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SYNTHETIC STUDIES IN THE ALKALOID FIELD—X[a]

PREPARATION AND STEREOSTRUCTURE DETERMINATION OF SEVERAL INDOLO[2,3-a]QUINOLIZINE DERIVATIVES

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Abstract—The C(12b)–C(1)–C(2)–C(3) stereochemical relationship in several racemic indolo[2,3-a]quinolizine derivatives has been determined by the application of conformational considerations to the ^{13}C NMR spectral analysis. The proper shift assignment was confirmed by recording the spectra of selectively deuterated derivatives. The C(12b)–C(1)–C(2)–C(3) stereochemical relationship in indolo[2,3-a]quinolizines obtained by acid-induced cyclization of partially hydrogenated 3,5-dimethoxycarbonyl-1-[2-(3-indolyl)ethyl]pyridine derivatives is discussed.

In connection with our studies[1] concerning the preparation of indole alkaloid models by Pd-catalyzed partial hydrogenation of 3,5 - dimethoxycarbonyl - 1 - [2 - (3 - indolyl)ethyl]pyridinium bromides, followed by acid-induced cyclization, we found the tetrahydropyridine derivative 1 (XV in Ref. 1) yielded only one of the possible diastereoisomers but the tetrahydropyridine derivative 2 (XVI in Ref. 1) yielded a mixture of two diastereoisomers. The analytical data confirming the gross structures 3 and 4 of the prepared compounds were given, but it was considered premature to draw conclusions about their stereochemistry.

The sodium dithionite reduction[2,3] of 3,5 - dimethoxycarbonyl - 1 - [2 - (3 - indolyl)ethyl]pyridinium bromide 5, followed by acid-induced cyclization and $NaBH_4$/acetic acid reduction,[4-6] provided all four possible stereoisomers of 3 available for analysis. Similar treatment of 3,5 - dimethoxycarbonyl - 4 - methyl - 1 - [2 - (3 - indolyl)ethyl]pyridinium bromide 6 permitted the preparation of the 1,3 - dimethoxycarbonyl - 2 - methyl - 1,2,3,4,6,7,12,12b - octahydroindolo[2,3-a]quinolizines 4a and 4b. Thus the time appeared ripe for a detailed determination of the stereostructures of 3a, 3b, 3c, 3d, 4a, 4b, as well as of 7a, 7b, 8a and 8b, and for a more detailed study of the effect of the D ring substituents on the C/D ring fusion (*vide infra*).

During recent years ^{13}C NMR analysis has been shown to be a powerful tool for the structure elucidation and analysis of organic compounds and the results described in the present report were mainly obtained by this method.

RESULTS

The sodium dithionite reduction[2,3] of the recently described[1] 3,5 - dimethoxycarbonyl - 1 - [2 - (3 - indolyl)ethyl]pyridinium bromides 5 and 6 (III and IV in Ref. 1) permitted the preparation of 1,4-dihydropyridines 9 and 10, which by acid-induced cyclization were trans-

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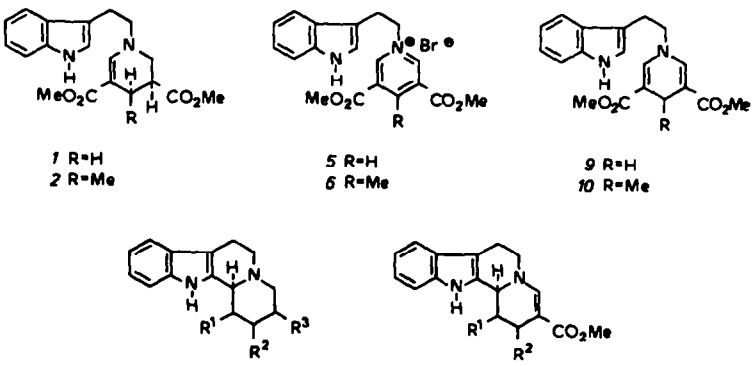


1 R=H
2 R=Me

5 R=H
6 R=Me

9 R=H
10 R=Me

3 $R^1=R^3=CO_2Me$; $R^2=H$
3a $R^1=\alpha$-CO_2Me; $R^2=H$; $R^3=\beta$-CO_2Me
3b $R^1=\alpha$-CO_2Me; $R^2=H$; $R^3=\alpha$-CO_2Me
3c $R^1=\beta$-CO_2Me; $R^2=H$; $R^3=\beta$-CO_2Me
3d $R^1=\beta$-CO_2Me; $R^2=H$; $R^3=\alpha$-CO_2Me
4 $R^1=R^3=CO_2Me$; $R^2=Me$
4a $R^1=\alpha$-CO_2Me; $R^2=\alpha$-Me, $R^3=\alpha$-CO_2Me
4b $R^1=\alpha$-CO_2Me; $R^2=\alpha$-Me; $R^3=\beta$-CO_2Me
11 $R^1=\alpha$-CO_2Me; $R^2=R^3=H$
12 $R^1=\alpha$-CO_2Me; $R^2=\beta$-Me; $R^3=\beta$-CO_2Me

