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SYNTHETIC STUDIES IN THE ALKALOID FIELD—IV†

THE SODIUM DITHIONITE REDUCTION OF 1-[2-(3-INDOLYL)-ETHYL]-3-METHOXYCARBONYL PYRIDINIUM BROMIDES

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Abstract—The preparation of racemic indolo[2,3-a]quinolizine derivatives by sodium dithionite reduction of appropriate pyridinium bromides has been studied. A method has been found of influencing with high degree of stereoselectivity the C(12b)–C(2) stereochemical relationship in the products formed. The determination of the stereochemistry of the products by comparative examination of their ^{13}C NMR spectra is described. The convenience of the sodium dithionite reduction method for the preparation of vallesiachotamine **1** models is discussed.

Résumé—La préparation des dérivés racémiques de l'indolo[2,3-a]quinolizine par la réduction des bromures de pyridinium appropriés par la dithionite de sodium, a été étudiée. Une méthode pour influencer, avec un haut degré de stéréosélectivité, sur le rapport stéréochimique de C(12b)-C(2) dans les produits formés, a été trouvée. La détermination de la stéréochimie des produits par l'examen comparatif de leurs spectres de rmn du ^{13}C est décrite. La convenance de la méthode de réduction par la dithionite de sodium pour la préparation des modèles de vallésiachotamine **1** est discutée.

In connection with our studies[1,2] concerning the preparation of indole alkaloid models of vallesiachotamine **1**[3] type we became interested in the preparation of 1,2,6,7,12,12b - hexahydro - 3 - methoxycarbonylindolo[2,3 - a] - quinolizine **2** derivatives by acid-induced cyclization of 1 - [2 - (3 - indolyl)ethyl] - 3 - methoxycarbonyl - 1,4 - dihydropyridines **3**. The sodium dithionite reduction of appropriate pyridinium salts seemed to be ideally suited for the preparation of the needed 1,4 - dihydropyridine intermediates because pyridinium salts containing an electron-withdrawing group at C(3) can be readily reduced[4,5] by sodium dithionite to the corresponding 1,4 - dihydropyridines.‡

In the present communication we describe the results obtained by sodium dithionite reduction of three 1 - [2 - (3 - indolyl)ethyl] - 3 - methoxycarbonyl pyridinium bromides **4a-c**, followed by acid-induced transformations of the resulting 1,4 - dihydro compounds into the corresponding indoloquinolizines. Since heretofore no pyridine derivative containing a functional group at C(4) had been employed in the preparation of indoloquinolizine derivatives by sodium dithionite reduction and by acid-induced cyclization, particular attention had to be paid to the C(12b)–C(2) stereochemical relationship in the indoloquinolizines prepared from **4b** and **4c**. The possibility of introducing the C(12b)H–C(2)H *trans* configuration,§ which is found in the indole alkaloids vallesiachotamine **1**[3], antirhine **5**[6-13] and its metho salts,[10,13] and hunterburnine α- and β-metho salts **6**,[14-17] was of special interest.

RESULTS

Several 1 - [2 - (3 - indolyl)ethyl] - 3 - methoxycarbonyl pyridinium bromides were needed for the present investigation. The preparation of pyridinium salt **4a** has been described recently.[1] Treatment of 3 - cyano - 2,6 - dihydroxy - 4 - methylpyridine **7b**[18] by phosphorous pentachloride yielded 3 - cyano - 2,5,6 - trichloro - 4 - methylpyridine **8b**, which was transformed by hydrogenolysis to 3 - cyano - 4 - methylpyridine **9b**.[18] Hydrolysis and esterification of **9b** gave 4 - methylnicotinic acid methyl ester **10b**,[19] which, by treatment with tryptophyl bromide,[20] yielded 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl - 4 - methyl pyridinium bromide **4b**. Similarly, 3 - cyano - 2,6 - dihydroxy - 4 - propylpyridine **7c**[12] yielded *via* 3 - cyano - 2,5,6 - trichloro - 4 - propylpyridine **8c**, 3 - cyano - 4 - propylpyridine **9c**,[12] and 4 - propylnicotinic acid methyl ester **10c**, 1 - [2 - (3 - indolyl)ethyl] - 3 - methoxycarbonyl - 4 - propyl pyridinium bromide **4c**.

Owing to the sufficient acidity of the reaction medium,[4] sodium dithionite reduction of the salts **4a-c** led directly to the indoloquinolizine derivatives **11a-c**, respectively. Buffering the reaction medium with sodium bicarbonate permitted the isolation of the 1,4-dihydro derivatives **3a-c** in high yield. Acid-induced cyclization of these derivatives **3a-c** led to the tetracyclic compounds **11a**, **12b** and **12c**, respectively. Trace amounts of **11b** and **11c** were also detected.

