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A NEW EFFICIENT SYNTHESIS OF ETHYL β-CARBOLINE-3-CARBOXYLATE (β-CCE) AND METHYL 4-METHYL-β-CARBOLINE-3-CARBOXYLATE (4-METHYL-β-CCM) STARTING FROM INDOLE-2 CARBOXALDEHYDE

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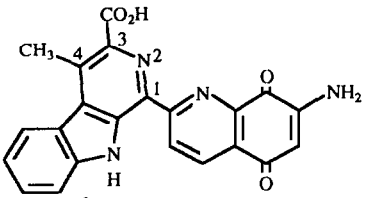
Abstract: Ethyl β-carboline-3-carboxylate (9) and methyl 4-methyl-β-carboline-3-carboxylate (15) were prepared in high yields by condensing indole-2-carboxaldehyde (5) (itself prepared by lithium aluminum hydride reduction of the Weinreb amide derived from indole-2-carboxylic acid) with ethyl 2-amino-3,3-diethoxypropionate (6) and methyl 2-amino-3,3-diethoxybutyrate (12), respectively, followed by reduction of the imine bonds formed with sodium cyanoborohydride and cyclization of the resulting amines (8 and 14, respectively) using titanium (IV) chloride.

β-Carboline-3-carboxylic acids (and esters) substituted at the 4 position with a methyl group are a pharmacologically interesting class of molecules. For instance, 4-methyl-β-carboline-3-carboxylic acid is a structural unit of the naturally occurring antitumor antibiotic lavendamycin **1**[1] while ethyl 4-methyl-5-isopropyloxy-β-carboline-3-carboxylate **2**, a synthetic molecule, shows significant memory enhancing effects in humans *via* its interaction with the benzodiazepine receptor of the central nervous system.[2,3]



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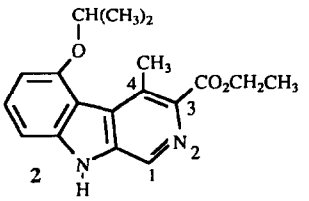

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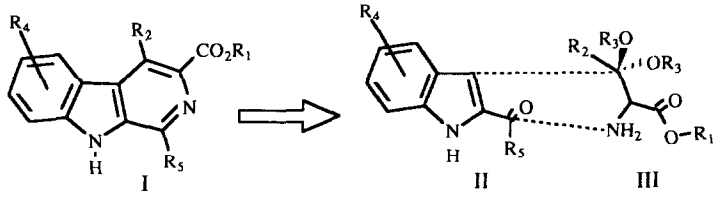
C-4 substituted 3-carboxy-β-carbolines (including C-4 methyl derivatives) have until now been synthesized almost exclusively by a Pictet-Spengler-type condensation[4] of an aldehyde or aldehyde equivalent with the corresponding β-substituted tryptophan derivative (for which non-stereoselective[5] as well as stereoselective[6] synthetic routes have been described) followed by aromatization of the intermediate 1,2,3,4-tetrahydro-β-carboline. Both the condensation and aromatization are often, however, low yielding steps. Low yields in aromatized C-4 substituted β-carbolines using the usual

reagents (palladium on carbon, manganese dioxide, DDQ or sulfur) are, in fact, often due to elimination of the substituent (instead of the hydrogenatom) at C-4.[7] In the particular case of lavendamycin (**1**) synthesis, these problems were circumvented by using either PPE-promoted cyclization of the amide formed from the methyl ester of β-methyltryptophan and a quinaldic acid derivative[8] or palladium (O)-catalyzed ring closure of a 3-amino-4-(2-bromophenyl)pyridine precursor.[9] More recently, the use of ortho-directed metalation techniques has been shown to allow direct introduction of various electrophiles at C-4 of 9-N-methyl-β-carboline-3-carboxamides.[10] However, this strategy has not yet been applied to β-carbolines having a blocking group more easily removed than methyl at N-9.