7a $R^1=\alpha$-CO_2Me; $R^2=H$
7b $R^1=\beta$-CO_2Me; $R^2=H$
8a $R^1=\alpha$-CO_2Me; $R^2=\alpha$-Me
8b $R^1=\beta$-CO_2Me, $R^2=\alpha$-Me

Fig. 1.

formed to the tetracyclic compounds **7a** and **7b**, and **8a** and **8b**, respectively. The $NaBH_4$/acetic acid reduction[4-6] of **7a**, **7b** and **8a** afforded **3a**, **3b**, **3c**, **3d**, **4a** and **4b**.

Selectively deuterated analogues of **3a**, **3b**, **4a** and **7a** were needed for comparison. The dithionite reduction[2,3] of **5** (III in Ref. 1) in D_2O/CH_3OD yielded 4 - deuterio - 3,5 - dimethoxycarbonyl - 1 - [2 - (3 - indolyl)ethyl] - 1,4 - dihydropyridine **9-4-d_1**, which was transformed by acid-induced cyclization to 2 - deuterio - 1α,3 - dimethoxycarbonyl - 1,2,6,7,12,12bα - hexahydroindolo[2,3-a]quinolizine **7a-2-d_1** and 2 - deuterio - 1β,3 - dimethoxycarbonyl - 1,2,6,7,12,12bα - hexahydroindolo[2,3-a]quinolizine **7b-2-d_1**. The $NaBH_4$/acetic acid reduction of **7a-2-d_1** yielded **3a-2-d_1** and **3b-2-d_1**; the $NaBD_4$/acetic acid reduction[6] of **7a**, **3a-4-d_1** and **3b-4-d_1**; and the $NaBD_4$/acetic acid reduction of **8a**, **4a-4-d_1** and **4b-4-d_1**.

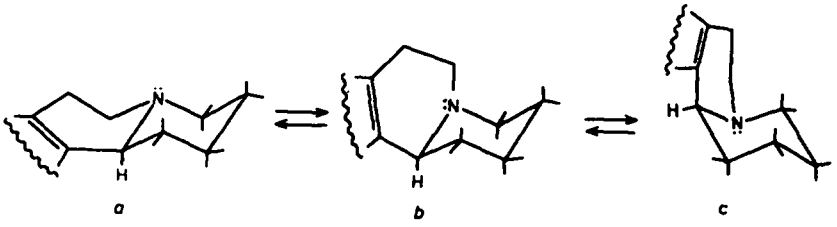
The 1,3-disubstituted 1,2,3,4,6,7,12,12b - octahydroindolo[2,3-a]quinolizine system can exist in twelve conformations (four configurations) with equilibration by nitrogen inversion and *cis*-decalin type ring interconversion (Scheme 1). In the 1,2,3-trisubstituted indolo[2,3-a]quinolizine analogues, the situation is similar, although more complicated (eight configurations).

[c]The contribution of conformer b is considered negligible.

Of the 1,3 - dimethoxycarbonylindolo[2,3-a]quinolizines **3a**, **3b**, **3c** and **3d**, the configurations **3a**, **3b** and **3c** can be expected to exist predominantly in the *trans*-fused C/D ring conformation (conformer a), but **3c**, where both methoxycarbonyl groups in the *trans*-fused conformation are axial (a strong 1,3-diaxial interaction is present), should exist with an overwhelming preponderance in the *cis*-fused conformation (conformer c).[c]

The preponderance of the *trans*-fused conformation (conformer a) in **3a**, **3b** and **3d** is supported by ^1H NMR spectroscopy. The absence of any signal downfield from δ 3.8 that could be assigned to H-12b is characteristic of a *trans*-fused conformation.[7-10] The H-12b signal of **3c** appears at δ 4.70 owing to the diamagnetic displacement effect of the electron pair of the basic nitrogen, which is in agreement with the preponderance of the *cis*-fused conformation. Moreover, the presence of the so-called Bohlmann bands[11] in the IR spectra of **3a**, **3b** and **3d**, and their absence in the IR spectrum of **3c** further support the conformational conclusions presented.

