).

^1H NMR: 1.65 (3H, s, $-CH_3$), 3.85 (1H, m, H-2'), 5.36 (1H, br s, H-5'), 6.84 (1H, d, J=2.4 Hz, H-2), 7.16-7.75 (4H, m, H-4, 5, 6, 7), 8.18 (1H, br s, NH).

MS: 265(M^+), 238, 144, 135 (100%), 130, 108; exact mass: 265.1595 (calc. for $C_{17}H_{19}N_3$: 265.1579).

Compound 2c:

Y. 96%. Amorphous material.

IR: 3440 (NH), 2270 (CN).

^1H NMR: 1.02 (9H, s, $-C(CH_3)_3$), 3.96 (1H, m, H-2'), 5.49 (1H, br s, H-5'), 6.90 (1H, d, J=2.4 Hz, H-2), 7.19-7.65 (4H, m, H-4, 5, 6, 7), 8.10 (1H, br s, NH).

MS: 307 (M^+), 280, 250, 177, 152 (100%), 144, 130; exact mass: 307.2056 (calc. for $C_{20}H_{25}N_3$: 307.2049).

Preparation of compounds 3a, 3b and 3c

Compound 2a, 2b or 2c (4.5 mmol) was dissolved in 50% AcOH (140 ml) and stirred at rt (Ar-atm) for 3d. After evaporation and neutralization (2N Na_2CO_3) the solution was extracted with CH_2Cl_2. The combined organic extracts were dried over Na_2SO_4. The crude product was purified by column chromatography (alumina, CH_2Cl_2).

Compound 3a:

Y. 48%. Amorphous material.

IR: 3440 (NH).

^1H NMR: 5.77 (2H, n m, H-2, 3), 7.00-7.56 (4H, m, H-8, 9, 10, 11), 7.72 (1H, br s, NH).

MS: 224 (M^+), 170 (100%), 169; exact mass: 224.1296 (calc. for $C_{15}H_{16}N_2$: 224.1313).

Compound 3b:

Y. 54%. Amorphous material.

IR: 3440 (NH).
^{1}H NMR: 1.69 (3H, s, $-CH_3$), 5.46 (1H, br s, H-3), 7.05-7.54 (4H, m, H-8, 9, 10, 11), 7.83 (1H, br s, NH).
MS: 238 (M^+), 170 (100%), 169; exact mass: 238.1460 (calc. for $C_{16}H_{18}N_2$: 238.1470).
Compound 3c:
Y. 54%. Amorphous material.
IR: 3440 (NH).
^{1}H NMR: 1.09 (9H, s, $-C(CH_3)_3$), 5.54 (1H, br s, H-3), 7.01-7.43 (4H, m, H-8, 9, 10, 11), 7.81 (1H, br s, NH).
MS: 280 (M^+), 279, 223, 170 (100%), 169; exact mass: 280.1937 (calc. for $C_{19}H_{24}N_2$: 280.1940).

Preparation of compounds 4a, 4b and 4c
Catalytic hydrogenation (PtO_2) of compounds 3a, 3b and 3c (1.00 mmol) in MeOH (30 ml) afforded compounds 4a, 4b and 4c, respectively. The crude product was purified by column chromatography (alumina, CH_2Cl_2).
Compound 4a:
Y. 76%. Mp. 153-155°C (EtOH) (lit.[14] Mp. 153-155°C).
Analytical data were identical with those obtained earlier[14].
Compound 4b:
Y. 72%. Mp. 165-166°C (EtOH) (lit.[14] Mp. 165-166°C).
Analytical data were identical with those obtained earlier[14].
Compound 4c:
Y. 70%. Mp.155-156°C (EtOH) (lit.[4] Mp. 157-158°C).
IR: 3430 (NH), 2830 and 2780 (Bohlmann bands).
^{1}H NMR: 0.90 (9H, s, $-C(CH_3)_3$), 7.07 - 7.52 (4H, m, H-8, 9, 10, 11), 7.90 (1H, br s, NH).
MS: 282 (M^+), 281, 225 (100%), 197, 184, 170, 169, 156; exact mass: 282.2077 (calc. for $C_{19}H_{26}N_2$: 282.2092).

