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Synthetic Studies in the Alkaloid Field. Part II.* On the Preparation of *N*-(β-Indolylethyl)-dihydro- and *N*-(β-Indolylethyl)-tetrahydropyridines by Catalytic Hydrogenation, and their Acid-induced Cyclization

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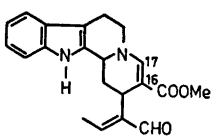
Four 1-[β-(3-indolyl)ethyl]-3-carbomethoxy pyridinium salts were converted into the corresponding *N*-alkyldihydro- and/or *N*-alkyltetrahydropyridines by palladium-catalyzed partial hydrogenation. The isolated *N*-alkyldihydropyridines were found to be 1,6-isomers.** The acid-induced cyclization of the obtained compounds into indoloquinolizidine derivatives is described.

Much of the work on indole alkaloid synthesis in recent years has involved utilization of the 1-[β-(3-indolyl)ethyl]tetrahydropyridines in acid-induced transformations into indoloquinolizidine derivatives (for a review article see Ref. 1). One of the common methods of preparing the starting compounds consists of catalytic hydrogenation of the corresponding 1-[β-(3-indolyl)ethyl]-pyridinium salts. Since catalytic hydrogenation of *N*-alkylpyridinium salts customarily yields *N*-alkylpiperidines [2] it was necessary to develop special experimental designs to permit hydrogenation stoppage at the tetrahydropyridine stage. Wenkert *et al.*[3–7] have shown that palladium-catalyzed hydrogenation of pyridines and their *N*-alkyl salts



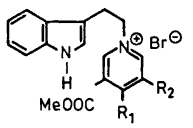
(I)

containing a wide variety of 3-acyl or related substituents yields the corresponding tetrahydropyridines.

In connection with our studies concerning the preparation of indole alkaloids of the vallesiachotamine (I) [8] type we became interested in *N*-alkyldihydro- and *N*-alkyltetrahydropyridines. In the present communication we describe the results obtained by palladium-catalyzed partial hydrogenation of four 1-[β-(3-indolyl)ethyl]-3-carbomethoxypyridinium salts (II–V), followed by the acid-induced transformation of the resulting compounds into indoloquinolizidine derivatives (XVIII–XXIV). Much interest was focused on the possibility of stopping the reduction at the dihydropyridine stage. In particular, it was hoped that the presence of a second carbomethoxy substituent at position 5 of salts (III), (IV), and (V) would permit the isolation of *N*-alkyldihydropyridines, which, especially in the case of 1,4-isomers, could be useful intermediates for the preparation of vallesiachotamine models.[9] Recently Eisner [10] has shown that catalytic hydrogenation of *N*-unsubstituted 3,5-diacyl pyridines can be stopped at the dihydropyridine

* Part I. M. Lounasmaa and C.-J. Johansson, *Tetrahedron Lett.* (1974) 2509.

** In an attempt to make the numbering of the partially hydrogenated pyridine derivatives uniform and thus facilitate their comparison with the tetrahydro compounds prepared earlier, products are numbered in such a way that the 1,2-dihydro compounds described here are referred to as 1,6-isomers.

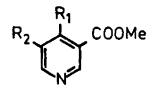


(II) $R_1 = R_2 = H$

(III) $R_1 = H$; $R_2 = COOMe$

(IV) $R_1 = CH_3$; $R_2 = COOMe$

(V) $R_1 = CH_2\text{-}COOMe$; $R_2 = COOMe$

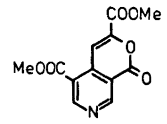


(VI) $R_1 = R_2 = H$

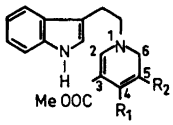
(VII) $R_1 = H$; $R_2 = COOMe$

(VIII) $R_1 = CH_3$; $R_2 = COOMe$

(X) $R_1 = CH_2\text{-}COOMe$; $R_2 = COOMe$



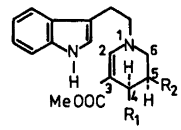
(IX)



