REACTION OF TETRAHYDRO-β-CARBOLINE-1-CARBOXYLIC ACID WITH ISOCYANATES AND ISOTHIOCYANATES. SYNTHESIS OF 1-ALKYL- OR ARYLCARBAMOYL-β-CARBOLINES†

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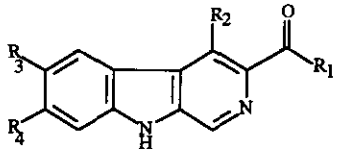
Abstract- The reaction of (±)- 1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid (**8**) with alkyl and aryl isocyanates formed the corresponding tetrahydro-β-carboline-hydantoin ring systems (**7**). However the reaction of **8** with isothiocyanates provided 2-alkyl- or arylthiocarbamoyl-1,2,3,4-tetrahydro-β-carbolines (**9**). The oxidation of **7** with selenium dioxide or dichlorodicyano-*p*-benzoquinone gave 1-substituted β-carbolines (**10**) related to β-carboline alkaloids.

INTRODUCTION

β-Carboline derivatives attracted high interest in medicinal chemistry when Braestrup and co-workers discovered that ethyl β-carboline-3-carboxylate (**1**) binds with affinity[1] at the benzodiazepine receptors in the mammalian central nervous system.[2-5]

† Dedicated to Professor Alan R. Katritzky on the ocassion of his 65th birthday.

β-Carbolines exhibit a wide range of psychopharmacological actions. Many of these effects are mediated through benzodiazepine receptors,[2-5] which are capable of selectively modulating activity at GABA-gated chloride channels.[6] Depending upon their intrinsic activity profiles, β-carbolines are classified as agonists [anxiolytic and anticonvulsant actions; i.e. ZK-93423 (**2**)],[7-12] inverse agonists [anxiogenic, somnolytic, convulsant, and proconvulsant properties; i.e. β-CCE (**1**), β-CCM (**3**), FG 7142 (**4**), DMCM (**5**)],[13-17] and antagonists.[18-19] In addition, there are examples of BzR ligands which do not exhibit the full range of agonists or inverse agonists actions,[6] making the synthesis of new β-carboline derivatives important tools to study benzodiazepine receptor function.



1 R_1=OCH_2CH_3, R_2=R_3=R_4=H (β-CCE)

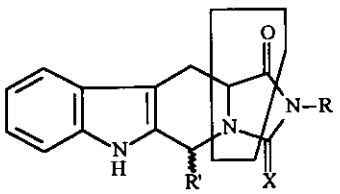
2 R_1=OCH_2CH_3, R_2=CH_2OCH_3, R_3=OCH_2Ph, R_4=H (ZK-93423)

3 R_1=OCH_3, R_2=R_3=R_4=H (β-CCM)

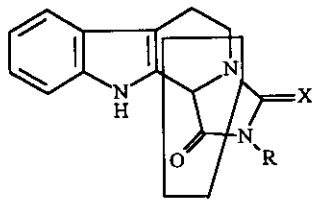
4 R_1=$NHCH_3$, R_2=R_3=R_4=H (FG 7142)

5 R_1=R_3=R_4=OCH_3, R_2=CH_2CH_3 (DMCM)

As a part of an ongoing program toward the development of new drugs acting on the central nervous system (CNS), we were interested in the synthesis of a new type of compounds (**6**) and (**7**) combining tetrahydro-β-carboline and hydantoin or thiohydantoin skeletons. In a previous work we have described the preparation[20] of **6** (X=O), and in this paper we report the synthesis of **7** (X=0) by reaction of tetrahydro-β-carboline-1-carboxylic acid (**8**) with isocyanates as well as the formation of 2-alkyl- or arylthiocarbamoyl-1,2,3,4-tetrahydro-β-carbolines (**9**) by a similar treatment with isothiocyanates. Furthermore, the oxidation of **7** with selenium dioxide or dichlorodicyano-*p*-benzoquinone (DDQ) gave 1-substituted β-carbolines (**10**) related to β-carboline alkaloids.



6 X = O, S



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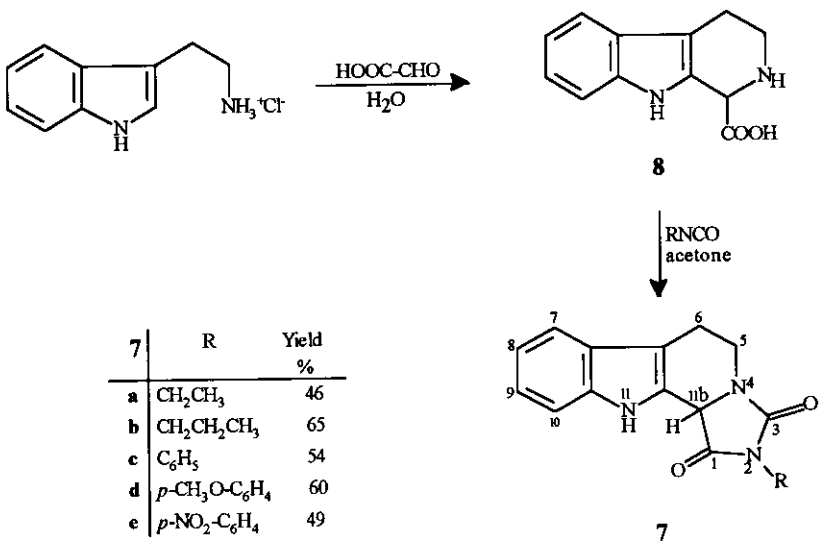
RESULTS AND DISCUSSION

(±)-1,2,3,4-Tetrahydro-β-carboline-1-carboxylic acid[21] **(8)** was prepared by reaction of tryptamine with glyoxylic acid; treatment of **8** with alkyl or aryl isocyanates in refluxing acetone gave the corresponding 2-substituted 5,6,11,11b-tetrahydro-1*H*-imidazo[1',5':1,2]pyrido[3,4-*b*]indole-1,3(2*H*)-diones **(7a-e)** (Scheme 1).