The stereochemical relationships proposed for **7a**, **7b**, **8a**, **8b**, **3a**, **3b**, **3c**, **3d**, **4a** and **4b** were mainly determined by ^{13}C NMR spectral analysis. The fully proton-decoupled spectra of **7a**, **7b**, **8a**, **8b**, **3a**, **3b**, **3c**, **3d**, **4a** and **4b**, and the intermediate 1,4-dihydropyridine derivatives **9** and **10**, all taken in $CDCl_3$, showed the chemical shifts



Scheme 1.

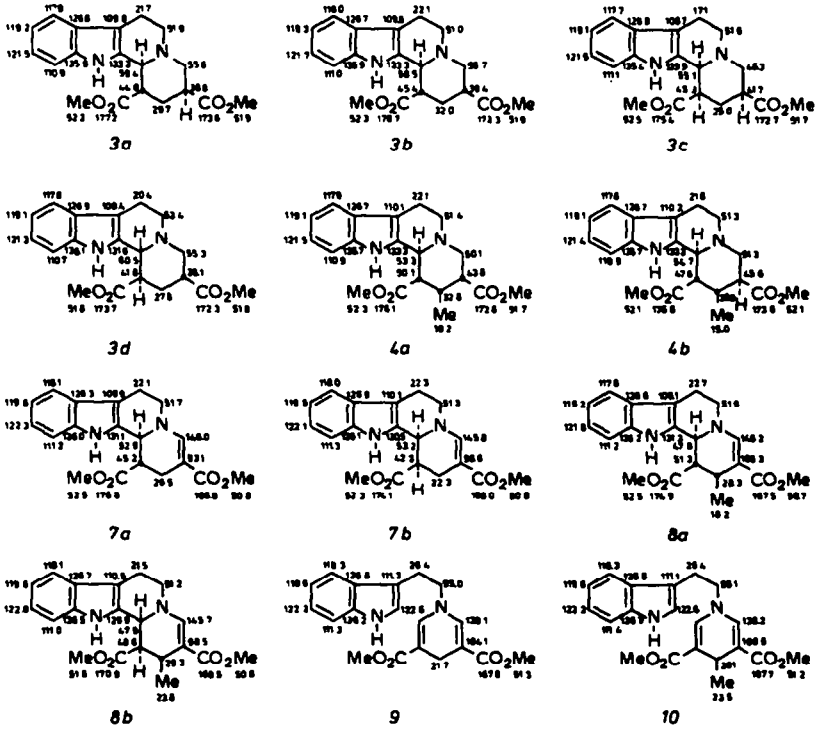


Fig. 2.

Table 1. ^{13}C chemical shifts of deuterated indolo[2,3-a]quinolizines.[a]

	3a-2-d_1	3b-2-d_1	3a-4-d_1	3b-4-d_1	4a-4-d_1	7a-2-d_1
C-1	43.9	45.3	44.0	45.4	50.1	45.3
C-2			29.7	32.0	32.8	
C-3	38.7	39.3	38.7	39.2	43.7	93.0
C-4	55.7	56.6				146.0
C-6	52.0	50.9	52.0	50.8	51.4	51.8
C-7	21.7	22.0	21.7	22.1	22.1	22.1
C-7a	109.8	109.7	109.9	109.7	110.1	110.0
C-7b	126.8	126.7	126.8	126.7	126.8	126.3
C-8	118.0	118.1	118.0	118.1	117.9	118.1
C-9	119.3	119.3	119.3	119.3	119.1	119.7
C-10	121.6	121.7	121.6	121.7	121.6	122.3
C-11	111.0	111.0	111.0	111.0	111.0	111.2
C-11a	135.9	135.9	136.0	136.0	135.7	136.0
C-12a	133.4	133.3	133.4	133.3	133.3	131.1
C-12b	59.4	58.5	59.4	58.4	53.3	52.9
-Me					10.2	
-OMe	52.0	51.9	52.0	51.9	51.7	50.8
-OMe	52.3	52.4	52.3	52.4	52.3	52.5
C = O	173.7	173.3	173.7	173.3	172.8	168.0
C = O	177.3	176.8	177.3	176.8	176.1	176.9

[a]All the spectra were recorded in $CDCl_3$ solution.
The δ values are in parts per million downfield from Me_4Si.

depicted on the formulas. The proper shift assignment was confirmed by recording single-frequency, off-resonance decoupled (aford) spectra and the spectra of selected deuterated derivatives (Table 1), and by comparison with the earlier shift assignment.[6,12-14]

