Structure and Spectral Properties of β-Carbolines. Part 3.[1] Synthesis and Stereochemistry of 1,2,3,4,6,7,9,10,15b,15c-Decahydropyrido[1″,2″:1′,2′]pyrazino[4′,3′:1,2]pyrido[3,4-*b*]indoles

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Diastereoisomers of a new heterocyclic system, *i.e.* 1,2,3,4,6,7,9,10,15b,15c-decahydropyrido-[1″,2″:1′,2′]pyrazino[4′,3′:1,2]pyrido[3,4-*b*]indoles (**7a**) and (**7b**), as well as their 6- and 7-oxo derivatives (**5a**),(**5b**) and (**2a**),(**2b**), respectively, were synthesized. The structure of individual diastereoisomers was determined using ^{1}H and ^{13}C NMR techniques.

Simple β-carboline alkaloids include many pharmacologically active compounds.[2] For several years we have synthesized a number of tetrahydro-β-carboline derivatives,[3] some of which show significant sedative,[3e] antidepressant,[3d,4] anticonvulsant,[3c,3f] or anxiolytic[3g] activity in animal tests. We also demonstrated that the toxicity and the sedative effect of some tetrahydro-β-carbolines depend quantitatively on the substitution pattern and the kind of substituent.[5] Recently we have focussed our attention towards the stereochemistry of compounds with the β-carboline moiety built into a fused ring system.[1,6]

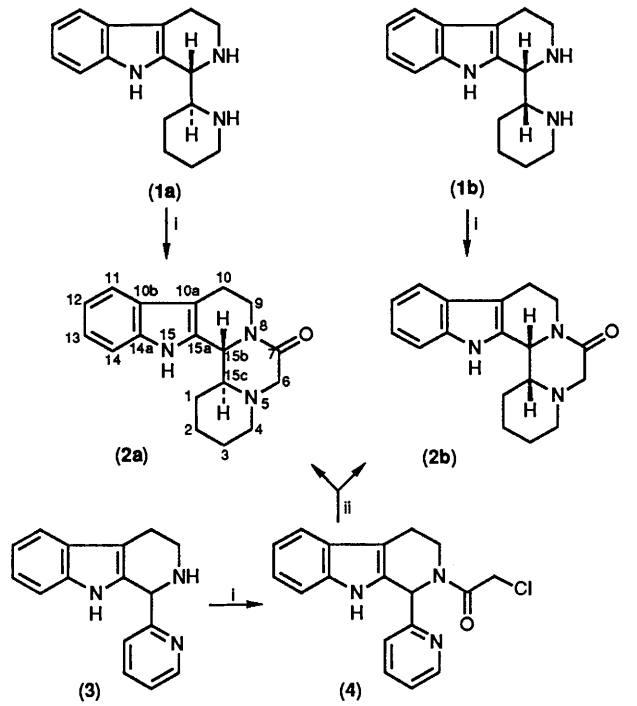
In order to expand our study we synthesized diastereoisomers of a new heterocyclic system, *i.e.* 1,2,3,4,6,7,9,10,15b,15c-decahydropyrido[1″,2″:1′,2′]pyrazino[4′,3′:1,2]pyrido[3,4-*b*]-indoles (**7a**) and (**7b**), as well as their 6- and 7-oxo derivatives (**5a**),(**5b**) and (**2a**),(**2b**), respectively.

Results and Discussion

Synthesis.—The two starting diastereoisomers (**1a**) and (**1b**) were obtained by catalytic hydrogenation of 1-(2-pyridyl)-1,2,3,4-tetrahydro-β-carboline (**3**)[7] and further separation by fractional crystallization as described previously.[8] The cyclocondensation reaction of compounds (**1a**) and (**1b**) with chloroacetyl chloride in acetone at −15 °C, in the presence of sodium carbonate, afforded the appropriate 7-oxo diastereoisomers (**2a**) and (**2b**). In order to determine the direction of chloroacetylation and thereby to evince the presence of the carbonyl group at position 7, compounds (**2a**) and (**2b**) were also obtained by an alternative route (Scheme 1). Reaction of compound (**3**) with chloroacetyl chloride under the above mentioned conditions at room temperature gave the 2-chloroacetyl derivative (**4**) in 92% yield. Catalytic reduction of the derivative (**4**) and treatment of the reaction mixture with ammonia yielded a mixture of 7-oxo compounds (**2a**) and (**2b**), which were separated by column chromatography.