8

7

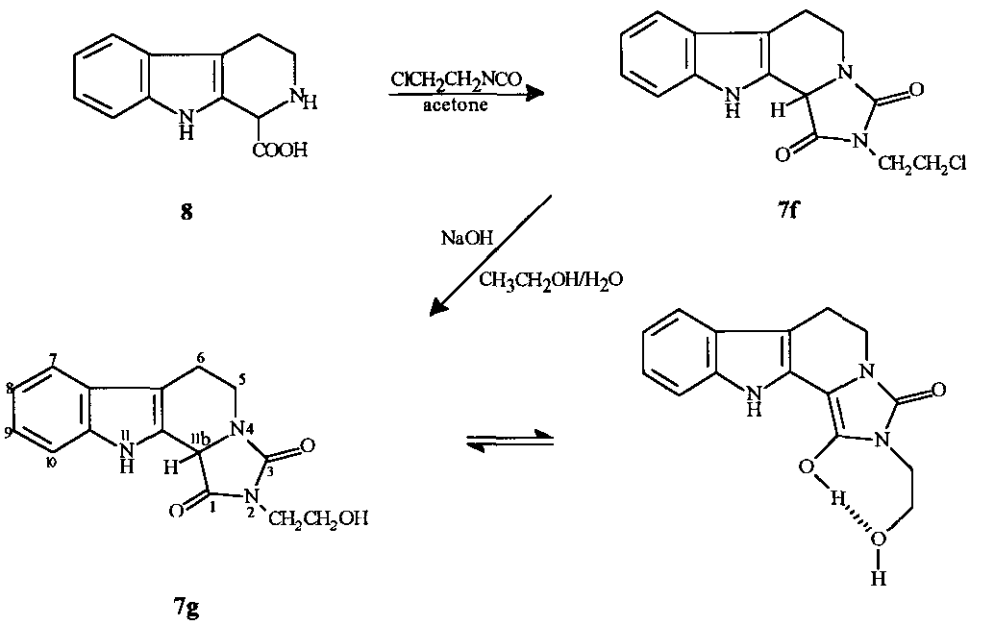
7	R	Yield %
a	CH_2CH_3	46
b	$CH_2CH_2CH_3$	65
c	C_6H_5	54
d	*p*-CH_3O-C_6H_4	60
e	*p*-NO_2-C_6H_4	49

Scheme 1

The structures of these compounds were confirmed from examination of the ^1H and ^{13}C nmr data. As an example, the ^1H nmr spectrum of **7a** showed a characteristic pattern for the tetrahydro-β-carboline-hydantoin moiety: $\delta(CDCl_3)$, 2.80 (1H, dd, J=15.6, 5.4 Hz, H-6a), 2.94 (1H, dddd, J=15.6, 11.1, 6.0, 2.4 Hz, H-6b), 3.21 (1H, ddd, J=13.8, 11.4, 5.1 Hz, H-5a), 4.53 (1H, dd, J=13.7, 5.1 Hz, H-5b), 5.18 (1H, br s, H-11b), 7.12 (1H, td, J=8.1, 1.2 Hz, H-8), 7.21 (1H, td, J=8.1, 1.2 Hz, H-9), 7.36 (1H, d, J=8.0 Hz, H-10), 7.49 (1H, d, J=7.6 Hz, H-7) and 8.72 (1H, s, NH). Compound **(7a)** appears to exist as a keto form in chloroform solution due to the signal at δ 5.18 to the methine proton H-11b. The ^{13}C nmr spectrum indicated the presence of two methylenes (C-6, C-5), a methine (C-11b) and two carbonyl groups at 20.32, 37.81, 56.04, 156.59 and 170.40 ppm, respectively. The carbon signals attributable to the indole ring were assigned on the basis of distortionless enhancement by polarization transfer (DEPT) method and reference data.[22] The ^{13}C nmr spectra of **7c-e** were recorded in solid state due to the low solubility of these structures.

Compound **(7g)** was synthesized by hydrolysis of the 2-chloroethyl derivate **(7f)**, which was prepared by the reaction of **8** with 2-chloroethyl isocyanate in dry acetone (Scheme 2). The infrared (ir) spectrum of **7g** exhibited a broad band at 3340 cm^{-1} and absorptions at 1780, 1710 cm^{-1}. The ^1H nmr spectrum (DMSO-d_6) showed the presence of a singlet at δ 2.10 (1H, exchangeable with D_2O) and four methylenes groups at δ 2.78-2.86 (2H, m, H-6), 3.32-3.46 (1H, m, H-5a), 3.80-3.83 (4H, m, NCH_2CH_2OH) and 4.28 ppm (1H, dd, J=13.8, 4.5 Hz, H-5b). The aromatic region showed the characteristic pattern for the indole ring. Furthermore at δ 7.82 and 11.30 ppm appeared two singlets, which are exchangeable with D_2O. Our attention was drawn to the absence of the signal at *ca.* 5.2 ppm due to the methine proton H-11b, suggesting that compound **(7g)** exists in DMSO-d_6 under the enol form. This fact was confirmed from examination of the ^{13}C nmr spectrum, in which the chemical shift of the 11b-carbon appears at 80.44 ppm, whereas in the case of **7a-f,** this carbon resonates at *ca.* 56 ppm. Additional data based in nmr spectra evidenced that compound **(7g)** exists in $CDCl_3$ and DMSO-d_6 in enol form, while compounds **(7a-f)** exist in both solvents under the keto form. These results may be interpreted in terms of an internal hidrogen bonding which stabilizes the enol form in **7g**, where a seven-membered ring can be created. This hidrogen bonding is unavailable to the structures **(7a-f)**. The