The fact that $NaBH_4$/acetic acid reductions of **7a** and **7b** yielded in both cases just two 1,2,3,4,6,7,12,12b - octahydroindolo[2,3-a]quinolizines (**3a** and **3b**, and **3c** and **3d**, respectively) shows that no epimerization takes place at C-1. Accordingly the products formed are two pairs of C-3 epimers. The upfield shifts of C-4 and C-7 in **3c** relative to **3a**, **3b** and **3d**, which are due to the 1,4-gauche interactions between the C-4 axial proton and the C-7 pseudoaxial proton (*cf.* conformational considerations), confirm the stereostructure of **3c**, and, as a consequence, the stereostructures of **7b** and **3d**. The C(12b)H–C(1)H *trans*-relationship for **7a**, **3a** and **3b** necessarily also follows.

[4]For an axial –$COOCH_3$ group, 14, 0 and – 3 ppm, respectively. For an equatorial –$COOCH_3$ group, 16, 2 and 0 ppm, respectively.[6]

The upfield shifts of C-12a in **3c** and **3d** relative to **3a** and **3b** are partly due to the γ-shielding effect of the C-1 methoxycarbonyl groups and partly a consequence of the C/D ring conformations present (*cf.* the corresponding signals reported in Ref. 6 for compounds **5a–d**).

With the chemical shifts found for **11** (**3a** in Ref. 15) as a basis,[15] the axial and equatorial –$COOCH_3$ group α-, β- and γ-parameters[4] were used to predict the chemical shifts of C-3, C-2, C-4 and C-1 in **3a** and **3b**. A comparison of the observed and calculated chemical shifts (Table 2), with the conformational considerations in mind, fully confirms the C(12b)–C(1)–C(3) stereochemical relationships presented for **3a** and **3b**.

Similarly, the stereostructures of **4a** and **4b**, and as a consequence, the stereostructure of **8a** could be settled by taking the chemical shifts found for **3a**, **3b**, **3c** and **3d** as a basis, and using the axial and equatorial Me group α-, β- and γ-parameters.[16] Moreover, as the ^{13}C NMR results indicate that **8a** and **8b** are C-1 epimers, the stereostructure of **8b** is also confirmed.

The compounds [XXII and XXIII (isomer B) in Ref. 1] obtained by palladium-catalyzed partial hydrogenation of

Table 2. Comparison of the observed and calculated ^{13}C chemical shifts for C-3, C-2, C-4 and C-1 in compounds **11**, **3a** and **3b**

	11[a]	Calc. for an ax. CO_2Me group	3a	3b	Calc. for an eq. CO_2Me group
C-3	23.8	37.8	38.8	39.4	39.8
C-2	30.2	30.2	29.7	32.0	32.2
C-4	55.2	55.2	55.6	56.7	57.2
C-1	46.8	43.8	44.0	45.4	46.8

[a]Taken from Ref. 15

3,5 - dimethoxycarbonyl - 1 - [2 - (3 - indolyl)-ethyl]pyridinium bromides **5** and **6**, followed by acid-induced cyclization, proved to be identical (TLC, ^{1}H NMR, ^{13}C NMR) with **3a** and **4a**, respectively, and their stereochemistry was thus settled. Moreover, as the ^{13}C NMR spectrum of **4a** permits the C- and D-ring signals for isomers A and B in the ^{13}C NMR spectrum of their diastereoisomeric mixture (Ref. 1, compound XXIII (isomers A and B)) to be distinguished, the shift values obtained for isomer A,* taken with the assumption that the catalytic hydrogenation of the pyridinium salts proceeds in a *cis*-manner,[17] permit the stereostructure **12** to be proposed for isomer A.

The present report shows the applicability of conformational considerations to the determination of the stereostructures of D-ring substituted 1,2,3,4,6,7,12,12b - octahydroindolo[2,3-a]quinolizines by ^{13}C NMR spectral analysis, expecially when a sufficient amount of stereoisomers are available.

EXPERIMENTAL

The IR spectra were measured on a Perkin–Elmer 237 apparatus and the UV spectra on a Perkin–Elmer 137 UV apparatus. The ^{1}H NMR spectra were taken with either a Jeol JNM-PMX-60 or a Jeol JNM-FX-100 instrument, and the ^{13}C NMR spectra with the Jeol JNM-FX-100 instrument operating at 25.20 MHz in the Fourier transform mode. TMS was used as internal standard. The mass spectra were recorded either on a Jeol JMS-D-100 Mass Spectrometer or on a Hitachi–Perkin–Elmer RMU 6E Mass Spectrometer at 70 eV, using direct sample insertion into the ion source, whose temp. was 120–140°. The elemental compositions when given for the molecular ions were confirmed by high-resolution mass measurements performed with a resolution of 10,000 (40% valley definition). The m.ps were determined in a Büchi capillary m.p. apparatus and are uncorrected.