Preparation of compounds 5a, 5b and 5c
50% NaOH (10 ml) was added to compound 3a, 3b or 3c (4.00 mmol) in toluene (15 ml), and then tetrabutylammonium hydrogen sulphate (350 mg). The two-phase system was stirred under argon for 5 min. Di-t-butyl dicarbonate (1.70 g, 2 equiv.) in toluene (5 ml) was added during 10 min and stirring was continued for 12 min. The organic layer was separated and the aqueous layer was washed several times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4 and evaporated. The crude product was purified by column chromatography (alumina, CH_2Cl_2).

Compound 5a:
Y. 98%. Viscous oil.
IR: 1730 (C=O).
^{1}H NMR: 1.65 (9H, s, $-C(CH_3)_3$), 4.12 (1H, br, d, H-12b), 5.79 (2H, n m, H-2, 3), 7.14-7.42 (3H, m, H-8, 9, 10), 8.08 (1H, m, H-11).
MS: 324 (M^+), 268, 267, 214 (100%), 170, 169; exact mass: 324.1844 (calc. for $C_{20}H_{24}N_2O_2$: 324.1838).
Compound 5b:
Y. 98%. Viscous oil.
IR: 1730 (C=O).
^{1}H NMR: 1.64 (12H, s, $-CH_3$ and $-C(CH_3)_3$), 4.12 (1H, br d, H-12b), 5.46 (1H, m, H-3), 7.14-7.52 (3H, m, H-8, 9, 10), 8.12 (1H, m, H-11).
MS: 338 (M^+), 282, 281, 237, 214 (100%), 170, 169; exact mass: 338.1988 (calc. for $C_{21}H_{26}N_2O_2$: 338.1990).
Compound 5c:
Y. 91%. Viscous oil.
IR: 1730 (C=O).
^{1}H NMR: 1.06 (9H, s, $-C(CH_3)_3$), 1.66 (9H, s, $-C(CH_3)_3$), 4.04 (1H, br d, H-12b), 5.51 (1H, m, H-3), 7.14-7.41 (3H, m, H-8, 9, 10), 8.07 (1H, m, H-11).
MS: 380 (M^+), 324, 323 (100%), 279, 214, 170, 169; exact mass: 380.2460 (calc. for $C_{24}H_{32}N_2O_2$: 380.2464).

Preparation of compounds 6a, 6b and 6c
Catalytic hydrogenation (PtO_2) of compounds 5a, 5b and 5c (2.00 mmol) in MeOH (50 ml) afforded compounds 6a, 6b and 6c, respectively. The crude product was purified by column chromatography (alumina, CH_2Cl_2).
Compound 6a:
Y. 82%. Amorphous material.
IR: 1730 (C=O).
^{1}H NMR: 1.64 (9H, s, $-C(CH_3)_3$), 4.01 (1H, m, H-12b), 7.12-7.37 (3H, m, H-8, 9, 10), 8.12 (1H, m, H-11).
MS: 326 (M^+), 269 (100%), 225; exact mass: 326.1989 (calc. for $C_{20}H_{26}N_2O_2$: 326.1990).
Compound 6b:
Y. 85%. Amorphous material.
IR: 1730 (C=O).
^{1}H NMR: 1.03 (3H, def, $-CH_3$), 1.66 (9H, s, $-C(CH_3)_3$), 4.31 (1H, m, H-12b), 7.12-7.49 (3H, m, H-8, 9, 10), 8.05 (1H, m, H-11).
MS: 340 (M^+), 283 (100%), 239, 215; exact mass: 340.2169 (calc. for $C_{21}H_{28}N_2O_2$: 340.2151).

Compound 6c:
Y. 83%. Amorphous material.
IR: 1730 (C=O).
^1H NMR: 0.85 (9H, s, $-C(CH_3)_3$), 1.66 (9H, s, $-C(CH_3)_3$), 4.65 (1H, m, H-12b), 7.15-7.53 (3H, m, H-8, 9, 10), 8.05 (1H, m, H-11).
MS: 382 (M^+), 325 (100%), 281, 269; exact mass: 382.2616 (calc. for $C_{24}H_{34}N_2O_2$: 382.2620.