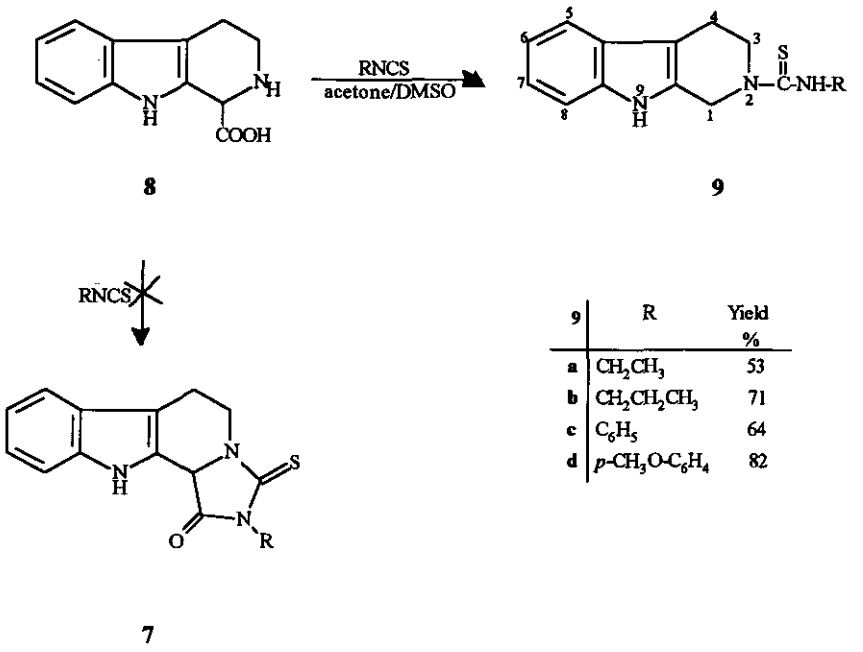
INSIGHT II program[23] on a Silicon Graphics IRIS computer has shown that the H···O distance is 1.77 Å.



Scheme 2

The reaction of **8** with alkyl or aryl isothiocyanates in refluxing acetone/DMSO did not afford the desired compounds **(7)** (X=S) but gave the corresponding 2-substituted thiocarbamoyl-1,2,3,4-tetrahydro-β-carbolines **(9a-d)** (Scheme 3). The structures of these compounds have been characterized on the basis of their ^{1}H and ^{13}C nmr data and all of them gave satisfactory elemental analyses. The ^{13}C signals were analyzed by the application of 2D heteronuclear correlation (HETCOR) spectrum.

The fact of obtaining the structures **(9a-d)** in the reaction of **8** with isothiocyanates instead of the desired tetrahydro-β-carboline-thiohydantoin derivatives can be explained by the decarboxylation of the acid **(8)** under the reaction conditions.



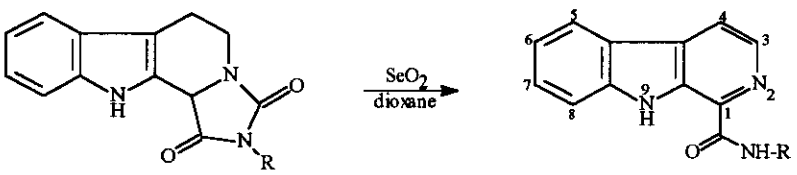
9	R	Yield %
a	CH_2CH_3	53
b	$CH_2CH_2CH_3$	71
c	C_6H_5	64
d	p-CH_3O-C_6H_4	82

Scheme 3

Then, we examined the effect of the oxidation in the indole area of some tetrahydro-β-carboline-hydantoin derivatives (**7**) for further biological testing. Compound (**7b**) was selected for this study and both selenium dioxide (SeO_2) and dichlorodicyano-*p*-benzoquinone (DDQ) have been used.

Treatment of **7b** with selenium dioxide in refluxing dioxane gave 1-propylcarbamoyl-β-carboline (**10b**) (Scheme 4). The ^1H nmr spectrum in $CDCl_3$ indicated the presence of a propyl and two NH groups. The aromatic protons appeared at δ 7.18 (1H, td, J=7.8, 1.2 Hz, H-6), 7.41 (1H, d, J=8.1 Hz, H-8), 7.46 (1H, td, J=7.8, 1.2 Hz, H-7), 7.95 (1H, d, J=5.1 Hz, H-4), 8.01 (1H, d, J=7.8 Hz, H-5) and 8.26 ppm (1H, d, J=5.1 Hz, H-3). The ^{13}C nmr spectrum was assigned by distortionless enhancement by polarization transfer (DEPT) method and by the application of 2D heteronuclear correlation spectroscopy (HETCOR).

In order to confirm the generality of this reaction, a number of different tetrahydro-β-carboline-hydantoin systems (**7**) have been oxidated with selenium dioxide to give 1-alkyl- or arylcarbamoyl-β-carbolines (**10b-e**) (Scheme 4).