The 6-oxo isomers (**5a**) and (**5b**) were obtained by condensation of appropriate diastereoisomers (**1a**) and (**1b**) with ethyl bromoacetate in ethanol in the presence of triethylamine (Scheme 2). Reaction of compound (**3**) with ethyl bromoacetate under the same conditions gave the 2-ethoxycarbonylmethyl derivative (**6**) in 70% yield. Products of the catalytic reduction of the derivative (**6**) cyclized simultaneously in alkaline medium to yield, after chromatographic resolution, the 6-oxo diastereoisomers (**5a**) and (**5b**).

Condensation of the specific diastereoisomers (**1a**) and (**1b**) with 1,2-dibromoethane in butan-1-ol in the presence of sodium carbonate yielded compounds (**7a**) and (**7b**), respectively

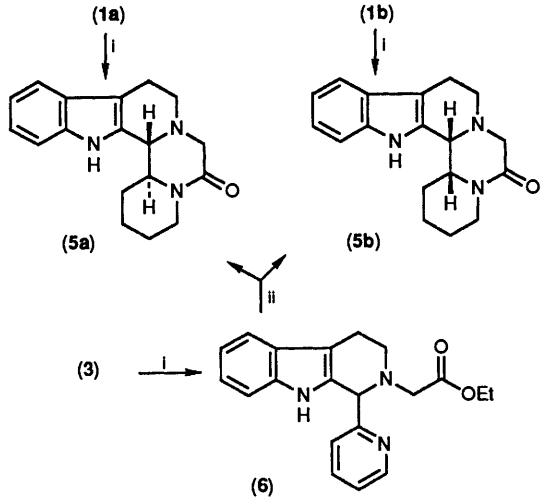


Scheme 1. *Reagents and conditions:* i, $ClCOCH_2Cl$, Na_2CO_3, acetone; ii, H_2, PtO_2, AcOH, 4 atm, room temp., 22 h; then aq. NH_3.

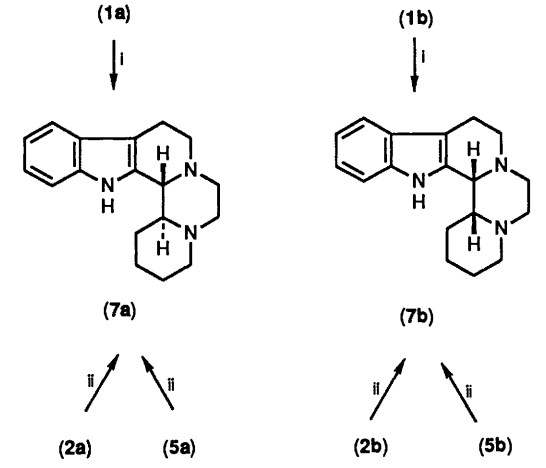
(Scheme 3). Reduction of the oxo derivatives (**2a**), (**5a**) and (**2b**), (**5b**) with $LiAlH_4$ also gave the appropriate diastereoisomers (**7a**) and (**7b**).

The identity of the respective compounds (**2a**), (**2b**), (**5a**), (**5b**), (**7a**), and (**7b**), synthesized by different methods, was confirmed by both TLC and ^{1}H and ^{13}C NMR techniques.

^{1}H *NMR Spectra.*—Although the ^{1}H NMR spectrum of the saturated fragment of the investigated compounds is fairly complex, the 15b-H signal is not overlapped by other signals and can be easily analysed. The chemical shift of the 15b-H atom and its vicinal coupling constant with the 15c-H atom is of the highest diagnostic value for structural elucidation. The resonance signal of 15b-H for compounds (**5a**) and (**5b**) is shifted only slightly downfield in relation to compounds (**7a**) and (**7b**). However, the same signals in structures (**2a**) and (**2b**) are shifted downfield by 1.17 and 1.49 ppm from their respective



Scheme 2. *Reagents and conditions:* i, $BrCH_2CO_2Et$, Et_3N, EtOH; ii, H_2, PtO_2, AcOH, 4 atm, room temp., 20 h; then KOH, 99.8% EtOH.



Scheme 3. *Reagents and conditions:* i, $BrCH_2CH_2Br$, Na_2CO_3, BuOH; ii, $LiAlH_4$, THF.

