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SYNTHETIC STUDIES IN THE ALKALOID FIELD—V†

DETERMINATION OF THE STEREOCHEMISTRY OF SEVERAL 1,2,3,4,6,7,12,12b-OCTAHYDRO-3-METHOXYCARBONYLINDOLO-[2,3-a]QUINOLIZINE DERIVATIVES BY ^{13}C NMR SPECTRAL ANALYSIS

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Abstract—The C(12b)–C(2)–C(3) stereochemical relationship in several racemic 1,2,3,4,6,7,12,12b-octahydro-3-methoxycarbonylindolo[2,3-a]quinolizine derivatives has been determined by ^{13}C NMR spectral analysis. The proper shift assignment was confirmed by recording the spectra of selectively deuterated derivatives. The shifts of specific carbons are found to be conformationally diagnostic. The C(12b)–C(2)–C(3) stereochemical relationship in indolo[2,3-a]quinolizines obtained by selective alkaline decarboalkoxylative cyclization of partially hydrogenated 1-[2-(3-indolyl)ethyl]3,5-dimethoxycarbonylpyridine derivatives is discussed.

In connection with our studies concerning the preparation of indole alkaloid models of vallesiachotamine 1 type by selective alkaline decarboalkoxylative cyclization of partially hydrogenated 1 - [2 - (3 - indolyl)ethyl]3,5 - dimethoxycarbonylpyridine derivatives,[1] we found the tetrahydropyridine derivative 2 (2 in Ref. 1; XV in Ref. 2) to yield both of the two possible diastereoisomers 3a and 3b, but the tetrahydropyridine derivative 4 (3 in Ref. 1; XVI in Ref. 2) only one of the four possible diastereoisomers 5a, 5b, 5c and 5d. The analytical data confirming the gross structures 3 and 5 (5 and 6, respectively, in Ref. 1) of the prepared compounds were given,[1] but it was considered premature to publish the results concerning their stereochemistry. Claims for the uniform formation of C(12b)H–C(2)H *trans* compounds in the alkaline decarboalkoxylative cyclization of appropriate tetrahydropyridines have been made,[3,4] but the recent ambiguity in the preparation of *dl*-18,19-dihydroantirhine by an analogous method[4,5] has clearly shown that the matter requires further investigation and makes a proper determination of the C(12b)–C(2) stereochemical relationship in compound 5 (6a in Ref. 1) of special interest.

Recently we have developed a method[6] permitting the C(12b)–C(2) relationship to be chosen with a high degree of stereoselectivity in the preparation of 1,2,6,7,12,12b - hexahydro - 2 - methyl - 3 - methoxycarbonylindolo[2,3-a]quinolizines 6 and 7 (11b and 12b, respectively, in Ref. 6). This method, combined with the $NaBH_4$/acetic acid reduction[7,8] of the formed C(2) epimers to the corresponding 1,2,3,4,6,7,12,12b-octahydrocompounds 5a, 5b, 5c and 5d, made all four possible stereoisomers available for analysis. Moreover, the $NaBH_4$/acetic acid reduction of the recently described[1,6] 1,2,6,7,12,12b - hexahydro - 3 - methoxycarbonylindolo[2,3-a]quinolizine 8 (8 in Ref. 1; 11a in Ref. 6) permitted the additional and easy preparation of compounds 3a and 3b. Thus the time appeared ripe for a detailed determination of the stereochemistry of all of the above-mentioned 1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizines, 3a, 3b, 5a, 5b, 5c and 5d.

During the last few years, ^{13}C NMR analysis has proven to be a powerful tool for the structure elucidation and analysis of organic compounds. The advances in the field of stereochemical determinations have been especially notable. Hence, ^{13}C NMR analysis seemed to be the *méthode de choix* for the determination of the stereochemistry of compounds 3a, 3b, 5a, 5b, 5c and 5d, and the results described in the present report were mainly obtained by this method.

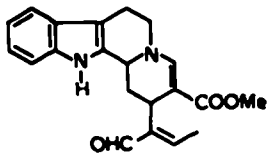
RESULTS

The $NaBH_4$/acetic acid reduction[7,8] of the recently described[1,6] 1,2,6,7,12,12b - hexahydro - 3 - methoxycarbonylindolo[2,3-a]quinolizine 8 (8 in Ref. 1; 11a in Ref. 6) afforded compounds 3a and 3b in good yield. Similar treatment of the recently described[6] C(2) epimeric 1,2,6,7,12,12b - hexahydro - 2 - methyl - 3 - methoxycarbonylindolo[2,3-a]quinolizines 6 and 7 (11b and 12b, respectively, in Ref. 6) yielded compounds 5a, 5b, 5c and 5d.