7 10

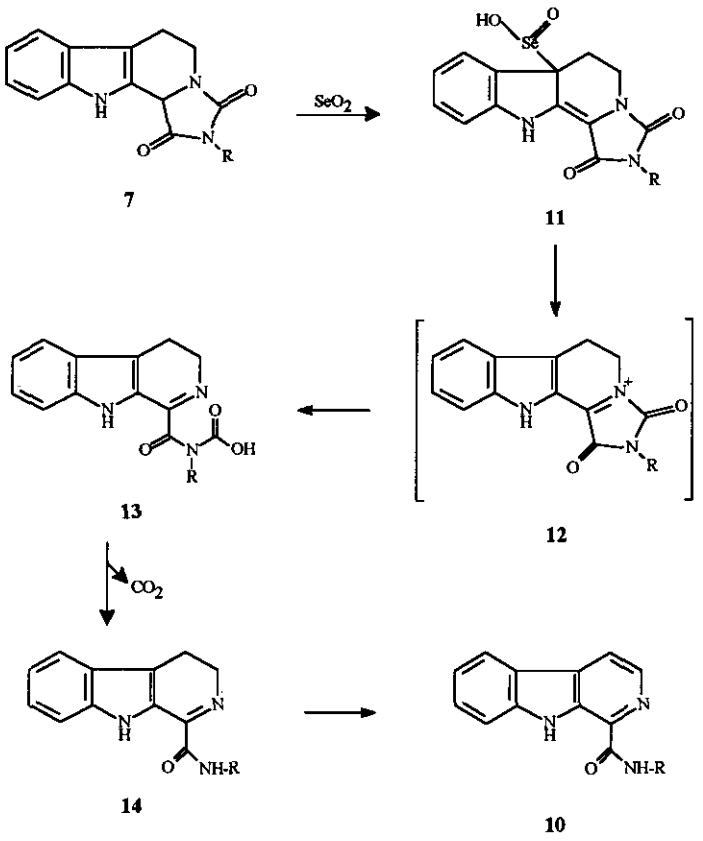
10	R	Yield %
b	$CH_2CH_2CH_3$	38
c	C_6H_5	45
d	p-CH_3O-C_6H_4	49
e	p-NO_2-C_6H_4	40

Scheme 4

The formation of **10** may occur through the mechanism formulated in Scheme 5. The initial step involves attack of the selenium dioxide at the indole 3-position to form **11,** followed by a [2,3]sigmatropic rearrangement to generate a Se^{II} ester,[24-26] which would transform through the intermediate **(12)** to a carbamic acid **(13)**. This acid break down to carbon dioxide and 3,4-dihydro-β-carboline **(14)**. Such a compound is know to aromatize readly with generation of the β-carboline system. Finally, the same 1-substituted β-carbolines **(10)** were also obtained by the oxidation of **7** with dichlorodicyano-*p*-benzoquinone (DDQ) in refluxing dioxane.

The approach methodology described here to afford a wide range of 1-carbamoyl-β-carbolines **(10)** in 3 steps, starting from tryptamine, represents an important contribution to the synthesis of new systems related to β-carboline alkaloids.

The affinities of the synthesized β-carboline-hydantoin hybrid systems for the central type benzodiazepine receptors were measured *in vitro* by a previously described procedure.[1] None of the hybrid molecules **(7)** showed any significant receptor binding.



7 11 12 13 14 10

Scheme 5

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. Ir spectra were recorded on a Perkin-Elmer 781 spectrophotometer. ^{1}H and ^{13}C nmr spectra were measured with a Varian VXR-300S spectrometer working at 299.949 MHz (^{1}H nmr) and 75.429 MHz (^{13}C nmr). Chemical shift data are given in ppm by reference to TMS (^{1}H nmr), $CDCl_3$ (^{13}C nmr; $\delta c = 76.9$) and DMSO-d_6 (^{13}C nmr; $\delta c = 39.6$). ^{13}C Nmr spectra of compounds (**7c-e**) were recorded in solid state with adamantane as external standard. Elemental analyses were performed by Centro Nacional de Química Orgánica (CSI).

(±)-1,2,3,4-Tetrahydro-β-carboline-1-carboxylic Acid (8)

Compound **(8)** was prepared according to the literature[21] method.

General Procedure for the Synthesis of 2-Substituted 5,6,11,11b-Tetrahydro-1*H*-imidazo[1',5':1,2]pyrido[3,4-*b*]indole-1,3(2*H*)-diones (7a-e)

To a suspension of the acid **(8)** (1.94 g, 9.0 mmol) in dry acetone (50 ml) was added 9.0 mmol of alkyl or aryl isocyanate. The reaction mixture was refluxed for 40 h. After filtration and evaporation of the solvent under reduced pressure, the residue was purified by silica gel column chromatography and the solid obtained was crystallized from an appropiate solvent.

2-Ethyl-5,6,11,11b-tetrahydro-1*H*-imidazo[1',5':1,2]pyrido[3,4-*b*]indole-1,3(2*H*)-dione (7a)

Column chromatography (ethyl acetate/hexane 1:1); mp 184° C (ethanol/water); ir (KBr): 3420, 1770, 1700 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 1.19 (3H, t, J=7.2 Hz, CH_3), 2.80 (1H, dd, J=15.6, 5.4 Hz, H-6a), 2.94 (1H, dddd, J=15.6, 11.1, 6.0, 2.4 Hz, H-6b), 3.21 (1H, ddd, J=13.8, 11.4, 5.1 Hz, H-5a), 3.56 (4H, q, J=7.2 Hz, CH_2), 4.53 (1H, dd, J=13.7, 5.1 Hz, H-5b), 5.18 (1H, br s, H-11b), 7.12 (1H, td, J=8.1, 1.2 Hz, H-8), 7.21 (1H, td, J=8.1, 1.2 Hz, H-9), 7.36 (1H, d, J=8.0 Hz, H-10), 7.49 (1H, d, J=7.6 Hz, H-7), 8.72 (1H, s, NH); ^{13}C nmr ($CDCl_3$) δ: 13.21 (CH_3), 20.32 (C-6), 34.04 (CH_2), 37.81 (C-5), 56.04 (C-11b), 109.2 (C-6a), 111.25 (C-10), 118.33 (C-7), 119.76 (C-8), 122.71 (C-9), 124.59 (C-6b), 126.22 (C-11a), 136.52 (C-10a), 156.59, 170.40 (C=O). Anal. Calcd for $C_{15}H_{15}N_3O_2$: C, 66.89; H, 5.61; N, 15.60. Found: C, 66.57; H, 5.41; N, 15.49.

