Short Synthesis of Tryptophane and β-Carboline Derivatives by Reaction of Indoles with N-(Diphenylmethylene)-α,β-didehydroamino Acid Esters

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The ethylaluminum dichloride catalyzed Michael-type addition of indoles **1a-h** to the *N*-(diphenylmethylene)-α,β-didehydroamino acid esters **2a-c** allows a new synthesis of β-methyltryptophanes **4l,m** and a new route for 1,1-diphenyl-3-carbalkoxy-1,2,3,4-tetrahydro-β-carbolines **5a-m**.

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The Lewis acid catalyzed addition of indoles **1a-f** to alkyl *N*-(diphenylmethylene)-α,β-didehydroalaninates **2a-b** (later on, diphenylmethylene = DPM), giving the protected tryptophanes **3a-f,i** in good yields, has been used to obtain both tryptophane [1] and *N*-benzydryltryptophane [2] derivatives.

The reaction inserts directly a protected alkyl α-aminoethylcarboxylate chain on the C-3 of indole, as well as on other aromatic systems. In the field of the synthesis of indole derivatives, this method is comparable with those giving tryptophanes by reaction of indoles with ethyl α-nitrosoacrylates [3] or azadienes [4], and with the method affording tryptamines by indole nitro-olefination [5].

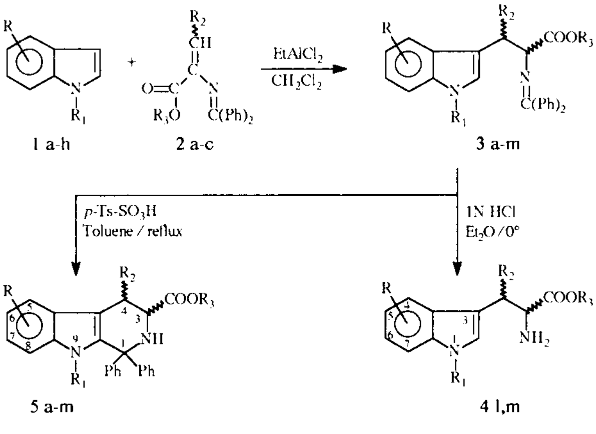
The alkyl *N*-(DPM)-α,β-didehydroalaninates **2** belong to a class of versatile intermediates for the organic synthesis. As a rule, the α,β-didehydroamino acids undergo additions of hydrogen [6-9], deuterium and tritium [10-11], radicals [12], 1,3-dipoles [13-15], 1,3-dienes [16], both ionic and neutral electrophiles [17], and nucleophiles [18] to their double bond. Thus, they have found many applications in the synthesis of optically active and inactive, unnatural, and labelled amino acids. Furthermore, the choice of an α,β-didehydroamino acid route is also encouraged by the practical preparation method reported for many of them [19].

As is well known, the α,β-didehydroamino acids are fairly stable only in the *N*-protected forms. To this end, acyl or other *N*-protective groups have been used; the ester derivatives have been usually employed in the practice.

The introduction of the *N*-(DPM) protection results in compounds **2a-c**, which are very reactive as Michael acceptors and are termically more stable [20] than the *N*-(phenylmethylene) analogues studied by others [21]. The *N*-(DPM) protection is compatible with many reaction media and the deblocking of the saturated amino acid derivatives has been quantitatively performed in very mild conditions (1*N* hydrochloric acid/diethyl ether, 0°) [22].

Accordingly, we decided to extend our work on the addition of indoles to α,β-didehydroamino acids toward a new diasterospecific synthesis of β-methyltryptophanes and a new route for 1,1-diphenyl-3-carboalkoxy-1,2,3,4-tetrahydro-β-carboline derivatives (see Scheme). The two points are linked by the shared synthetic pathway and by the structural correlations we found helpful in assigning the configuration to the diastereoisomers **3,4m**.