Several selectively deuterated analogues of compounds 3a, 3b, 5a, 5b, 5c and 5d were needed for comparison. The replacement of $NaBH_4$ by $NaBD_4$ in the $NaBH_4$/acetic acid reduction (*vide supra*) permitted the preparation of monodeuterioderivatives 3a-4-d_1, 3b-4-d_1, 5a-4-d_1, 5b-4-d_1, 5c-4-d_1 and 5d-4-d_1 with high deuterium content.‡ The dithionite reduction[6] of 1 - [2 - (3 - indolyl)ethyl] - 3 - methoxycarbonyl pyridinium bromide 9 (II in Ref. 2; 4a in Ref. 6) in D_2O/CH_3OD afforded 4 - deuterio - 1 - [2 - (3 - indolyl)ethyl] - 3 - methoxycarbonyl - 1,4 - dihydropyridine 10-4-d_1, which was transformed by acid-induced cyclization to 2 - deuterio - 1,2,6,7,12,12b - hexahydro - 3 - methoxycarbonylindolo[2,3-a]quinoliz-

†IV. M. Lounasmaa and C.-J. Johansson, *Tetrahedron* 33, 113 (1977). This work was first presented as a part of a series of lectures by M. L. at the University of Helsinki (Autumn 1976).

‡The possible *cis* and/or *trans* C(12b)H–C(2)D or C(12b)H–C(4)D relationship in the prepared tetracyclic monodeuterioderivatives was without importance for the present work and was not determined.



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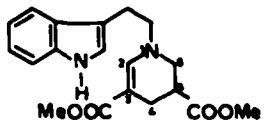

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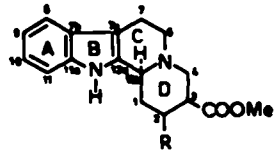
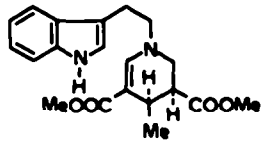


3 R = H
3a R = H, 3α-COOMe
3b R = H, 3β-COOMe
4 R = Me
4a R = Me, 2α-Me, 3α-COOMe
4b R = Me, 2α-Me, 3β-COOMe
4c R = Me, 2β-Me, 3α-COOMe
4d R = Me, 2β-Me, 3β-COOMe



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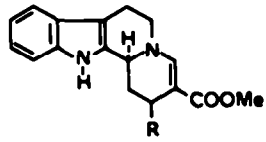
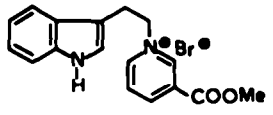


6 R = Me; 2α-Me
7 R = Me; 2β-Me
8 R = H



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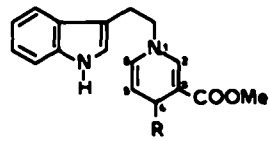
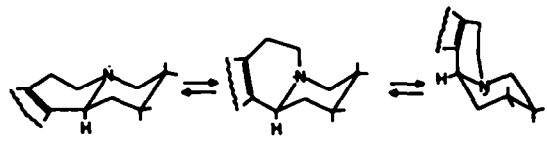


10 R = H
11 R = Me

ine 6-2-d_1. The $NaBH_4$/acetic acid reduction yielded monodeuterioderivatives 3a-2-d_1 and 3b-2-d_1.

Compounds 3a–b and 5a–d can exist in conformational equilibrium by nitrogen inversion and *cis*-decalin type ring interconversion (Scheme 1; only one enantiomer is illustrated). The conformer with a *trans* diaxial C/D ring juncture is not possible. Ring C is assumed to be in the half-chair conformation and only the chair forms of ring D are considered.

The *trans* C/D quinolizine ring juncture can be estimated to be 10.9 kJ/mol more stable than the *cis* ring juncture.† This supports the preponderance of conformation a in the conformational equilibrium of all compounds examined except 5b, where the equilibrium is slightly shifted in favour of conformation c.‡



9 8 c

Scheme 1. Conformational equilibrium of compounds 3a–b and 5a–d.