The double bond in the D ring of all tetracyclic compounds described can be fixed at the 3,4-position owing to the strong absorption in the UV spectra at about 290 nm ($\rangle$N–C=C–COOCH$_3$ chromophoric system).

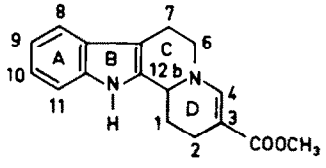
The fact that the treatment of the salt **4a** affords the same tetracyclic compound **11a** whether the buffer is present or not, suggests that compounds **11b** and **12b**, and **11c** and **12c** are both racemic pairs of C(2) epimers.

Compounds **11a-c–12b, c** can exist in conformational equilibrium by nitrogen inversion and half-chair ring

†III. M. Lounasmaa, C.-J. Johansson and J. Svensson, *Acta Chem. Scand.* **B30**, 251 (1976). This work was first presented as a part of a series of lectures by M. L. at the University of Helsinki (Autumn 1975).

‡It has been shown[6] that in certain special cases the dithionite reduction yields 1,2- and/or 1,6 - dihydropyridines.

§Corresponding to the C(3)H–C(15)H *trans* configuration when the biogenetic numbering is utilized for compounds **1**, **5** and **6**.



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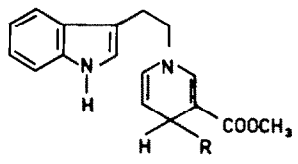
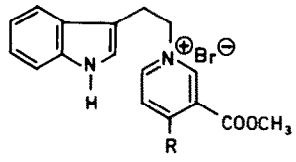
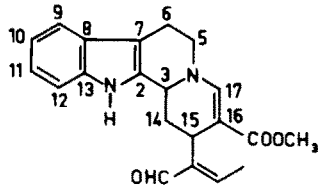


3a R = H
b R = CH_3
c R = CH_2-CH_2-CH_3



4a R = H
b R = CH_3
c R = CH_2-CH_2-CH_3

Fig. 1.



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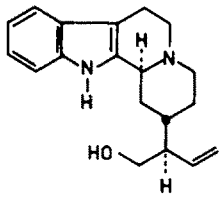

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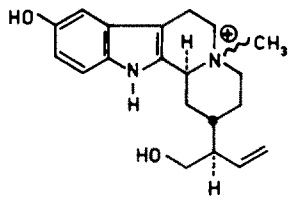

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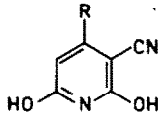
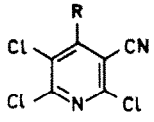
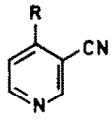


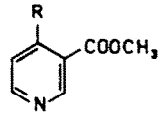
7b R = CH_3
7c R = CH_2-CH_2-CH_3



8b R = CH_3
8c R = CH_2-CH_2-CH_3

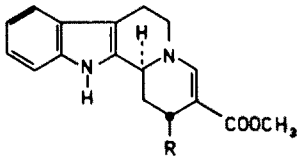


9b R = CH_3
9c R = CH_2-CH_2-CH_3

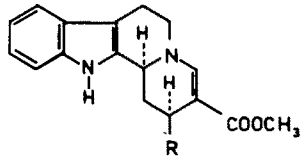


10b R = CH_3
10c R = CH_2-CH_2-CH_3

Fig. 2.



11a R = H
b R = CH_3
c R = CH_2-CH_2-CH_3



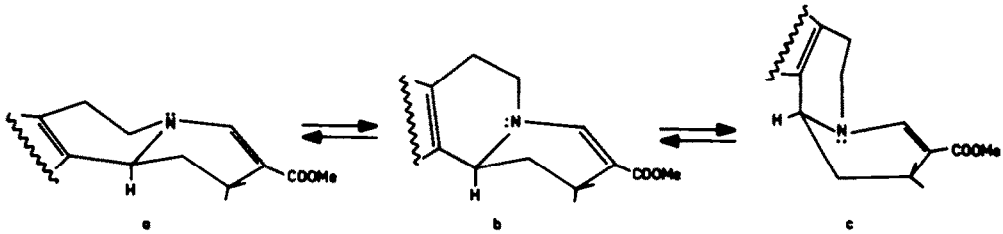
12b R = CH_3
c R = CH_2-CH_2-CH_3

Fig. 3.

interconversion (Scheme 1, only one enantiomer is illustrated). The conformer with a *trans* diaxial C/D ring juncture is not possible. In all conformations examined, rings C and D are assumed by analogy with cyclohexene to be in half-chair conformations.