Scheme



Compd	R	R$_1$	R$_2$	R$_3$
1 a	H	H	–	–
1 b	4-OMe	H	–	–
1 c	5-OMe	H	–	–
1 d	5-Me	H	–	–
1 e	5-F	H	–	–
1 f	H	Me	–	–
1 g	5,6-OMe	H	–	–
1 h	7-Me	H	–	–
2 a	–	–	H	Et
2 b	–	–	H	Me
2 c	–	–	Me	Me
3 a	H	H	H	Me
3 b	4-OMe	H	H	Me
3 c	5-OMe	H	H	Me
3 d	5-Me	H	H	Me
3 e	5-F	H	H	Me
3 f	H	Me	H	Me
3 g	5,6-OMe	H	H	Me
3 h	7-Me	H	H	Me
3 i	H	H	H	Et
3,4 l *	H	H	Me	Me
3,4 m *	5-Me	H	Me	Me
5 a	H	H	H	Me
5 b	5-OMe	H	H	Me
5 c	6-OMe	H	H	Me
5 d	6-Me	H	H	Me
5 e	6-F	H	H	Me
5 f	H	Me	H	Me
5 g	6,7-OMe	H	H	Me
5 h	8-Me	H	H	Me
5 i	H	H	H	Et
5 l *	H	H	Me	Me
5 m *	6-Me	H	Me	Me

* Both the (2SR,3RS) and (2RS,3RS) diastereoisomers.

Synthesis of β-Methyltryptophanes.

The amino acid β-methyltryptophane is a component or a methabolic precursor of natural products such as telomycin [23], streptonigrin [24] and lavendomycin [25]. The only efficient synthesis of the natural diasteroisomeric form **4l** (2*SR*,3*RS*) of this amino acid has been recently reported [26] as an improvement of previous methods [27-29].

Recently, in our laboratory a stereospecific synthesis of β-substituted *N*-(DPM)-α,β-didehydroamino acid esters was pointed out [30]. In this way the (*E*) and (*Z*) isomers of β-methyl derivative **2c** became available. Therefore, we envisaged to apply the cited coupling reaction to the synthesis of the epimers of the β-methyltryptophanes **4l,m**, by means of a presumably stereospecific addition. The stereoisomers (*E*)-**2c** and (*Z*)-**2c** were thus allowed to react with indoles **1a,d** in the presence of ethylaluminum dichloride as catalyst, obtaining the derivatives **3l,m** in 70% and 50% yields respectively. Whether starting from (*E*)-**2c** or from (*Z*)-**2c**, the reaction afforded the 2*SR*,3*RS* (natural) and 2*RS*,3*RS* diastereoisomers in almost equimolecular amounts. The diastereoisomers were separated by flash-chromatography on silica gel.

The configuration of epimeric compounds **3l** and **4l** were assigned after *N*-(DPM) deprotection by comparison with authentical samples of compounds **4l** (2*SR*,3*RS*) and **4l** (2*RS*,3*RS*) [26]. In order to establish the configuration of the epimers of **3m** (and consequently of **4m**), the compounds **3m** were converted into the corresponding β-carboline derivatives **5m**, whose ^{1}H nmr spectra were interpreted unambiguously. In fact, the measured $J_{H-3,H-4}$ values are consistent with those obtained from the Karplus equation for similar cyclic systems [31]; to an approximately syn-periplanar geometry of **5m** (3*SR*,4*RS*) corresponds a value of $J = 3.96$, and to an approximately anti-periplanar geometry of **5m** (3*RS*,4*RS*) corresponds a value of $J = 9.41$. Furthermore, the J values compare with those of β-carboline analogues **5l** prepared from **3l**.

The aim of a stereospecific synthesis has not been reached, nevertheless the method is useful, since it is less troublesome than the already mentioned ones [27-29]. If compared to the synthesis of Behforouz and co-workers [26], it allows to obtain in one step β-methyltryptophane derivatives bearing substituents on the indole ring, starting directly from the many substituted indoles commercially available. The extension to a general synthesis of tryptophanes alkyl or aryl β-substituted is predictable without apparent problems.

Synthesis of Tetrahydro-β-carboline Derivatives.

As for the second point, the prepared new compounds **3g,h,l,m** and the elsewhere described **3a-f,i** [1,2] were then used for the synthesis of the new β-carboline derivatives **5a-m** (see Scheme). It is known that the tetrahydro-β-carboline structure is a common nucleus of many indole alkaloids biosynthetically correlated to tryptophane [32]. The synthetic derivatives of β-carboline are of increasing interest in medicinal chemistry because of their important biological effects, such as inhibition of monoammine oxidase, antiviral activity, carcinogenic properties, and because of their binding to benzodiazepine (Bdz) receptors [33].