The preponderance of conformation a in all tetracyclic compounds examined except 5b, is also supported by ^1H NMR spectroscopy. The absence of any signal downfield from δ 3.8 that could be assigned to the C(12b)H is characteristic of conformation a (*trans*-quinolizine juncture).[11-14] Owing to the diamagnetic displacement effect of the electron pair of the basic nitrogen, it can be expected that in conformations b and c (*cis*-quinolizine junctures) the C(12b)H signal appears at about 0.5 ppm lower field.[13]§

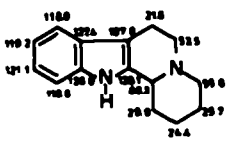
Moreover, the intensities found for the so-called Bohlmann bands[16] in the IR spectra of the tetracyclic compounds examined are in agreement with the conformational conclusions presented (*vide infra*).

The C(12b)–C(2)–C(3) stereochemical relationships proposed for 3a–b and 5a–d were determined by ^{13}C NMR spectral analysis. The fully proton-decoupled spectra of 3a, 3b, 5a, 5b, 5c 5d and 12, as well as of the intermediate 1,4-dihydropyridine derivatives 10 and 11, taken in $CDCl_3$, showed the chemical shifts depicted on the formulas. The proper shift assignment was confirmed by single-frequency, off-resonance decoupled (sford)

†The *trans* diequatorial juncture in quinolizine itself has been shown to be 10.9 kJ/mol (2.6 kcal/mol) more stable than the *cis* juncture.[9]

‡About 60% of c. Based on an A-value difference of 0.8 kJ/mol. A-values used for a methyl group and a methoxycarbonyl group are 7.1 kJ/mol (1.7 kcal/mol) and 4.6 kJ/mol (1.1 kcal/mol), respectively.[10] As a first approximation, the A-values are assumed to be additive. The small nonbonded interactions present in conformers b and c of several compounds, which further favour conformer a, are not taken into account.

§In mobile systems where several conformations are possible the chemical shift of any given proton will be the weighted time average of its chemical shifts in the pure conformations in question, provided that the conformational interchange is rapid. The C(12b)H signal appearing at δ 4.10 in the ^1H NMR spectrum of 5b is in full agreement with the conformational considerations presented (*vide supra*).



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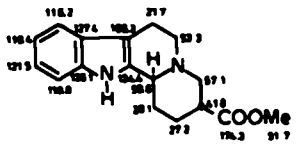
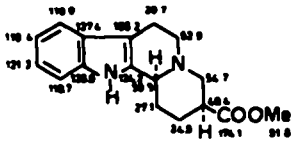
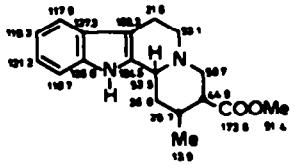


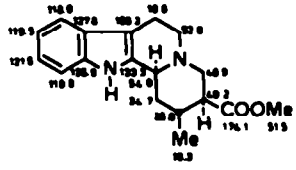
3a



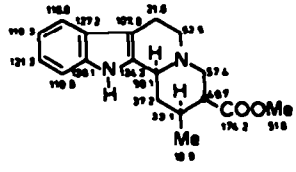
3b



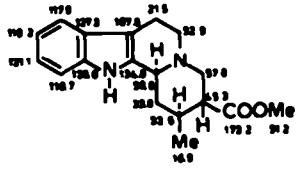
5a



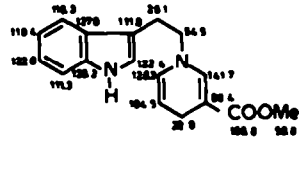
5b



5c



5d



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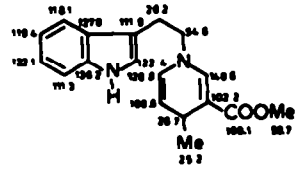

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Table 1. ^{13}C Chemical shifts of deuterated indolo-[2,3-a]-