Table 1. Comparison of ^1H NMR chemical shifts (δ) and vicinal coupling constants (J) of the 15b-H atom, and dihedral angles (φ, H_{15b}–C_{15b}–C_{15c}–H_{15c}) for structures (**2**), (**5**), and (**7**).

Compound	δ	$J_{15b\text{-}H,15c\text{-}H}$ (Hz)	φ(°) Calc.[a]	φ(°) Estim.[b]
(**2a**)	4.67	9.0	171	180
(**2b**)	5.08	1.8	59	60
(**5a**)	3.65	9.2	177	180
(**5b**)	3.90	1.0	66 < φ < 90	70
(**7a**)	3.50	9.0	171	180
(**7b**)	3.59	1.8	59	60

[a] Calculated from observed $J_{15b\text{-}H,15c\text{-}H}$ using equation (1). [b] Measured from Dreiding models.

positions in compounds (**7a**) and (**7b**) (Table 1). The observed chemical-shift changes depend on the position of the carbonyl group.[9,10] Therefore the 7-oxo structure should be ascribed to diastereoisomers (**2a**) and (**2b**), with the isomeric 6-oxo structure to compounds (**5a**) and (**5b**). These findings explicitly confirm our synthetic conclusions.

The signal of the 15b-H atom appears as a doublet or as a broad singlet [the latter only in the case of compound (**5b**)], in

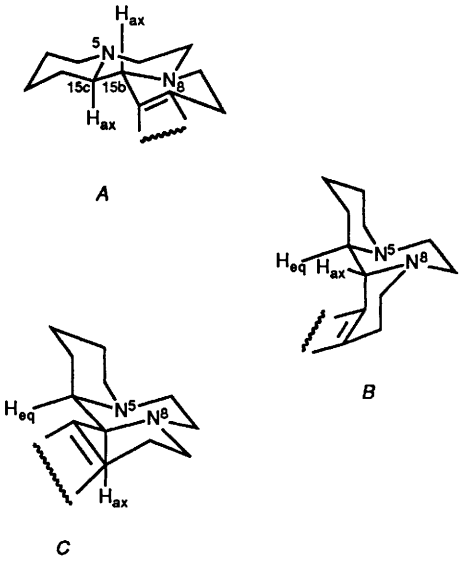


Figure. Observed conformations of the decahydropyridopyrazino skeleton: *A* 8,15b-*trans*, 5,15c-*trans* [(**2a**), (**5a**), (**7a**)]; *B* 8,15b-*cis*, 5,15c-*cis* [(**2b**), (**7b**)]; *C* 8,15b-*trans*, 5,15c-*cis* [(**5b**)].

the spectra of the investigated compounds, and the vicinal coupling constants $J_{15b\text{-}H,15c\text{-}H}$ are shown in Table 1. The dihedral angle (φ) between H_{15b}–C_{15b}–C_{15c}–H_{15c} was estimated using a basic Karplus equation (1).[11] The calculated values of

$$J^{vic} = 4.5\cos 2\varphi - 0.5\cos\varphi + 4.22 \quad (1)$$

the dihedral angle were compared with those estimated from Dreiding models, as shown in Table 1. The above results indicate that 15b-H (axial) and 15c-H (axial) atoms in structures (**2a**), (**5a**), and (**7a**) are in a *trans* position. However, 15b-H (axial) and 15c-H (equatorial) atoms in structures (**2b**), (**5b**), and (**7b**) are arranged in a *cis* position, as illustrated in the Figure.

^{13}C *NMR Spectra.*—The ^{13}C NMR chemical shifts for the studied compounds (**2a**), (**2b**), (**5a**), (**5b**), (**7a**), and (**7b**) are listed in Table 2. These were assigned by comparison with the spectra of other tetrahydro-β-carbolines,[10,12] quinolizidine,[13] and piperazines,[14] and by analysis of the signal multiplicity obtained from proton-coupled spectra. The signals of the indole moiety carbon atoms (10a–15a) were found at their typical values and within a narrow range from those values expected ($0.4 \leqslant \Delta\delta \leqslant 2.7$ ppm).[6,12] The observed differences in the ^{13}C NMR spectra between particular diastereoisomers (Table 2) may be explained by steric relations in the rigid decahydrodipyridopyrazino skeleton (Figure). The quinolizidine system seems to be a good approximation of this tricyclic skeleton. The stereochemistry of the quinolizidine ring is well established and can be determined by ^{13}C NMR spectroscopy.[13,15] In general, particular carbon atoms of the saturated skeleton in compounds (**2b**) and (**7b**) resonate upfield in relation to those in compounds (**2a**) and (**7a**), due to a compression effect.[14] However, chemical shifts of these atoms in isomers (**5a**) and (**5b**) are comparable. Resonance signals of C-1, C-3, and C-10 in the diastereoisomers (**2b**) and (**7b**) are shifted upfield by 3.5–7.3 ppm from their respective positions in isomers (**2a**) and (**7a**), while the same resonances in the diastereoisomer (**5b**) are shifted slightly downfield by 0.2–0.9 ppm in relation to those for diastereoisomer (**5a**). The observed upfield shifts arise from a steric hindrance and additional γ-*syn* and γ-*gauche* interactions[14] found in conformation *B*, but which are not