Sodium dithionite reductions

General procedure. Sodium dithionite was added in small portions during 1 hr to a magnetically stirred soln of pyridinium bromide derivative and $NaHCO_3$ in aqueous MeOH under N_2. The mixture was stirred for 6 hr, the MeOH evaporated off under vacuum, and the mixture extracted several times with CH_2Cl_2. The extracts were washed with water, dried over Na_2SO_4 and evaporated under vacuum. The residue was chromatographed on alumina (act. IV).

3,5 - *Dimethoxycarbonyl* - 1 - [2 - (3 - *indolyl*)*ethyl*] - 1,4 - *dihydropyridine* **9**. Reaction between 500 mg of **5**,[1] 1.5 g of $NaHCO_3$, and 1.5 g of sodium dithionite in 150 ml of aqueous MeOH yielded 374 mg (92%) of **9**. M.p. 179–181° (MeOH). IR (KBr): NH 3330 (s), C=O 1690 (s), C=C 1585 (s) cm^{-1}. UV [EtOH 94% (*e*)] λ_{max} 205 (infl.) (17,900), 224 (32,600), 261 (10,700), 282 (8100), 291 (6800) and 392 (6800) nm. λ_{min} 207 (infl.), 245, 279, 289 and 320 nm. ^{1}H NMR (60 MHz, DMSO-d_6) δ 3.60 (6 H, s, both –$COOCH_3$), 7.04 (2 H, s, H-2 and H-6) and 7.60 (1 H, s, NH). MS M$^+$ at *m/e* 340 corresponding to $C_{19}H_{20}N_2O_4$.

4 - *Deuterio* - 3,5 - *dimethoxycarbonyl* - 1 - [2 - (3 - *indolyl*)*ethyl*] - 1,4 - *dihydropyridine* **9**-4-d_1. Reaction between 300 mg of **5**,[1] 1 g of $NaHCO_3$, and 1 g of sodium dithionite in 20 ml of D_2O/CH_3OD (5/1, D_2O/CH_3OD) yielded 198 mg (81%) of **9**-4-d_1. M.p. 180–182° (MeOH). MS M$^+$ at *m/e* 341.

3,5 - *Dimethoxycarbonyl* - 4 - *methyl* - 1 - [2 - (3 - *indolyl*)*ethyl*] - 1,4 - *dihydropyridine* **10**. Reaction between 1.5 g of **6**,[1] 3.0 g of $NaHCO_3$ and 3.0 g of sodium dithionite in 250 ml of aqueous MeOH yielded 1100 mg (89%) of **10** as an oil. IR (film): NH 3350 (s), C=O 1690 (s), C=C 1580 (s) cm^{-1}. UV [EtOH 94% (*e*)] λ_{max} 205 (infl.) (18,000), 223 (35,800), 259 (11,800), 284 (8000), 291 (7100) and 374 (8800) nm. λ_{min} 206 (infl.), 245, 279, 289 and 314 nm. ^{1}H NMR (100 MHz, $CDCl_3$) δ 1.02 (3 H, d, *J* 7 Hz, –CH_3), 3.64 (6 H, s, both –$COOCH_3$), 6.90 (2 H, s, H-2 and H-6) and 8.42 (1 H, s, NH). MS M$^+$ at *m/e* 354 corresponding to $C_{20}H_{22}N_2O_4$.

Cyclizations

General procedure. The 1,4-dihydropyridine derivative was stirred for 12 hr in a soln of anhyd MeOH presaturated with dry HCl gas. The soln was then poured slowly into a suspension of $NaHCO_3$ in CH_2Cl_2. The inorganic salts were filtered off and the dried filtrate evaporated under vacuum. The residue was chromatographed on alumina (act. IV).

1*α*,3 - *Dimethoxycarbonyl* - 1,2,6,7,12,12b*α* - *hexahydroindolo*[2,3-a]*quinolizine* **7a** *and* 1*β*,3 - *dimethoxycarbonyl* - 1,2,6,7,12,12b*α* - *hexahydroindolo*[2,3-a]*quinolizine* **7b**. Cyclization of 170 mg of **9** yielded a mixture of **7a** and **7b**.