	3a-2-d_1	3b-2-d_1	3a-4-d_1	3b-4-d_1	5a-4-d_1	5b-4-d_1	5c-4-d_1	5d-4-d_1
C(1)	29.2	27.2	29.0	27.0	36.1	34.6	37.4	33.6
C(2)			27.1	24.4	28.7	28.0	33.1	32.5
C(3)	41.9	40.4	41.6	40.3	44.9	48.9	49.6	45.1
C(4)	57.1	54.8						
C(6)	53.3	53.0	53.1	52.8	53.1	51.7	52.5	52.9
C(7)	21.8	20.8	21.7	20.5	21.6	18.2	21.7	21.5
C(7a)	108.1	108.4	108.1	108.1	108.4	107.8	107.7	107.8
C(7b)	127.2	127.6	127.2	127.5	127.3	127.6	127.2	127.3
C(8)	118.2	118.1	118.0	118.0	118.0	117.9	118.1	118.0
C(9)	119.5	119.5	119.3	119.3	119.3	119.3	119.4	119.3
C(10)	121.5	121.4	121.3	121.3	121.3	121.3	121.4	121.2
C(11)	110.8	110.8	110.7	110.7	110.7	110.8	110.7	110.7
C(11a)	136.0	136.1	136.0	135.9	136.0	135.7	136.0	136.0
C(12a)	134.5	134.3	134.3	134.0	134.4	133.1	134.1	134.8
C(12b)	59.5	58.6	59.4	58.3	53.6	53.7	59.1	59.6
-Me					13.9	19.3	20.0	19.0
-OMe	51.6	51.7	51.7	51.7	51.5	51.5	51.6	51.2
C = O	174.2	174.0	174.1	174.0	173.6	174.1	174.1	173.2

† All the spectra were recorded in $CDCl_3$ solution.

The δ values are in parts per million downfield from Me_4Si.

spectra, by recording the spectra of selected deuterated derivatives (Table 1),† and by comparison with the earlier shift assignment.[17-19]

The replacement of one of the two hydrogens by deuterium on a C atom causes a strong disturbance in the corresponding ^{13}C signal. This effect follows from the increased spin-lattice relaxation time (T_1) of the deuterated carbon, from the increased complexity due to the ^{13}C–D splitting, and from the decreased intensity due to the decreased nuclear Overhauser effect (NOE). The signals of the partly deuterated carbons show, in general, an upfield shift of 0.2–0.5 ppm. The carbons adjacent to the deuterated ones show a similar, although smaller shift. In consequence of this, great caution needs to be exercised in interpreting by deuteration the signals of carbons possessing very similar chemical shifts.‡

†The proper shift assignment of C(4) (22.0 ppm) in compound 10 was confirmed by the spectrum of the 4-d_1 counterpart of 10.

‡An excellent illustration of this is the interpretation of the spectrum of compound 5b: the signals of the carbons C(3) and C(4) of the nondeuterated compound appear at 49.2 and 48.9 ppm, respectively, but in the spectrum of the 4-d_1 counterpart at 48.9 and 48.5 (apparent triplet) ppm. In the present case the correct assignment of the signals could be confirmed by single-frequency, off-resonance decoupled (sford) spectrum of compound 5b-4-d_1.

A comparison of the chemical shifts of C(3), C(2), C(4) and C(1) in 12, 3a and 3b gives clear evidence of the stereostructures depicted in the formulas. Especially, the γ-shielding effect at C(1) in 3b is characteristic. The results seem to indicate that equatorial methoxycarbonyl groups cause α-, β- and γ-deshielding effects of *ca.* 16, 2 and 0 ppm, respectively, and that axial methoxycarbonyl groups cause α- and β-deshielding effects of *ca.* 14 and 0 ppm, respectively, but a γ-shielding effect of *ca.* 3 ppm. However, the conformational considerations (*vide supra*) must be taken into account.

Taking the chemical shifts found for 3a and 3b as a basis, the equatorial and axial Me group α-, β- and γ-parameters† were used to predict the chemical shifts of C(2), C(1), C(3), C(12b) and C(4) in 5c and 5a, and 5d and 5b, respectively. A comparison of the observed and calculated chemical shifts‡ (Table 2), keeping the conformational considerations (*vide supra*) in mind, fully confirms the C(12b)–C(2)–C(3) stereochemical relationships presented for 5a–d.

The chemical shift of C(7) reflects the contribution of different conformations to the conformational equilibrium (due to the involvement of C(7) with C(4)), whereas the chemical shift of C(12b) is in the first place influenced by the γ-effect of the C(2) methyl substituent.

