β-Carbolines as Agonistic or Antagonistic Benzodiazepine Receptor Ligands. 1. Synthesis of some 5-, 6- and 7-Amino Derivatives of 3-Methoxycarbonyl-β-carboline (β-CCM) and of 3-Ethoxycarbonyl-β-carboline (β-CCE)

Guido Settimj*, Maria Rosaria Del Giudice, Rosella Ferretti and Franco Gatta

Laboratorio di Chimica del Farmaco, Istituto Superiore di Sanità, Viale Regina Elena 299, 00161 Roma, Italy

Received January 22, 1988

Condensation of diethyl formylamino- or diethyl acetylaminomalonate with 4-, 5- or 6-nitrogramine **1** afforded the diethyl formylamino- or the diethyl acetylamino[(nitroindol)-3-ylmethyl]malonates **2**; reduction of the nitro group followed by *N*-formylation or acetylation of the resulting amino compounds **3**, led to the 4-, 5-and 6-acylamino derivatives **4**.

Cyclization of **4** in the presence of polyphosphoric esters gave the 3,3-bis(ethoxycarbonyl)-3,4-dihydro-β-carbolines **5**, which underwent lithium chloride/water catalyzed monodeethoxycarbonylation to the corresponding 5-, 6- and 7-acylamino-3-ethoxycarbonyl-β-carbolines **6**, whose acidic hydrolysis led finally to the 5-, 6- and 7-amino-3-ethoxycarbonyl-β-carbolines **9**. The 6-amino compounds **9b-e** were obtained also by direct nitration of 3-methoxycarbonyl-β-carboline **7a** and of 3-ethoxycarbonyl-β-carboline **7c**, followed by the nitro group reduction of the resulting nitro carbolines **8**.

Preliminary studies of the binding to rabbit brain benzodiazepine receptor sites indicate compounds **9b** and **9c** to inhibit the ^{3}H-diazepam binding at 10^{-8} *M* concentrations.

J. Heterocyclic Chem., **25**, 1391 (1988).

Evidence has been brought out that the pharmacological effects of the benzodiazepines are mediated through central nervous system specific binding sites. Only a small number of compounds chemically different from the benzodiazepines bind to these "benzodiazepine receptors" with a high affinity comparable with that of the pharmacologically and clinically active benzodiazepines [1-4]. Such is the case of the β-carboline moiety, some derivatives of which have been related to the postulated endogenous ligand of the benzodiazepine receptor [5,6]. Quite remarkable benzodiazepine receptor affinities have been reported for some β-carboline-3-carboxylates [7-9], making them important tools to study benzodiazepine receptor function [10-12].

Particularly, the high benzodiazepine receptor affinities (low nanomolar range) of 3-methoxycarbonyl-β-carboline **7a** (β-CCM) [8], of 3-ethoxycarbonyl-β-carboline **7c** (β-CCE) [7b] and of 6,7-dimethoxy-4-ethyl-3-methoxycarbonyl-β-carboline (DMCM) [8] prompted us to prepare some derivatives of **7a** and of **7c** bearing new functions at the phenyl ring of the carboline moiety.

We chose the amino function because of its electron donor properties similar to those of the methoxy groups of DMCM, and because it could be easily substituted by other functional groups. Ar-amino derivatives of either **7a** or **7c** appear hitherto not to have been studied, as only a Schering Patent [13] reports their preparation, but no data are given.

This paper describes the synthesis and physical properties of some 5-, 6- and 7-amino derivatives of **7a** and of **7c**, which were prepared to study their binding to rabbit brain benzodiazepine receptor sites.

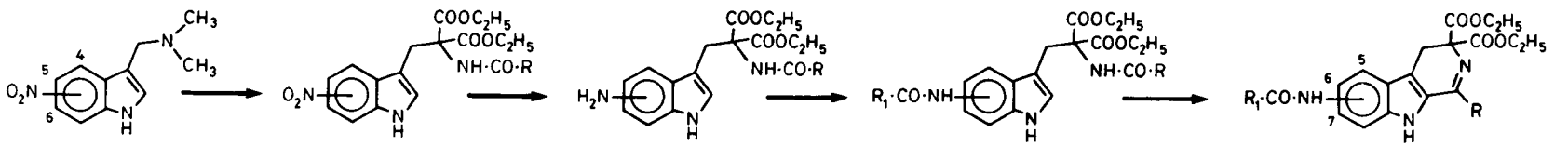
The synthetical pathways to the new amino carbolines are summarized in Scheme 1.

The synthesis of 4- and 6-nitrogramine **1a** and **1c** [14], 5-nitrogramine **1b** [15], diethyl formylamino- and diethyl acetylamino[(5-nitroindol)-3-ylmethyl]malonate **2b** [16] and **2c** [15], diethyl formylamino- and diethyl acetylamino-[(6-nitroindol)-3-ylmethyl]malonate **2d** [16] and **2e** [17], diethyl acetylamino[(5-aminoindol)-3-ylmethyl]malonate **3c** [18] and diethyl acetylamino[(6-aminoindol)-3-ylmethyl]-malonate **3e** [17] have been reported elsewhere. 3-Methoxycarbonyl- and 3-ethoxycarbonyl-β-carboline **7a** and **7c** have been prepared according to the method of Lippke *et al.* [19] with minor modifications [20]; their 1-methyl analogues **7b** [21] and **7d** [22] were prepared in a simlar manner.

According to the synthetic pathway A outlined in Scheme 1, the nitrogramines **1a-c** were allowed to react with diethyl formylamino- or diethyl acetylaminomalonate [23], according to the previously cited literature, to give the nitroindol-3-ylmethylmalonates **2a-e**. Difficulties were met with the reduction of compounds **2** to their related aminoindol-3-ylmethylmalonates **3a-e** (and of the nitro-β-carbolines **8** to the amino-β-carbolines **9** as well) in good agreement with literature reports: nitro arenes are known to undergo incomplete hydrogenation to amino arenes in the presence of palladium-charcoal catalyst [24], while catalytic hydrogenation of nitroindol derivatives on platinum oxide [25,26], nickel Raney, palladium on alumina or lithium aluminium hydride [27] gave poor yields of amino indoles. Satisfactory yields are reported when high quantities of platinum oxide [18] or nickel Raney [28,29] catalyst were employed: yet, a rapid oxidation of the prepared amino indoles was observed with formation of dark tar material.

SCHEME 1

A)



1 a : 4 - nitro
b : 5 - nitro
c : 6 - nitro

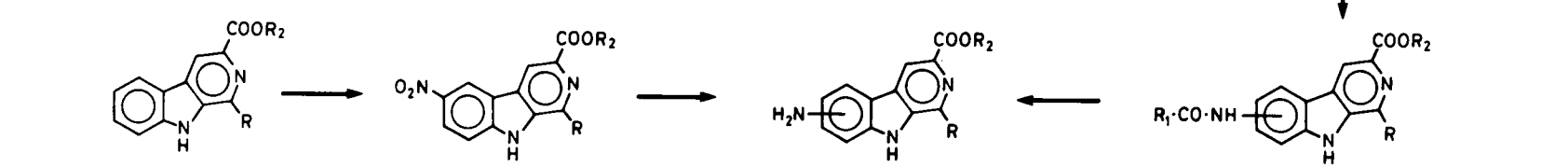
2 a : 4-nitro ; R = H
b : 5-nitro ; R = H
c : „ ; R = CH_3
d : 6-nitro ; R = H
e : „ ; R = CH_3

3 a : 4-amino ; R = H
b : 5-amino ; R = H
c : „ ; R = CH_3
d : 6-amino ; R = H
e : „ ; R = CH_3