2-Propyl-5,6,11,11b-tetrahydro-1*H*-imidazo[1',5':1,2]pyrido[3,4-*b*]indole-1,3(2*H*)-dione (7b)

Column chromatography (ethyl acetate/hexane 9:1); mp 167° C (ethanol/water); ir (KBr): 3360, 1770, 1710 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 0.87 (3H, t, J=7.5 Hz, CH_3), 1.62 (2H, sext, J=7.5 Hz, CH_2), 2.70-2.85 (1H, m, H-6a), 2.90-3.10 (1H, m, H-6b), 3.17-3.24 (1H, m, H-5a), 3.46 (2H, t, J=7.5 Hz, CH_2), 4.52 (1H, dd, J=13.8, 5.7 Hz, H-5b), 5.18 (1H, s, H-11b), 7.12 (1H, td, J=7.8, 1.0 Hz, H-8), 7.21 (1H, td, J=8.1, 1.1 Hz, H-9), 7.35 (1H, d, J=8.1 Hz, H-10), 7.49 (1H, d, J=7.8 Hz, H-7), 8.96 (1H, s, NH); ^{13}C nmr ($CDCl_3$) δ: 10.96 (CH_3), 20.32, 21.15 (C-6 or CH_2), 37.86 (C-5), 40.60 (CH_2), 56.04 (C-11b), 109.00 (C-6a), 111.27

(C-10), 118.33 (C-7), 119.73 (C-8), 122.68 (C-9), 124.62 (C-6b), 126.22 (C-11a), 136.56 (C-10a), 156.84, 170.70 (C=O). Anal. Calcd for $C_{16}H_{17}N_3O_2$: C, 67.82; H, 6.04; N, 14.83. Found: C, 67.60; H, 5.92; N, 14.77.

2-Phenyl-5,6,11,11b-tetrahydro-1*H*-imidazo[1',5':1,2]pyrido[3,4-*b*]indole-1,3(2*H*)-dione (7c)

Column chromatography (ethyl acetate/hexane 7:3); mp 245° C; ir (KBr): 3420, 1780, 1710 cm^{-1}; ^{13}C nmr (solid state) δ: 21.20 (C-6), 28.97 (C-5), 55.56 (C-11b), 108.54, 111.26, 116.75, 118.99, 121.13, 123.32, 125.75, 128.23, 137.17 (indole, phenyl), 156.56, 170.46 (C=O). Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.92; H, 4.73; N, 13.25. Found: C, 71.87; H, 4.65; N, 13.18.

2-(*p*-Methoxyphenyl)-5,6,11,11b-tetrahydro-1*H*-imidazo[1',5':1,2]pyrido[3,4-*b*]indole-1,3(2*H*)-dione(7d)

Column chromatography (ethyl acetate/hexane 7:3); mp 258° C; ir (KBr): 3380, 1770, 1710 cm^{-1}; ^{13}C nmr (solid state) δ: 21.30 (C-6), 27.90 (C-5), 55.60 (OCH_3), 60.36 (C-11b), 109.64, 112.45, 113.92, 115.86, 119.90, 121.43, 124.83, 126.32, 132.64, 136.18, 153.15 (indole, phenyl), 156.11, 170.80 (C=O). Anal. Calcd for $C_{20}H_{17}N_3O_3$: C, 69.16; H, 4.90; N, 12.10. Found: C, 68.80; H, 4.81; N, 11.90.

2-(*p*-Nitrophenyl)-5,6,11,11b-tetrahydro-1*H*-imidazo[1',5':1,2]pyrido[3,4-*b*]indole-1,3(2*H*)-dione (7e)

Column chromatography (ethyl acetate/hexane 8:2); mp 275° C; ir (KBr): 3400, 1780, 1720 cm^{-1}; ^{13}C nmr (solid state) δ: 21.15 (C-6), 28.06 (C-5), 65.75 (C-11b), 111.46, 113.54, 114.77, 119.59, 123.27, 125.87, 129.65, 136.88, 145.85, 146.61 (indole, phenyl), 155.10, 168.92 (C=O). Anal. Calcd for $C_{19}H_{14}N_4O_4$: C, 62.98; H, 3.87; N, 15.47. Found: C, 62.70; H, 3.71; N, 15.31.

2-(2-Chloroethyl)-5,6,11,11b-tetrahydro-1*H*-imidazo[1',5':1,2]pyrido[3,4-*b*]indole-1,3(2*H*)-dione (7f)

To a suspension of the acid (**8**) (1.5g, 7.0 mmol) in dry acetone (50 ml) was added 2-chloroethyl isocyanate (1.48 g, 14.0 mmol). The reaction mixture was refluxed under nitrogen for 48 h. After evaporation of the solvent under reduced pressure, the residual oil was purified by silica gel column chromatography (ethyl acetate/hexane 7:3) to afford **7f** (1.1g, 50%), mp 190-192° C (methanol); ir (KBr): 3430, 1775, 1710 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 2.81 (1H, dd, J=15.9, 5.1 Hz, H-6a), 2.93 (1H, dddd, J=15.9, 11.1, 5.7, 2.4 Hz, H-6b), 3.22 (1H, ddd, J=13.8, 11.4, 5.1 Hz, H-5a), 3.67 (2H, t, J=6.6 Hz, CH_2), 3.83, (2H, t, J=6.3 Hz, CH_2),