Some of us previously prepared a number of 1,1-diphenyl-1,2,3,4-tetrahydro-β-carbolines and tested them as Bdz receptor ligands; however, the compounds did not show any interaction with these receptors [34]. These results could be only partly ascribed to the unfavourable steric hindrance at C-1. Indeed, a qualitative structure-activity relationships study [35] on the β-carbolinic ligands to Bdz established the carboalkoxy group at C-3 as necessary for the binding. Since these molecules do not fulfill this requirement, we thought it of interest to prepare from **3a-m** the new 1,1-diphenyl-3-carboalkoxy-1,2,3,4-tetrahydro-β-carbolines **5a-m** in order to submit them to a further binding study.

The reactions were made in the typical condition of the Pictet-Spengler cyclization in aprotic media [36]. Refluxing toluene was used as solvent, and *p*-toluenesulfonic acid as catalyst. Better yields were obtained when the commercial *p*-toluenesulfonic acid monohydrate was azeotropically dehydrated, before the use, by a Dean-Stark apparatus in the same reaction solvent.

The structure of the β-carboline derivatives has been confirmed by ^{1}H nmr and ms spectroscopy. The ms fragmentation patterns of all the compounds are very similar, apart from the minor quantitative differences in the relative abundance of some peaks. This is indicative of the close structural correlation existing among the compounds. All the spectra display the molecular ion and some of them an MH^+ signal, which may indicate a strong hydration process prior to the ionization. The base-peak in all the spectra is associated to the loss of C_6H_5; the loss of $COOR^3$ from both M^+ and $M^+-C_6H_5$ rules the successive fragmentation process.

EXPERIMENTAL

Dichloromethane and toluene were distilled over calcium hydride; all the other solvents and reagents were the highest grade commercially available and were used without additional purification. Evaporations *in vacuo* were conducted on a Büchi rotavapor at water aspirator pressures. Column chromatography purifications were performed under "flash" conditions [37] using Merck 230-400 mesh silica gel. Melting points (mp) were taken on a Büchi SMP-510 capillary apparatus, and are uncorrected. Infrared spectra (ir) were obtained on a Perkin-Elmer 257 spectrometer. Mass spectra (ms) (EI, 70 eV) were taken on a GC-MS HP 5995 instrument; diagnostic peaks are reported in the order:

M^+, M^+-COOR^3, M^+-C_6H_5 (relative abundance %). Nuclear magnetic resonance (^{1}H nmr) spectra were recorded in deuteriochloroform on a Bruker AC 200 spectrometer.

General Procedure for *N*-(Diphenylmethylene)tryptophane Derivatives **3a-m**.

The compounds were prepared by partial modification of the method previously reported [1,2], and all of these reactions were carried out under a nitrogen atmosphere. To a stirred and cooled (0°) solution of appropriate compound, **2a-c**, [1,30] (10 mmoles) and suitable indole, **1a-h**, (20 mmoles) in dry dichloromethane (100 ml), a 1*M* solution of ethylaluminum dichloride in hexane (20 ml) was added, and the reaction mixture was stirred at 0° for 1 hour (2 hours to obtain the compounds **3l,m**). The mixture was then carefully poured into an ice-cold saturated sodium bicarbonate solution (100 ml); the resultant suspension of aluminum hydroxide was filtered on Celite, the organic layer was separated, washed with water, dried (anhydrous sodium sulfate) and evaporated *in vacuo* to yield a crude product which was purified by flash-chromatography (cyclohexane-ethyl acetate 8:2 as eluent).

For the chemical and spectral data of compounds **3a-f** and **3i**, see literature references [2] and [1] respectively.

Methyl *N*-(Diphenylmethylene)-5,6-dimethoxytryptophanate (**3g**).