A retrosynthetic scheme (Scheme 1) suggested that multi-substituted 3-carboxy-β-carbolines I should also be obtainable *via* condensation of a 2-acylindole derivative II with the dialkyl ketal (or acetal for R_2=H) derivative III of an α-amino-β-ketoacid followed by intramolecular cyclization between C-3 of the indole and the carbon atom of the ketal function. In this paper, we report the application of this simple strategy to an efficient synthesis of ethyl β-carboline-3-carboxylate (β-CCE, **9**) and methyl 4-methyl-β-carboline-3-carboxylate (4-methyl β-CCM, **15**). The latter compound is a particularly worthwhile objective since, in addition to its pharmacological importance as stated above, it has been shown that the benzylic type C-4 methyl group can be easily brominated and transformed into a variety of functional groups.[4a,11]

Scheme 1

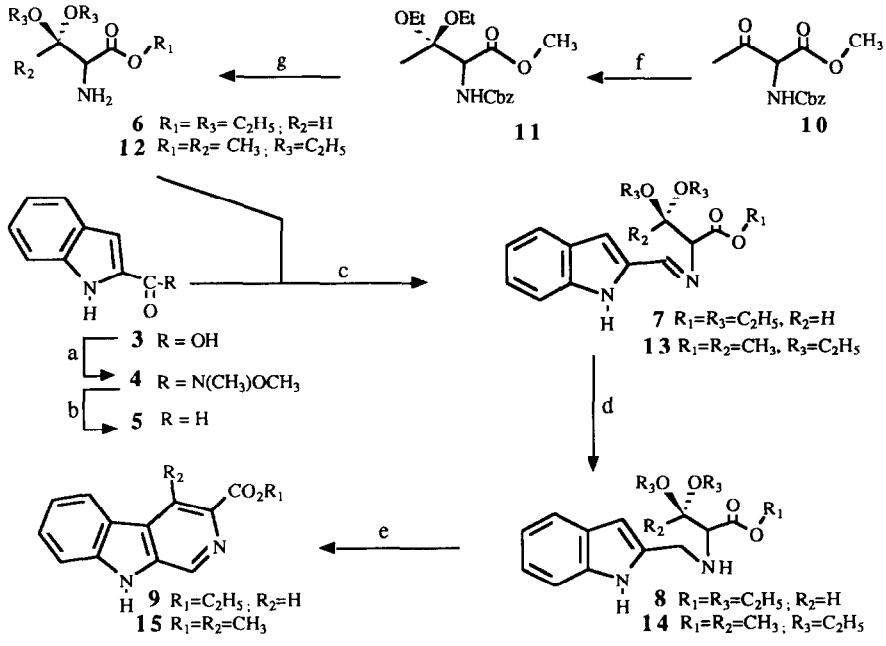


The preparation of a β-carboline derivative carrying only a hydrogen atom at C-1 (i.e. I, R_5 = H) required that our starting indole be the 2-carboxaldehyde **5** (Scheme 2). Though a number of methods are known for forming indole-2-carboxaldehydes (by reduction of indole-2-carboxylic esters to an alcohol followed by oxidation to an aldehyde ;[12] by based-catalyzed decomposition of p-toluenesulfonyl hydrazides ;[13] by lithiation of an N-protected indole followed by reaction with N,N-dimethylformamide[14]), we chose to innovate by making use of the well known property of Weinreb amides to be easily reduced to aldehydes.[15] Thus, indole-2-carboxylic acid (**3**) was treated with 1 eq each of N,O-dimethylhydroxylamine and DCC in dichloromethane to give a 70% yield of the N-methoxy-N-methylindole-2-carboxamide **4**. This amide was cleanly reduced to indole-2-carboxaldehyde **5** in 95% yield using 1 eq of lithium aluminum hydride in THF at -30°C. This method of preparing an indole carboxaldehyde from its carboxylic acid precursor has never, to our knowledge, been described and represents a mild, efficient alternative to the procedures previously cited.

Condensation of aldehyde **5** with ethyl 2-amino-3,3-diethoxypropionate **6** (prepared from glycine by the method of Belleau[16]) in the presence of 4 Å molecular sieves gave imine **7** almost quantitatively. We initially attempted to cyclize imine **7** directly to β-carboline **9** using the conditions previously employed for 6-azaindole synthesis (i.e. titanium (IV) tetrachloride in refluxing benzene[17]). However, this led only to degradation of the starting material. The imine function of **7** was thus saturated by use of

sodium cyanoborohydride in ethanol, yielding the amine **8**. Treatment of the latter with titanium (IV) tetrachloride now afforded ethyl β-carboline-3-carboxylate **9** in 57% yield, identical in all respects with the same compound prepared from tryptophan.[18]