A study of the nonbonded interactions of each conformer of compound **11a**, made with the aid of Dreiding models, reveals that in conformer **b** there is an interaction between the C(1) axial hydrogen and the C(6) axial hydrogen, and in conformer **c** between the C(2) pseudoaxial hydrogen and the N(12) hydrogen and/or lone electron pair,† whereas in conformer **a** no appreciable nonbonded interactions are present. This favours the preponderance of conformer **a** in the conformational

†It has been shown[21] that an H atom and a nitrogen lone electron pair are, in the sense being considered, of comparable size.



a b c

Scheme 1. Conformational equilibrium of compounds **11a-c–12b, c.**

equilibrium between **a**, **b** and **c** (Scheme 1). Conformer **b** is further disfavoured by the low possibility of the lone electron pair of the basic nitrogen (N(5)) conjugating with the α,β-unsaturated methoxycarbonyl system.

In the case of compounds **12b** and **12c**, where the C(2) alkyl group occupies in conformers **a** and **b** a pseudoequatorial position, it can be supposed, as a first approximation (the small allylic strain possible is overlooked), that the contribution of the different conformers to the conformational equilibrium is nearly the same as in compound **11a**. In the case of compounds **11b** and **11c**, where the C(2) alkyl group occupies in conformers **a** and **b** a pseudoaxial position, the contribution of conformer **c** to the conformational equilibrium will be more pronounced.

The C(12b)–C(2) stereochemical relationships proposed for **11b** and **12b** were determined by ^{13}C NMR spectral analysis. The fully proton-decoupled spectra of **11a**, **11b** and **12b**, 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) spectra and by comparison with the earlier shift assignment.[22,23] The chemical shifts found for homoallyl effect.[23]

The fundamental study of Dalling and Grant[24] on the effect of Me substitution on the carbon shifts of the cyclohexane ring permits the shift values in several ring systems to be predicted. Equatorial Me groups cause α-, β- and γ-deshielding effects (+5.6, +8.9 and 0.0 ppm, respectively), whereas axial Me groups cause α- and β-deshielding effects (+1.1 and +5.2 ppm, respectively) but a γ-shielding effect (−5.4 ppm). Based on the conformational considerations (*vide supra*) it can be expected, that, taking the chemical shifts found for **11a** as a basis, the equatorial Me group parameters allow a fairly accurate prediction of the chemical shifts of C(2), C(1) and C(12b) in **12b**, while the axial Me group parameters serve less well for the prediction of the corresponding shifts in **11b**. A comparison of the observed and calculated chemical shifts (Table 1) fully confirms the C(12b)–C(2) stereochemical relationships presented for **11b** and **12b**. The stereochemistry proposed for **11c** and **12c** was arrived at by analogy.

The C(12b)–C(2) stereochemical relationships found can be rationalized by the known fact[25] that the dithionite reduction of pyridinium salts proceeds via an intermediate sodium sulfinate. In the absence of a buffer the cyclization is apparently so rapid that it takes place before the decomposition of the intermediate sodium sulfinate leading to C(12b)H–C(2)H *trans* configuration. In the cases where the 1,4-dihydro derivative is isolated the C(4) alkyl group comes into the thermodynamically more favoured position which corresponds to C(12b)H–C(2)H *cis* configuration.

CONCLUSIONS

Sodium dithionite reduction of 1-[2-(3-indolyl)ethyl]-3-methoxycarbonyl pyridinium salts to the corresponding 1,4-dihydropyridine derivatives, followed by acid-induced cyclization to tetracyclic compounds, represents a convenient method for the preparation of 1,2,6,7,12,12b-hexahydro-3-methoxycarbonyl-indolo[2,3-a]-quinolizines, of which **11b** and **11c** in particular, which possess the C(12b)H–C(2)H *trans* configuration, are relatively good vallesiachotamine **1** models.

Compared with some other methods (mercuric acetate oxidation of appropriate N-alkylpiperidines,[26] catalytic hydrogenation of suitable pyridinium salts,[27] modified Polonovski reaction,[12] and Zn/HCl reduction of appropriate preprepared immonium salts[28]), the sodium dithionite reduction has the advantage of permitting the C(12b)–C(2) stereochemical relationship to be chosen with a high degree of stereoselectivity by slight modification of the last step of the synthesis. It can be expected that interesting applications of the sodium dithionite reduction will be found also in the preparation of indole alkaloid models that possess the more general C(12b)H–C(2)H *cis* configuration.