4.52 (1H, dd, J=13.8, 5.7 Hz, H-5b), 5.25 (1H, br s, H-11b), 7.11 (1H, td, J=7.8, 1.2 Hz, H-8), 7.21 (1H, td, J=8.2, 1.2 Hz, H-9), 7.35 (1H, d, J=7.8 Hz, H-10), 7.48 (1H, d, J=7.8 Hz, H-7), 8.65 (1H, s, NH); ^{1}H *nmr* (DMSO-d_6) δ: 2.72-2.81 (2H, m, H-6), 3.20 (1H, ddd, J=13.8, 11.4, 5.4 Hz, H-5a), 3.75-3.82 (4H, m, N-CH_2-CH_2-Cl), 4.31 (1H, dd, J=13.8, 4.5 Hz, H-5b), 5.60 (1H, s, H-11b), 6.97 (1H, td, J=7.8, 1.0 Hz, H-8), 7.10 (1H, td, J=7.8, 1.2 Hz, H-9), 7.37 (1H, d, J=7.8 Hz, H-10), 7.48 (1H, d, J=8.7 Hz, H-7), 11.30 (1H, s, NH); ^{13}C nmr (DMSO-d_6) δ: 20.39 (C-6), 37.80 (C-5), 40.15, 41.11 (N-CH_2-CH_2-Cl), 56.30 (C-11b), 107.78 (C-6a), 111.84 (C-10), 118.21 (C-7), 118.97 (C-8), 121.85 (C-9), 125.38 (C-6b), 126.05 (C-11a), 136.86 (C-10a), 156.21, 170.17 (C=O). Anal. Calcd for $C_{15}H_{14}N_3O_2Cl$: C, 59.31; H, 4.65; N, 13.83. Found: C, 59.13; H, 4.76; N, 13.77.

2-(2-Hidroxyethyl)-5,6,11,11b-tetrahydro-1*H*-imidazo[1',5':1,2]pyrido[3,4-*b*]indole-1,3(2*H*)-dione (7g)

A solution of **7f** (0.40 g, 1.3 mmol) in 80% aqueous ethanol (25 ml) was stirred at room temperature for 2 h. Then, 15 ml of sodium hydroxide (0.07 N) was added and stirred for 2 h. After filtration and evaporation of the filtrate under reduced pressure, the residual oil was purified by silica gel column chromatography (toluene/ethyl acetate 7:3) to give **7g** (0.22 g, 59.5%), mp 238° C (chloroform); ir (KBr): 3340 (broad), 1780, 1710 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 1.65 (1H, s, OH), 2.82 (1H, dd, J=15.9, 4.2 Hz, H-6a), 2.96 (1H, ddd, J=15.9, 11.4, 6.0 Hz, H-6b), 3.45 (1H, ddd, J=13.8, 11.7, 5.4 Hz, H-5a), 3.67 (2H, t, J=6.6 Hz, CH_2), 3.83 (2H, t, J=6.3 Hz, CH_2), 4.36 (1H, s, OH), 4.41 (1H, dd, J=13.8, 4.8 Hz, H-5b), 7.14 (1H, td, J=8.1, 1.2 Hz, H-8), 7.26 (1H, td, J=8.1, 1.2 Hz, H-9), 7.38 (1H, d, J=8.4 Hz, H-10), 7.52 (1H, d, J=7.5 Hz, H-7), 8.87 (1H, s, NH); ^{1}H nmr (DMSO-d_6) δ: 2.10 (1H, s, OH, exchangeable with D_2O), 2.78-2.86 (2H, m, H-6), 3.32-3.46 (1H, m, H-5a), 3.80-3.83 (4H, m, N-CH_2-CH_2-OH), 4.28 (1H, dd, J=13.8, 4.5 Hz, H-5b), 7.07 (1H, td, J=7.5, 1.0 Hz, H-8), 7.21 (1H, td, J=8.1, 1.1 Hz, H-9), 7.48 (1H, d, J=8.4 Hz, H-10), 7.54 (1H, d, J=7.8 Hz, H-7), 7.82 (1H, s, OH, exchangeable with D_2O), 11.30 (1H, s, NH, exchangeable with D_2O); ^{13}C nmr (DMSO-d_6) δ: 20.30 (C-6), 35.68 (C-5), 40.41, 40.96 (N-CH_2-CH_2-OH), 80.44 (C-11b), 110.09 (C-6a), 112.03 (C-10), 118.72 (C-7), 118.86 (C-8), 122.46 (C-9), 125.12 (C-6b), 127.70 (C-11a), 136.79 (C-10a), 154.66 (C=O), 170.63 (C-1). Anal. Calcd for $C_{15}H_{15}N_3O_3$: C, 62.15; H, 5.26; N, 14.73. Found: C, 61.90; H, 5.30; N, 14.65.

General Procedure for the Synthesis of 2-Substituted 1,2,3,4-Tetrahydro-β-carbolines (9a-d).

To a suspension of the acid **(8)** (1.94 g, 9.0 mmol) in dry acetone (35 ml) and dry DMSO (15 ml) was added 9.0 mmol of alkyl or aryl isothiocyanate. The reaction mixture was refluxed for 40 h. After filtration and evaporation of the solvent under reduced pressure, the residual oil was purified by silica gel column chromatography and the solid obtained was crystallized from an appropiate solvent.

2-Ethylthiocarbamoyl-1,2,3,4-tetrahydro-β-carboline (9a)

Column chromatography (ethyl acetate/hexane 7:3); mp 195° C (ethanol); ir (KBr): 3400, 3280, 1550 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 1.13 (3H, t, J=7.0 Hz, CH_3), 2.74 (2H, t, J=5.1 Hz, H-4), 3.57 (2H, quint, J=6.0 Hz, CH_2), 4.06 (2H, t, J=5.3 Hz, H-3), 5.08 (2H, s, H-1), 6.96 (1H, td, J=8.2, 1.0 Hz, H-6), 7.04 (1H, td, J=8.0, 1.1 Hz, H-7), 7.31 (1H, d, J=7.7 Hz, H-8), 7.39 (1H, d, J=7.5 Hz, H-5), 7.88 (1H, t, J=5.2 Hz, NH), 10.89 (1H, s, NH-indole); ^{13}C nmr (DMSO-d_6) δ: 14.62 (q, CH_3), 20.84 (t, C-4), 40.20 (t, CH_2), 45.37 (t, C-3), 46.58 (t, C-1), 107.09 (s, C-4a), 111.06 (d, C-8), 117.55 (d, C-5), 118.55 (d, C-6), 120.78 (d, C-7), 126.53 (s, C-4b), 131.66 (s, C-9a), 136.11 (s, C-8a), 181.50 (C=S). Anal. Calcd for $C_{14}H_{17}N_3S$: C, 64.82; H, 6.60; N, 16.20. Found: C, 65.02; H, 6.58; N, 16.42.