Scheme 2



a) DCC, $HN(CH_3)OCH_3.HCl$, Et_3N, CH_2Cl_2 ; b) $LiAlH_4$, THF, -30° C
c) 4 Å molecular sieve, CH_2Cl_2 ; d) $NaBH_3CN$, EtOH ; e) $TiCl_4$, benzene, Δ
f) $HC(OC_2H_5)_3$, Amberlyst-15 ; g) H_2, Pd/C, EtOH

The more important problem of preparing the 4-methyl derivative of **9**, that is, **15**, using this methodology was next addressed. The retrosynthetic sequence (Scheme 1) indicated that an amino acid derivative of type III (R_2 = methyl) would first have to be prepared. As shown in Scheme 2 such a ketal (i.e., **12**) was synthesized starting from the recently described 2-benzyloxycarbonylamino acetoacetate **10**.[19] Thus, treatment of the latter with triethyl orthoformate in the presence of Amberlyst-15 resin[20] as acid catalyst first gave ketal **11**. Although these conditions have been observed in some cases to give enol ethers instead of ketals, the spectral data for compound **11** was entirely compatible with a ketal structure. Moreover, there was no evidence in the reaction mixture of any product resulting from transesterification. Removal of the benzyloxycarbonyl blocking group of **11** by hydrogenolysis proceeded cleanly to give the desired amino ketal **12**.

Following the same sequence of reactions as for the preparation of β-carboline **9**, condensation of amine **12** with indole-2-carboxaldehyde **5** afforded imine **13** which, after reduction with sodium cyanoborohydride, gave amine **14**. The latter was cyclized by treatment with $TiCl_4$, affording the desired methyl 4-methyl-β-carboline-3-carboxylate **15** in 58% overall yield starting from indole **5**.

It is interesting to note that the Lewis acid catalyzed cyclizations of **8** and **14** gave in neither case products arising from attack of the indolic NH (instead of C-3) on the ketal functions.[17] This obviates the need to protect (and eventually deprotect) the indole nitrogen, thereby increasing the overall efficiency of the reaction scheme.

In conclusion, a new short, high yielding route to pharmacologically interesting and synthetically useful β-CCE (**9**) and 4-methyl-β-CCM (**15**) is now available. Application of this methodology to the synthesis of multiply substituted β-carboline derivatives is currently under study.

EXPERIMENTAL

Melting points were determined on a Büchi apparatus and are uncorrected. IR spectra of samples were obtained either as KBr pellets (for solids) or as films (for oils) with a Nicolet 205 FT-IR spectrometer. ^{1}H-NMR and ^{13}C-NMR spectra were determined on a Bruker 250 MHz instrument. Chemical shifts are given as δ values with reference to Me_4Si as internal standard. Electron impact and chemical ionization mass spectra were recorded on an AEI MS-50 and AEI MS-9 spectrometer, respectively. High-resolution mass spectra were obtained using a Kratos MS-80 spectrometer. Thin-layer chromatography was performed on Merck silica gel 60 plates with fluorescent indicator. The plates were visualized with UV light (254 nm). All column chromatography was conducted on Merck 60 silica gel (230-400 mesh) at medium pressure (200 mbar). All reagents were purchased from the Aldrich Chemical Co. and were used without further purification. Elemental analyses were performed at the ICSN, CNRS, Gif-sur-Yvette, France.