EXPERIMENTAL

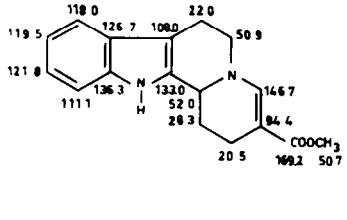
The IR spectra were measured on a Perkin–Elmer 237 apparatus and the UV spectra on a Perkin–Elmer 137 UV apparatus. The ^1H NMR spectra were taken with a Jeol JNM-PMX-60 instrument and the ^{13}C NMR spectra with a Jeol JNM-PS/PFT-100 instrument operating at 25.20 MHz in the Fourier transform mode. TMS was used as internal standard. The mass spectra were recorded on a Jeol JMS-D-100 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 performed on a Hitachi Perkin–Elmer RMU 6E instrument. The m.pts were determined in a Büchi capillary m.p. apparatus and are uncorrected.

Preparation of 3-*cyano*-2,6-*dihydroxy*-4-*alkylpyridines* **7b** *and* **7c**

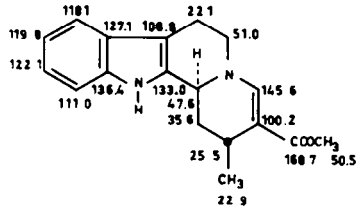
General procedure. A mixture of ethylacetate derivative, cyanoacetamide, and piperidine in MeOH was refluxed for 45 hr. The solvent was evaporated under vacuum to half of its original volume and the mixture allowed to cool. The abundant ppt formed was separated, washed with MeOH, and dissolved in hot water. Concd HCl was added and the mixture was allowed to cool. The ppt was filtered off and washed with ice-water.

3-*Cyano*-2,6-*dihydroxy*-4-*methylpyridine* **7b**. Reaction between 158 ml of ethylacetoacetate, 105 g of cyanoacetamide, and 125 ml of piperidine in 400 ml of MeOH yielded 143 g (76%) of **7b**, m.p. 286–288° (lit.[18] 295–300°); IR (KBr) CN 2225 (m) cm^{-1}; MS M^+ at *m/e* 150.

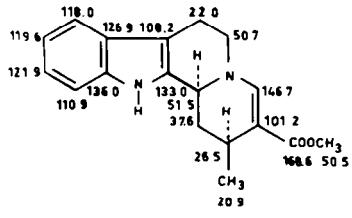
3-*Cyano*-2,6-*dihydroxy*-4-*propylpyridine* **7c**. Reaction between 40 ml of ethylbutyroacetate, 21 g of cyanoacetamide, and



11a



11b



12b

Fig. 4.

25 ml of piperidine in 80 ml of MeOH yielded 24 g (54%) of **7c**, m.p. 280–283° dec (lit.[12] > 260°); IR (KBr) CN 2225 (m) cm^{-1}; MS M^+ at *m/e* 178.

Preparation of 3 - *cyano* - 2,5,6 - *trichloro* - 4 - *alkylpyridines* **8b** *and* **8c**

General procedure. A mixture of pyridine derivative and PCl_5 was heated at 160° and the formed $POCl_3$ was allowed to pass over. After 18 hr the mixture was cooled, the contents were transferred cautiously and with manual stirring onto cracked ice, and the residue was extracted with dichloromethane. The extract was washed with ice-water, dried over Na_2SO_4, and evaporated under vacuum. The residue was chromatographed on silica gel.

3 - *Cyano* - 2,5,6 - *trichloro* - 4 - *methylpyridine* **8b**. Reaction between 20 g of **7b**[18] and 100 g of PCl_5 yielded 16 g (61%) of **8b**, m.p. 120–122° (MeOH); IR (KBr) CN 2230 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.72 (3 H, s, $-CH_3$); MS M^+ at *m/e* 226, 224, 222 and 220.

3 - *Cyano* - 2,5,6 - *trichloro* - 4 - *propylpyridine* **8c**. Reaction between 14 g of **7c**[12] and 75 g of PCl_5 yielded 9.5 g (52%) of **8c** as an oil; IR (film) CN 2230 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 1.06 (3 H, t, J = 7 Hz, $-CH_2-CH_2-\underline{CH_3}$), 1.70 (2 H, m, $-CH_2-\underline{CH_2}-CH_3$), and 3.04 (2 H, t, J = 7 Hz, $-\underline{CH_2}-CH_2-CH_3$); MS M^+ at *m/e* 254, 252, 250 and 248.