4 a : 4-amido ; R = R_1 = H
b : „ ; R = H ; R_1 = CH_3
c : 5-amido ; R = R_1 = H
d : „ ; R = H ; R_1 = CH_3
e : „ ; R = R_1 = CH_3
f : 6-amido ; R = R_1 = H
g : „ ; R = H ; R_1 = CH_3
h : „ ; R = R_1 = CH_3

5 a : 5-amido ; R = R_1 = H
b : „ ; R = H ; R_1 = CH_3
c : 6-amido ; R = H ; R_1 = CH_3
d : „ ; R = R_1 = CH_3
e : 7-amido ; R = R_1 = H
f : „ ; R = H ; R_1 = CH_3
g : „ ; R = R_1 = CH_3

B)



7 a : R = H ; R_2 = CH_3
b : R = R_2 = CH_3
c : R = H ; R_2 = C_2H_5
d : R = CH_3 ; R_2 = C_2H_5

8 a : R = H ; R_2 = CH_3
b : R = R_2 = CH_3
c : R = H ; R_2 = C_2H_5
d : R = CH_3 ; R_2 = C_2H_5

9 a : 5-amino ; R = H ; R_2 = C_2H_5
b : 6-amino ; R = H ; R_2 = CH_3
c : „ ; R = H ; R_2 = C_2H_5
d : „ ; R = R_2 = CH_3
e : „ ; R = CH_3 ; R_2 = C_2H_5
f : 7-amino ; R = H ; R_2 = C_2H_5
g : „ ; R = CH_3 ; R_2 = C_2H_5

6 a : 5-amido ; R = R_1 = H ; R_2 = C_2H_5
b : „ ; R = H ; R_1 = CH_3 ; R_2 = C_2H_5
c : 6-amido ; R = H ; R_1 = R_2 = CH_3
d : „ ; R = H ; R_1 = CH_3 ; R_2 = C_2H_5
e : „ ; R = R_1 = CH_3 ; R_2 = C_2H_5
f : 7-amido ; R = R_1 = H ; R_2 = C_2H_5
g : „ ; R = H ; R_1 = CH_3 ; R_2 = C_2H_5
h : „ ; R = R_1 = CH_3 ; R_2 = C_2H_5

We found sodium borohydride/palladium on charcoal [30] in methanol to be the most effective hydrogenation reagent for our purposes, the limiting factor being represented by the poor solubility of the nitro adducts - particularly the nitro-carbolines **8** - in methanol. The reductions could nevertheless be accomplished in this solvent at room temperature on the finely powdered suspended nitro compounds and gave good to satisfactory yields (see Experimental).

The protection of the amino group of compounds **3** was achieved by *N*-formylation or acetylation: while *N*-acetylation to the intermediates **4** was carried out according to conventional methods, *N*-formylation was advantageously accomplished by refluxing **3** with formic acid in toluene [31]; indeed, formylation with the formic-acetic mixed anhydride [32] led also to a partial *N*-acetylation.

The Bischler-Napieralski cyclization of **4** with polyphosphoric esters [33] in chloroform gave the 3,4-dihydro-β-carbolines **5**; the diethyl formylaminomalonates **4a,d,f,g**, gave higher yields than their diethyl acetylamino analogues **4e,h** (see Experimental). Monodeethoxycarbonylation of **5** with lithium chloride/water in dimethylsulfoxide [34] led directly to the 5-, 6- or 7-acylamino-β-carbolines **6**, the acidic hydrolysis of which afforded the corresponding 5-, 6- or 7-amino-β-carbolines **9**.

The cyclization and aromatization steps from intermediates **4** to the β-carbolines **6** were also followed by uv spectra of compounds **4**, **5** and **6** in acetonitrile solutions (see Experimental). The appearance of a band at 316-366 nm and the absence of the indole 282 nm band in the 3,4-dihydro-β-carbolines **5** is in good agreement with literature data [21]. In the 5-substituted indole derivatives **4c**, **4d** and **4e**, however, the 282 nm band was not observed.

The 6-amino-3-ethoxycarbonyl-β-carbolines **9c,e** could also be prepared, like their 3-methoxycarbonyl analogues **9b,d**, according to pathway B of Scheme 1. Nitration of the 3-methoxycarbonyl- or of the 3-ethoxycarbonyl-β-carbolines **7a-d** gave the 6-nitro derivatives **8a-d** (in agreement with literature reports on nitration of 6-unsubstituted β-carbolines [28,29]) in good yields, followed by reduction of **8** with sodium borohydride/palladium on charcoal under the aforementioned conditions.

Preliminary binding studies on membrane preparations from rabbit brain cortex indicate compounds **9b** and **9c** to bind with high affinity at the benzodiazepine receptors. In the presence of γ-aminobutyric acid (GABA) a slight decrease of their affinity is noticed. The ratio between the 50% inhibition concentration (IC_{50}) value found in the absence over the value found in the presence of GABA suggests that these two compounds can be included within the group of the so called inverse benzodiazepine agonists with a weak efficacy.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ^{1}H nmr spectra were determined on a T-60 Varian spectrometer in dimethyl sulfoxide-d_6 solutions, unless otherwise specified, with tetramethylsilane as internal standard. Chemical shifts are given in δ units. Abbreviations are as follows: at = apparent triplet; d = doublet; dd = doublet of doublets; dm = doublet of multiplets; m = multiplet; q = quadruplet; t = triplet; s = singlet. The uv spectra were recorded on a Perkin-Elmer 554 spectrometer in acetonitrile solutions; tlc (Carlo Erba plates) was employed under two main conditions: alumina plates/ethyl acetate for compounds **2**, **3** and **4**; silicagel/ethyl acetate with 3% methanol for compounds **5**, **6** and **9** (as the bases). The drying agent used was sodium sulfate.

Diethyl Formylamino[(4-nitroindol)-3-ylmethyl]malonate **2a**.

To a stirred solution of sodium (1.75 g, 0.076 g-atom) in absolute ethanol (80 ml) diethyl formylaminomalonate (15.4 g, 0.076 mole) was first added followed by 4-nitrogramine (18.0 g, 0.076 mole). The mixture was first heated at 40° and, while stirring, dimethylsulfate (13.9 g, 0.11 mole) was added dropwise at such a rate as to maintain the internal temperature at about 45°, then kept overnight at room temperature. The mixture was then poured onto crushed ice, and the resulting yellow precipitate filtered, rinsed with ice water and crystallized from ethanol, yield 10.1 g (35%), mp 215-218°; ^{1}H nmr: δ 11.80 (broad, 1H, indole N*H*), 8.35 (broad, 1H, N*H*-CHO), 7.86 (s, 1H, C*H*O), 7.70 (broad, 2H, H_5+H_7), 7.36 (broad, 1H, H_3), 7.16 (at, 1H, H_6), 4.00 (q, 4H, CH_2-CH$_3$), 3.73 (s, 2H, CH_2), 1.05 (t, 6H, CH$_2$-CH_3).

Anal. Calcd. for $C_{17}H_{19}N_3O_7$: C, 54.11; H, 5.08; N, 11.14. Found: C, 54.35; H, 5.16; N, 11.08.

Diethyl Formylamino[(5-nitroindol)-3-ylmethyl]malonate **2b**.

This compound, prepared according to literature [16], had mp 191-194° (ethyl acetate), lit, mp 183-185° (ethanol); ^{1}H nmr: δ 11.67 (broad, 1H, indole N*H*), 8.55 (broad, 1H, N*H*-CHO), 8.30 (d, 1H, H_4), 8.03 (s, 1H, C*H*O), 7.95 (dd, 1H, H_6), 7.48 (d, 1H, H_7), 7.30 (broad, 1H, H_2), 4.16 (q, 4H, CH_2-CH$_3$), 3.70 (s, 2H, CH_2), 1.16 (t, 6H, CH$_2$-CH_3).

Diethyl Acetylamino[(5-nitroindol)-3-ylmethyl]malonate **2c**.