N-Methoxy-N-methyl-1H-indole-2-carboxamide (**4**). To a solution of indole-2-carboxylic acid **3** (1.02 g, 6.32 mmol) in anhydrous dichloromethane was added N,O-dimethylhydroxylamine hydrochloride (618 mg, 6.32 mmol) and triethylamine (0.89 mL, 6.32 mmol). The mixture was stirred for 5 min, dicyclohexylcarbodiimide (1.3 g, 6.32 mmol) was added and stirring was continued for 3 h. The solvent was then removed under vacuum, the residue was suspended in a minimum volume of acetone and the insoluble white solid was removed by filtration. The filtrate was evaporated to dryness and the operation with acetone was repeated twice more to remove the last traces of urea. Compound **4** was thus obtained as a white powder in 70% yield, mp 147-149°C (CH_2Cl_2/EtOH) ; IR (ν_{max} cm^{-1}) : 3285(NH), 1608(C=O) ; EIMS : m/z 204 (M^+), 144(M^+- $NCH_3(OCH_3)$) ; ^{1}H-NMR ($CDCl_3$) : δ 3.44 (s, 3H, NCH_3), 3.83 (s, 3H, OCH_3), 7.11 (t, 1H, J = 8.0 Hz, H-6), 7.28 (t, 1H, H-5), 7.45 (d, 1H, J = 8.0 Hz, H-7), 7.70 (d, 1H, H-4), 9.85 (br s, 1H, exchangeable with D_2O, NH) ; ^{13}C-NMR ($CDCl_3$) : δ 33.3, 61.3, 108.0, 112.0, 120.3, 122.5, 124.7, 128.0, 128.2, 136.2, 161.8. Anal. Calcd for $C_{11}H_{12}N_2O_2$: C, 64.70 ; H, 5.88 ; N, 13.72. Found : C, 64.84 ; H, 5.71 ; N, 13.81.

1H-Indole-2-carboxaldehyde (**5**). A solution of amide **4** (510 mg, 2.5 mmol) in anhydrous THF (10 mL) at - 30°C was treated dropwise under a nitrogen atmosphere with a 1M solution of lithium aluminum hydride in THF (2.5 mL). The reaction mixture was stirred for 1 h and ice water was then added to destroy excess hydride. The reaction mixture was evaporated under vacuum until most of the THF was removed and the aqueous residue was extracted with dichloromethane (3 x 25 mL). The combined organic fractions were dried over Na_2SO_4 and the solvents were removed under vacuum leaving compound **5** as a white powder (340 mg, 95%) which was recrystallized from aqueous methanol, mp 140°C (lit.[12a] mp 141-142°C) ; IR (ν_{max} cm^{-1}) : 3400(NH), 1656(C=O) ; EIMS : m/z 145(M^+), 116(M^+-CHO) ; ^{1}H-NMR ($CDCl_3$) : δ 7.18 (dd, 1H, J = 1.2 Hz and 7.7 Hz, H-6), 7.29 (d, 1H, J = 1.2 Hz, H-3),

7.40 (dd, 1H, H-5), 7.46 (d, 1H, J = 7.7 Hz, H-7), 7.75 (d, 1H, H-4), 9.21 (br s, 1H, exchangeable with D_2O, NH), 9.86 (s, 1H, CHO) ; ^{13}C-NMR ($CDCl_3$) : δ 112.7, 115.2, 121.4, 123.5, 125.0, 127.5, 136.2, 138.4, 182.4. Anal. Calcd for C_9H_7NO : C, 74.48 ; H, 4.82 ; N, 9.65. Found : C, 74.26 ; H, 5.04 ; N, 9.89.

Ethyl 3,3-diethoxy-2-[(1H-indol-2-yl)methylene]aminopropionate **(7)**. To a solution of aldehyde **5** (58 mg, 0.4 mmol) in anhydrous dichloromethane (3 mL) were added 4 Å molecular sieves (300 mg) followed by a solution of ethyl 2-amino-3,3-diethoxypropionate **6**[16] (123 mg, 0.6 mmol) in dichloromethane (0.5 mL). The reaction mixture was stirred for 12 h at room temperature and then filtered through a pad of Celite. The filtrate was washed with water, dried over sodium sulfate and the solvent was evaporated under vacuum, leaving imine **7** as a yellow oil (130 mg, 98%) : IR (ν_{max} cm^{-1}) : 3409(NH), 1737(C=O), 1645(C=N) ; EIMS : m/z 332 (M^+) ; ^{1}H-NMR ($CDCl_3$) : δ 1.12 (t, 3H, J = 7.2Hz, $CO_2CH_2C\underline{H}_3$), 1.21-1.34 (m, 6H, 2 x $OCH_2C\underline{H}_3$), 3.50-3.75 (m, 4H, 2 x $OC\underline{H}_2CH_3$), 4.15 (d, 1H, J = 7.2 Hz, NC<u>H</u>), 4.26 (q, 2H, $CO_2C\underline{H}_2CH_3$), 4.97 (d, 1H, C<u>H</u>OC_2H_5), 6.86 (d, 1H, J = 1.0 Hz, indole H-3), 7.12 (dt, 1H, J = 1.0 Hz and 8.0 Hz, indole H-6), 7.28 (dt, 1H, indole H-5), 7.35 (d, 1H, J = 8.0 Hz, indole H-7), 7.66 (d, 1H, indole H-4), 8.29 (s, 1H, C<u>H</u> = N), 9.36 (s, 1H, exchangeable with D_2O, NH). Anal. Calcd for $C_{18}H_{24}N_2O_4.1/3\ H_2O$: C, 63.90 ; H, 7.29 ; N, 8.28. Found : C, 63.93 ; H, 7.23 ; N, 8.39.