Taking the chemical shifts found for C(7) in *cis*- and *trans* - indolo[2,3 - a]quinolizine systems (21.8 and 16.8 ppm, respectively)§ as a basis, the present conformational equilibrium between conformers a and c (the contribution of conformer b is considered to be negligible) can be estimated with a relatively high degree of accuracy (*vide supra*).¶

The compounds (5a, 5b and 6a in Ref. 1) obtained by selective alkaline decarboalkoxylative cyclization[1] of partially hydrogenated 1 - [2 - (3 - indolyl)ethyl] - 3,5 - dimethoxycarbonylpyridine derivatives proved to be identical (m.p., TLC, ^{13}C NMR) with 3a, 3b and 5a, respectively, and thus their stereochemistry was settled. The stereochemistry found for 5a (6a in Ref. 1) indicates that in the case of 1 - [2 - (3 - indolyl)ethyl] - 3,5 - dimethoxycarbonyl - 4 - methyl - 1,4,5,6 - tetrahydropyridine 4 (3 in Ref. 1; XVI in Ref. 2) the alkaline decarboalkoxylative cyclization leads to C(12b)H–C(2)H *trans* configuration, which, however, in all evidence is a consequence of the C(4)H–C(5)H *cis* relationship in the

Table 2. Comparison of the observed and calculated ^{13}C chemical shifts for C(2), C(1), C(3), C(12b) and C(4) in compounds 3a, 3b, 5a, 5b, 5c and 5d

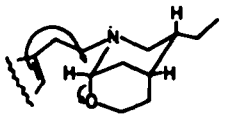
	3a	5c	Calc. for an eq. CH_3-group	Calc. for an ax. CH_3-group	5a	3b	5d	Calc. for an eq. CH_3-group	Calc. for an ax. CH_3-group	5b
C(2)	27.2	33.1	32.8	28.3	28.7	24.5	32.6	30.1	23.6	28.0
C(1)	29.1	37.2	36.0	34.3	36.0	27.1	33.6	36.0	32.3	34.7
C(3)	41.8	49.7	50.7	47.0	44.9	40.4	45.3	49.3	45.6	49.2
C(12b)	39.4	39.1	39.6	34.2	33.5	38.5	39.8	38.5	33.1	34.0
C(4)	57.1	57.4	57.1	51.7	50.7	54.7	57.8	54.7	48.3	48.9

†For an equatorial Me group, 5.6, 8.9 and 0.0 ppm, respectively. For an axial Me group, 1.1, 5.2 and −5.4 ppm, respectively.[20]

‡For calculations the compounds were considered, as a first approximation, to be totally in the conformation a.

§The values 21.8 and 16.8 ppm represent the shifts found for the signals of C(7) in *cis*- and *trans* - 2 - t - butyl - 1,2,3,4,6,7,12,12b - octahydroindolo[2,3-a]quinolizine, respectively (2 and 3 in Ref. 17). It has been estimated that in the case of the *cis*-2-t-butyl derivative the contribution of conformer a to the conformational equilibrium is at least 95%, whereas in the case of the *trans*-2-t-butyl derivative the contribution of conformer c exceeds 99.9%. It is assumed, that the values 21.8 and 16.8 ppm represent relatively well also the chemical shifts of C(7) in pure conformations a and c of 5b and 3b.

¶Correlation of the value 18.6 ppm, found for the signal of C(7) in compound 5b, with the values 21.8 and 16.8 ppm indicates that the contribution of conformer c to the conformational equilibrium between a and c is about 60%. This is in good agreement with the thermodynamic calculations (*vide supra*). Similarly, the value 20.7 ppm found for the signal of C(7) in compound 3b indicates that the contribution of conformer c to the conformational equilibrium is about 20–25%.



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intermediate 1,4,5,6-tetrahydropyridine derivative 4,[1,2]† and thus cannot be used by way of analogy to resolve the ambiguity existing in the preparation of *dl*-18,19-dihydroantirhine (*vide supra*).

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 a Jeol JNM-PMX-60 instrument and the ^{13}C NMR spectra with a 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 100–120°. The elemental compositions when given for the molecular ions were confirmed by high-resolution mass measurements. The m.ps were determined in a Büchi capillary m.p. apparatus and are uncorrected.