Preparation of 3 - *cyano* - 4 - *alkylpyridines* **9b** *and* **9c**

General procedure. A mixture of pyridine derivative, anhyd NaOAc, and Pd–C (10%) in MeOH was hydrogenated at atmospheric pressure. After the calculated amount of H_2 has been introduced the hydrogenolysis was interrupted. The catalyst was filtered off, the filtrate evaporated under vacuum, and the residue extracted with dichloromethane. The extract was washed with water, dried over Na_2SO_4 and evaporated under vacuum. The residue was chromatographed on alumina (act. II-III).

3 - *Cyano* - 4 - *methylpyridine* **9b**. Reaction between 2.5 g of **8b**, 2.0 g of anhyd NaOAc and 600 mg of Pd–C (10%) in 100 ml of MeOH yielded 760 mg (62%) of **9b**, m.p. 41–43° (hexane) (lit. 43–44°,[29] 45–46°[18]); IR (KBr) CN 2230 (m) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.56 (3 H, s, $-CH_3$), 7.24 (1 H, d, J = 5 Hz, C-5-H), 8.57 (1 H, d, J = 5 Hz, C-6-H), and 8.68 (1 H, s, C-2-H). MS M^+ at *m/e* 118.

3 - *Cyano* - 4 - *propylpyridine* **9c**. Reaction between 3.1 g of **8c**, 3.0 g of anhyd NaOAc, and 600 mg of Pd–C (10%) in 100 ml of MeOH yielded 1.4 g (77%) of **9c**[12] as an oil; IR (film) CN 2225 (m) cm^{-1}); ^1H NMR ($CDCl_3$) δ 1.00 (3 H, t, J = 7 Hz, $-CH_2-CH_2-\underline{CH_3}$), 1.75 (2 H, m, $-CH_2-\underline{CH_2}-CH_3$), 2.83 (2 H, t, J = 7 Hz, $-\underline{CH_2}-CH_2-CH_3$), 7.27 (1 H, d, J = 5 Hz, C-5-H), 8.63 (1 H, d, J = 5 Hz, C-6-H) and 8.73 (1 H, s, C-2-H); MS M^+ at *m/e* 146.

Preparation of 4 - *alkylnicotinic acid methyl esters* **10b** *and* **10c**

General procedure. A mixture of pyridine derivative and 75% H_2SO_4 was kept at 130° under N_2 for 18 hr. The soln was cooled to about 65°, MeOH was added, and the heating was continued for 4 hr. The soln was then cooled, $NaHCO_3$ added, and the mixture filtered. The filtrate was evaporated to dryness under vacuum and ice-water added. After the soln was saturated with K_2CO_3, it was extracted several times with ether, The ppt was dissolved in a minimum quantity of water and the soln saturated with K_2CO_3 and extracted several times with ether. The combined ether fractions from both treatments were dried over K_2CO_3 and evaporated under vacuum. The residue was chromatographed on alumina (act. II-III).

4-*Methylnicotinic acid methyl ester* **10b**. Reaction between 2.0 g of **9b** and 40 ml of 75% H_2SO_4 yielded 2.0 g (73%) of **10b** as an oil; IR (film) C=O 1735 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.59 (3 H, s, $-CH_3$), 3.88 (3 H, s, $-COOCH_3$), 7.09 (1 H, d, J = 5 Hz, C-5-H), 8.45 (1 H, d, J = 5 Hz, C-6-H), and 8.96 (1 H, s, C-2-H); MS M^+ at *m/e* 151.

4-*Propylnicotinic acid methyl ester* **10c**. Reaction between 3.0 g of **9c** and 60 ml of 75% H_2SO_4 yielded 2.5 g (68%) of **10c** as an oil; IR (film) C=O 1730 (s) cm^{-1}; ^1H NMR ($CDCl_3$) δ 0.98 (3 H, t, J = 7 Hz, $-CH_2-CH_2-\underline{CH_3}$), 1.67 (2 H, m, J = 7 Hz, $-CH_2-\underline{CH_2}-CH_3$), 2.95 (2 H, t, J = 7 Hz, $-\underline{CH_2}-CH_2-CH_3$), 3.90 (3 H, s, $-COOCH_3$), 7.13 (1 H, d, J = 5 Hz, C-5-H), 8.50 (1 H, d, J = 5 Hz, C-6-H), and 8.97 (1 H, s, C-2-H); MS M^+ at *m/e* 179.