(XI) $R_1 = H$; $R_2 = COOMe$

(XII) $R_1 = CH_3$; $R_2 = COOMe$

(XIII) $R_1 = CH_2\text{-}COOMe$; $R_2 = COOMe$



(XIV) $R_1 = R_2 = H$

(XV) $R_1 = H$; $R_2 = COOMe$

(XVI) $R_1 = CH_3$; $R_2 = COOMe$

(XVII) $R_1 = CH_2\text{-}COOMe$; $R_2 = COOMe$

stage, yielding mainly 1,6-isomers, however. Moreover, it is known that *N*-alkyldihydropyridines can be obtained, *e.g.* by complex metal hydride [11] and alkaline dithionite [11,12] reductions of pyridinium salts.

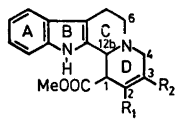
Several pyridines had to be prepared for the present investigation. Methyl nicotinate (VI) and 3,5-dimethyl dinicotinate (VII) were obtained by esterification of the corresponding acids. Dimethyl 4-methylpyridine-3,5-dicarboxylate (VIII), was synthesized as described recently,[13] and transferred by partial alkaline hydrolysis to the corresponding monoacid. Treatment with oxalylchloride and methanol yielded the esterlactone (IX),[14] which by alkaline hydrolysis, alkaline hydrogen peroxide treatment, and esterification was transformed to dimethyl 4-carbomethoxymethylpyridine-3,5-dicarboxylate (X).

Tryptophyl bromide, prepared according to Hoshino and Shimodaira,[15] was treated with appropriate pyridines to give the 1-[β-(3-indolyl)ethyl]-3-carbomethoxy pyridinium salts (II – V).

The next step consisted of palladium-catalyzed hydrogenation of the 1-[β-(3-indolyl)-ethyl]-3-carbomethoxy pyridinium salts in methanol in the presence of triethylamine. In the cases of salts (III – V), which contain a second carbomethoxy substituent in position 5, the reduction took place in two distinct steps, thereby permitting the isolation of dihydro derivatives in reasonable yields. The first mol of hydrogen was taken up within a few hours while the second one required a much longer time. In the case of salt (II), which unlike salts (III – V) does not contain a second carbomethoxy substituent in position 5, the hydrogen uptake was less step-wise, leading mostly to the tetrahydro derivative. Even when hydrogenation was interrupted before 1 mol of hydrogen had been taken up, the reaction mixture contained, besides starting material, mainly the tetrahydro derivative. However, the presence of some 1,6-dihydro derivative was indicated by NMR (multiplet at δ 4.13).

It seems evident to us from these results that clear interruption of the palladium-catalyzed hydrogenation of 1-[β-(3-indolyl)ethyl]-3-carbomethoxy pyridinium salts at the dihydro stage demands a supplementary stabilizing agent, which in the examined cases was the carbomethoxy substituent at position 5.

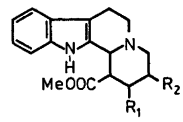
The NMR spectra (*cf.* Experimental part) of the isolated dihydro compounds (XI), (XII), and (XIII) clearly indicate that they are 1,6-isomers, showing characteristic signals due to the α-methylene groups at δ 4.18 – 4.33. Moreover,



(XVIII) $R_1 = H$; $R_2 = COOMe$

(XIX) $R_1 = CH_3$; $R_2 = COOMe$

(XX) $R_1 = CH_2\text{-}COOMe$; $R_2 = COOMe$



(XXI) $R_1 = R_2 = H$

(XXII) $R_1 = H$; $R_2 = COOMe$

(XXIII) $R_1 = CH_3$; $R_2 = COOMe$

(XXIV) $R_1 = CH_2\text{-}COOMe$; $R_2 = COOMe$

the appearence of two distinct methoxy group signals is in agreement with the 1,6-dihydro structure.

The above results, which at least *a priori* seem unfortunate for the preparation of vallesiachotamine models containing a $\Delta^{3(4)}$ ($\Delta^{16(17)}$ in the biogenetic nomenclature of vallesiachotamine) double bond, are in agreement with the results of Eisner.[10] Investigation of the main by-products of the hydrogenation reaction revealed that the 1,4-dihydro compounds (blue fluorescence on thin layer; *cf.* Ref. 16) were present in very low concentration.