Table 2. ^{13}C NMR chemical shifts of compounds (**2a**), (**2b**), (**5a**), (**5b**), (**7a**), and (**7b**) in $CDCl_3$.

Carbon[a]	(2a)	(2b)	(5a)	(5b)	(7a)	(7b)
C-1	31.5	24.6	31.4	32.3	28.7	25.2
C-2	23.5	20.7	23.5	24.0	24.1	21.5
C-3	24.7	17.4[b]	24.6	24.8	25.0	18.7[b]
C-4	54.9	49.7	58.6	58.1	56.1[b]	54.6[c]
C-6	40.2	39.0	166.2	166.3	54.1[b]	52.7[c]
C-7	166.3	167.2	40.3	41.8	52.2[b]	50.5[c]
C-9	58.7	52.4	54.9	49.8	48.8	45.1
C-10	21.1	17.1[b]	21.1	21.4	22.0	18.4[b]
C-10a	112.0	111.0	110.6	110.2	110.4	109.7
C-10b	126.6	126.7	126.7	126.8	126.8	127.3
C-11	118.4	118.2	118.4	118.4	118.0	118.0
C-12	120.1	119.7	120.0	119.9	119.1	119.2
C-13	122.6	122.1	122.5	122.3	121.5	121.3
C-14	110.9	110.9	111.0	110.9	110.6	110.8
C-14a	136.1	136.7	136.0	136.3	136.0	136.3
C-15a	131.0	129.7	131.5	131.3	132.4	132.3
C-15b	62.3	59.0	59.7	59.3	62.5[c]	59.1
C-15c	59.7	56.6	62.3	61.1	62.4[c]	55.2

[a] Numbering scheme corresponds to that shown in structure (**2a**). [b,c] Assignments may be reversed in any column.

observed in the case of conformers *A* and *C*. Moreover, Gribble and Levy reported chemical shifts for C-10 in *trans*- (21.8 ppm) and *cis*- (16.8 ppm) quinolizidine systems *A*, *C*, and *B*, respectively.[15a] The above mentioned chemical shifts are also of a strong diagnostic value for structural determination, and are in good agreement with those observed for the C-10 atom of the investigated compounds (Table 2).

Experimental

M.p.s were determined on a Boetius apparatus and are uncorrected. Microanalyses were performed on a Perkin-Elmer 240 Elemental Analyser in the Institute of Organic Chemistry, PAS, Warsaw. EI mass spectra at 70 eV were taken with a LKB 9005 spectrometer, and IR spectra were recorded in KBr pellets on a Specord 71 IR spectrophotometer. ^1H (200 MHz) and ^{13}C (125 MHz) NMR spectra were recorded on Bruker spectrometers for solutions in $CDCl_3$ with tetramethylsilane as internal standard. Column chromatography was performed using Kieselgel 60 (Art. 7734, Merck). TLC was conducted on precoated Kieselgel $60F_{254}$ plates [Art. 5554, and Art. 5717 for preparative TLC (PLC), Merck]. Spots on TLC were detected by their absorption under UV light. Syntheses of the starting compounds are described as follows: (**1a**), (**1b**),[8] and (**3**).[7]