This compound was obtained as white crystals (benzene-hexane), mp 91-92°, yield 79%; ir (chloroform): ν 3470 (NH), 1730 (C=O) cm^{-1}; ^{1}H nmr: δ 1.76 (m, 2H, ABX, C*H*$_2$-CH), 3.38 (m, 1H, ABX, CH$_2$-C*H*), 3.60, 3.65, 3.75 (3s, 9H, 5,6-OC*H*$_3$, COOC*H*$_3$), 6.40-7.33 (m, 13H arom), 8.03 (br s, 1H, N*H*).

Anal. Calcd. for $C_{27}H_{26}N_2O_4$: C, 73.29; H, 5.92; N, 6.33. Found: C, 72.91; H, 5.99; N, 6.11.

Methyl *N*-(Diphenylmethylene)-7-methyltryptophanate (**3h**).

This compound was obtained as white crystals (diethyl ether-hexane), mp 150-151°, yield 72%; ir (chloroform): ν 3480 (NH), 1735 (C=O) cm^{-1}; ^{1}H nmr: δ 2.45 (s, 3H, 7-C*H*$_3$), 3.17, 3.59 (2m, 3H, ABX, C*H*$_2$-CH), 3.87 (s, 3H, COOC*H*$_3$), 6.66-7.65 (m, 14H arom), 7.91 (br s, 1H, N*H*).

Anal. Calcd. for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07. Found: C, 78.71; H, 6.15; N, 7.05.

Methyl *N*-(Diphenylmethylene)-β-methyltryptophanate (**3l**, 2*SR*,3*RS*).

This compound was obtained as white prisms (ether-pentane), mp 124-125°, yield 37%; ir (nujol): ν 3330 (NH), 1710 (C=O) cm^{-1}; ^{1}H nmr: δ 1.52 (d, 3H, CH-C*H*$_3$), 3.66 (s, 3H, COOC*H*$_3$), 3.95 (m, 1H, C*H*-COOCH$_3$), 4.42 (d, 1H, C*H*-CH$_3$, J = 5.35 Hz), 6.56-7.66 (m, 15H arom), 7.94 (br s, 1H, N*H*).

Anal. Calcd. for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07. Found: C, 78.48; H, 6.18; N, 6.95.

Methyl *N*-(Diphenylmethylene)-β-methyltryptophanate (**3l**, 2*RS*,3*RS*).

This compound was obtained as colorless prisms (diethyl ether-hexane), mp 120-121°, yield 33%; ir (nujol): ν 3330 (NH), 1715 (C=O) cm^{-1}; ^{1}H nmr: δ 1.38 (d, 3H, CH-C*H*$_3$), 3.63 (s, 3H, COOC*H*$_3$), 3.80 (m, 1H, C*H*-CH$_3$), 4.39 (d, 1H, C*H*-COOCH$_3$, J = 6.78 Hz), 6.74-7.57 (m, 15H arom), 7.97 (br s, 1H, N*H*).

Anal. Calcd. for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07. Found: C, 78.80; H, 6.12; N, 7.02.

Methyl *N*-(Diphenylmethylene)-β-methyl-5-methyltryptophanate (**3m**, 2*SR*,3*RS*).

This compound was obtained as an oil, yield 27%; ir (chloroform): ν 3470 (NH), 1725 (C=O) cm^{-1}; ^{1}H nmr: δ 1.54 (d, 3H, CH-C*H*$_3$), 2.33 (s, 3H, 5-C*H*$_3$), 3.68 (s, 3H, COOC*H*$_3$), 3.93 (m, 1H, C*H*-CH$_3$), 4.51 (d, 1H, C*H*-COOCH$_3$, J = 5.46 Hz), 6.61-7.60 (m, 14H arom), 7.93 (br s, 1H, N*H*).

Anal. Calcd. for $C_{27}H_{26}N_2O_2$: C, 79.00; H, 6.38; N, 6.82. Found: C, 79.31; H, 6.44; N, 6.66.

Methyl *N*-(Diphenylmethylene)-β-methyl-5-methyltryptophanate (**3m**, 2*RS*,3*RS*).

This compound was obtained as an oil, yield 25%; ir (chloroform): ν 3470 (NH), 1725 (C=O) cm^{-1}; ^{1}H nmr: δ 1.44 (d, 3H, CH-C*H*$_3$), 2.38 (s, 3H, 5-C*H*$_3$), 3.71 (s, 3H, COOC*H*$_3$), 3.78 (m, 1H, C*H*-CH$_3$), 4.47 (d, 1H, C*H*-COOCH$_3$, J = 7.31 Hz), 6.63-7.61 (m, 14H arom), 8.02 (br s, 1H, N*H*).