Compound **2c**, prepared as described [15], had mp 197-203° (ethyl acetate), lit mp 196-198° (raw material); ^{1}H nmr: δ 11.58 (broad, 1H, indole N*H*), 8.22 (d, 1H, H_4), 8.05 (s, 1H, N*H*-CO), 7.93 (dd, 1H, H_6), 7.47 (d, 1H, H_7), 7.27 (broad, 1H, H_2), 4.13 (q, 4H, CH_2-CH$_3$), 3.67 (s, 2H, CH_2), 1.92 (s, 3H, COCH_3), 1.15 (t, 6H, CH$_2$-CH_3).

Diethyl Formylamino[(6-nitroindol)-3-ylmethyl]malonate **2d**.

This compound, prepared as described [16], had mp 204-206° (ethanol), lit mp 196-198° (ethanol); ^{1}H nmr: δ 11.67 (broad, 1H, indole N*H*), 8.53 (broad, 1H, N*H*-CHO), 8.27 (d, 1H, H_7), 8.00 (d, 1H, C*H*O), 7.87 (dd, 1H, H_5), 7.47 (broad, 1H, H_2), 7.43 (d, 1H, H_4), 4.13 (q, 4H, CH_2-CH$_3$), 3.67 (s, 2H, CH_2), 1.13 (t, 6H, CH$_2$-CH_3).

Diethyl Acetylamino[(6-nitroindol)-3-ylmethyl]malonate **2e**.

This compound, prepared according to the literature [17], had mp 224-226° (ethanol); lit mp 225-226° (chloroform or acetonitrile); ^{1}H nmr: δ 11.67 (broad, 1H, indole N*H*), 8.30 (d, 1H, H_7), 8.05 (s, 1H, N*H*-CO), 7.88 (dd, 1H, H_5), 7.42 (d, 1H, H_4 and d, 1H, H_2), 4.12 (q, 4H, CH_2-CH$_3$), 3.65 (s, 2H, CH_2), 1.92 (s, 3H, CO-CH_3), 1.13 (t, 6H, CH$_2$-CH_3).

Diethyl Formylamino[(4-aminoindol)-3-ylmethyl]malonate **3a**.

To a stirred solution (or suspension) of **2a** (6.0 g, 0.016 mole) in methanol (600 ml) kept at 15° under nitrogen atmosphere, sodium borohydride (1 g, 0.026 mole) was added followed by a small amount of 10% palladium on charcoal catalyst suspended in methanol. After hydrogen evolution had ceased, two more portions of sodium borohydride and of the catalyst were added, and the resulting solution turned colourless. The solution was filtered under nitrogen and evaporated under reduced pressure at no more than 30°, the residue obtained was

suspended in water (200 ml), thoroughly extracted with ethyl acetate (4 x 200 ml; the product is slightly soluble), the solvent evaporated, and the resulting crude product crystallized from methanol, yield 4.1 g (74%), mp 197-199°; ^{1}H nmr: δ 10.60 (broad, 1H, indole N*H*), 8.72 (broad, 1H, N*H*-CHO), 7.98 (d, 1H, C*H*O), 6.67 (m, 2H, H_6+H_7), 6.63 (d, 1H, H_2), 6.17 (dd, 1H, H_5), 4.60 (broad, 2H, NH_2), 4.13 (q, 4H, CH_2-CH$_3$), 3.70 (s, 2H, CH_2), 1.12 (t, 6H, CH$_2$-CH_3).

Anal. Calcd. for $C_{17}H_{21}N_3O_5$: C, 58.78; H, 6.09; N, 12.10. Found: C, 59.00; H, 6.20; N, 12.03.

Diethyl Formylamino[(5-aminoindol)-3-ylmethyl]malonate **3b**.

This compound was obtained by reduction of **2b** under the same conditions described for **3a** in 65% yield, mp 148-150° (1-butanol); ^{1}H nmr: δ 10.37 (broad, 1H, indole N*H*), 8.45 (broad, 1H, N*H*-CHO), 8.00 (d, 1H, C*H*O), 6.97 (d, 1H, H_7), 6.80 (d, 1H, H_4), 6.50 (s, 1H, H_2), 6.43 (dd, 1H, H_6), 4.37 (broad, 2H, NH_2), 4.13 (q, 4H, CH_2-CH$_3$), 3.52 (s, 2H, CH_2), 1.17 (t, 6H, CH$_2$-CH_3).

Anal. Calcd. for $C_{17}H_{21}N_3O_5$: C, 58.78; H, 6.09; N, 12.10. Found: C, 58.55; H, 6.25; N, 12.11.

Diethyl Acetylamino[(5-aminoindol)-3-ylmethyl]malonate **3c**.

This compound prepared by reduction of **2c** had mp 209-211° (ethyl acetate); lit [18] mp 198-199° (ethanol); ^{1}H nmr: δ 10.30 (broad, 1H, indole N*H*), 7.87 (s, 1H, N*H*-CO-CH$_3$), 7.00 (d, 1H, H_7), 6.95 (d, 1H, H_4), 6.52 (s, 1H, H_2), 6.45 (dd, 1H, H_6), 4.30 (broad, 2H, NH_2), 4.08 (q, 4H, CH_2-CH$_3$), 3.48 (s, 2H, CH_2), 1.93 (s, 3H, CO-CH_3), 1.13 (t, 6H, CH$_2$-CH_3).

Diethyl Formylamino[(6-aminoindol)-3-ylmethyl]malonate **3d**.

This compound was obtained in 72% yield by reduction of **2d** under the same aforementioned conditions, mp 136-138° (ethyl acetate); ^{1}H nmr: δ 10.30 (broad, 1H, indole N*H*), 8.43 (broad, 1H, N*H*-CHO), 7.98 (broad, 1H, C*H*O), 6.82 (d, 1H, H_4), 6.65 (broad, 1H, H_7), 6.47 (broad, 1H, H_2), 6.35 (dm, 1H, H_5), 4.60 (broad, 2H, NH_2), 4.13 (q, 4H, CH_2-CH$_3$), 3.52 (s, 2H, CH_2), 1.17 (t, 6H, CH$_2$-CH_3).

Anal. Calcd. for $C_{17}H_{21}N_3O_5$: C, 58.78; H, 6.09; N, 12.10. Found: C, 58.98; H, 6.02; N, 12.05.

Diethyl Acetylamino[(6-aminoindol)-3-ylmethyl]malonate **3e**.

Compound **3e** prepared by reduction of **2e** had mp 174-176° (ethyl acetate- *n*-hexane), lit [17] mp 176-177° (acetonitrile); ^{1}H nmr: δ 10.22 (broad, 1H, indole N*H*), 7.90 (s, 1H, N*H*-CO-CH$_3$), 6.98 (d, 1H, H_4), 6.65 (d, 1H, H_7), 6.52 (d, 1H, H_2), 6.37 (dd, 1H, H_5), 4.60 (s, 2H, NH_2), 4.15 (q, 4H, CH_2-CH$_3$), 3.50 (s, 2H, CH_2), 1.88 (s, 3H, CO-CH_3), 1.13 (t, 6H, CH$_2$-CH_3).

Diethyl Formylamino[(4-formylaminoindol)-3-ylmethyl]malonate **4a**.

A mixture of **3a** (2.7 g, 7.8 mmoles) and 98% formic acid (2.1 g, 45.6 mmoles) in anhydrous toluene (150 ml) was refluxed for 1 hour, and the water formed was collected in a Dean-Stark trap. More toluene (50 ml) and formic acid (2.0 g) were then added and the mixture allowed to reflux for another hour. After cooling the separated grey crystals were collected and crystallized from ethyl acetate to yield 1.8 g (62%), mp 181-182°; uv: λ max 220 and 282 nm; ^{1}H nmr: δ 10.67 (broad, 1H, indole N*H*), 9.37 (broad, 1H, aromatic N*H*-CHO), 8.53 (broad, 1H, malonic N*H*-CHO), 8.22 (broad, 1H, aromatic NH-C*H*O), 7.92 (broad, 1H, malonic NH-C*H*O), 7.03 (m, 4H, $H_2+H_5+H_6+H_7$), 4.10 (q, 4H, CH_2-CH$_3$), 3.78 (s, 2H, CH_2), 1.08 (t, 6H, CH$_2$-CH_3).