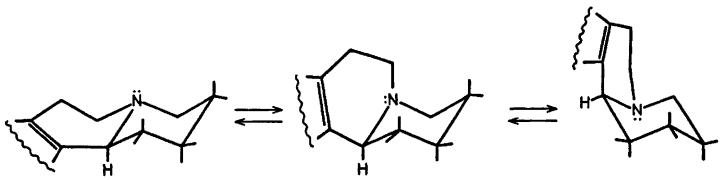
The obtained dihydro (XI–XIII) and tetrahydro (XIV–XVII) derivatives were subjected in anhydrous methanol to acid-induced cyclizations which gave tetracyclic compounds (XVIII–XXIV) in good yields. The mass spectra of the tetracyclic compounds prepared showed, besides the corresponding molecular peaks, *inter al.* typical tetrahydro-β-carboline peaks at *m/e* M–1, 184, 170, 169, and 156.[17–19]

The double bond in the D ring of compounds (XVIII), (XIX), and (XX) can be fixed at the 2,3-position on the basis of several experimental results. Firstly, the intense peak at *m/e* 170 in the mass spectra of compounds (XVIII), (XIX), and (XX) strongly supports the 2,3-position, because only in such a case can the corresponding ion be formed by a retro-Diels-Alder process.[20] Secondly, it would be expected that, due to the relatively strong diamagnetic shielding effect of a double bond either at the 1,2- or at the 3,4-position on the C-12b proton, the NMR signal of the C-12b proton would appear downfield from δ 4.0. The fact that this is not the case in the NMR spectra of compounds (XVIII), (XIX), and (XX) (*cf.* Experimental part and Discussion later) strongly favours the 2,3-position. Thirdly, the C-2 methyl and methylene group signals in the NMR spectra of compounds (XIX) and (XX), respectively, are singlets, which indicates that there are no protons directly attached to C-2 thus eliminating the 3,4-position in these cases. Moreover, if the double bond occupied the 3,4-position there would be strong absorption in the UV spectra of compounds (XVIII), (XIX), and (XX) at about 290 nm, due to the presence of a

$$\backslash \\ N-C=C-COOCH_3 \\ /$$

chromophoric system. The fact that the UV spectra obtained (*cf.* Experimental part) are typical of 2,3-disubstituted indoles,[21] showing only relatively weak absorption in the 280–290 nm region, clearly indicates that the double bond cannot occupy the 3,4-position.

Compounds (XXI–XXIV) can exist in a conformational equilibrium by nitrogen in-



a b c

Scheme 1.

version and *cis*-decalin type ring inversion (Scheme 1; only one enantiomer is illustrated).* Ring C is assumed to be in the half chair conformation and only the chair forms of ring D are considered.[22]

A similar conformational examination can be presented for compounds (XVIII – XX) considering ring D to be in half chair forms.

The presence of the so-called Bohlmann bands**[22–26] in the IR spectra of all tetracyclic compounds prepared (XVIII – XXIV) indicates that conformation *a*, which means *trans*-quinolizidine juncture of C/D rings, dominates the conformational equilibrium between *a*, *b*, and *c* (Scheme 1)***.

In a recent paper Potier and co-workers [20] have indicated that similar compounds having a double bond at 2,3-position (14,15-position in their nomenclature) show Bohlmann bands. From the presence of these bands the French investigators have concluded that introduction of a double bond at 2,3-position has no notable effect on the conformation of the *trans* diaxial hydrogens at C-12b, C-4, and C-6 (C-21, C-3, and C-5 in their nomenclature) in relation to the lone electron pair of the basic nitrogen.