Condensation of Diastereoisomers (**1a**) *and* (**1b**) *with Chloroacetyl Chloride.*—To a solution of the appropriate diastereoisomer (**1a**) or (**1b**) (0.255 g, 1 mmol) in acetone (30 ml) was added sodium carbonate (0.2 g). The suspension was cooled to −15 °C, and a solution of chloroacetyl chloride (0.12 g, 1 mmol) in acetone (4 ml) was added dropwise. The reaction mixture was stirred for 30 min, then treated with water (50 ml) and the precipitate was filtered off. The filtrate was evaporated under reduced pressure to give (i) (±)-threo-1,2,3,4,9,10,15b,15c-*octahydropyrido*[1″,2″:1′,2′]*pyrazino*-[4′,3′:1,2]*pyrido*[3,4-*b*]*indol*-7(6H)-*one* (**2a**) as crystals from ethanol (0.18 g, 60%), m.p. 259–261 °C (Found: C, 71.0; H, 7.1; N, 13.6. $C_{18}H_{21}N_3O{\cdot}0.5H_2O$ requires C, 71.0; H, 7.3; N, 13.8%); R_f 0.47 [$CHCl_3$–MeOH (9:1)]; ν_{max} 1 645 cm^{-1} (CO); δ_H 7.98 (1 H, s, NH), 7.51 (1 H, d, *J* 7.0 Hz, 14-H), 7.36 (1 H, d, *J* 7.2 Hz, 11-H), 7.20 (1 H, t, *J* 7.0 Hz, 12-H), 7.13 (1 H, t, *J* 7.2 Hz, 13-H), 5.09 (1 H, ddd, *J* 12.2, 7.5, and 1.5 Hz, 9-H^{eq}), 4.67 (1 H, d, *J* 9.0 Hz, 15b-H), 3.54 (1 H, d, *J* 16.8 Hz, 6-H^{eq}), 3.05–2.70 (5 H, m, 6- and 9-H^{ax}, 10-H_2, and 15c-H), and 2.50–1.40 (8 H, m, 1-, 2-, 3-, and 4-H_2); *m/z* 295 (M^+, 32%), 212 (49), 170 (100), and 156 (3).

(ii) (±)-erythro-1,2,3,4,9,10,15b,15c-*Octahydropyrido*-[1″,2″:1′,2′]*pyrazino*[4′,3′:1,2]*pyrido*[3,4-*b*]*indol*-7(6H)-*one* (**2b**), as crystals from benzene–hexane (1:1) (0.15 g, 50%), m.p. 218–220 °C (Found: C, 71.4; H, 7.1; N, 13.5%); R_f 0.24 [$CHCl_3$–MeOH (9:1)]; ν_{max} 1 645 cm^{-1} (CO); δ_H 8.04 (1 H, s, NH), 7.52 (1 H, d, *J* 7.3 Hz, 14-H), 7.36 (1 H, d, *J* 7.3 Hz, 11-H), 7.20 (1 H, t, *J* 7.6 Hz, 12-H), 7.13 (1 H, t, *J* 7.6 Hz, 13-H), 5.10 (1 H, br d, *J* 10.5 Hz, 9-H^{eq}), 5.08 (1 H, d, *J* 1.8 Hz, 15b-H), 3.80 (1 H, d, *J* 17.7 Hz, 6-H^{eq}), 3.49 (1 H, d, *J* 17.7 Hz, 6-H^{ax}), 3.38 (1 H, m, 9-H^{ax}), 3.05–2.75 (5 H, m, 4- and 10-H_2, and 15c-H), and 1.90–0.80 (6 H, m, 1-, 2-, and 3-H_2); *m/z* (M^+, 34%), 212 (56), 170 (100), and 156 (3).

2-*Chloroacetyl*-1-(2-*pyridyl*)-1,2,3,4-*tetrahydro*-β-*carboline* (**4**).—To a solution of 1-(2-pyridyl)-1,2,3,4-tetrahydro-β-carboline (**3**) (1.0 g, 4 mmol) in acetone (50 ml) was added sodium carbonate (2.0 g), and then a solution of chloroacetyl chloride (0.8 g, 7 mmol) in acetone (14 ml) was added dropwise. The reaction mixture was stirred for 40 min at room temperature, poured into water (150 ml), and cooled down to 0 °C. The precipitate was filtered off and dried over P_2O_5 to give compound (**4**) as pale yellow crystals from acetone–water (8:2) (1.2 g, 92%), m.p. 220–222 °C (Found: C, 66.5; H, 4.65; N, 12.8. $C_{18}H_{16}ClN_3O$ requires C, 66.4; H, 4.95; N, 12.9%); ν_{max} 3 280, 1 640, 1 580, 1 470, 1 445, 1 215, 750, and 690 cm^{-1}; *m/z* 327 (M + 2, 11%), 325 (M^+, 31), 289 [(M − HCl)$^+$, 47], and 248 [(M − $COCH_2Cl$)$^+$, 100].