Anal. Calcd. for $C_{18}H_{21}N_3O_6$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.39; H, 5.67; N, 11.06.

Diethyl Formylamino[(4-acetylaminoindol)-3-ylmethyl]malonate **4b**.

This compound was obtained in 56% yield by allowing **3a** to react with acetic anhydride in pyridine at room temperature according to the procedure described for **4d** (see below), mp 177-179° (ethyl acetate); ^{1}H nmr: δ 10.87 (broad, 1H, indole N*H*), 9.13 (broad, 1H, N*H*-COCH$_3$), 8.50 (broad, 1H, N*H*-CHO), 7.88 (s, 1H, NH-C*H*O), 6.92 (m, 4H, $H_2+H_5+H_6+H_7$), 4.08 (q, 4H, CH_2-CH$_3$), 3.70 (s, 2H, CH_2), 2.02 (s, 3H, CO-CH_3), 1.03 (t, 6H, CH$_2$-CH_3).

Anal. Calcd. for $C_{19}H_{23}N_3O_6$: C, 58.60; H, 5.95; N, 10.79. Found: C, 58.78; H, 5.95; N, 10.56.

Diethyl Formylamino[(5-formylaminoindol)-3-ylmethyl]malonate **4c**.

This compound was obtained from **3b**, following the procedure reported for **4a**, in 60% yield, mp 221-224° (methanol); ^{1}H nmr: δ 10.80 (broad, 1H, indole N*H*), 9.80 (broad, 1H, aromatic N*H*-CHO), 8.43 (broad, 1H, malonic N*H*-CHO), 8.17 (d, 1H, aromatic NH-C*H*O), 8.02 (d, 1H, malonic NH-C*H*O), 7.68 (broad, 1H, H_4), 7.18 (s, 1H, H_2), 7.00 (m, 2H, H_6+H_7), 4.13 (q, 4H, CH_2-CH$_3$), 3.57 (s, 2H, CH_2), 1.12 (t, 6H, CH$_2$-CH_3).

Anal. Calcd. for $C_{18}H_{21}N_3O_6$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.61; H, 5.79; N, 11.28.

Diethyl Formylamino[(5-acetylaminoindol)-3-ylmethyl]malonate **4d**.

To a solution of **3b** (1.0 g, 28.8 mmoles) in anhydrous pyridine (3 ml) acetic anhydride (3 ml) was added and the mixture allowed to react at room temperature for 2 hours. The solution was then diluted with ethyl ether (30 ml), kept overnight at room temperature, and the obtained solid was crystallized from ethyl acetate-ethyl ether mixture to give 0.6 g (54%), mp 148-150°; uv: λ max 195 and 236 nm; ^{1}H nmr: δ 10.80 (broad, 1H, indole N*H*), 9.62 (broad, 1H, N*H*-COCH$_3$), 8.48 (broad, 1H, N*H*-CHO), 8.03 (broad, 1H, NH-C*H*O), 7.65 (broad, 1H, H_4), 7.18 (broad, 1H, H_2), 7.08 (m, 2H, H_6+H_7), 4.13 (q, 4H, CH_2-CH$_3$), 3.58 (s, 2H, CH_2), 2.02 (s, 3H, CO-CH_3), 1.15 (t, 6H, CH$_2$-CH_3).

Anal. Calcd. for $C_{19}H_{23}N_3O_6$: C, 58.60; H, 5.95; N, 10.79. Found: C, 58.66; H, 5.92; N, 10.86.

Diethyl Acetylamino[(5-acetylaminoindol)-3-ylmethyl]malonate **4e**.

This compound was obtained in the same manner as **4d** by acetylation of **3c** at room temperature for 1 hour, mp 205-209° (ethyl acetate); uv: λ max 195 and 238 nm; ^{1}H nmr: δ 10.72 (broad, 1H, indole N*H*), 9.60 (broad, 1H, aromatic N*H*-COCH$_3$), 7.92 (s, 1H, malonic N*H*-COCH$_3$), 7.63 (broad, 1H, H_4), 7.17 (s, 1H, H_2), 7.03 (m, 2H, H_6+H_7), 4.08 (q, 4H, CH_2-CH$_3$), 3.53 (s, 2H, CH_2), 1.83 and 1.77 (two s, 6H, two CO-CH_3), 1.12 (t, 6H, CH$_2$-CH_3).

Anal. Calcd. for $C_{20}H_{25}N_3O_6$: C, 59.54; H, 6.25; N, 10.42. Found: C, 59.72; H, 6.46; N, 10.26.

Diethyl Formylamino[(6-formylaminoindol)-3-ylmethyl]malonate **4f**.

This compound resulted by formylation of **3d** in the same conditions described for **4a**, yield 66%, mp 182-185° (ethanol); ^{1}H nmr: δ 10.82 (broad, 1H, indole N*H*), 9.95 (broad, 1H, aromatic N*H*-CHO), 8.48 (broad, 1H, malonic N*H*-CHO), 8.20 (d, 1H, aromatic NH-C*H*O), 8.00 (d, 1H, malonic NH-C*H*O), 7.88 (broad, 1H, H_7), 7.25 (d, 1H, H_4), 6.97 (m, 2H, H_2+H_5), 4.13 (q, 4H, CH_2-CH$_3$), 3.60 (s, 2H, CH_2), 1.13 (t, 6H, CH$_2$-CH_3).

Anal. Calcd. for $C_{18}H_{21}N_3O_6$: C, 57.59; H, 5.64; N, 11.20. Found: C, 57.72; H, 5.60; N, 10.94.

Diethyl Formylamino[(6-acetylaminoindol)-3-ylmethyl]malonate **4g**.

Compound **3d** was allowed to react for 1 hour at room temperature with acetic anhydride in pyridine to give a 77% yield of **4g**, mp 214-216° (ethanol); uv: λ max 238 and 282 nm; ^{1}H nmr: δ 10.73 (broad, 1H, indole N*H*), 9.67 (broad, 1H, N*H*-COCH$_3$), 8.43 (broad, 1H, N*H*-CHO), 7.97 (d, 1H, NH-C*H*O), 7.87 (broad, 1H, H_7), 7.18 (d, 1H, H_4), 6.97 (m, 2H, H_2+H_5), 4.12 (q, 4H, CH_2-CH$_3$), 3.58 (s, 2H, CH_2), 2.03 (s, 3H, COCH_3), 1.15 (t, 6H, CH$_2$-CH_3).

Anal. Calcd. for $C_{19}H_{23}N_3O_6$: C, 58.60; H, 5.95; N, 10.79. Found: C, 58.85; H, 5.96; N, 10.68.

Diethyl Acetylamino[(6-acetylaminoindol)-3-ylmethyl]malonate **4h**.

This compound was obtained in 75% yield by acetylation of **3e** at room temperature for 1 hour, mp 223-225° (ethanol-ethyl ether); ^{1}H nmr: δ 10.75 (broad, 1H, indole N*H*), 9.70 (s, 1H, aromatic N*H*-COCH$_3$), 8.13 (s, 1H, H_7), 8.10 (s, 1H, malonic N*H*-COCH$_3$), 7.20 (d, 1H, H_4), 7.00 (dd, 1H, H_5), 6.90 (d, 1H, H_2), 4.17 (q, 4H, CH_2-CH$_3$), 3.57 (s, 2H, CH_2), 2.02 and 1.90 (two s, 6H, two COCH_3), 1.12 (t, 6H, CH$_2$-CH_3).