Ethyl 3,3-diethoxy-2-[(1H-indol-2-yl)methyl]amino propionate **(8)**. A solution of imine **7** (130 mg, 0.39 mmol) and sodium cyanoborohydride (20 mg, 0.31 mmol) in ethanol (2 mL) was stirred at room temperature for 30 min. The reaction mixture was then made basic with aqueous saturated sodium hydrogen carbonate and the solution was extracted with dichloromethane (3 x 5 mL). The combined organic extracts were dried (Na_2SO_4) and evaporated leaving amine **8** as a yellow oil (123 mg, 94%) which was used without further purification in the following step : IR (ν_{max} cm^{-1}) : 3407(NH), 3334(NH), 1731(C=O) ; EIMS : m/z 334 (M^+) ; ^{1}H-NMR ($CDCl_3$) : δ 1.16-1.29 (m, 9H, 3 x CH_3), 2.14 (br s, 1H, exchangeable with D_2O, N<u>H</u>CH), 3.42 (d, 1H, J = 4.0 Hz, NHC<u>H</u>), 3.51-3.78 (m, 4H, 2 x $OC\underline{H}_2CH_3$), 3.86 (d, 1H, J_{gem} = 15 Hz, C<u>H</u>aNH), 4.21 (q, 2H, J = 7.0 Hz, $CO_2C\underline{H}_2$), 4.22 (d, 1H, C<u>H</u>$_b$NH), 4.66 (d, 1H, J = 4.0 Hz, <u>H</u>COC_2H_5), 6.29 (s, 1H, indole H-3), 7.01-7.12 (m, 2H, indole H-5, H-6), 7.30 (d, 1H, J = 7.5 Hz, indole H-7), 7.52 (d, 1H, indole H-4), 8.98 (br s, 1H, exchangeable with D_2O, indole NH) ; ^{13}C-NMR ($CDCl_3$) : δ 14.3, 15.2, 15.4, 45.2, 61.1, 63.1, 63.9, 64.1, 100.3, 103.1, 110.8, 119.6, 120.1, 121.4, 128.8, 136.1, 137.3, 172.1. HREIMS : Calcd for $C_{18}H_{26}N_2O_4$: m/z 334.1893. Found : m/z 334.1894.

Ethyl β-carboline-3-carboxylate **(9)**. A solution of amine **8** (119 mg, 0.35 mmol) and titanium (IV) chloride (100 μL, 0.90 mmol) in anhydrous benzene (2 ml) was refluxed for 10 min under nitrogen with exclusion of moisture. The reaction mixture was cooled, ethyl acetate (10 mL) and saturated aqueous sodium hydrogen carbonate (10 mL) were added and the organic phase was separated. The aqueous phase was extracted with ethyl acetate (3 x 15 mL), the combined organic extracts were dried (Na_2SO_4) and the solvents were evaporated, leaving a brown solid. The crude reaction product was purified by chromatography on silica gel using ethyl acetate-heptane (1:1) as developer, affording compound **9** as a white solid (48 mg, 57%), mp 225-227°C (CH_2Cl_2) (lit[18] mp : 231-232°C) ; ^{1}H-NMR ($CDCl_3$) : δ 1.48 (t, 3H, J = 7.5 Hz, $CH_2C\underline{H}_3$), 4.53 (q, 2H, J = 7.5 Hz, $C\underline{H}_2CH_3$), 7.34 (t, 1H, J = 8 Hz, H-7), 7.58 (t, 1H, H-6), 7.72 (d, 1H, J = 8 Hz, H-5), 8.19 (d, 1H, J = 8 Hz, H-8), 8.92 (s, 1H, H-4), 9.17 (s, 1H, H-1), 10.95 (br s, 1H, exchangeable with D_2O, NH).