Anal. Calcd. for $C_{27}H_{26}N_2O_2$: C, 79.00; H, 6.38; N, 6.82. Found: C, 79.12; H, 6.45; N, 6.71.

General Procedure for *N*-Deblocking of Compounds **3l,m** into the Corresponding Methyl β-Methyltryptophanates **4l,m**.

The compounds were prepared by partial modification of the previously reported method [1,22]. A solution of the suitable *N*-(diphenylmethylene)-β-methyltryptophane derivative **3l,m** (5 mmoles) in diethyl ether (10 ml) was stirred overnight at 0° with 1*N* hydrochloric acid (6 ml). The layers were separated, the aqueous phase was washed with diethyl ether, then alkalized with 14% aqueous ammonium hydroxide (*p*H ≅ 9), and extracted with ethyl acetate. The combined organic extracts were dried (anhydrous sodium sulfate) and evaporated *in vacuo* to yield a crude product (**4l,m**) which was purified by crystallization.

For chemical and spectral data of compounds **4l** (2*SR*,3*RS*) and **4l** (2*RS*,3*RS*), see literature reference [26].

Methyl β-Methyl-5-methyltryptophanate (**4m**, 2*SR*,3*RS*).

This compound was obtained as white crystals (ethyl acetate-hexane), mp 136-137°, yield 92%; ir (nujol): ν 3370, 3295 (NH$_2$), 1740 (C=O) cm^{-1}; ^{1}H nmr: δ 1.31 (d, 3H, CH-C*H*$_3$), 1.45 (br s, 2H, N*H*$_2$), 2.48 (s, 3H, 5-C*H*$_3$), 3.67 (m, 1H, C*H* -CH$_3$), 3.77 (s, 3H, COOC*H*$_3$), 3.96 (d, 1H, C*H*-COOCH$_3$, J = 3.82 Hz), 7.03-7.46 (m, 4H arom), 8.06 (br s, 1H, N*H*).

Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.51; H, 7.50; N, 11.22.

Methyl β-Methyl-5-methyltryptophanate (**4m**, 2*RS*,3*RS*).

This compound was obtained as white crystals (diethyl ether-hexane), mp 130-131°, yield 90%; ir (nujol): ν 3340, 3280 (NH$_2$), 1750 (C=O) cm^{-1}; ^{1}H nmr: δ 1.45 (d, 3H, CH-C*H*$_3$), 1.47 (br s, 2H, N*H*$_2$), 2.46 (s, 3H, 5-C*H*$_3$), 3.53 (m, 1H, C*H*-CH$_3$), 3.69 (s, 3H, COOC*H*$_3$), 3.77 (d, 1H, C*H*-COOCH$_3$, J = 6.81 Hz), 6.99-7.39 (m, 4H arom), 8.03 (br s, 1H, N*H*).

Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37. Found: C, 68.21; H, 7.32; N, 11.45.

General Procedure for 1,1-Diphenyl-1,2,3,4-tetrahydro-β-carbolines Derivatives **5a-m**.

A mixture of the suitable *N*-(diphenylmethylene)tryptophane derivative **3a-m** (5 mmoles) and anhydrous *p*-toluenesulfonic acid (1 mmole, 0.172 g) in toluene (20 ml) was refluxed (10 hours). After cooling at room temperature, the organic solution was washed with a saturated sodium bicarbonate solution and with water, then dried (anhydrous sodium sulfate) and evaporated *in vacuo* to yield a crude product **5l,m** which was purified by crystallization.

Commercial *p*-toluenesulfonic acid monohydrate was azeotropically dehydrated, before the use, by refluxing (4 hours, Dean-Stark trap) in the same reaction solvent.

1,1-Diphenyl-3-carbomethoxy-1,2,3,4-tetrahydro-β-carboline (**5a**).