4 - *Deuterio* - 1 - [2 - (- *indolyl*)*ethyl*] - 3 - *methoxycarbonyl* - 1,4 - *dihydropyridine* **10-4-d_1**. 2.2 g of sodium dithionite was added in small portions during 1 hr to a magnetically stirred soln of **9** (810 mg) and $NaHCO_3$ (3.5 g) in 40 ml of D_2O/CH_3OD (1:1) under N_2. The mixture was stirred for 20 hr, the CH_3OD evaporated off under vacuum, and the mixture extracted several times with dichloromethane. The extracts were washed with water, dried over Na_2SO_4, and evaporated under vacuum. The residue was chromatographed on alumina (act. IV), giving 496 mg (78%) of a solid whose recrystallization from MeOH yielded **10-4-d_1** as yellow crystals, m.p. 119–123°; MS M$^+$ at *m/e* 283. Other noteworthy peaks at *m/e* 282, 268, 252, 153, 144 and 130.

2 - *Deuterio* - 1,2,6,7,12,12*b* - *hexahydro* - 3 - *methoxycarbonylindolo*[2,3-*a*]*quinolizine* **8-2-d_1**. A soln of **10-4-d_1** (496 mg) in anhyd MeOH was saturated with dry HCl gas during a 2 hr period. The soln was left standing at room temp. for 18 hr and then slowly poured into a suspension of $NaHCO_3$ in dichloromethane. The inorganic salts were filtered off and the dried filtrate evaporated under vacuum. The residue was chromatographed on alumina (act. IV), giving 489 mg (98%) of a solid whose recrystallization from MeOH yielded **8-2-d_1** as yellow crystals, m.p. 170–172°; MS M$^+$ at *m/e* 283. Other noteworthy peaks at *m/e* 282, 252 and 224.

$NaBH_4$/*acetic acid reductions.*

General procedure. Sodium borohydride (or sodium borodeuteride) 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 slowly poured into a suspension of $NaHCO_3$ in dichloromethane. The inorganic salts were filtered off and the dried filtrate evaporated under vacuum. The residue was chromatographed on alumina (act. IV). The components were separated by preparative silicagel plates.‡

1,2,3,4,6,7,12,12*ba* - *Octahydro* - 3*α* - *methoxycarbonylindolo*[2,3-*a*]*quinolizine* **3a** *and* 1,2,3,4,6,7,12,12*ba* - *octahydro* - 3*β* - *methoxycarbonylindolo*[2,3-*a*]*quinolizine* **3b**. Reaction between **8** (230 mg) $NaBH_4$ (2.0 g) and 60 ml glacial AcOH yielded a mixture of **3a** and **3b**.

Compound **3a** (100 mg), m.p. 192–194° (MeOH); IR ($CHCl_3$) Bohlmann bands 2810 (m) and 2760 (m) C=O 1730 (s) cm^{-1}; UV (EtOH 94%) λ_{max} 205 (infl.) (*ε* 18,450), 226 (*ε* 40,350), 284 (*ε* 9100) and 291 (*ε* 7950) nm. λ_{min} 206 (infl.), 249 and 289 nm; ^{1}H NMR ($CDCl_3$) *δ* 3.72 (3H, s, $-COOCH_3$) and 8.41 (1H, s, N–H); MS M$^+$ at *m/e* 284 corresponding to $C_{17}H_{20}N_2O_2$. Other noteworthy peaks at *m/e* 283, 269, 253, 225, 184, 170, 169 and 156.

Compound **3b** (70 mg), m.p. 223–225° (MeOH); IR ($CHCl_3$) Bohlmann bands 2805 (w) and 2760 (w) C=O 1730 cm^{-1}; UV (EtOH 94%) λ_{max} 205 (*ε* 14,050), 227 (*ε* 28,400), 285 (*ε* 6670) and 292 (*ε* 5960) nm. λ_{min} 207, 250 and 289 nm; ^{1}H NMR (DMSO-d_6) *δ* 3.59 (3H, s, $-COOCH_3$). MS M$^+$ at *m/e* 284 corresponding to $C_{17}H_{20}N_2O_2$. Other noteworthy peaks at *m/e* 283, 269, 253, 225, 184, 170, 169 and 156.