Compound **7a** (61 mg), m.p. 146–147° (Et_2O). IR (KBr) NH 3410 (s), C=O 1715 (s) and 1680 (s), C=C 1630 (s) cm^{-1}. UV [EtOH 94% (*e*)] λ_{max} 206 (23,300), 223 (22,800) and 292 (20,000) nm. λ_{min} 213 and 250 nm. ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.63 (3 H, s, –$COOCH_3$), 3.73 (3 H, s, –$COOCH_3$), 4.73 (1 H, br m, H-12b), 7.42 (1 H, s, H-4) and 8.32 (1 H, s, NH). MS M$^+$ at *m/e* 340 corresponding to $C_{19}H_{20}N_2O_4$. Other noteworthy peaks at *m/e* 339, 325, 309 and 281.

Compound **7b** (63 mg), m.p. 186–188° (Et_2O). IR (KBr) NH 3350 (s), C=O 1720 (s) and 1680 (s), C=C 1615 (s) cm^{-1}. UV [EtOH 94% (*e*)] λ_{max} 204 (infl.) (10,200), 224 (20,500) and 293 (21,800) nm. λ_{min} 205 (infl.) and 255 nm. ^{1}H NMR (60 MHz, $CDCl_3$) δ 3.59 (3 H, s, –$COOCH_3$), 3.61 (3 H, s, –$COOCH_3$) 4.75 (1 H, br s, H-12b), 7.38 (1 H, s, H-4) and 8.85 (1 H, s, NH). MS M$^+$ at *m/e* 340 corresponding to $C_{19}H_{20}N_2O_4$. Other noteworthy peaks at *m/e* 339, 325, 309 and 281.

2 - *Deuterio* - 1*α*,3 - *dimethoxycarbonyl* - 1,2,6,7,12,12b*α* - *hexahydroindolo*[2,3-a]*quinolizine* **7a**-2-d_1 *and* 2 - *deuterio* - 1*β*,3 - *dimethoxycarbonyl* - 1,2,6,7,12,12b*α* - *hexahydroindolo*[2,3-a]*quinolizine* **7b**-2-d_1. Cyclisation of 70 mg of **9**-4-d_1 yielded a mixture of **7a**-2-d_1 and **7b**-2-d_1.

Compound **7a**-2-d_1 (25 mg), m.p. 147–149° (Et_2O). MS M$^+$ at *m/e* 341. Other noteworthy peaks at *m/e* 340, 326, 310 and 282.

Compound **7b**-2-d_1 (20 mg), m.p. 184–185° (Et_2O). MS M$^+$ at *m/e* 341. Other noteworthy peaks at *m/e* 340, 326, 310 and 282.

1*α*,3 - *Dimethoxycarbonyl* - 2*α* - *methyl* - 1,2,6,7,12,12b*α* - *hexahydroindolo*[2,3-a]*quinolizine* **8a** *and* 1*β*,3 - *dimethoxycarbonyl* - 2*α* - *methyl* - 1,2,6,7,12,12b*α* - *hexahydroindolo*[2,3-a]*quinolizine* **8b**. Cyclization of 230 mg of **10** yielded a mixture of **8a** and **8b**.

Compound **8a** (124 mg), m.p. 195–197° (Et_2O). IR (KBr) NH 3365 (s), C=O 1730 (s) and 1680 (s), C=C 1610 (s) cm^{-1}. UV [EtOH 94% (*e*)] λ_{max} 206 (infl.) (18,000), 223 (27,000) and 293 (25,500) nm. λ_{min} 207 (infl.) and 251 nm. ^{1}H NMR (60 MHz, $CDCl_3$) δ 0.72 (3 H, d, *J* 7 Hz, –CH_3), 3.62 (3 H, s, –$COOCH_3$), 3.80 (3 H, s, –$COOCH_3$), 4.94 (1 H, m, H-12b), 7.37 (1 H, s, H-4) and 9.30 (1 H, s, NH). MS M$^+$ at *m/e* 354 corresponding to $C_{20}H_{22}N_2O_4$. Other noteworthy peaks at *m/e* 353, 339, 323 and 295.

Compound **8b** (10 mg), m.p. 240–243° (MeOH). IR (KBr) NH 3275 (s), C=O 1740 (s) and 1665 (s), C=C 1580 (s) cm^{-1}. UV [EtOH 94% (*e*)] λ_{max} 206 (infl.) (20,500), 223 (27,300) and 293 (26,000) nm. λ_{min} 208 (infl.) and 251 nm. ^{1}H NMR (60 MHz, $CDCl_3$) δ 1.28 (3 H, d, *J* 7 Hz, –CH_3), 3.30 (3 H, s, –$COOCH_3$), 3.67 (3 H, s, –$COOCH_3$), 4.65 (1 H, br s, H-12b), 7.50 (1 H, s, H-4) and 8.12 (1 H, s, NH). MS M$^+$ at *m/e* 354 corresponding to $C_{20}H_{22}N_2O_4$. Other noteworthy peaks at *m/e* 353, 339, 323 and 295.