Reduction of 2-*Chloroacetyl*-1-(2-*pyridyl*)-1,2,3,4-*tetrahydro*-β-*carboline* (**4**).—A mixture of compound (**4**) (0.5 g, 1.5 mmol), PtO_2 (0.04 g), and glacial acetic acid (10 ml) was reduced with hydrogen (4 atm) in an autoclave at room temperature for 22 h. The catalyst was then filtered off, and the solvent was evaporated off under reduced pressure. The oily residue was dissolved in chloroform (5 ml), and the solution was made alkaline with 25% ammonia to pH 11 and extracted with chloroform (3 × 5 ml). The extract was dried over anhydrous potassium carbonate and concentrated to *ca.* 5 ml. Purification of the obtained mixture by column chromatography with chloroform–methanol (8:2) as eluant, followed by crystallization, afforded the (±)-*threo*-compound (**2a**) from ethanol (0.066 g, 15%), m.p. 259–261 °C; R_f 0.47 [$CHCl_3$–MeOH (9:1)] and the (±)-*erythro*-compound (**2b**) from benzene–hexane (1:1) (0.033 g, 7%), m.p. 218–220 °C; R_f 0.24 [$CHCl_3$–MeOH (9:1)].

Condensation of Diastereoisomers (**1a**) *and* (**1b**) *with Ethyl Bromoacetate.*—A mixture of the appropriate diastereoisomer (**1a**) or (**1b**) (0.13 g, 0.5 mmol), ethyl bromoacetate (0.125 ml, 1 mmol), triethylamine (0.15 ml, 1 mmol), and ethanol (5 ml) was refluxed for 1 h. Powdered potassium hydroxide (0.03 g) was then added, and the reaction mixture was stirred at room temperature for 45 min, poured into water (5 ml), and extracted with chloroform (3 × 3 ml). The extract was dried over anhydrous potassium carbonate and then evaporated under reduced pressure. The crude product was purified by column chromatography with chloroform–methanol (9:1) as eluant and crystallized to yield (i) (±)-threo-1,2,3,4,9,10,15b,15c-*octahydropyrido*[1″,2″:1′,2′]*pyrazino*[4′,3′:1,2]*pyrido*[3,4-b]-*indol*-6(7H)-*one* (**5a**) as crystals from ethanol–water (9:1) (0.03 g, 20%), m.p. 205–207 °C (Found: C, 73.3; H, 7.1; N, 13.8. $C_{18}H_{21}N_3O$ requires C, 73.2; H, 7.2; N, 14.2%); R_f 0.51 [$CHCl_3$–MeOH] (9:1)]; ν_{max} 1 640 cm^{-1} (CO); δ_H 7.94 (1 H, s, NH), 7.52 (1 H, d, *J* 7.2 Hz, 14-H), 7.36 (1 H, d, *J* 7.3 Hz, 11-H), 7.21 (1 H, t, *J* 7.3 Hz, 12-H), 7.13 (1 H, t, *J* 7.4 Hz, 13-H), 4.82 (1 H, br d, *J* 11.9 Hz, 4-H^{eq}), 3.65 (1 H, d, *J* 9.2 Hz, 15b-H), 3.60 (1

H, d, *J* 16.5 Hz, 7-H^{eq}), 3.52 (1 H, br d, *J* 11.3 Hz, 4-H^{ax}), 3.42 (1 H, d, *J* 16.5 Hz, 7-H^{ax}), 3.17 (1 H, ddd, *J* 11.0, 9.3, and 1.2 Hz, 15c-H), 2.95–2.65 (4 H, m, 9-and 10-H_2), and 2.50–1.50 (6 H, m, 1-, 2-, and 3-H_2); *m/z* 295 (M^+, 31%), 184 (100), 170 (10), and 156 (24).