Anal. Calcd. for $C_{20}H_{25}N_3O_6$: C, 59.54; H, 6.25; N, 10.42. Found: C, 59.48; H, 6.30; N, 10.22.

3,3-bis(Ethoxycarbonyl)-5-formylamino-3,4-dihydro-β-carboline **5a**.

A mixture of **4a** (1.6 g, 4.3 mmoles) and polyphosphoric esters (9.6 g) [33] in absolute chloroform (50 ml) was kept at room temperature in the dark for 48 hours in which time the adduct gradually dissolved. The solvent was then evaporated, ice water was added to the residue, the suspension stirred for 1 hour, made carefully alkaline with concentrated ammonia, then extracted with ethyl acetate (3 x 100 ml). The combined organic layers were washed with water until neutral to litmus, dried and evaporated. The resulting residue was crystallized from methanol to give 1.5 g of **5a** (98%), mp 220-222° (from methanol); uv: λ max 242 and 316 nm; ^{1}H nmr: δ 11.20 (broad, 1H, indole N*H*), 9.67 (broad, 1H, N*H*-CHO), 8.50 (s, 1H, H_1), 8.37 (m, 1H, NH-C*H*O), 7.23 (m, 3H, $H_6+H_7+H_8$), 4.13 (q, 4H, CH_2-CH$_3$), 3.63 (broad, 2H, C$_4$-H_2), 1.13 (t, 6H, CH$_2$-CH_3).

Anal. Calcd. for $C_{18}H_{19}N_3O_5$: C, 60.49; H, 5.36; N, 11.76. Found: C, 60.23; H, 5.34; N, 11.72.

5-Acetylamino-3,3-bis(ethoxycarbonyl)-3,4-dihydro-β-carboline **5b**.

This compound was obtained by polyphosphoric esters catalyzed cyclization of **4b** under the same aforementioned conditions, yield 98% of crude, unstable material with an ill-defined mp, employed as such for the preparation of **6b** (see below); ^{1}H nmr (deuteriochloroform): δ 10.06 (broad, 1H, indole N*H*), 8.13 (s, 1H, H_1), 7.83 (broad, 1H, N*H*-COCH$_3$), 7.00 (broad, 3H, $H_6+H_7+H_8$), 4.15 (q, 4H, CH_2-CH$_3$), 3.62 (broad, 2H, C$_4$-H_2), 2.20 (s, 3H, CO-CH_3), 1.15 (t, 6H, CH$_2$-CH_3).

6-Acetylamino-3,3-bis(ethoxycarbonyl)-3,4-dihydro-β-carboline **5c**.

This compound was likewise obtained from **4d**, yield 63%, mp 133-135° (ethyl acetate); uv: λ max 220, 244 and 326 nm; ^{1}H nmr: δ 11.28 (broad, 1H, indole N*H*), 9.68 (broad, 1H, N*H*-COCH$_3$), 8.43 (s, 1H, H_1), 7.85 (broad, 1H, H_5), 7.26 (m, 2H, H_7+H_8), 4.10 (q, 4H, CH_2-CH$_3$), 3.37 (broad, 2H, C$_4$-H_2), 2.00 (s, 3H, COCH_3), 1.10 (t, 6H, CH$_2$-CH_3).

Anal. Calcd. for $C_{19}H_{21}N_3O_5$: C, 61.44; H, 5.70; N, 11.32. Found: C, 61.32; H, 5.63; N, 11.17.

6-Acetylamino-3,3-bis(ethoxycarbonyl)-1-methyl-3,4-dihydro-β-carboline **5d**.

This compound was obtained by allowing **4e** to cyclize in refluxing chloroform for 11 hours in the presence of polyphosphoric esters and working up the reaction mixture as described for **5g** (see below), yield 28% of crude, unstable material with an ill-defined mp employed as such for the preparation of **6e** (see below); ^{1}H nmr: δ 11.30 (broad, 1H, indole N*H*), 9.67 (broad, 1H, N*H*-COCH$_3$), 7.83 (broad, 1H, H_5), 7.30 (m, 2H, H_7+H_8), 4.10 (q, 4H, CH_2-CH$_3$), 3.30 (broad, 2H, C$_4$-H_2), 2.37 (s, 3H, C$_1$-CH_3), 2.00 (s, 3H, COCH_3), 1.12 (t, 6H, CH$_2$-CH_3).

3,3-bis(Ethoxycarbonyl)-7-formylamino-3,4-dihydro-β-carboline **5e**.

This compound was obtained in the same manner described for **5a** from adduct **4f**: yield 40%, mp 224-226° (methanol); ^{1}H nmr: δ 11.30 (broad, 1H, indole N*H*), 10.13 (broad, 1H, N*H*CHO), 8.48 (s, 1H, H_1), 8.27 (d, 1H, C*H*O), 7.98 (m, 1H, H_8), 7.53 (d, 1H, H_5), 7.07 (dm, 1H, H_6), 4.13 (q, 4H, CH_2-CH$_3$), 3.40 (s, 2H, C$_4$-H_2), 1.12 (t, 6H, CH$_2$-CH_3).

Anal. Calcd. for $C_{18}H_{19}N_3O_5$: C, 60.49; H, 5.36; N, 11.76. Found: C, 60.38; H, 5.22; N, 11.90.

7-Acetylamino-3,3-bis(ethoxycarbonyl)-3,4-dihydro-β-carboline **5f**.

This compound was likewise obtained from **4g**, yield 50%, mp 199-200° (ethyl acetate); uv: λ max 244 and 336 nm; ^{1}H nmr: δ 11.25 (broad, 1H, indole N*H*), 10.20 (broad, 1H, N*H*-COCH$_3$), 8.47 (s, 1H, H_1), 8.00 (m, 1H, H_6), 7.50 (d, 1H, H_5), 7.07 (dd, 1H, H_6), 4.13 (q, 4H, CH_2-CH$_3$), 3.42 (s, 2H, C$_4$-H_2), 2.07 (s, 3H, COCH_3), 1.13 (t, 6H, CH$_2$-CH_3).

Anal. Calcd. for $C_{19}H_{21}N_3O_5\cdot H_2O$: C, 58.60; H, 5.95; N, 10.79. Found: C, 58.94; H, 5.62; N, 11.06.

7-Acetylamino-3,3-bis(ethoxycarbonyl)-1-methyl-3,4-dihydro-β-carboline **5g**.

A mixture of **4h** (2.0 g, 5.0 mmoles) and of polyphosphoric esters (12.0 g) in absolute chloroform (50.0 ml) was heated for 4 hours in an oil bath kept at 80°. After cooling, the solvent was evaporated at reduced pressure, and the obtained viscous residue worked up as described for **5a**. The resulting new residue from the ethyl acetate extraction layer was suspended in 0.1 *N* hydrogen chloride (150 ml: almost all dissolved); the acidic phase was first thoroughly shaken with ethyl acetate (3 x 100 ml), then made alkaline with concentrated ammonia, extracted with ethyl acetate (2 x 100 ml), and the organic solvent evaporated; 1.3 g of crude **5g** was thus obtained, which, after crystallization from methanol (5.0 ml), weighed 0.7 g (35%), mp 240-243°; ^{1}H nmr: δ 11.30 (broad, 1H, indole N*H*), 9.87 (broad, 1H, N*H*-COCH$_3$), 8.03 (d, 1H, H_8), 7.52 (d, 1H, H_5), 7.08 (dd, 1H, H_6), 4.13 (q, 4H, CH_2-CH$_3$), 3.33 (broad, 2H, C$_4$-H_2), 2.33 (s, 3H, C$_1$-CH_3), 2.03 (s, 3H, COCH_3), 1.10 (t, 6H, CH$_2$-CH_3).