$NaBH_4$/AcOH Reductions

General procedure. $NaBH_4$ (or $NaBD_4$) was added in small portions to an externally cooled, magnetically stirred soln of 1,2,6,7,12,12b - hexahydroindolo[2,3-a]quinolizine derivative in glacial AcOH. The soln was allowed to reach room temp. and the stirring was continued for 1 hr. Water was cautiously added and the soln then slowly poured into a suspension of $NaHCO_3$ in CH_2Cl_2. The inorganic salts were filtered off and the dried filtrate evaporated under vacuum. The residue was chromatographed on

*δ 49.2 (C-1), 36.4 (C-2), 44.6 (C-3), 57.6 (C-4), 51.4 (C-6), 21.9 (C-7), 109.8 (C-7a), 133.2 (C-12a) and 60.5 (C-12b).

alumina (act. IV). The components were separated by preparative silica gel plates.

1α,3β - Dimethoxycarbonyl - 1,2,3,4,6,7,12,12bα - octahydroindolo[2,3-a]quinolizine **3a** *and 1α,3α - dimethoxycarbonyl - 1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-a]quinolizine* **3b**. Reaction between 172 mg of **7a**, 2 g of $NaBH_4$ and 40 ml of glacial AcOH yielded a mixture of **3a** and **3b**.

Compound **3a** (54 mg), m.p. 178–179° (MeOH). IR (KBr) NH 3420 (s), Bohlmann bands 2815 (vw) and 2770 (vw), C=O 1730 (s) and 1715 (s) cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$) δ 3.70 (3 H, s, $-COOCH_3$), 3.79 (3 H, s, $-COOCH_3$) and 8.15 (1 H, br s, NH). MS M^+ at *m/e* 342 corresponding to $C_{19}H_{22}N_2O_4$. Other noteworthy peaks at *m/e* 341, 311, 283, 256, 255, 170 and 169.

Compound **3b** (60 mg), m.p. 142–143° (Et_2O). Identical (IR, ^1H NMR, ^{13}C NMR, MS, TLC) with the sample described earlier (Ref. 1, compound XXII).

2 - Deuterio - 1α,3β - dimethoxycarbonyl - 1,2,3,4,6,7,12,12bα - octahydroindolo[2,3-a]quinolizine **3a**-2-d_1 *and 2 - deuterio - 1α,3α - dimethoxycarbonyl - 1,2,3,4,6,7,12,12bα - octahydroindolo[2,3-a]quinolizine* **3b**-2-d_1. Reaction between 135 mg of **7a**-2-d_1, 1.5 g of $NaBH_4$ and 30 ml of glacial AcOH yielded a mixture of **3a**-2-d_1 and **3b**-2-d_1.

Compound **3a**-2-d_1 (27 mg), m.p. 178–180° (MeOH). MS M^+ at *m/e* 343. Other noteworthy peaks at *m/e* 342, 312, 284, 256, 255, 170 and 169.

Compound **3b**-2-d_1 (30 mg), m.p. 140–141° (Et_2O). MS M^+ at *m/e* 343. Other noteworthy peaks at *m/e* 342, 312, 284, 256, 255, 170 and 169.

4 - Deuterio - 1α,3β - dimethoxycarbonyl - 1,2,3,4,6,7,12,12bα - octahydroindolo[2,3-a]quinolizine **3a**-4-d_1 *and 4 - deuterio - 1α,3α - dimethoxycarbonyl - 1,2,3,4,6,7,12,12bα - octahydroindolo[2,3-a]quinolizine* **3b**-4-d_1. Reaction between 64 mg of **7a**, 900 mg of $NaBD_4$ and 20 ml of glacial AcOH yielded a mixture of **3a**-4-d_1 and **3b**-4-d_1.

Compound **3a**-4-d_1 (20 mg), m.p. 179–181° (MeOH). MS M^+ at *m/e* 343. Other noteworthy peaks at *m/e* 342, 341, 312, 284, 257, 256, 170 and 169.

Compound **3b**-4-d_1 (23 mg), m.p. 140–142° (Et_2O). MS M^+ at *m/e* 343. Other noteworthy peaks at *m/e* 342, 341, 312, 284, 257, 256, 170 and 169.