2-Propylthiocarbamoyl-1,2,3,4-tetrahydro-β-carboline (9b)

Column chromatography (ethyl acetate/hexane 6:4); mp 196° C (chloroform/hexane); ir (KBr): 3380, 3260, 1540 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 0.86 (3H, t, J=7.4 Hz, CH_3), 1.58 (2H, sext, J=7.3 Hz, CH_2), 2.74 (2H, t, J=5.0 Hz, H-4), 3.50 (2H, q, J=6.6 Hz, CH_2), 4.06 (2H, t, J=5.3 Hz, H-3), 5.10 (2H, s, H-1), 6.96 (1H, td, J=7.5, 1.0 Hz, H-6), 7.04 (1H, td, J=8.1, 1.2 Hz, H-7), 7.31 (1H, d, J=7.8 Hz, H-8), 7.39 (1H, d, J=7.5 Hz, H-5), 7.87 (1H, t, J=5.2 Hz, NH), 10.84 (1H, s, NH-indole); ^{13}C nmr (DMSO-d_6) δ: 11.28 (CH_3), 20.75 (C-4), 21.90 (CH_2), 45.25 (C-3), 46.55 (C-1), 47.05 (CH_2), 106.94 (C-4a), 110.92 (C-8), 117.41 (C-5), 118.40 (C-6), 120.63 (C-7), 126.37 (C-4b), 131.57 (C-9a), 135.95 (C-8a), 181.47 (C=S). Anal. Calcd for $C_{15}H_{19}N_3S$: C, 65.89; H, 7.00; N, 15.63. Found: C, 66.04; H, 6.89; N, 15.65.

2-Phenylthiocarbamoyl-1,2,3,4-tetrahydro-β-carboline (9c)

Column chromatography (ethyl acetate); mp 182° C (ethanol/water); ir (KBr): 3400, 3300, 1550 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 2.85 (2H, t, J=4.9 Hz, H-4), 4.26 (2H, t, J=5.0 Hz, H-3), 5.16 (2H, s, H-1), 6.96-7.34 (8H,

m, H-6, H-7, H-8, phenyl), 7.43 (1H, d, J=7.6 Hz, H-5), 9.54 (1H, s, NH), 10.93 (1H, s, NH-indole); ^{13}C nmr (DMSO-d_6) δ: 20.77 (C-4), 46.48 (C-3), 47.13 (C-1), 106.93 (C-4a), 110.96 (C-8), 117.48 (C-5), 118.47 (C-6), 120.74 (C-7), 126.28 (C-4b), 131.05 (C-9a), 135.97 (C-8a), 124.33, 125.34, 127.95, 140.91 (phenyl), 181.84 (C=S). Anal. Calcd for $C_{18}H_{17}N_3S$: C, 70.33; H, 5.53; N, 13.67. Found: C, 70.15; H, 5.35; N, 13.38.

2-(*p*-Methoxyphenylthiocarbamoyl)-1,2,3,4-tetrahydro-β-carboline (9d)

Column chromatography (ethyl acetate/hexane 7:3); mp 202° C (ethanol/water); ir (KBr): 3390, 3220, 1530, 1510 cm^{-1}; ^{1}H nmr (DMSO-d_6) δ: 2.83 (2H, t, J=4.9 Hz, H-4), 3.74 (3H, s, OCH_3), 4.21 (2H, t, J=5.2 Hz, H-3), 5.17 (2H, s, H-1), 6.88 (2H, d, J=8.7 Hz, H-3 and H-5 phenyl), 6.98 (1H, t, J=7.5 Hz, H-6), 7.06 (1H, t, J=7.8 Hz, H-7), 7.18 (2H, d, J=8.7 Hz, H-2 and H-6 phenyl), 7.31 (1H, d, J=7.8 Hz, H-8), 7.43 (1H, d, J=7.5 Hz, H-5), 9.41 (1H, s, NH), 10.94 (1H, s, NH-indole); ^{13}C nmr (DMSO-d_6) δ: 20.99 (C-4), 46.37 (C-3), 47.20 (C-1), 55.22 (OCH_3), 107.12 (C-4a), 111.11 (C-8), 117.63 (C-5), 118.60 (C-6), 120.86 (C-7), 126.49 (C-4b), 131.41 (C-9a), 136.15 (C-8a), 113.31, 127.68, 133.95, 156.62 (phenyl), 182.20 (C=S). Anal. Calcd for $C_{19}H_{19}N_3OS$: C, 67.63; H, 5.63; N, 12.46. Found: C, 67.38; H, 5.45; N, 12.20.

General Procedure for the Synthesis of 1-Substituded β-carbolines (10b-e)

A solution of **7b-e** (3.0 mmol) in dioxane (80 ml) was treated with selenium dioxide (0.66 g, 6.0 mmol) and the reaction mixture was stirred at reflux temperature until tlc indicated the absence of the starting material. The hot suspension was filtered over Celite and the filtrate was evaporated under reduced pressure. The residual oil was purified by silica gel column chromatography and the solid obtained was crystallized from an appropiate solvent.