The preponderance of conformation *a* in the conformational equilibrium of compounds (XVIII – XXIV) is also supported by NMR spectroscopy. The absence of any signal downfield from δ 3.8 that could be assigned to the C-12b proton is characteristic of conformation *a* (*trans*-quinolizidine juncture).[20,23,25–28] 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*-quinolizidine junctures) the C-12b proton signal appears at about 0.5 ppm lower field.*

The relative stereochemistry at C-12b and C-1, as well as that at C-2 and C-3 when asymmetric, has not been determined with certainty. The magnitude of the coupling constant (10 Hz) (*cf.* Experimental part) for the interaction between the adjacent C-12b and C-1 protons in the NMR spectrum of compound (XXI) seems to support the *trans* diaxial relationship between these protons. As a consequence, the carbomethoxy group at C-1 would be equatorial in the predominant conformation (conformation *a*). A similar relationship is indicated by the NMR spectrum of compound (XXII), though less clearly, owing to the partial masking of the C-12b – H signal by the peaks of the carbomethoxy groups. Despite these results, confirmation of the relative stereochemistry at C-12b and C-1 must await more rigorous proofs. On the other hand, it can be assumed that the catalytic hydrogenation of the salts proceeds in a *cis*-manner [4] and, as a consequence, that compounds (XXIII) and (XXIV) are 2,3-*cis* products.

According to NMR spectroscopy (*cf.* Experimental part) the cyclization of (XVI) yielded a mixture of two diastereoisomers, which were not separated, whereas in all other cases only one of the possible diastereoisomers was found.

EXPERIMENTAL

The UV spectra were measured on a Perkin-Elmer 137 UV apparatus and the IR spectra on a Perkin-Elmer 237 apparatus. The NMR spectra were taken with a Varian A-60 instrument using TMS as internal standard. The mass spectra were recorded on a Perkin-Elmer 270 mass spectrometer at 70 eV using direct sample insertion into the ion source whose temperature was 80 – 90 °C. The melting points were deter-

* The conformation with a *trans* diaxial C/D ring juncture is not possible.

** The prerequisite for the occurrence of the Bohlmann bands is that the C-12b hydrogen and at least one more adjacent C hydrogen are *trans* diaxial to the lone electron pair of the basic nitrogen.[22]

*** Strictly speaking the IR spectra of compounds (XXI – XXIII) taken in crystalline form (*cf.* Experimental part), where interconversion of various conformations is stopped, only indicate that these compounds crystallize, at least mainly, in conformation *a*. However, it seems evident to us that conformation *a* is predominant even in solution (*cf.* NMR results).

* 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 pure conformations in question, provided that conformational interchange is rapid. The C – 12b – H signal of compound (XXII), which is partly masked by peaks of the carbomethoxy groups, appears at about δ 3.9 (*cf.* Experimental part). Although this value, which reflects *inter alia* the contribution of conformation(s) *b* and/or *c* to the conformational equilibrium, is slightly downfield from δ 3.8, it is considered, nevertheless, to support the predominance of conformation *a*.

mined in a capillary melting point apparatus (Büchi) and are uncorrected.

Esterlactone (IX). 18 g of the diester (VIII) [13] was partially hydrolyzed to the corresponding monoacid (15 g) (MS M+ at *m/e* 195 corresponding to $C_9H_9NO_4$) by the procedure described in the literature.[14] A solution of 25 ml of freshly distilled oxalyl chloride in 25 ml of chloroform was dropped during one hour into an ice-cold mixture of the monoacid and 25 ml of triethylamine in 1000 ml of dry chloroform. The solution was allowed to reach room temperature and stirred for an additional hour. Methanol (125 ml) and chloroform (500 ml) were added and the solution was left to stir overnight. The solution was filtered and the filtrate washed with a sodium bicarbonate solution and dried over anhydrous potassium carbonate. The solvent was evaporated and the residue washed several times with chloroform, giving 10.4 g of esterlactone (IX) (52 %), m.p. 196–197 °C (lit.[14] 196–197 °C). IR (KBr) C=O 1745 (s), 1715 (s), C=C 1635 (s) cm^{-1}. NMR ($CDCl_3$) δ 3.99 (3 H, s, $-COOCH_3$), 4.04 (3 H, s, $-COOCH_3$), 8.52 (1 H, s, vinylic), 9.48 (1 H, s, aromatic), and 9.62 (1 H, s, aromatic). MS M+ at *m/e* 263 corresponding to $C_{12}H_9NO_6$.