(ii) (±)-erythro-1,2,3,4,9,10,15b,15c-*Octahydropyrido*-[1″,2″:1′,2′]*pyrazino*[4′,3′:1,2]*pyrido*[3,4-b]*indol*-6(7H)-*one* (**5b**), as crystals from ethanol–water (9:1) (0.036 g, 24%), m.p. 213–216 °C (Found: C, 73.1; H, 7.2; N, 14.1%); R_f 0.59 [$CHCl_3$–MeOH (9:1)]; ν_{max} 1 645 cm^{-1} (CO); δ_H 8.01 (1 H, s, NH), 7.52 (1 H, d, *J* 7.2 Hz, 14-H), 7.35 (1 H, d, *J* 7.1 Hz, 11-H), 7.19 (1 H, t, *J* 7.1 Hz, 12-H), 7.12 (1 H, t, *J* 7.2 Hz, 13-H), 4.79 (1 H, br d, *J* 12.6 Hz, 4-H^{eq}), 3.90 (1 H, br s, 15b-H), 3.71 (1 H, m, 15c-H), 3.65 (1 H, d, *J* 16.2 Hz, 7-H^{eq}), 3.20 (1 H, d, *J* 16.2 Hz, 7-H^{ax}), 3.15–2.45 (5 H, m, 4-H^{ax}, 9- and 10-H_2), and 1.95–1.25 (6 H, m, 1-, 2-, and 3-H_2); *m/z* 295 (M^+, 32%), 184 (100), 170 (11), and 156 (32).

*2-Ethoxycarbonylmethyl-1-(2-pyridyl)-1,2,3,4-tetrahydro-β-carboline** (**6**).—A mixture of 1-(2-pyridyl)-1,2,3,4-tetrahydro-β-carboline (**3**) (0.5 g, 2 mmol), ethyl bromoacetate (0.73 g, 4 mmol), triethylamine (0.44 g, 1 mmol), and ethanol (5 ml) was refluxed for 45 min. The reaction mixture was then poured into water (10 ml) and extracted with benzene (3 × 7 ml). The extract was dried over anhydrous sodium sulphate and then evaporated under reduced pressure. The residue was crystallized from ethanol to give the *title ether* (**6**) as crystals (0.48 g, 71%), m.p. 144–146 °C (Found: C, 71.6; H, 6.2; N, 12.5. $C_{20}H_{21}N_3O_2$ requires C, 71.6; H, 6.3; N, 12.5%); ν_{max} 3 200, 1 735, 1 600, 1 500, 1 475, 1 440, and 1 280 cm^{-1}; *m/z* 335 (M^+, 72%), 262 [(M – CO_2Et)$^+$, 17], 257 (63), 248 [(M – CH_2CO_2Et)$^+$, 34], and 219 (100).

Reduction of 2-Ethoxycarbonylmethyl-1-(2-pyridyl)-1,2,3,4-tetrahydro-β-carboline (**6**).—A mixture of compound (**6**) (0.4 g, 1.2 mmol), PtO_2 (0.04 g), and glacial acetic acid (10 ml) was reduced with hydrogen (4 atm) in an autoclave at room temperature for 20 h. The catalyst was filtered off and the solvent was evaporated off under reduced pressure. The oily residue was dissolved in chloroform (3 ml), the solution was made alkaline with 25% ammonia to pH 11 and extracted with chloroform (3 × 5 ml), and the extract was evaporated under reduced pressure. The residue was dissolved in 99.8% ethanol (10 ml), powdered potassium hydroxide (0.12 g) was added, and the mixture was refluxed for 45 min before being treated with water (10 ml) and extracted with chloroform (3 × 5 ml). The extract was dried over anhydrous potassium carbonate and evaporated. Purification of the residue by column chromatography with ethyl acetate–methanol (3.5:0.5) as eluant, followed by crystallization from ethanol–water (9:1), afforded the (±)-*threo*-compound (**5a**) (0.05 g, 15%), m.p. 205–207 °C; R_f 0.51 [$CHCl_3$–MeOH (9:1)], and the (±)-*erythro*-compound (**5b**) (0.04 g, 12%), m.p. 214–216 °C; R_f 0.59 [$CHCl_3$–MeOH (0:1)].