Table 1. Comparison of the observed and calculated ^{13}C NMR chemical shifts for C(2), C(1) and C(12b) in compounds **11a**, **11b** and **12b**

	11a	11b	12b	Calc. for an eq. CH_3-group	Calc. for an ax. CH_3-group
C(2)	20.5	25.5	26.5	26.1	21.6
C(1)	28.3	35.6	37.6	37.2	33.5
C(12b)	52.0	47.6	51.5	52.0	46.6

Preparation of 1 - [2 - (3 - *indolyl*)*ethyl*] - 3 - *methoxycarbonyl* - 4 - *alkyl pyridinium bromides* **4b** *and* **4c**

General procedure. A mixture of nicotinic acid derivative and tryptophyl bromide[20] was heated under N_2 at 100° for 1 hr. The mixture was allowed to cool, crushed to grains, and stirred in abs ether for 1 hr. The mixture was filtered.

1 - [2 - (3 - *Indolyl*)*ethyl*] - 3 - *methoxycarbonyl* - 4 - *methyl pyridinium bromide* **4b**. Reaction between 1.057 g of **10b** and 1.725 g of tryptophyl bromide yielded 2.250 g (86%) of **4b** m.p. 199–201° dec. (MeOH); IR (KBr) NH 3430 (m), C=O 1735(s), and C=C 1645 (s) cm^{-1}.

1 - [2 - (3 - *Indolyl*)*ethyl*] - 3 - *methoxycarbonyl* - 4 - *propyl pyridinium bromide* **4c**. Reaction between 358 mg of **10c** and 493 mg of tryptophyl bromide yielded 710 mg (88%) of **4c**, m.p. 152–155° dec (MeOH); IR (KBr) NH 3400 (m), C=O 1740 (s), and C=C 1645 (s) cm^{-1}.

Preparation of 1 - [2 - (3 - *indolyl*)*ethyl*] - 3 - *methoxycarbonyl* - 1,4 - *dihydropyridines* **3a**, **3b** *and* **3c**

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 (1:2, H_2O: MeOH) under N_2. The mixture was stirred for 20 hr, filtered, and the filtrate evaporated under vacuum. The residue was 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).

1 - [2 - (3 - *Indolyl*)*ethyl*] - 3 - *methoxycarbonyl* - 1,4 - *dihydropyridine* **3a**. Reaction between 704 mg of **4a**,[1] 3.0 g of $NaHCO_3$, and 2.0 g of sodium dithionite in 150 ml of aqueous MeOH yielded 370 mg (67%) of **3a** as an oil; IR (film) NH 3320 (s), C=O 1680 (s) and C=C 1600 (s) cm^{-1}; UV (EtOH 94%) λ_{max} 207 (infl.) (log ϵ 4.36), 223 (log ϵ 4.50), 285 (log ϵ 3.72), 293 (log ϵ 3.69) and 356 (log ϵ 3.71) nm. λ_{min} 209 (infl.), 254, 290 and 310 nm. ^1H NMR ($CDCl_3$)δ 3.63 (3 H, s, $-COOCH_3$), 4.69 (1 H, m, C-5-H), 5.61 (1 H, dd, J_1 = 8 Hz, J_2 = 1 Hz, C-6-H), 6.92 (1 H, d, J = 2 Hz, indolyl α-H), 6.98 (1 H, d, J = 1 Hz, C-2-H) and 8.60 (1 H, s, N–H); MS M^+ at *m/e* 282 corresponding to $C_{17}H_{18}N_2O_2$.

1 - [2 - (3 - *Indolyl*)*ethyl*] - 3 - *methoxycarbonyl* - 4 - *methyl* - 1,4 - *dihydropyridine* **3b**. Reaction between 1011 mg of **4b**, 4.0 g of $NaHCO_3$, and 3.0 g of sodium dithionite in 150 ml of aqueous MeOH yielded 390 mg (49%) of **3b** as an oil; IR (film) NH 3330 (s), C=O 1675 (s)and C=C 1590 (s) cm^{-1}; UV (EtOH 94%) λ_{max} 206 (infl.) (log ϵ 4.37), 222 (log ϵ 4.50), 284 (log ϵ 3.72), 292 (log ϵ 3.68) and 350 (log ϵ 3.78) nm. λ_{min} 209 (infl.), 260, 289 and 307 nm; ^1H NMR ($CDCl_3$) δ 1.07 (3 H, d, J = 7 Hz, $-CH_3$), 3.62 (3 H, s, $-COOCH_3$), 4.68 (1 H, dd, J_1 = 8 Hz, J_2 = 4 Hz, C-5-H), 5.63 (1 H, dd, J_1 = 8 Hz, J_2 = 1 Hz, C-6-H), 6.84 (1 H, d, J = 2 Hz, indolyl α-H), 6.99 (1 H, d, J = 1 Hz, C-2-H) and 8.48 (1 H, s, N–H); MS M^+ at *m/e* 296 corresponding to $C_{18}H_{20}N_2O_2$.