Anal. Calcd. for $C_{20}H_{23}N_3O_5\cdot\frac{1}{2}H_2O$: C, 60.90; H, 6.13; N, 10.65. Found: C, 60.61; H, 6.31; N, 10.36.

3-Ethoxycarbonyl-5-formylamino-β-carboline **6a**.

A mixture of **5a** (600 mg, 1.68 mmoles), water (60 μl, 3.3 mmoles), lithium chloride (72 mg, 1.7 mmoles) in dimethyl sulfoxide (10 ml) was heated for 7-9 hours in an oil bath kept at 170°. After cooling, water was added (100 ml), the mixture thoroughly extracted with ethyl acetate (3 x 100 ml), the organic layers washed with water and dried. After removal of the ethyl acetate, the obtained residue was first rinsed with warm methanol, then crystallized from dimethylformamide-ethyl ether, yield 143 mg (30%), mp 292-294°; uv: λ max 212, 222 (shoulder) and 266 nm; ^{1}H nmr: δ 12.11 (broad, 1H, indole N*H*), 10.33 (broad, 1H, N*H*-CHO), 8.93 (broad, 2H, H_1+H_4), 8.55 (broad, 1H, C*H*O), 7.53 (m, 3H, $H_6+H_7+H_8$), 4.42 (q, 2H, CH_2-CH$_3$), 1.38 (t, 3H, CH$_2$-CH_3).

Anal. Calcd. for $C_{15}H_{13}N_3O_3\cdot\frac{1}{2}H_2O$: C, 61.63; H, 4.83; N, 14.38. Found: C, 61.98; H, 4.81; N, 14.60.

5-Acetylamino-3-ethoxycarbonyl-β-carboline **6b**.

This compound was prepared from **5b** under the same conditions reported for **6a**, yield 30%, mp 310-312° (dimethylformamide); ^{1}H nmr: δ 13.05 (broad, 1H, indole N*H*), 10.47 (broad, 1H, N*H*-COCH$_3$), 9.13 (s, 1H, H_1), 8.76 (s, 1H, H_4), 7.63 (m, 3H, $H_6+H_7+H_8$), 4.55 (q, 2H, CH_2-CH$_3$), 2.30 (s, 3H, COCH_3), 1.48 (t, 3H, CH$_2$-CH_3).

Anal. Calcd. for $C_{16}H_{15}N_3O_3$: C, 64.63; H, 5.09; N, 14.14. Found: C, 64.65; H, 5.20; N, 14.35.

9-Acetyl-6-acetylamino-3-methoxycarbonyl-β-carboline.

Acetylation of **9b** (see below) in an acetic anhydride-pyridine mixture for 2 hours at room temperature gave, instead of **6c**, its N_9-acetyl derivative in 40% yield, mp 302-305° (dimethylformamide-ethyl acetate); ^{1}H nmr: δ 10.06 (broad, 1H, N*H*-COCH$_3$), 9.33 (s, 1H, H_1), 8.35 (d, 1H, H_5), 8.32 (s, 1H, H_4), 7.93 (d, 1H, H_8), 7.53 (dd, 1H, H_7), 3.92 (s, 3H, COOCH_3), 2.82 (s, 3H, N$_9$-COCH_3), 1.93 (s, 3H, NH-COCH_3).

Anal. Calcd. for $C_{17}H_{15}N_3O_4$: C, 62.76; H, 4.65; N, 12.92. Found: C, 62.59; H, 4.85; N, 12.79.

6-Acetylamino-3-ethoxycarbonyl-β-carboline **6d**.

This compound was prepared either by monodeethoxycarbonylation of the 3,4-dihydro-β-carboline **5c**, or by acetylation of 6-amino-3-ethoxycarbonyl-β-carboline **9c** (see below).

A) Compound **5c** was reacted with lithium chloride and water in dimethyl sulfoxide at 170° for 8 hours following the procedure described for **6a**, yield 42%, mp 305-308° (dimethylformamide-ethyl acetate).

B) Compound **9c** was allowed to react at room temperature for 15 hours with acetic anhydride in pyridine and the resulting mixture worked up as described for the following compound **6e**, yield 50%, mp 306-308° (dimethylformamide-ethyl acetate); uv: λ max 240 and 276 nm; ^{1}H nmr: δ 11.85 (broad, 1H, indole N*H*), 9.93 (broad, 1H, N*H*-COCH$_3$), 8.88 (s, 1H, H_1), 8.70 (s, 1H, H_4), 8.53 (broad, 1H, H_5), 7.60 (broad, 2H, H_7+H_8), 4.37 (q, 2H, CH_2-CH$_3$), 2.08 (s, 3H, COCH_3), 1.37 (t, 3H, CH$_2$-CH_3).

Anal. Calcd. for $C_{16}H_{15}N_3O_3$: C, 64.63; H, 5.09; N, 14.14. Found: C, 64.68; H, 5.11; N, 13.94.

6-Acetylamino-3-ethoxycarbonyl-1-methyl-β-carboline **6e**.

This compound was prepared in the same manner as **6a**, from **5d** (1.35 g, 3.5 mmoles), water (0.13 ml, 7.0 mmoles) and lithium chloride (0.15 g, 3.5 mmoles) in dimethylsulfoxide (10 ml), yield 0.33 g (30%), mp

309-311° (dimethylformamide-ethyl ether). The same compound was also obtained from a mixture of **9e** (1.4 g) and acetic anhydride (1.0 ml) in anhydrous pyridine (7.0 ml) kept overnight at room temperature, ice water was then added, and the separated solid collected, rinsed with water and crystallized from dimethylformamide-ethyl ether, yield 0.9 g (56%), mp 309-311°. ^{1}H nmr: δ 11.83 (broad, 1H, indole N*H*), 9.97 (broad, 1H, N*H*-COCH$_3$), 8.57 (s, 1H, H_4), 8.53 (broad, 1H, H_5), 7.60 (sharp m, 2H, H_7+H_8), 4.40 (q, 2H, C*H*$_2$-CH$_3$), 2.82 (s, 3H, C$_1$-C*H*$_3$), 2.15 (s, 3H, COC*H*$_3$), 1.40 (t, 3H, CH$_2$-C*H*$_3$).

Anal. Calcd. for $C_{17}H_{17}N_3O_3\cdot H_2O$: C, 61.99; H, 5.82; N, 12.76. Found: C, 62.15; H, 5.48; N, 12.87.

3-Ethoxycarbonyl-7-formylamino-β-carboline **6f**.

This compound was prepared from **5e**, following the procedure described for **6a**, yield 30%, mp 298-300° (methanol); ^{1}H nmr: δ 11.88 (broad, 1H, indole N*H*), 10.42 (broad, 1H, N*H*-CHO), 8.87 (s, 1H, H_1), 8.87 (broad, 1H, C*H*O), 8.78 (s, 1H, H_4), 8.38 (broad, 1H, H_8), 8.33 (d, 1H, H_5), 7.33 (dm, 1H, H_6), 4.40 (q, 2H, C*H*$_2$-CH$_3$), 1.38 (t, 3H, CH$_2$-C*H*$_3$).

Anal. Calcd. for $C_{15}H_{13}N_3O_3$: C, 63.59; H, 4.63; N, 14.83. Found: C, 63.61; H, 4.63; N, 14.63.

7-Acetylamino-3-ethoxycarbonyl-β-carboline **6g**.

This compound was likewise prepared from **5f**, yield 34%, mp 276-278° (ethyl acetate); uv: λ max 225, 258 and 278 nm; ^{1}H nmr: δ 11.82 (broad, 1H, indole N*H*), 10.10 (broad, 1H, N*H*-COCH$_3$), 8.82 (s, 1H, H_1), 8.72 (s, 1H, H_4), 8.18 (d, 1H, H_5), 8.18 (broad, 1H, H_8), 7.27 (dm, 1H, H_6), 4.35 (q, 2H, C*H*$_2$-CH$_3$), 2.10 (s, 3H, COC*H*$_3$), 1.35 (t, 3H, CH$_2$-C*H*$_3$).