Dimethyl 4-carbomethoxymethylpyridine-3,5-dicarboxylate (X). A mixture of 5.0 g of esterlactone (IX) and 5.0 g potassium hydroxide dissolved in 35 ml of water was stirred at room temperature for 0.5 h. The resulting solution was cooled to 5 °C and 6.75 ml of 30 % hydrogen peroxide was added in 0.75 ml portions at 3 h intervals. After a total reaction time of 27 h the solution was concentrated to dryness under vacuum at 40 °C. The residue was dried in a vacuum desiccator overnight, cooled to −70 °C, and treated with 400 ml of methanol saturated with hydrogen chloride and precooled to −20 °C. The mixture was allowed to reach room temperature slowly. After standing for 48 h the mixture was poured slowly onto a suspension of excess of sodium bicarbonate in methylene chloride. The mixture was filtered and the filtrate evaporated under vacuum. The residue was chromatographed on alumina (act. II–III), giving 0.75 g (15 %) of a solid whose crystallization from hexane yielded (X) as colorless crystals. M.p. 61–63 °C. IR (KBr) C=O 1735 (s, broad) cm^{-1}. NMR ($CDCl_3$) δ 3.71 (3 H, s, $-CH_2-COOCH_3$), 3.92 (6 H, s, two $-COOCH_3$), 4.51 (2 H, s, $-CH_2-COOCH_3$) and 9.18 (2 H, s, H-2, H-6). MS M+ at *m/e* 267 corresponding to $C_{12}H_{13}NO_6$.

Preparation of 1-[β-(3-indolyl)-ethyl]-3-carbomethoxy pyridinium salts

General procedure. A mixture of the pyridine derivative and tryptophyl bromide [15] in methanol was stirred under nitrogen atmosphere. After completion of the reaction (TLC) the solution was concentrated to dryness under vacuum and the residue washed with abs. ether.

1-[β-(3-Indolyl)ethyl]-3-carbomethoxy pyridinium bromide (II). Reaction between 425 mg of methyl nicotinate and 770 mg of tryptophyl bromide in 15 ml of methanol gave after 18 h reaction time at room temperature a solid whose crystallization from methanol yielded 1.0 g (84 %) of salt (II). M.p. 213–215 °C (lit.[4] 212–213 °C). IR (KBr) NH 3340 (m) C=O 1740 (s) cm^{-1}.

1-[β-(3-Indolyl)ethyl]-3,5-dicarbomethoxy pyridinium bromide (III). Reaction between 3.5 g of 3,5-dimethyl dinicotinate (VII) and 3.5 g of tryptophyl bromide in 50 ml of methanol gave after 18 h reaction time at room temperature a solid whose crystallization from ether-methanol (1/1) yielded 5.5 g (84 %) of salt (III). M.p. 220–221 °C. IR (KBr) NH 3410 (m) C=O 1740 (s) cm^{-1}.

1-[β-(3-Indolyl)ethyl]-3,5-dicarbomethoxy-4-methyl pyridinium bromide (IV). Reaction between 760 mg of dimethyl 4-methylpyridine-3,5-dicarboxylate (VIII) and 760 mg of tryptophyl bromide in 20 ml of methanol gave after 7 h reaction time at 65 °C a solid whose crystallization from methanol yielded 1.2 g (81 %) of salt (IV). M.p. 193–195 °C. IR (KBr) NH 3440 (m) C=O 1730 (s) cm^{-1}.

1-[β-(3-Indolyl)ethyl]-3,5-dicarbomethoxy-4-carbomethoxymethyl pyridinium bromide (V). Reaction between 193 mg of dimethyl 4-carbomethoxymethylpyridine-3,5-dicarboxylate (X) and 200 mg of tryptophyl bromide in absence of methanol gave after 1 h reaction time at 100 °C 350 mg (71 %) of a solid, which, although essentially pure salt (V), failed to crystallize. IR (KBr) NH 3200 (m) C=O 1740 (s) cm^{-1}.