1 - [2 - (3 - *Indolyl*)*ethyl*] - 3 - *methoxycarbonyl* - 4 - *propyl* - 1,4 - *dihydropyridine* **3c**. Reaction between 890 mg of **4c**, 4.0 g of $NaHCO_3$, and 2.5 g of sodium dithionite in 150 ml of aqueous MeOH yielded 359 mg (50%) of **3c** as an oil; IR (film) NH 3330 (s), C=O 1670 (s) and C=C 1585 (s) cm^{-1}; UV (EtOH 94%) λ_{max} 207 (infl.) (log ϵ 4.39), 222 (log ϵ 4.46), 285 (log ϵ 3.78), 292 (log ϵ 3.78) and 343 (log ϵ 3.77) nm. λ_{min} 210 (infl.), 251, 289 and 310 nm; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, def., $-CH_2-CH_2-\underline{CH_3}$), 3.62 (3 H, s, $-COOCH_3$), 4.71 (1 H, dd, J_1 = 8 Hz, J_2 = 4 Hz, C-5-H), 5.71 (1 H, dd, J_1 = 8 Hz, J_2 = 1 Hz, C-6-H), 6.86 (1 H, d, J = 2 Hz, indolyl α-H), 7.04 (1 H, d, J = 1 Hz, C-2-H) and 8.28 (1 H, s, N–H); MS M^+ at *m/e* 324 corresponding to $C_{20}H_{24}N_2O_2$.

Preparation of 1,2,6,7,12,12*b* - *hexahydro* - 3 - *methoxycarbonyl* - *indolo*[2,3 - *a*]*quinolizines* **11a**, **11b** *and* **11c**

General procedure. Sodium dithionite was added in small portions during 1 hr to a magnetically stirred soln of pyridinium bromide derivative in aqueous MeOH (1:2, H_2O:MeOH) under N_2. The mixture was stirred for 20 hr, filtered, and the filtrate evaporated under vacuum to 1/10 of its original volume. $NaHCO_3$ was added 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).

1,2,6,7,12,12*b* - *Hexahydro* - 3 - *methoxycarbonylindolo*[2,3 - *a*]*quinolizine* **11a**. Reaction between 520 mg of **4a**[1] and 1.5 g of sodium dithionite in 120 ml of aqueous MeOH yielded 255 mg (62%) of **11a**, m.p. 170–172° (MeOH)(lit.[2] 170–172°); IR (KBr) NH 3300 (s), C=O 1665 (s) and C=C 1610 (s) cm^{-1}; UV (EtOH 94%) λ_{max} 205 (infl.)(log ϵ 4.21), 224 (log ϵ 4.50) and 293 (log ϵ 4.52) nm λ_{min} 206 (infl.) and 254 nm; ^1H NMR ($CDCl_3$:DMSO-d_6, 1:1) δ 3.60 (3 H, s, $-COOCH_3$), 4.39 (1 H, br d, J = 11 Hz, C-12b-H) and 7.41 (1 H, s, C-4-H); MS M^+ at *m/e* 282 corresponding to $C_{17}H_{18}N_2O_2$. Other noteworthy peaks at *m/e* 281, 251 and 223.

1,2,6,7,12,12*bα* - *Hexahydro* - 2*α* - *methyl* - 3 - *methoxycarbonylindolo*[2,3 - *a*]*quinolizine* **11b**. Reaction between 826 mg of **4b** and 2.5 g of sodium dithionite in 120 ml of aqueous MeOH yielded 391 mg (60%) of **11b**, m.p. 238–240° (MeOH); Ir (KBr)† NH 3260 (s), C=O 1680 (s) and 1660 (s) and C=C 1585 (s) cm^{-1}; IR ($CHCl_3$) C=O 1675 (s) cm^{-1}, UV (EtOH 94% λ_{max} 205 (infl.)(log ϵ 4.22), 224 (log ϵ 4.52) and 293 (log ϵ 4.58) nm. λ_{min} 206 (infl.) and 253 nm; ^1H NMR (DMSO-d_6) δ 1.17 (3 H, d, J = 6 Hz, $-CH_3$), 3.56 (3 H, s, $-COOCH_3$), 4.52 (1 H, br d, J = 10 Hz, C-12b-H) and 7.48 (1 H, s, C-4-H); MS M^+ at *m/e* 296 corresponding to $C_{18}H_{20}N_2O_2$. Other noteworthy peaks at *m/e* 295, 281, 265 *and* 237.