Anal. Calcd. for $C_{16}H_{15}N_3O_3\cdot\frac{1}{2}H_2O$: C, 62.73; H, 5.27; N, 13.72. Found: C, 62.62; H, 4.98; N, 13.55.

7-Acetylamino-3-ethoxycarbonyl-1-methyl-β-carboline **6h**.

Compound **6h** was analogously prepared from **5g**, yield 31%, mp 302-305° (ethyl acetate); ^{1}H nmr: δ 11.80 (broad, 1H, indole N*H*), 10.12 (broad, 1H, N*H*-COCH$_3$), 8.60 (s, 1H, H_4), 8.23 (broad, 1H, H_8), 8.17 (d, 1H, H_5), 7.27 (dm, 1H, H_6), 4.37 (q, 2H, C*H*$_2$-CH$_3$), 2.77 (s, 3H, C$_1$-C*H*$_3$), 2.12 (s, 3H, COC*H*$_3$), 1.35 (t, 3H, CH$_2$-C*H*$_3$).

Anal. Calcd. for $C_{17}H_{17}N_3O_3\cdot\frac{1}{2}H_2O$: C, 63.74; H, 5.66; N, 13.12. Found: C, 63.92; H, 5.62; N, 12.87.

3-Methoxycarbonyl-6-nitro-β-carboline **8a**.

3-Methoxycarbonyl-β-carboline **7a** [19,20] (4.0 g, 17.7 mmoles) was added in small portions to stirred 86% nitric acid (30 ml) keeping the internal temperature at no more than 4° throughout the entire addition (about 1 hour). The resulting reddish solution was kept at 2° for 3 hours, poured onto crushed ice and concentrated ammonia (75 ml), the resulting yellow precipitate filtered and rinsed with water until rinsings were neutral, then dried under reduced pressure. The dried crude material of good purity grade weighed 4.4 g (92%). The product, crystallized from dimethylformamide, melted at 314-315°; the compound is practically insoluble in the commonly employed organic solvents, except dimethylformamide and acetic acid; ^{1}H nmr (trifluoroacetic acid): δ 9.47 (d, 1H, H_5), 9.42 (s, 1H, H_1), 9.37 (s, 1H, H_4), 8.77 (dm, 1H, H_7), 7.97 (d, 1H, H_8), 4.33 (s, 3H, COOC*H*$_3$).

Anal. Calcd. for $C_{13}H_9N_3O_4$: C, 57.56; H, 3.34; N, 15.49. Found: C, 57.90; H, 3.48; N, 15.46.

3-Methoxycarbonyl-1-methyl-6-nitro-β-carboline **8b**.

This compound resulted from nitration of 3-methoxycarbonyl-1-methyl-β-carboline **7b** [21] under the same aforementioned conditions described for **8a**, yield 97%, mp 313-316° (dimethylformamide); ^{1}H nmr: δ 12.57 (broad, 1H, indole N*H*), 9.25 (d, 1H, H_5), 8.83 (s, 1H, H_4), 8.33 (dd, 1H, H_7), 7.63 (d, 1H, H_8), 3.90 (s, 3H, COOC*H*$_3$), 2.78 (s, 3H, C$_1$-C*H*$_3$).

Anal. Calcd. for $C_{14}H_{11}N_3O_4$: C, 58.94; H, 3.89; N, 14.73. Found: C, 58.78; H, 4.17; N, 14.70.

3-Ethoxycarbonyl-6-nitro-β-carboline **8c**.

Nitration of 3-ethoxycarbonyl-β-carboline **7c** [19,20] afforded compound **8c** in 97% yield, mp 333-335° (dimethylformamide); ^{1}H nmr (trifluoroacetic acid): δ 9.48 (d, 1H, H_5), 9.45 (s, 1H, H_1), 9.40 (s, 1H, H_4), 8.80 (dd, 1H, H_7), 8.05 (d, 1H, H_8), 4.82 (q, 2H, C*H*$_2$-CH$_3$), 1.63 (t, 3H, CH$_2$-C*H*$_3$).

Anal. Calcd. for $C_{14}H_{11}N_3O_4$: C, 58.94; H, 3.89; N, 14.73. Found: C, 58.99; H, 4.06; N, 14.79.

3-Ethoxycarbonyl-1-methyl-6-nitro-β-carboline **8d**.

This compound was obtained in 94% yield by nitration of 3-ethoxycarbonyl-1-methyl-β-carboline **7d** [22], mp 330° (dimethylformamide); ^{1}H nmr: δ 12.75 (broad, 1H, indole N*H*), 9.47 (d, 1H, H_5), 9.03 (s, 1H, H_4), 8.55 (dd, 1H, H_7), 7.87 (d, 1H, H_8), 4.57 (q, 2H, C*H*$_2$-CH$_3$), 2.95 (s, 3H, C$_1$-C*H*$_3$), 1.55 (t, 3H, CH$_2$-C*H*$_3$).

Anal. Calcd. for $C_{15}H_{13}N_3O_4$: C, 60.19; H, 4.38; N, 14.04. Found: C, 59.89; H, 4.53; N, 14.08.

5-Amino-3-ethoxycarbonyl-β-carboline Dihydrochloride **9a**.

Compound **6a** (100 mg) was refluxed for 3 hours in 1 *N* ethanolic hydrogen chloride (10 ml). After cooling, the resulting precipitate was filtered off and the clear ethanolic solution diluted with ethyl ether to opalescence and allowed to stand overnight at room temperature. The obtained solid was filtered and crystallized from ethanol-ethyl ether added with a drop concentrated hydrogen chloride, yield 50 mg (46%), mp 180-182°; ^{1}H nmr: δ 13.40 (broad, 1H, indole N*H*), 9.22 (s, 1H, H_1), 9.02 (s, 1H, H_4), 8.50 (broad, amino groups + water), 7.52 (q, 1H, H_7), 7.27 (d, 1H, H_8), 7.02 (d, 1H, H_6), 4.50 (q, 2H, C*H*$_2$-CH$_3$), 1.43 (t, 3H, CH$_2$-C*H*$_3$).

Anal. Calcd. for $C_{14}H_{13}N_3O_2\cdot 2HCl\cdot 1\frac{1}{2}H_2O$: C, 47.33; H, 5.11; N, 11.83; Cl, 19.96. Found: C, 47.31; H, 4.80; N, 11.65; Cl, 19.70.

6-Amino-3-methoxycarbonyl-β-carboline Dihydrochloride **9b**.

To a stirred suspension of **8a** (0.5 g) in methanol (200 ml) kept under nitrogen atmosphere at 15°, sodium borohydride (0.2 g) and palladium on charcoal catalyst (a spatula's tip) were added and allowed to react until hydrogen evolution had ceased; three like portions of sodium borohydride and of catalyst were then successively added, each time after the hydrogen evolution had ceased (entire time: 3 hours). The reddish suspension turned to greenish while the suspended adduct slowly dissolved. The mixture was then filtered, the solvent evaporated at reduced pressure at no more than 30°, water (150 ml) was added to the obtained residue, the aqueous suspension extracted with ethyl acetate (3 x 150 ml), the solvent evaporated and the new residue taken into warm 1-butanol (10 ml) filtering from undissolved matter. Upon addition of a few drops concentrated hydrogen chloride an orange solid separated, which was collected and crystallized from aqueous 80% ethanol added with a few drops hydrogen chloride, yield 350 mg (60%), mp 229-232°; ^{1}H nmr (deuterium oxide): δ 8.92 (s, 1H, H_1), 8.73 (s, 1H, H_4), 8.22 (broad, 1H, H_5), 7.73 (m, 2H, H_7+H_8), 4.00 (s, 3H, COOC*H*$_3$).