1-Propylcarbamoyl-β-carboline (10b)

Column chromatography (ethyl acetate/toluene 7:3); mp 174° C (ethanol); ir (KBr): 3420, 3360, 1650, 1620, 1530 cm^{-1}; ^{1}H nmr ($CDCl_3$) δ: 0.94 (3H, t, J=7.2 Hz, CH_3), 1.62 (2H, sext, J=7.2 Hz, CH_2), 3.42 (2H, q, J=6.6 Hz, CH_2), 7.18 (1H, td, J=7.8, 1.2 Hz, H-6), 7.41 (1H, d, J=8.1 Hz, H-8), 7.46 (1H, td, J=7.8, 1.2 Hz, H-7), 7.95 (1H, d, J=5.1 Hz, H-4), 8.01 (1H, d, J=7.8 Hz, H-5), 8.14 (1H, br t, NH), 8.26 (1H, d, J=5.1 Hz, H-3), 10.73 (1H, s, NH); ^{13}C nmr ($CDCl_3$) δ: 11.69 (CH_3), 23.17 (CH_2), 40.98 (CH_2), 112.01 (C-8), 117.75 (C-4), 120.28 (C-6), 121.89 (C-5), 129.20 (C-7), 120.69, 131.40, 132.26, 135.60 (C-4a, C-4b,

C-8a, C-9a), 137.24 (C-3), 141.16 (C-1), 168.60 (C=O). Anal. Calcd for $C_{15}H_{15}N_3O$: C, 71.14; H, 5.93; N, 16.60. Found: C, 71.02; H, 5.89; N, 16.41.

1-Phenylcarbamoyl-β-carboline (10c)

Column chromatography (ethyl acetate/toluene 7:3); mp 232° C (ethanol/water); ir (KBr): 3340(broad), 1665, 1630, 1600, 1520 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 7.17 (1H, tt, J=7.5, 0.9 Hz, H-4 phenyl), 7.28 (1H, td, J=8.1, 1.5 Hz, H-6), 7.40 (2H, td, J=8.1, 1.2 Hz, H-3 and H-5 phenyl), 7.51 (1H, d, J=7.8 Hz, H-8), 7.56 (1H, td, J=8.4, 1.2 Hz, H-7), 7.82 (2H, dd, J=8.4, 0.9 Hz, H-2 and H-6 phenyl), 8.07 (1H, d, J=5.1 Hz, H-4), 8.10 (1H, d, J=8.1 Hz, H-5), 8.40 (1H, d, J=5.1 Hz, H-3), 10.09 (1H, s, NH), 10.33 (1H, s, NH); ^{13}C nmr ($CDCl_3$) δ: 111.79 (C-8), 117.91 (C-4), 120.27 (C-6), 121.70 (C-5), 129.16 (C-7), 120.39, 131.47, 131.55, 135.56 (C-4a, C-4b, C-8a, C-9a), 136.94 (C-3), 140.93 (C-1), 119.55, 124.20, 128.99, 137.51 (phenyl), 164.20 (C=O). Anal. Calcd for $C_{18}H_{13}N_3O$: C, 75.24; H, 4.56; N, 14.62. Found: C, 75.04; H, 4.61; N, 14.43.

1-(*p*-Methoxyphenylcarbamoyl)-β-carboline (10d)

Column chromatography (ethyl acetate/toluene 7:3); mp 226° C (ethanol/water); ir (KBr): 3360, 3320, 1660, 1630, 1600, 1520 cm^{-1}; ^1H nmr ($CDCl_3$) δ: 3.80 (3H, s, OCH_3), 6.93 (2H, d, J=9.0 Hz, H-3 and H-5 phenyl), 7.27 (1H, td, J=7.9, 1.1 Hz, H-6), 7.47 (1H, d, J=8.1 Hz, H-8), 7.55 (1H, td, J=7.8, 1.2 Hz, H-7), 7.71 (2H, d, J=9.0 Hz, H-2 and H-6 phenyl), 8.04 (1H, d, J=5.1 Hz, H-4), 8.09 (1H, d, J=7.8 Hz, H-5), 8.37 (1H, d, J=4.9 Hz, H-3), 9.92 (1H, s, NH), 10.38 (1H, s, NH); ^{13}C nmr ($CDCl_3$) δ: 55.29 (OCH_3), 111.75 (C-8), 117.68 (C-4), 120.13 (C-6), 121.62 (C-5), 129.04 (C-7), 120.34, 131.34, 131.69, 135.45 (C-4a, C-4b, C-8a, C-9a), 136.83 (C-3), 140.93 (C-1), 114.06, 121.11, 130.70, 156.21 (phenyl), 163.84 (C=O). Anal. Calcd for $C_{19}H_{15}N_3O_2$: C, 71.90; H, 4.76; N, 13.20. Found: C, 71.54; H, 4.75; N, 2.70.

1-(*p*-Nitrophenylcarbamoyl)-β-carboline (10e)

Column chromatography (ethyl acetate/toluene 7:3); mp 211° C (ethanol/water); ir (KBr): 3415, 3310, 1660, 1620, 1600, 1540 cm^{-1}; ^1H nmr (DMSO-d_6) δ: 7.31 (1H, td, J=7.8, 1.0 Hz, H-6), 7.61 (1H, td, J=8.4, 1.2 Hz, H-7), 7.82 (1H, d, J=8.4 Hz, H-8), 8.31-8.33 (5H, m, phenyl and H-5), 8.47 (1H, d, J=4.8 Hz, H-4), 8.54 (1H, d, J=5.1 Hz, H-3), 11.39 (1H, s, NH), 11.95 (1H, s, NH); ^{13}C nmr (DMSO-d_6) δ: 113.20 (C-8),

119.12 (C-4), 120.03 (C-6), 122.07 (C-5), 129.27 (C-7), 120.27, 131.40, 131.55, 135.09 (C-4a, C-4b, C-8a, C-9a), 136.96 (C-3), 141.91 (C-1), 120.15, 124.94, 142.71, 144.95 (phenyl), 164.99 (C=O). Anal. Calcd for $C_{18}H_{12}N_4O_3$: C, 65.06; H, 3.61; N, 16.87. Found: C, 64.81; H, 3.57; N, 16.68.

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