Methyl 2-(N-benzyloxycarbonyl)amino-3,3-diethoxybutyrate **(11)**. To a solution of ketone **10**[19] (730 mg, 2.75 mmol) in triethyl orthoformate (3 mL) was added calcium sulfate (900 mg) and Amberlyst-15 (H^+) resin (400 mg). The reaction mixture was stirred for 10 h at room temperature after which it was filtered through a pad of Celite. The filtrate was concentrated under vacuum and the residue was purified by chromatography on silica gel (ethyl acetate-heptane 1:1) yielding, in addition to unreacted starting material **10** (400 mg, 55%), the acetal **11** (354 mg, 85% based on consumed starting material).

Compound **11** was crystallized from ethanol, affording amorphous white crystals, mp 36-38°C ; IR (ν_{max} cm^{-1}) : 3363(NH), 1732(C=O ester), 1720(C=O carbamate) ; CIMS : m/z 294(MH^+- EtOH) ; ^{1}H-NMR ($CDCl_3$) : δ 1.15 (t, 6H, J = 7.0 Hz, 2 x $OCH_2\underline{CH_3}$), 1.35 (s, 3H, CH_3), 3.45-3.61 (m, 4H, 2 x $O\underline{CH_2}CH_3$), 3.75 (s, 3H, OCH_3), 4.56 (d, 1H, J = 8.0 Hz, CH), 5.10 (s, 2H, CH_2), 5.44 (d, 1H, exchangeable with D_2O, NH), 7.32 (s, 5H, H_{arom}) ; ^{13}C-NMR ($CDCl_3$) : δ 15.2, 15.3, 19.7, 52.2, 56.9, 57.2, 58.8, 67.2, 100.6, 128.2, 128.6, 136.4, 155.9, 170.9. Anal. Calcd for $C_{17}H_{25}NO_6$: C, 60.17 ; H, 7.37 ; N, 4.13. Found : C, 60.47 ; H, 7.47 ; N, 3.94.

Methyl 2-amino-3,3-diethoxybutyrate **(12).** A solution of compound **11** (540 mg, 1.6 mmol) in ethanol (12 mL) containing 10% palladium on carbon (108 mg) was hydrogenated at atmospheric pressure for 2 h. The reaction mixture was then filtered through Celite, the filtrate was evaporated under vacuum and the residue was crystallized from ethanol yielding amine **12** as amorphous needles (235 mg, 72%) ; IR (ν_{max} cm^{-1}) : 3436, 3381(NH_2), 1743(C=O) ; CIMS : m/z 206 (MH^+) ; ^{1}H-NMR ($CDCl_3$) : δ 1.14-1.23 (m, 6H, 2 x $OCH_2\underline{CH_3}$), 1.35 (s, 3H, CH_3), 2.62 (br s, 2H, exchangeable with D_2O, NH_2), 3.45-3.56 (m, 4H, 2 x $O\underline{CH_2}CH_3$), 3.76 (s, 3H, OCH_3), 3.85 (s, 1H, $C\underline{H}NH_2$) ; ^{13}C-NMR ($CDCl_3$) : δ 15.0, 17.9, 51.8, 55.9, 56.3, 58.5, 101.2, 171.8. HRCIMS : Calcd for $C_9H_{20}NO_4$: m/z 206.1412. Found : m/z 206.1393. Anal. Calcd for $C_9H_{19}NO_4$: C, 52.88 ; H, 9.27 ; N, 6.83. Found : C, 52.55 ; H, 9.07 ; N, 6.62.