Preparation of compounds 7a, 7b and 7c
Compounds 6a (=8a), 6b and 6c (1.00 mmol) were stirred in HCOOH (12 ml) for 30 h (rt, Ar-atm). After evaporation and neutralization (10% Na_2CO_3) the solution was extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and evaporated to yield 7a, 7b and 7c, respectively.
Compound 7a (=4a):
Y. 92%. Mp. 153-155°C (EtOH) (lit.[14] 153-155°C).
Analytical data were identical with those of compound 4a (vide supra).
Compound 7b:
Y. 95%. Mp. 154-155°C (C_6H_6, petroleum ether addition) (lit.[15] Mp. 128-130°C).
IR: 3430 (C=O).
^1H NMR: 1.03 (3H, def, $-CH_3$), 3.86 (1H, m, H-12b), 6.98-7.54 (4H, m, H-8, 9, 10, 11), 7.98 (1H, br s, NH).
MS: 240 (M^+), 239 (100%), 171; exact mass: 240.1639 (calc. for $C_{16}H_{20}N_2$: 240.1626).
Compound 7c:
Y. 92%. Amorphous material (lit.[4] Amorphous material).
IR: 3400 (C=O).
^1H NMR: 0.85 (9H, s, $-C(CH_3)_3$), 4.46 (1H, m, H-12b), 7.09-7.46 (4H, m, H-8, 9, 10, 11), 7.91 (1H, br s, NH).
MS: 282 (M^+, 100%), 281, 225; exact mass: 282.2077 (calc. for $C_{19}H_{26}N_2$: 282.2092).

Preparation of compounds 8a, 8b and 8c
Compounds 4a, 4b and 4c were BOC-protected using the procedure described for compounds 5a, 5b and 5c (vide supra).
Compound 8a (=6a):
Y. 80%. Viscous oil.
Analytical data were identical with those of 6a (vide supra).
Compound 8b:
Y. 78%. Viscous oil.

IR: 1730 (C=O).
^{1}H NMR: 0.95 (3H, d, J=5.0 Hz, $-CH_3$), 1.64 (9H, s, $-C(CH_3)_3$), 3.98 (1H, m, H-12b), 7.11-7.37 (3H, m, H-8, 9, 10), 8.12 (1H, m, H-11).
MS: 340 (M^+), 283 (100%), 239; exact mass: 340.2160 (calc. for $C_{21}H_{28}N_2O_2$: 340.2151).
Compound 8c:
Y. 76%. Viscous oil.
IR: 1720 (C=O).
^{1}H NMR: 0.88 (9H, s, $-C(CH_3)_3$), 1.66 (9H, s, $-C(CH_3)_3$), 3.99 (1H, m, H-12b), 7.13-7.48 (3H, m, H-8, 9, 10), 8.08 (1H, m, H-11).
MS: 382 (M^+), 325 (100%), 281, 280, 269; exact mass: 382.2644 (calc. for $C_{24}H_{34}N_2O_2$: 382.2620).

Preparation of compounds 9a, 9b and 9c
Pyridinium salts 1a, 1b and 1c were catalytically hydrogenated (PtO_2) to the corresponding piperidine derivatives 9a, 9b and 9c.
Compound 9a:
Y. 89%. Mp. 151-152°C (EtOH) (lit.[35] Mp. 151-152°C).
IR: 3430 (NH).
^{1}H NMR: 6.93 (1H, s, H-2), 7.03-7.67 (4H, m, H-4, 5, 6, 7), 8.61 (1H, br s, NH).
MS: 228 (M^+), 144, 130, 99, 98 (100%); exact mass: 228.1624 (calc. for $C_{15}H_{20}N_2$: 228.1626).
Compound 9b:
Y. 90%. Mp. 110-111°C (EtOH).
IR: 3420 (NH).
^{1}H NMR: 0.94 (3H, def., $-CH_3$), 6.87 (1H, s, H-2), 7.07-7.65 (4H, m, H-4, 5, 6, 7), 8.75 (1H, br s, NH).
MS: 242 (M^+), 144, 130, 113, 112 (100 %); exact mass: 242.1785 (calc. for $C_{16}H_{22}N_2$: 242.1783).
Compound 9c:
Y. 95%. Mp. 158-159°C (EtOH) (lit.[13] Mp. 157°C).
IR: 3500 (NH).
^{1}H NMR: 0.85 (9H, s, $-C(CH_3)_3$), 6.90 (1H, s, H-2), 7.03-7.66 (4H, m, H-4, 5, 6, 7), 8.55 (1H, br s, NH).
MS: 284 (M^+), 154 (100%), 144, 130; exact mass: 284.2266 (calc. for $C_{19}H_{28}N_2$: 284.2253).

Preparation of compounds 10a, 10b and 10c
Compounds 9a, 9b and 9c were BOC-protected using the procedure described for compounds 5a, 5b and 5c (vide supra).