1β,3β - Dimethoxycarbonyl - 1,2,3,4,6,7,12,12bα - octahydroindolo[2,3-a]quinolizine **3c** *and 1β,3α - dimethoxycarbonyl - 1,2,3,4,6,7,12,12bα-octahydroindolo[2,3-a]quinolizine* **3d**. Reaction between 170 mg of **7b**, 2 g of $NaBH_4$ and 35 ml of glacial AcOH yielded a mixture of **3c** and **3d**.

Compound **3c** (85 mg), m.p. 137–139° (MeOH), IR (KBr) NH 3405 (s), no Bohlmann bands, C=O 1725 (s) and 1715 (s) cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$) δ 3.60 (3 H, s, $-COOCH_3$), 3.86 (3 H, s, $-COOCH_3$), 4.70 (1 H, br d, *J* 4 Hz, H-12b) and 8.80 (1 H, br s, NH). MS M^+ at *m/e* 342 corresponding to $C_{19}H_{22}N_2O_4$. Other noteworthy peaks at *m/e* 341, 311, 283, 256, 255, 170 and 169.

Compound **3d** (60 mg), m.p. 170–172° (MeOH). IR (KBr) NH 3370 (s), Bohlmann bands 2800 (w) and 2755 (w), C=O 1720 (s) and 1710 (s) cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$) δ 3.48 (3 H, s, $-COOCH_3$), 3.72 (3 H, s, $-COOCH_3$) and 8.00 (1 H, br s, NH). MS M^+ at *m/e* 342 corresponding to $C_{19}H_{22}N_2O_4$. Other noteworthy peaks at *m/e* 341, 311, 283, 256, 255, 170 and 169.

1α,3α - Dimethoxycarbonyl - 2α - methyl - 1,2,3,4,6,7,12,12bα - octahydroindolo[2,3-a]quinolizine **4a** *and 1α,3β - dimethoxycarbonyl - 2α - methyl - 1,2,3,4,6,7,12,12bα - octahydroindolo[2,3-a]quinolizine* **4b**. Reaction between 155 mg of **8a**, 2 g of $NaBH_4$ and 35 ml of glacial AcOH yielded a mixture of **4a** and **4b**.

Compound **4a** (57 mg), m.p. 143–146° (MeOH). IR (KBr) NH 3450 (s), Bohlmann band 2785 (w), C=O 1730 (s) and 1710 (s) cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$) δ 0.92 (3 H, d, *J* 7 Hz, $-CH_3$), 3.66 (3 H, s, $-COOCH_3$), 3.77 (3 H, s, $-COOCH_3$) and 8.40 (1 H, s, NH). MS M^+ at *m/e* 356 corresponding to $C_{20}H_{24}N_2O_4$. Other noteworthy peaks at *m/e* 355, 325, 297, 256, 255, 170 and 169. Identical (^1H NMR, ^{13}C NMR, TLC) with the sample described earlier (Ref. 1, compound XXIII isomer B).

Compound **4b** (32 mg), m.p. 195–196° (MeOH). IR (KBr) NH 3450 (s), Bohlmann bands 2815 (w) and 2780 (w), C=O 1725 (s) and 1710 (s) cm^{-1}. ^1H NMR (100 MHz, $CDCl_3$) δ 1.05 (3 H, d, *J* 7 Hz, $-CH_3$), 3.70 (3 H, s, $-COOCH_3$), 3.80 (3 H, s, $-COOCH_3$) and 8.40 (1 H, s, NH). MS M^+ at *m/e* 356 corresponding to $C_{20}H_{24}N_2O_4$. Other noteworthy peaks at *m/e* 355, 325, 297, 256, 255, 170 and 169.

4-Deuterio - 1α,3α - dimethoxycarbonyl - 2α - methyl - 1,2,3,4,6,7,12,12bα - octahydroindolo[2,3-a]quinolizine **4a**-4-d_1 *and 4 - deuterio - 1α,3β - dimethoxycarbonyl - 2α - methyl - 1,2,3,4,6,7,12,12bα - octahydroindolo[2,3-a]quinolizine* **4b**-4-d_1. Reaction between 80 mg of **8a**, 400 mg of $NaBD_4$ and 20 ml of glacial AcOH yielded a mixture of **4a**-4-d_1 and **4b**-4-d_1.

Compound **4a**-4-d_1 (31 mg), m.p. 142–145° (MeOH). MS M^+ at *m/e* 357. Other noteworthy peaks at *m/e* 356, 355, 326, 298, 257, 256, 170 and 169.

Compound **4b**-4-d_1 (6 mg), m.p. 193–195° (MeOH). MS M^+ at *m/e* 357. Other noteworthy peaks at *m/e* 356, 355, 326, 298, 257, 256, 170 and 169.

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