This compound was obtained as white crystals (dichloromethane-petroleum ether), mp 234-235°, yield 72%; ir (chloroform): ν 3450 (NH), 3330 (NH), 1735 (C = O) cm^{-1}; ^{1}H nmr: δ 1.60 (br s, 1H, N*H*), 3.15 (m, 2H, ABX, C*H*$_2$-CH), 3.75 (m, 1H, ABX, CH$_2$-C*H*), 3.80 (s, 3H, COOC*H*$_3$), 7.20-7.60 (m, 14H arom, 1H, N*H* indole); ms: (m/z) 382 (19), 323 (8), 305 (100).

Anal. Calcd. for $C_{25}H_{22}N_2O_2$: C, 78.51; H, 5.80; N, 7.32. Found: C, 78.86; H, 5.73; N, 7.24.

1,1-Diphenyl-3-carbomethoxy-5-methoxy-1,2,3,4-tetrahydro-β-carboline (**5b**).

This compound was obtained as white crystals (benzene-petroleum ether), mp 228-229°, yield 83%; ir (chloroform): ν 3460 (NH), 3330 (NH), 1730 (C = O) cm^{-1}; ^{1}H nmr: δ 2.94 (br s, 1H, N*H*), 3.21, 3.50 (m, 2H, ABX, C*H*$_2$-CH), 3.68 (m, 1H, ABX, CH$_2$-C*H*), 3.77, 3.94 (2s, 6H, 5-OC*H*$_3$, COOC*H*$_3$), 6.50-7.50 (m, 13H arom, 1H, N*H* indole); ms: (m/z) 412 (30), 353 (3), 335 (100).

Anal. Calcd. for $C_{26}H_{24}N_2O_3$: C, 75.71; H, 5.86; N, 6.79. Found: C, 75.90; H, 5.91; N, 6.73.

1,1-Diphenyl-3-carbomethoxy-6-methoxy-1,2,3,4-tetrahydro-β-carboline (**5c**).

This compound was obtained as white crystals (benzene-petroleum ether), mp 247-248°, yield 80%; ir (nujol): ν 3425 (NH), 3350 (NH), 1730 (C = O) cm^{-1}; ^{1}H nmr: δ 2.96 (br s, 1H, N*H*), 3.12 (m, 2H, ABX, C*H*$_2$-CH), 3.71 (m, 1H, ABX, CH$_2$-C*H*), 3.78, 3.87 (2s, 6H, 6-OC*H*$_3$, COOC*H*$_3$), 6.80-7.49 (m, 13H arom, 1H, N*H* indole); ms: (m/z) 412 (27), 353 (8), 335 (100).

Anal. Calcd. for $C_{26}H_{24}N_2O_3$: C, 75.71; H, 5.86; N, 6.79. Found: C, 75.91; H, 5.81; N, 6.70.

1,1-Diphenyl-3-carbomethoxy-6-methyl-1,2,3,4-tetrahydro-β-carboline (**5d**).

This compound was obtained as white crystals (benzene-petroleum ether), mp 246-247°, yield 77%; ir (chloroform): ν 3460 (NH), 3330 (NH), 1735 (C = O) cm^{-1}; ^{1}H nmr: δ 1.65 (br s, 1H, N*H*), 2.48 (s, 3H, 6-C*H*$_3$), 3.05-3.18 (m, 2H, ABX, C*H*$_2$-CH), 3.71 (m, 1H, ABX, CH$_2$-C*H*), 3.78 (s, 3H, COOC*H*$_3$), 6.98-7.50 (m, 13H arom, 1H, N*H* indole); ms: (m/z) 396 (25), 337 (9), 319 (100).

Anal. Calcd. for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07. Found: C, 79.11; H, 6.22; N, 7.01.

1,1-Diphenyl-3-carbomethoxy-6-fluoro-1,2,3,4-tetrahydro-β-carboline (**5e**).

This compound was obtained as white crystals (dichloromethane-hexane), mp 253-254°, yield 80%; ir (nujol): ν 3465 (NH), 3325 (NH), 1730 (C = O) cm^{-1}; ^{1}H nmr: δ 3.08 (m, 2H, ABX, C*H*$_2$-CH, 1H, N*H*), 3.69 (m, 1H, ABX, CH$_2$-C*H*), 3.77 (s, 3H, COOC*H*$_3$), 6.85-7.49 (m, 13H arom, 1H, N*H* indole); ms: (m/z) 400 (22), 341 (24), 323 (100).