2 - *Deuterio* - 1,2,3,4,6,7,12,12*ba* - *octahydro* - 3*α* - *methoxycarbonylindolo*[2,3-*a*]*quinolizine* **3a-2-d_1** *and* 2 - *deuterio* - 1,2,3,4,6,7,12,12*ba* - *octahydro* - 3*β* - *methoxycarbonylindolo*[2,3-*a*]*quinolizine* **3b-2-d_1**. Reaction between **8-2-d_1** (425 mg), $NaBH_4$ (3.0 g) and 90 ml glacial AcOH yielded a mixture of **3a-2-d_1** and **3b-2-d_1**.

Compound **3a-2-d_1** (121 mg), m.p. 194–195° (MeOH); MS M$^+$ at *m/e* 285. Other noteworthy peaks at *m/e* 284, 270, 254, 226, 184, 170, 169 and 156.

Compound **3b-2-d_1** (114 mg), m.p. 226–227° (MeOH); MS M$^+$ at *m/e* 285. Other noteworthy peaks at *m/e* 284, 270, 254, 226, 184, 170, 169 and 156.

4 - *Deuterio* - 1,2,3,4,6,7,12,12*ba* - *octahydro* - 3*α* - *methoxycarbonylindolo*[2,3-*a*]*quinolizine* **3a-4-d_1** *and* 4 - *deuterio* - 1,2,3,4,6,7,12,12*ba* - *octahydro* - 3*β* - *methoxycarbonylindolo*[2,3-*a*]*quinolizine* **3b-4-d_1**. Reaction between **8** (297 mg), $NaBD_4$ (2.0 g) and 60 ml glacial AcOH yielded a mixture of **3a-4-d_1** and **3b-4-d_1**.

Compound **3a-4-d_1** (135 mg), m.p. 191–192° (MeOH); MS M$^+$ at *m/e* 285. Other noteworthy peaks at *m/e* 284, 270, 254, 226, 184, 170, 169 and 156.

Compound **3b-4-d_1** (79 mg), m.p. 225–226° (MeOH); MS M$^+$ at *m/e* 285. Other noteworthy peaks at *m/e* 284, 270, 254, 226, 184, 170, 169 and 156.

1,2,3,4,6,7,12,12*ba* - *Octahydro* - 2*α* - *methyl* - 3*α* - *methoxy* - *carbonylindolo*[2,3-*a*]*quinolizine* **5a** *and* 1,2,3,4,6,7,12,12*ba* - *octahydro* - 2*α* - *methyl* - 3*β* - *methoxycarbonylindolo*[2,3-*a*]*quinolizine* **5b**. Reaction between **6** (305 mg), $NaBH_4$ (2.0 g) and 60 ml glacial AcOH yielded a mixture of **5a** and **5b**.

Compound **5a** (74 mg), m.p. 172–174° (MeOH); IR ($CHCl_3$) Bohlmann 2820 (w) and 2770 (w) C=O 1730 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 1.06 (3H, d, *J* = 6 Hz, $-CH_3$), 3.72 (3H, s, $-COOCH_3$), 3.90 (1H, m, C(12b)–H, partly masked) and 7.88 (1H, br s, N–H); MS M$^+$ at *m/e* 298 corresponding to $C_{18}H_{22}N_2O_2$. Other noteworthy peaks at *m/e* 297, 283, 267, 239, 184, 170, 169 and 156.

Compound **5b** (54 mg) m.p. 186–187° (MeOH); IR ($CHCl_3$) Bohlmann 2810 (vw) and 2760 (vw) C=O 1730 (s) cm^{-1}; ^{1}H NMR ($CDCl_3$) *δ* 0.98 (3H, d, *J* = 6 Hz, $-CH_3$), 3.59 (3H, s, $-COOCH_3$), 4.10 (1H, br s, C(12b)–H) and 7.78 (1H, br s, N–H); MS M$^+$ at *m/e* 298 corresponding to $C_{18}H_{22}N_2O_2$. Other noteworthy peaks at *m/e* 297, 283, 267, 239, 184, 170, 169 and 156.