Reductions

General procedure. A mixture of the 1-[β-(3-indolyl)ethyl]-3-carbomethoxy pyridinium salt, palladium-charcoal (10 %), and triethylamine in abs. methanol was hydrogenated at atmospheric pressure. After the calculated amount of hydrogen had been introduced the hydrogenation was interrupted. The catalyst was filtered, the filtrate evaporated under vacuum, and the residue extracted with methylene chloride. The extract was washed with water, dried over anhydrous sodium sulfate, and evaporated under vacuum. The residue was purified by column chromatography (Al_2O_3; act. IV).

Dihydropyridines. Hydrogenation of a mixture of 400 mg of the salt (III), 100 mg of palladium-charcoal (10 %), and 0.2 ml of triethylamine in 150 ml of abs. methanol gave after 1 h reaction time 184 mg (56 %) of a solid whose crystallization from methanol yielded (XI) as yellowish crystals. M.p. 175–178 °C. IR (KBr) NH 3345 (s) C=O 1700 (s), 1670 (s) C=C 1645 (s) cm^{-1}. NMR (DMSO-d_6) δ 3.56 (3 H, s, $-COOCH_3$), 3.67 (3 H, s, $-COOCH_3$),

4.34 (2 H, s, C-6-H_2), 7.10 (1 H, d, J = 2 Hz, indolyl α-H), and 7.37 (1 H, s, C-2-H). MS M+ at m/e 340 corresponding to $C_{19}H_{20}N_2O_4$.

Hydrogenation of a mixture of 320 mg of the salt (IV), 100 mg of palladium-charcoal (10 %), and 0.15 ml of triethylamine in 100 ml of abs. methanol gave after 2.5 h reaction time 74 mg (31 %) of (XII) as an oil. NMR ($CDCl_3$) δ 2.53 (3 H, s, $-CH_3$), 3.59 (3 H, s, $-COOCH_3$), 3.70 (3 H, s, $-COOCH_3$), 4.18 (2 H, s, C-6-H_2), 6.92 (1 H, d, J = 2 Hz, indolyl α-H), and 7.38 (1, H s, C-2-H). Owing to the product's instability in air (*e.g.* it rapidly discolors) it was used in acid-induced cyclization (*cf.* later) without further analysis.

Hydrogenation of a mixture of 200 mg of the salt (V), 70 mg of palladium-charcoal (10 %), and 0.1 ml of triethylamine in 100 ml of abs. methanol gave after 3 h reaction time 44 mg (27 %) of (XIII) as an oil. NMR ($CDCl_3$) δ 3.56 (3 H, s, $-CH_2-COOCH_3$), 3.68 (3 H, s, $-COOCH_3$), 3.71 (3 H, s, $-COOCH_3$), 4.24 (2 H, s, C-6-H_2 or $-CH_2-COOCH_3$), 4.32 (2 H, s, $-CH_2-COOCH_3$ or C-6-H_2), 6.98 (1 H, d, J = 2 Hz, indolyl α-H), and 7.37 (1 H, s, C-2-H). Owing to the product's instability in air (*e.g.*, it rapidly discolors) it was used in acid-induced cyclization (*cf.* later) without further analysis.

Tetrahydropyridines. Hydrogenation of a mixture of 500 mg of the salt (II), 150 mg of palladium-charcoal (10 %), and 0.25 ml of triethylamine in 150 ml of abs. methanol gave after 12 hours reaction time 274 mg (70 %) of a solid whose crystallization from benzene-hexane yielded (XIV) as colorless crystals. M.p. 106–107 °C* (lit.[4] 117–118 °C). IR (KBr) NH 3270 (s) C=O 1665 (s) C=C 1590 (s) cm^{-1}. NMR ($CDCl_3$) δ 3.66 (3 H, s, $-COOCH_3$), 6.90 (1 H, d, J = 2 Hz, indolyl α-H), and 7.37 (1 H, s, C-2-H). MS M+ at m/e 284 corresponding to $C_{17}H_{20}N_2O_2$.