Anal. Calcd. for $C_{25}H_{21}FN_2O_2$: C, 74.98; H, 5.29; N, 7.00. Found: C, 74.98; H, 5.26; N, 7.05.

1,1-Diphenyl-3-carbomethoxy-9-methyl-1,2,3,4-tetrahydro-β-carboline (**5f**).

This compound was obtained as yellow crystals (dichloromethane-hexane), mp 209-210°, yield 46%; ir (nujol): ν 3340 (NH), 1735 (C = O) cm^{-1}; ^{1}H nmr: δ 2.91 (br s, 1H, N*H*), 2.99 (s, 3H, N-C*H*$_3$), 3.16 (m, 2H, ABX, C*H*$_2$-CH), 3.56 (m, 1H, ABX, CH$_2$-C*H*), 3.74 (s, 3H, COOC*H*$_3$), 7.15-7.63 (m, 14H arom); ms: (m/z) 396 (51), 337 (16), 319 (100).

Anal. Calcd. for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07. Found: C, 78.92; H, 6.15; N, 7.02.

1,1-Diphenyl-3-carbomethoxy-6,7-dimethoxy-1,2,3,4-tetrahydro-β-carboline (**5g**).

This compound was obtained as white crystals (benzene-petroleum ether), mp 227°, yield 65%; ir (chloroform): ν 3450 (NH), 3330 (NH), 1730 (C = O) cm^{-1}; ^{1}H nmr: δ 2.92 (br s, 1H, N*H*), 3.10 (m, 2H, ABX, C*H*$_2$-CH), 3.70 (m, 1H, ABX, CH$_2$-C*H*), 3.77, 3.85, 3.94 (3s, 9H, 6,7-OC*H*$_3$, COOC*H*$_3$), 6.79-7.49 (m, 12H arom, 1H, N*H* indole); ms: (m/z) 442 (20), 383 (4), 365 (100).

Anal. Calcd. for $C_{27}H_{26}N_2O_4$: C, 73.29; H, 5.92; N, 6.33. Found: C, 73.25; H, 5.29; N, 6.19.

1,1-Diphenyl-3-carbomethoxy-8-methyl-1,2,3,4-tetrahydro-β-carboline (**5h**).

This compound was obtained as white crystals (benzene-petroleum ether), mp 231-232°, yield 85%; ir (nujol): ν 3430 (NH), 3380 (NH), 1730 (C = O) cm^{-1}; ^{1}H nmr: δ 2.37 (s, 3H, 8-C*H*$_3$), 2.94 (br s, 1H, N*H*), 3.13 (m, 2H, ABX, C*H*$_2$-CH), 3.72 (m, 1H, ABX, CH$_2$-C*H*), 3.78 (s, 3H, COOC*H*$_3$), 6.97-7.52 (m, 13H arom, 1H, N*H* indole); ms: (m/z) 396 (25), 337 (9), 319 (100).

Anal. Calcd. for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07. Found: C, 78.47; H, 6.21; N, 7.01.

1,1-Diphenyl-3-carbethoxy-1,2,3,4-tetrahydro-β-carboline (**5i**).

This compound was obtained as white crystals (benzene-petroleum ether), mp 206°, yield 75%; ir (nujol): ν 3440 (NH), 3390 (NH), 1730 (C = O) cm^{-1}; ^{1}H nmr: δ 1.34 (t, 3H, CH$_2$-C*H*$_3$), 3.00 (br s, 1H, N*H*), 3.15 (m, 2H, ABX, C*H*$_2$-CH), 3.73 (m, 1H, ABX, CH$_2$-C*H*), 4.25 (q, 2H, C*H*$_2$-CH$_3$), 7.14-7.53 (m, 14H arom, 1H, N*H* indole); ms: (m/z) 396 (21), 323 (23), 319 (100).

Anal. Calcd. for $C_{24}H_{24}N_2O_2$: C, 77.39; H, 6.49; N, 7.52. Found: C, 77.01; H, 6.56; N, 7.41.