4 - *Deuterio* - 1,2,3,4,6,7,12,12*ba* - *octahydro* - 2*α* - *methyl* - 3*α* - *methoxycarbonylindolo*[2,3-*a*]*quinolizine* **5a-4-d_1** *and* 4 - *deuterio* - 1,2,3,4,6,7,12,12*ba* - *octahydro* - 2*α* - *methyl* - 3*β* - *methoxycarbonylindolo*[2,3-*a*]*quinolizine* **5b-4-d_1**. Reaction between **6** (321 mg), $NaBD_4$ (2.0 g) and 60 ml glacial AcOH yielded a mixture of **5a-4-d_1** and **5b-4-d_1**.

Compound **5a-4-d_1** (111 mg), m.p. 171–173° (MeOH); MS M$^+$ at *m/e* 299. Other noteworthy peaks at *m/e* 298, 284, 268, 240, 184, 170, 169 and 156.

Compound **5b-4-d_1** (69 mg), m.p. 185–186° (MeOH); MS M$^+$ at *m/e* 299. Other noteworthy peaks at *m/e* 298, 284, 268, 240, 184, 170, 169 and 156.

1,2,3,4,6,7,12,12*ba* - *Octahydro* - 2*β* - *methyl* - 3*α* - *methoxy* - *carbonylindolo*[2,3-*a*]*quinolizine* **5c** *and* 1,2,3,4,6,7,12,12*ba* -

†Similar stereochemical results have been obtained by Wenkert[21] in the preparation of *dl*-3-isocoryantheidol (31a in Ref. 21) by alkaline decarboalkoxylative cyclization of the appropriate tetrahydropyridine derivative (30 in Ref. 21). In this case the C(12b)H–C(2)H *trans* configuration found (corresponding to the C(3)H–C(15)H *trans* configuration when the biogenetic numbering is utilized) is in all evidence also a consequence of the C(4)H–C(5)H *cis* relationship in the intermediate 1,4,5,6-tetrahydropyridine derivative used, although an intermediate carbinolamine ether I cannot be completely excluded.

‡The ratio found between the amounts of different C(3) epimers varies slightly due to the easy epimerization of C(3).

octahydro - 2β - methyl - 3β - methoxycarbonylindolo[2,3-a]quinolizine **5d**. Reaction between **7** (250 mg), $NaBH_4$ (2.0 g) and 60 ml glacial AcOH yielded a mixture of **5c** and **5d**.

Compound **5c** (71 mg), m.p. 170–171° (MeOH); IR ($CHCl_3$) Bohlmann 2810 (m) and 2760 (m) C=O 1730 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (3H, d, J = 6 Hz, $-CH_3$), 3.67 (3H, s, $-COOCH_3$) and 7.87 (1H, br s, N–H); MS M^+ at *m/e* 298 corresponding to $C_{18}H_{22}N_2O_2$. Other noteworthy peaks at *m/e* 297, 283, 267, 239, 184, 170, 169 and 156.

Compound **5d** (49 mg), m.p. 171–173° (MeOH); IR ($CHCl_3$) Bohlmann 2805 (w) and 2760 (w) C=O 1730 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.10 (3H, d, J = 6 Hz, $-CH_3$), 3.67 (3H, s, $-COOCH_3$), 3.90 (1H, m, C(12b)–H, partly masked) and 8.14 (1H, br s, N–H); MS M^+ at *m/e* 298 corresponding to $C_{18}H_{22}N_2O_2$. Other noteworthy peaks at *m/e* 297, 283, 267, 239, 184, 170, 169 and 156.

4 - Deuterio - 1,2,3,4,6,7,12,12bα - octahydro - 2β - methyl - 3α - methoxycarbonylindolo[2,3-a]quinolizine **5c-4-d_1** *and 4 - deuterio - 1,2,3,4,6,7,12,12bα - octahydro - 2β - methyl - 3β - methoxycarbonylindolo[2,3-a]quinolizine* **5d-4-d_1**. Reaction between **2** (151 mg), $NaBD_4$ (1.0 g) and 30 ml glacial AcOH yielded a mixture of **5c-4-d_1** and **5d-4-d_1**.

Compounds **5c-4-d_1** (52 mg), m.p. 170–171° (MeOH); MS M^+ at *m/e* 299. Other noteworthy peaks at *m/e* 298, 284, 268, 240, 184, 170, 169 and 156.

Compound **5d-4-d_1** (26 mg), m.p. 171–172° (MeOH); MS M^+ at *m/e* 299. Other noteworthy peaks at *m/e* 298, 284, 268, 240, 184, 170, 169 and 156.

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