Compound 10a:
Y. 90%. Viscous oil.
IR: 1730 (C=O).
^1H NMR: 1.64 (9H, s, $-C(CH_3)_3$), 7.10-7.57 (4H, m, H-4, 5, 6, 7), 7.42 (1H, s, H-2).
MS: 328 (M^+), 271, 255, 144, 130, 99, 98 (100%); exact mass: 328.2148 (calc. for $C_{20}H_{28}N_2O_2$: 328.2151).
Compound 10b:
Y. 85%. Viscous oil.
IR: 1730 (C=O).
^1H NMR: 0.94 (3H, def, $-CH_3$), 1.64 (9H, s, $-C(CH_3)_3$), 7.17-7.62 (4H, m, H-4, 5, 6, 7), 7.41 (1H, s, H-2).
MS: 342 (M^+), 285, 269, 144, 130, 112 (100%); exact mass: 342.2281 (calc. for $C_{21}H_{30}N_2O_2$: 342.2307).
Compound 10c:
Y. 85%. Viscous oil.
IR: 1730 (C=O).
^1H NMR: 0.87 (9H, s, $-C(CH_3)_3$), 1.64 (9H, s, $-C(CH_3)_3$), 7.17-7.60 (4H, m, H-4, 5, 6, 7), 7.39 (1H, s, H-2).
MS: 384 (M^+), 327, 311, 154 (100%), 144, 130; exact mass: 384.2773 (calc. for $C_{24}H_{36}N_2O_2$: 384.2777).

Preparation of compounds 11a, 11b and 11c
Compounds 10a, 10b and 10c were transformed by successive treatments with H_2O_2, TFAA (modified Polonovski reaction) and KCN to compounds 11a, 11b and 11c, respectively.
Compound 11a:
Y. 55%. Viscous oil.
IR: 2270 (CN), 1735 (C=O).
^1H NMR: 1.63 (9H, s, $-C(CH_3)_3$), 3.83 (1H, br s, H-2'), 7.16-7.54 (4H, m, H-2, 4, 5, 6), 8.15 (1H, m, H-7).
MS: 353 (M^+), 326, 296, 280, 144, 130, 123 (100%), 96; exact mass: 353.2084 (calc. for $C_{21}H_{27}N_3O_2$: 353.2103).
Compound 11b:
Y. 56%. Viscous oil.
IR: 2270 (CN), 1730 (C=O).
^1H NMR: 0.93 (3H, d, J=6.5 Hz, $-CH_3$), 1.64 (9H, s, $-C(CH_3)_3$), 3.92 (1H, br s, H-2'), 7.18-7.60 (4H, m, H-2, 4, 5, 6), 8.15 (1H, m, H-7).
MS: 367 (M^+), 341, 340, 310, 294, 144, 137 (100%), 130, 110; exact mass: 367.2262 (calc. for $C_{22}H_{29}N_3O_2$: 367.2260).

Compound 11c:
Y. 62%. Viscous oil.
IR: 2270 (CN), 1730 (C=O).
^1H NMR: 0.83 (9H, s, $-C(CH_3)_3$), 1.65 (9H, s, $-C(CH_3)_3$), 3.96 (1H, br s, H-2'), 7.14-7.57 (4H, m, H-2, 4, 5, 6), 8.15 (1H, m, H-7).
MS: 409 (M^+), 382, 325, 269, 179 (100%), 144, 130; exact mass: 409.2706 (calc. for $C_{25}H_{35}N_3O_2$: 409.2729).

Alternative preparation of compounds 7a, 7b, and 7c
Treatment of compound 11a, first with $AgBF_4$ and then with HCl/MeOH afforded compound 7a (column chromatography, alumina, CH_2Cl_2), which was identical with compound 7a prepared from compound 6a (vide supra). Considerable amounts of dimeric material were found. Similar treatment of compounds 11b and 11c yielded compounds 7b and 7c, respectively, which were identical with 7b and 7c prepared from 6b and 6c.
Compound 7a:
Y. 35%. Mp. 153-155°C (EtOH) (lit.[14] Mp. 153-155°C).
Compound 7b:
Y. 32%. Mp. 154-155°C (C_6H_6, petroleum ether addition) (lit.[15] Mp. 128-130°C).
Compound 7c:
Y. 41%. Amorphous material (lit.[4] Amorphous material).

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