1,1-Diphenyl-3-carbomethoxy-4-methyl-1,2,3,4-tetrahydro-β-carboline (**5l**, 3*SR*,4*RS*).

This compound was obtained as white crystals (trichloromethane-petroleum ether), mp 249°, yield 81%; ir (nujol): ν 3395 (NH), 3340 (NH), 1715 (C = O) cm^{-1}; ^{1}H nmr: δ 1.40 (d, 3H, CH-C*H*$_3$), 1.74 (br s, 1H, N*H*), 3.52 (m, 1H, C*H*-CH$_3$), 3.78 (s, 3H, COOC*H*$_3$), 3.82 (d, 1H, C*H*-COOC*H*$_3$, J = 3.96 Hz), 7.10-7.58 (m, 14H arom), 7.61 (br s, 1H, N*H* indole); ms: (m/z) 396 (38), 337 (12), 319 (100).

Anal. Calcd. for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07. Found: C, 78.51; H, 6.16; N, 7.00.

1,1-Diphenyl-3-carbomethoxy-4-methyl-1,2,3,4-tetrahydro-β-carboline (**5l**, 3*RS*,4*RS*).

This compound was obtained as white crystals (benzene-petroleum ether), mp 212-213°, yield 84%; ir (nujol): ν 3445 (NH), 3330 (NH), 1730 (C = O) cm^{-1}; ^{1}H nmr: δ 1.45 (d, 3H, CH-C*H*$_3$), 1.70 (br s, 1H, N*H*), 3.32 (d, 1H, C*H*-COOCH$_3$, J = 9.45 Hz), 3.52 (m, 1H, C*H*-CH$_3$), 3.75 (s, 3H, COOC*H*$_3$), 7.10-7.70 (m, 14H arom), 7.49 (br s, 1H, N*H* indole); ms: (m/z) 396 (38), 337 (23), 319 (100).

Anal. Calcd. for $C_{26}H_{24}N_2O_2$: C, 78.76; H, 6.10; N, 7.07. Found: C, 78.93; H, 6.03; N, 7.24.

1,1-Diphenyl-3-carbomethoxy-4,6-dimethyl-1,2,3,4-tetrahydro-β-carboline (**5m**, 3*SR*,4*RS*).

This compound was obtained as white crystals (benzene-petroleum ether), mp 215-216°, yield 81%; ir (chloroform): ν 3450 (NH), 3330 (NH), 1730 (C=O) cm^{-1}; ^{1}H nmr: δ 1.38 (d, 3H, CH-CH_3), 2.46 (s, 3H, 6-CH$_3$), 2.77 (br s, 1H, N*H*), 3.50 (m, 1H, C*H*-CH$_3$), 3.77 (s, 3H, COOCH_3), 3.80 (d, 1H, C*H*-COOCH$_3$, J = 3.96 Hz), 7.00-7.55 (m, 13H arom, 1H, N*H* indole); ms: (m/z) 410 (28), 351 (8), 33 (100).

Anal. Calcd. for $C_{27}H_{26}N_2O_2$: C, 79.00; H, 6.38; N, 6.82. Found: C, 79.19; H, 6.28; N, 6.66.

1,1-Diphenyl-3-carbomethoxy-4,6-dimethyl-1,2,3,4-tetrahydro-β-carboline (**5m**, 3*RS*,4*RS*).

This compound was obtained as white crystals (benzene-petroleum ether), mp 233-234°, yield 84%; ir (chloroform): ν 3450 (NH), 3325 (NH), 1730 (C=O) cm^{-1}; ^{1}H nmr: δ 1.44 (d, 3H, CH-CH_3), 2.47 (s, 3H, 6-CH$_3$), 2.79 (br s, 1H, N*H*), 3.31 (d, 1H, C*H*-COOCH$_3$, J = 9.41 Hz), 3.51 (m, 1H, C*H*-CH$_3$), 3.75 (s, 3H, COO-CH_3), 6.97-7.47 (m, 13H arom, 1H, N*H* indole); ms: (m/z) 410 (32), 351 (18), 33 (100).

Anal. Calcd. for $C_{27}H_{26}N_2O_2$: C, 79.00; H, 6.38; N, 6.82. Found: C, 79.21; H, 6.25; N, 6.85.

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