Hydrogenation of a mixture of 500 mg of the salt (III), 150 mg of palladium-charcoal (10 %), and 0.2 ml of triethylamine in 150 ml of abs. methanol gave after 24 h reaction time 290 mg (71 %) of (XV) as an oil. IR (film) NH 3350 (m) C=O 1735 (s), 1670 (s) C=C 1615 (s) cm^{-1}. NMR ($CDCl_3$) δ 3.67 (6 H, s, two $-COOCH_3$), 6.91 (1 H, d, J = 2 Hz, indolyl α-H), and 7.36 (1 H, s, C-2-H). MS M+ at m/e 342 corresponding to $C_{19}H_{22}N_2O_4$.

Hydrogenation of a mixture of 270 mg of the salt (IV), 80 mg of palladium-charcoal (10 %), and 0.1 ml of triethylamine in 100 ml of abs. methanol gave after 24 h reaction time 190 mg (85 %) of (XVI) as an oil. IR (film) NH 3320 (s) C=O 1735 (s), 1670 (s) C=C 1610 (s) cm^{-1}. NMR ($CDCl_3$) δ 0.90 (3 H, d, J = 6.5 Hz, $-CH_3$), 3.64 (3 H, s, $-COOCH_3$), 3.68 (3 H, s, $-COOCH_3$), 6.88 (1 H, d, J = 2 Hz, indolyl α-H), and 7.29 (1 H, s, C-2-H). MS M+ at m/e 356 corresponding to $C_{20}H_{24}N_2O_4$.

* Indicated melting point was not altered by repeated crystallizations.

Hydrogenation of a mixture of 175 mg of the salt (V), 120 mg of palladium-charcoal (10 %), and 0.1 ml of triethylamine in 100 ml of abs. methanol gave after 70 h reaction time 47 mg (32 %) of (XVII) as an oil. IR (film) NH 3320 (m) C=O 1735 (s), 1675 (s) C=C 1615 (s) cm^{-1}. NMR ($CDCl_3$) δ 2.29 (2 H, d, J = 6 Hz, $-CH_2-COOCH_3$), 3.62 (6 H, s, two $-COOCH_3$), 3.69 (3 H, s, $-COOCH_3$), 6.98 (1 H, d, J = 2 Hz, indolyl α-H), and 7.31 (1 H, s, C-2-H). MS M+ at m/e 414 corresponding to $C_{22}H_{26}N_2O_6$.

Cyclizations

General procedure. A solution of the reduction product in anhydrous methanol was saturated with dry hydrogen chloride gas during a 2 h period. The solution was left standing at room temperature for 16 h and then was poured slowly into a suspension of sodium bicarbonate in methylene chloride. The inorganic salts were separated and the dried filtrate was evaporated under vacuum. The residue was purified by column chromatography (Al_2O_3; act. IV).

Dihydropyridines. Cyclization of 40 mg of (XI) gave 35 mg (87 %) of (XVIII) as an oil. UV (EtOH 94 %) λ_{max} 208 (ε 27 600), 223 (ε 30 100), 286 (ε 12 700), and 291 (ε 12 500) nm. λ_{min} 213, 255, and 289 nm. IR (film) NH 3430 (m) Bohlmann bands 2815 and 2770, C=O 1720 (s, broad), C=C 1660 (s) cm^{-1}. NMR ($CDCl_3$) δ 3.71 (3 H, s, $-COOCH_3$) and 3.82 (3 H, s, $-COOCH_3$). MS M+ at m/e 340 corresponding to $C_{19}H_{20}N_2O_4$. Other noteworthy peaks at m/e 339, 184, 170, 169, and 156.

Cyclization of 50 mg of (XII) gave 34 mg (68 %) of (XIX) as an oil. UV (EtOH 94 %) λ_{max} 208 (infl.) (ε 24 000), 224 (ε 30 900), 284 (ε 7 670), and 291 (ε 7 080) nm. λ_{max} 211 (infl.), 256, and 289 nm. IR (film) NH 3400 (m) Bohlmann bands 2810 and 2765, C=O 1725 (s), C=C 1655 (m) cm^{-1}. NMR ($CDCl_3$) δ 2.11 (3 H, s, $-CH_3$), 3.81 (3 H, s, $-COOCH_3$), and 3.92 (3 H, s, $-COOCH_3$). MS M+ at m/e 354 corresponding to $C_{20}H_{22}N_2O_4$. Other noteworthy peaks at m/e 353, 184, 170, 169, and 156.