1,2,6,7,12,12*bα* - *Hexahydro* - 2*α* - *propyl* - 3 - *methoxycarbonylindolo*[2,3 - *a*]*quinolizine* **11c**. Reaction between 820 mg of **4c** and 2.5 g of sodium dithionite in 120 ml of aqueous MeOH yielded 390 mg (58%) of **11c**, m.p. 226–228° (MeOH); IR (KBr) NH 3275 (s), C=O 1665 (s) and C=C 1595 (s) cm^{-1}; UV (EtOH 94%) λ_{max} 205 (infl.)(log ϵ 4.26), 224 (log ϵ 4.52) and 293 (log ϵ 4.58) nm. λ_{min} 207 (infl.) and 252 nm; ^1H NMR ($CDCl_3$) δ 0.88 (3 H, t, def., $-CH_2-CH_2-\underline{CH_3}$), 3.67 (3 H, s, $-COOCH_3$), 4.50 (1 H, br d, J = 10 Hz, C-12b-H), 7.47 (1 H, s, C-4-H) and 8.57 (1 H, s, N-H); MS M^+ at *m/e* 324 corresponding to $C_{20}H_{24}N_2O_2$. Other noteworthy peaks at *m/e* 323, 293, 281 and 265.

Preparation of 1,2,6,7,12,12*b* - *hexahydro* - 3 - *methoxycarbonyl* - *indolo*[2,3 - *a*]*quinolizines* **11a**, **12b** *and* **12c**

General procedure. A soln of 1,4 - dihydropyridine derivative 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 poured slowly 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).

1,2,6,7,12,12*b* - *Hexahydro* - 3 - *methoxycarbonylindolo*[2,3 - *a*]*quinolizine* **11a**. Cyclization of 490 mg of **3a** yielded 460 mg (94%) of **11a**, m.p. 170–172° (MeOH); IR, UV, ^1H NMR, MS and TLC were identical with those of the sample above.

1,2,6,7,12,12*bα* - *Hexahydro* - 2*β* - *methyl* - 3 - *methoxycarbonylindolo*[2,3 - *a*]*quinolizine* **12b**. Cyclization of 367 mg of **3b** yielded 335 mg (91%) of **12b**, m.p. 173–174° (MeOH); IR (KBr) NH 3350 (s), C=O 1660 (s) and C=C 1615 (s) cm^{-1}; UV (EtOH 94%) λ_{max} 206 (infl.)(log ϵ 4.08), 223 (log ϵ 4.49) and 293 (log ϵ 4.49) nm. λ_{min} 207 (infl.) and 252 nm; ^1H NMR (DMSO-d_6) δ 1.08 (3 H, d, J = 6 Hz, $-CH_3$), 3.57 (3 H, s, $-COOCH_3$), 4.46 (1 H, br, d, J = 6 Hz, C-12b-H), 7.42 (1 H, s, C-4-H) and 10.90 (1 H, br s, N-H); MS M^+ at *m/e* 296 corresponding to $C_{18}H_{20}N_2O_2$. Other noteworthy peaks at *m/e* 295, 281, 265 and 237.

†The occurrence of a doublet in the carbonyl stretching region in the spectrum taken into the solid state, is probably due to polymorphism.

1,2,6,7,12,12*bα* - *Hexahydro* - 2*β* - *propyl* - 3 - *methoxycarbonylindolo*[2,3 - *a*]*quinolizine* **12c**. Cyclization of 320 mg of **3c** yielded 275 mg (86%) of **12c** as an oil; IR (film) NH 3300 (s), C=O 1660 (s), and C=C 1610 (s) cm^{-1}; UV (EtOH 94%) λ_{max} 206 (infl.)(log ϵ 4.30), 225 (log ϵ 4.50) and 293 (log ϵ 4.48) nm. λ_{min} 207 (infl.) and 252 nm. ^1H NMR ($CDCl_3$) δ 0.82 (3 H, t, def., $-CH_2-CH_2-CH_3$), 3.61 (3 H, s, $-COOCH_3$), 4.35 (1 H, br d, J = 6 Hz, C-12b-H), 7.39 (1 H, s, C-4-H) and 8.18 (1 H, br s, N-H); MS M^+ at *m/e* 324 corresponding to $C_{20}H_{24}N_2O_2$. Other noteworthy peaks at *m/e* 323, 293, 281 and 265.

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