Condensation of Diastereoisomers (**1a**) *and* (**1b**) *with* 1,2-*Dibromoethane*.—A mixture of the appropriate diastereoisomer (**1a**) or (**1b**) (0.05 g, 0.2 mmol), 1.2-dibromoethane (0.8 g, 0.5 mmol), sodium carbonate (0.1 g), and butan-1-ol (5 ml) was refluxed for 2 h. The reaction mixture was then poured into water (30 ml), acidified with hydrochloric acid to pH 1, and the organic layer was separated. The aqueous layer was extracted with chloroform (3 × 5 ml). The organic layers were combined, dried over anhydrous sodium sulphate, and evaporated under reduced pressure, and the residue was crystallized from ethanol–water (9:1) to give (i) (±)-threo-1,2,3,4,6,7,9,10,15b,15c-*decahydropyrido*[1″,2″:1′,2′]*pyrazino*[4′,3′:1,2]*pyrido*[3,4-b]-*indole* (**7a**) as crystals (0.01 g, 18%), m.p. 172–174 °C (Found: C, 76.4; H, 8.5; N, 14.5. $C_{18}H_{23}N_3$ requires C, 76.8; H, 8.2; N, 14.9%); R_f 0.19 (MeOH); δ_H 8.14 (1 H, s, NH), 7.40 (1 H, d, *J* 7.8 Hz, 14-H), 7.22 (1 H, d, *J* 8.2 Hz, 11-H), 7.05 (1 H, t, *J* 7.1 Hz, 12-H), 6.99 (1 H, t, *J* 7.8 Hz, 13-H), 3.50 (1 H, d, *J* 9.0 Hz, 15b-H), 3.25–3.10 (2 H, m, 4- and 9-H), 2.94 (1 H, br d, *J* 9.8 Hz, 15c-H), 2.85–2.00 (8 H, m, 4- and 9-H, and 6-, 7-, and 10-H_2), and 1.80–1.15 (6 H, m, 1-, 2-, and 3-H_2); *m/z* 281 (M^+, 83%), 197 (51), 170 (91), 156 (15), and 83 (100).

(ii) (±)-erythro-1,2,3,4,6,7,9,10,15b,15c-*Decahydropyrido*-[1″,2″:1′,2′]*pyrazino*[4′,3′:1,2]*pyrido*[3,4-b]*indole* (**7b**), as crystals (0.16 g, 29%), m.p. 153–155 °C (Found: C, 74.5; H, 8.2; N, 14.4. $C_{18}H_{23}N_3$·0.5H_2O requires C, 74.4; H, 8.3; N, 14.4%); R_f 0.12 (MeOH); δ_H 8.40 (1 H, br s, NH), 7.47 (1 H, d, *J* 7.6 Hz, 14-H), 7.30 (1 H, d, *J* 8.2 Hz, 11-H), 7.12 (1 H, t, *J* 7.0 Hz, 12-H), 7.08 (1 H, t, *J* 7.1 Hz, 13-H), 3.59 (1 H, d, *J* 1.8 Hz, 15b-H), 3.35–3.25 (2 H, m, 4- and 9-H), 3.05–2.45 (9 H, m, 4-, 9-, and 15c-H, and 6-, 7-, and 10-H_2), and 1.90–0.95 (6 H, m, 1-, 2-, and 3-H_2); *m/z* 281 (M^+, 100%), 197 (44), 170 (69), 156 (14), and 83 (77).

Reduction of (±)-threo-*Oxo Isomers* (**2a**) *and* (**5a**).—To a solution of a (±)-*threo*-oxo isomer (**2a**) or (**5a**) (0.02 g, 0.06 mmol) in diethyl ether–tetrahydrofuran (THF) (1:1) was added $LiAlH_4$ (0.02 g), and the reaction mixture was stirred at room temperature for 30 min. The unchanged $LiAlH_4$ was decomposed on addition of a few drops of water. The reaction mixture was filtered, the filtrate was evaporated under reduced pressure, and the residue was crystallized from ethanol to yield (±)-*threo*-diastereoisomer (**7a**) (0.01 g, 59%), m.p. 172–174 °C; R_f 0.19 (MeOH).

Reduction of (±)-erythro-*Oxo Isomers* (**2b**) *and* (**5b**).—To a solution of a (±)-*erythro*-oxo isomer (**2b**) or (**5b**) (0.03 g, 0.1 mmol) in diethyl ether–THF (1:1) was added $LiAlH_4$ (0.03 g), and the reaction mixture was stirred at room temperature for 15 min. The unchanged $LiAlH_4$ was decomposed on addition of a few drops of water. The reaction mixture was filtered and the filtrate was evaporated under reduced pressure. The residue was dissolved in methanol (1 ml) and purified by PLC to afford (±)-*erythro*-diastereoisomer (**7b**) (0.012 g, 66%), m.p. 152–154 °C; R_f 0.12 (MeOH).

* Ethyl 1-(2-pyridyl)-1,2,3,4-tetrahydropyrido[3,4-*b*]indole-2-acetate.

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