Cyclization of 44 mg of (XIII) gave 40 mg (91 %) of (XX) as an oil. UV (EtOH 94 %) λ_{max} 209 (ε 21 400), 225 (ε 27 850), 284 (ε 7 150), and 292 (ε 6 870) nm. λ_{min} 211, 253, and 290 nm. IR (film) NH 3400 (m) Bohlmann bands 2810 and 2770, C=O 1730 (s, broad) C=C 1655 (m) cm^{-1}. NMR ($CDCl_3$) δ 3.68 (5 H, apparent s, $-CH_2-COOCH_3$ and $-CH_2-COOCH_3$), 3.75 (3 H, s, $-COOCH_3$), and 3.84 (3 H, s, $-COOCH_3$). MS M+ at m/e 412 corresponding to $C_{22}H_{24}N_2O_6$. Other noteworthy peaks at m/e 411, 184, 170, 169, and 156.

Tetrahydropyridines. Cyclization of 170 mg of (XIV) gave 130 mg (76 %) of a solid whose crystallization from ether yielded (XXI) as colorless crystals. M.p. 143–145 °C (lit.[4] 133–134 °C). IR (KBr) NH 3450 (s) Bohlmann bands

2815, and 2760, C=O 1720 (s) cm^{-1}. NMR ($CDCl_3$) δ 3.77 (3 H, s, $-COOCH_3$), and 3.79 (1 H, d, $J=10$ Hz, axial C-12b–H). MS M+ at *m/e* 284 corresponding to $C_{17}H_{20}N_2O_2$. Other noteworthy peaks at *m/e* 283, 184, 170, 169, and 156.

Cyclization of 120 mg of (XV) gave 98 mg (82 %) of a solid whose crystallization from ether yielded (XXII) as colorless crystals. M.p. 142–143 °C. IR (KBr) NH 3440 (s) Bohlmann bands 2810 and 2770, C=O 1730 (s) cm^{-1}. NMR ($CDCl_3$) δ 3.70 (3 H, s, $-COOCH_3$), 3.81 (3 H, s, $-COOCH_3$), and ~3.9 (1 H, d, $J\approx10$ Hz, axial C-12b–H). MS M+ at *m/e* 342 corresponding to $C_{19}H_{22}N_2O_4$. Other noteworthy peaks at *m/e* 341, 184, 170, 169, and 156.

Cyclization of 160 mg of (XVI) gave 134 mg (84 %) of (XXIII) as a mixture of two diastereoisomers A and B (60/40). IR (KBr) NH 3430 (m) Bohlmann bands 2810 and 2780, C=O 1730 (s) cm^{-1}. NMR* ($CDCl_3$) δ 0.92 (3 H, d, $J=7$ Hz, isomer B $-CH_3$), 1.08 (3 H, d, $J=7$ Hz, isomer A, $-CH_3$), 3.66 (3 H, s, isomer B, $-COOCH_3$), 3.68 (3 H, s, isomer A, $-COOCH_3$), 3.77 (3 H, s, isomer B, $-COOCH_3$), and 3.81 (3 H, s, isomer A, $-COOCH_3$). MS M+ at *m/e* 356 corresponding to $C_{20}H_{24}N_2O_4$. Other noteworthy peaks at *m/e* 355, 184, 170, 169, and 156.

Cyclization of 40 mg of (XVII) gave 35 mg (87 %) of (XXIV) as an oil. IR (film) NH 3440 (m) Bohlmann bands 2815 and 2775, C=O 1735 (s, broad) cm^{-1}. NMR ($CDCl_3$) δ 2.76 (2 H, d, $J=7$ Hz, $-CH_2-COOCH_3$), 3.68 (6 H, s, two $-COOCH_3$), and 3.77 (3 H, s, $-COOCH_3$). MS M+ at *m/e* 414 corresponding to $C_{22}H_{26}N_2O_6$. Other noteworthy peaks at *m/e* 413, 184, 170, 169, and 156.

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* The relative intensities given represent the two isomers independently.