Methyl 3,3-diethoxy-2-[(1H-indol-2-yl)methylene]aminobutyrate **(13).** The title compound, prepared in the same manner as **7** starting from indole-2-carboxaldehyde **5** and amine **12**, was isolated as an orange syrup in 95% yield ; IR (ν_{max} cm^{-1}) : 3350(NH), 1741(C=O), 1635(C=N) ; CIMS : m/z 333$(MH)^+$, 287$(MH\text{-}OEt)^+$; ^{1}H-NMR ($CDCl_3$) : δ 1.18 (m, 6H, 2 x $OCH_2\underline{CH_3}$), 1.60 (s, 3H, CH_3), 3.40-3.70 (m, 4H, 2 x $O\underline{CH_2}CH_3$), 3.77 (s, 3H, CO_2CH_3), 4.38 (s, 1H, $NC\underline{H}$), 6.82 (s, 1H, indole H-3), 7.06 (t, 1H, J = 8.0 Hz, indole H-6), 7.26 (t, 1H, indole H-5), 7.32 (d, 1H, J = 8.0 Hz, indole H-7), 7.63 (d, 1H, indole H-4), 8.22 (s, 1H, $C\underline{H}$=N), 9.33 (s, 1H, exchangeable with D_2O, NH) ; ^{13}C-NMR ($CDCl_3$) : δ 15.1, 15.3, 19.2, 52.0, 56.2, 56.7, 76.5, 102.0, 109.1, 111.7, 120.2, 121.8, 124.8, 127.9, 134.7, 137.2, 155.3, 174.6. HRCIMS : Calcd for $C_{18}H_{25}N_2O_4$: m/z 333.1793. Found : m/z 333.1814.

Methyl 3,3-diethoxy-2-[(1H-indol-2-yl)methyl]aminobutyrate **(14).** The title compound, prepared from imine **13** following the same procedure as for **8**, was obtained as a yellow oil in 95% yield and was used without further purification in the following step : IR (ν_{max} cm^{-1}) : 3370(NH), 3345(NH), 1740(C=O) ; EIMS : m/z 334(M^+) ; ^{1}H-NMR ($CDCl_3$) : δ 1.12 (t, 3H, J = 7.0 Hz, $OCH_2\underline{CH_3}$), 1.24 (t, 3H, $OCH_2\underline{CH_3}$), 1.41 (s, 3H, $C\underline{H_3}$), 2.38 (br s, 1H, exchangeable with D_2O, $N\underline{H}CH$), 3.30-3.57 (m, 4H, 2 x $O\underline{CH_2}CH_3$), 3.63 (s, 1H, $NHC\underline{H}$), 3.70 (s, 3H, $CO_2C\underline{H_3}$), 3.75 (d, 1H, J_{gem} = 15 Hz, $C\underline{H_a}NH$), 4.11 (d, 1H, $C\underline{H_b}NH$), 6.31 (s, 1H, indole H-3), 7.12 (m, 2H, indole H-5, H-6), 7.32 (d, 1H, J = 7.5 Hz, indole H-7), 7.54 (d, 1H, indole H-4), 9.01 (s, 1H, exchangeable with D_2O, indole NH) ; ^{13}C-NMR ($CDCl_3$) : δ 15.3, 15.4, 18.7, 45.5, 51.9, 56.3, 56.7, 65.1, 100.5, 102.7, 110.9, 119.6, 120.2, 121.5, 137.1. Anal. Calcd for $C_{18}H_{26}N_2O_4$: C, 64.67 ; H, 7.78 ; N, 8.38. Found : C, 64.60 ; N, 7.84 ; N, 8.15.

Methyl 4-methyl-β-carboline-3-carboxylate **(15).** The title compound was prepared in 64% yield from amine **14** following the same procedure as for **9**, mp 242-244°C (CH_2Cl_2) (lit[21] mp 243-246°C) ; IR (ν_{max} cm^{-1}) : 3313(NH), 1718(C=O) ; EIMS : m/z 240(M^+) ; ^{1}H-NMR ($CDCl_3$) : δ 3.18 (s, 3H, CH_3), 4.02 (s, 3H, CO_2CH_3), 7.36 (m, 1H, H-6), 7.58 (m, 2H, H-7, H-8), 8.32 (d, 1H, J = 8.0 Hz, H-5), 8.82 (s, 1H, H-1), 9.19 (br s, 1H, exchangeable with D_2O, NH) ; ^{13}C-NMR ($CDCl_3$) : δ 17.3, 52.6, 111.9, 121.1, 124.3, 128.4, 130.9. Anal. Calcd for $C_{14}H_{12}N_2O_2.1/6\ H_2O$: C, 69.13 ; H, 5.07 ; N, 11.52. Found : C 69.21; H, 5.23 ; N, 11.46.

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