Anal. Calcd. for $C_{13}H_{11}N_3O_2\cdot 2HCl\cdot\frac{1}{2}H_2O$: C, 48.31; H, 4.37; N, 13.00; Cl, 21.94. Found: C, 48.52; H, 4.63; N, 12.78; Cl, 21.82.

6-Amino-3-ethoxycarbonyl-β-carboline Dihydrochloride **9c**.

This compound was prepared either by palladium catalyzed reduction with sodium borohydride of **8c** (see above **9b**) in 65% yield, or by acidic hydrolysis of **6d** (see above **9a**) in 60% yield, mp 240-242° (aqueous 80% ethanol added with a few drops hydrogen chloride); ^{1}H nmr (dimethylsulfoxide-d$_6$): δ 13.23 (broad, 1H, indole N*H*), 9.13 (s, 2H, H_1+H_4), 9.13 (broad, 2H, N*H*$_2$), 8.50 (broad, 1H, H_5), 7.78 (broad, 2H, H_7+H_8), 4.47 (q, 2H, C*H*$_2$-CH$_3$), 1.42 (t, 3H, CH$_2$-C*H*$_3$); (deuterium oxide): δ 8.93 (broad, 1H, H_1), 8.83 (broad, 1H, H_4), 8.27 (broad, 1H, H_5), 7.77 (broad, 2H, H_7+H_8), 4.53 (q, 2H, C*H*$_2$-CH$_3$), 1.48 (t, 3H, CH$_2$-C*H*$_3$).

Anal. Calcd. for $C_{14}H_{13}N_3O_2\cdot 2HCl\cdot\frac{1}{2}H_2O$: C, 49.86; H, 4.78; N, 12.46; Cl, 21.03. Found: C, 50.00; H, 4.99; N, 12.50; Cl, 21.02.

6-Amino-3-methoxycarbonyl-1-methyl-β-carboline Dihydrochloride **9d**.

This compound was obtained by sodium borohydride reduction of **8b** in 58% yield, mp 250-252° (aqueous 80% ethanol added with a few drops hydrogen chloride); ^{1}H nmr (deuterium oxide): δ 9.08 (s, 1H, H_4), 8.52 (broad, 1H, H_5), 7.97 (broad, 2H, H_7+H_8), 4.22 (s, 3H, COOC*H*$_3$), 3.13 (s, 3H, C$_1$-C*H*$_3$).

Anal. Calcd. for $C_{14}H_{13}N_3O_2 \cdot 2HCl \cdot \frac{1}{2}H_2O$: C, 49.86; H, 4.78; N, 12.46; Cl, 21.03. Found: C, 50.18; H, 4.99; N, 12.09; Cl, 20.80.

6-Amino-3-ethoxycarbonyl-1-methyl-β-carboline Dihydrochloride **9e**.

This compound was analogously prepared by sodium borohydride reduction of **8d** in 73% yield, mp 270-271° (methanol-1-butanol 1:2, acidified with hydrogen chloride); ^{1}H nmr (deuterium oxide): δ 8.88 (s, 1H, H_4), 8.45 (broad, 1H, H_5), 7.95 (broad, 2H, H_7+H_8), 4.83 (q, 2H, CH_2-CH_3), 3.13 (s, 3H, C_1-CH_3), 1.82 (t, 3H, CH_2-CH_3).

Anal. Calcd. for $C_{15}H_{15}N_3O_2 \cdot 2HCl$: C, 52.64; H, 5.01; N, 12.28; Cl, 20.72. Found: C, 52.52; H, 5.13; N, 12.15; Cl, 20.61.

7-Amino-3-ethoxycarbonyl-β-carboline Dihydrochloride **9f**.

This compound was obtained from the 7-formylamino derivative **6f** by acidic hydrolysis in the dark at room temperature for 24 hours, and work up as described below; yield 70%, mp 255-256° (methanol-1-butanol 1:2 added with concentrated hydrogen chloride). The same compound **9f** resulted by refluxing **6g** (0.1 g) for 2 hours in 1 *N* ethanolic hydrogen chloride (15 ml). After cooling, the mixture was diluted with water (50 ml), made alkaline with ammonia, extracted with ethyl acetate (3 x 50 ml), the organic layer washed with water, dried and evaporated. The obtained residue was dissolved in 1-butanol and a few drops concentrated hydrogen chloride were added. A solid precipitate formed, which was crystallized from methanol-1-butanol 1:2 mixture added with a drop concentrated hydrogen chloride, yield 50 mg (45%), mp 255-256°; ^{1}H nmr: δ 13.10 (broad, 1H, indole N*H*), 8.93 (s, 1H, H_1), 8.90 (s, 1H, H_4), 8.30 (d, 1H, H_5), 7.92 (broad, amino groups + water), 7.23 (broad, 1H, H_8), 7.07 (dm, 1H, H_6), 4.48 (q, 2H, CH_2-CH_3), 1.43 (t, 3H, CH_2-CH_3).

Anal. Calcd. for $C_{14}H_{13}N_3O_2 \cdot 2HCl$: C, 51.23; H, 4.61; N, 12.80; Cl, 21.61. Found: C, 51.26; H, 4.61; N, 12.67; Cl, 21.55.

7-Amino-3-ethoxycarbonyl-1-methyl-β-carboline Dihydrochloride **9g**.

This compound was prepared in 70% yield by refluxing **6h** in 1 *N* ethanolic hydrogen chloride, mp 238-240° (methanol-1-butanol 1:2, acidified with hydrogen chloride); ^{1}H nmr: δ 13.30 (broad, 1H, indole N*H*), 8.60 (s, 1H, H_4), 8.27 (d, 1H, H_5), 7.20 (broad, 1H, H_8), 7.00 (dm, 1H, H_6), 6.37 (broad, amino groups + water), 4.47 (q, 2H, CH_2-CH_3), 3.03 (s, 3H, C_1-CH_3), 1.42 (t, 3H, CH_2-CH_3).

Anal. Calcd. for $C_{15}H_{15}N_3O_2 \cdot 2HCl \cdot H_2O$: C, 50.01; H, 5.32; N, 11.66; Cl, 19.68. Found: C, 50.24; H, 4.98; N, 11.69; Cl, 19.73.

Acknowledgment.

We wish to thank Sig. R. Piergallini for microanalyses, and Sig. F. Ponti for technical assistance.

REFERENCES AND NOTES

[1] C. Braestrup and M. Nielsen, *Arzneim.-Forsch.*, **30**, 852 (1980).

[2] H. Moehler and T. Okada, *Br. J. Psychiatry*, **133**, 261 (1978).

[3] J. F. Tallmann, S. M. Paul, P. Skolnik and D. W. Gallager, *Science*, **207**, 274 (1980).

[4] W. E. Mueller, *Pharmacology*, **22**, 153 (1981).

[5] H. Rommelspacher, C. Nanz, H. O. Borbe, K. J. Fehske, W. E. Mueller and U. Wollert, *Eur. J. Pharmacol.*, **70**, 409 (1981).

[6] W. E. Mueller, K. J. Fehske, H. O. Borbe, U. Wollert, C. Nanz and H. Rommelspacher, *Pharmacol. Biochem. Behav.*, **14**, 693 (1981).

[7a] C. Braestrup, M. Nielsen and C. E. Olsen, *Proc. Natl. Acad. Sci. U. S. A.*, **77**, 2288 (1980); [b] S. S. Tenen and J. D. Hirsch, *Nature*, **208**, 609 (1980).

[8] C. Braestrup, R. Schmiechen, G. Neef, M. Nielsen and E. N. Petersen, *Science*, **216**, 1241 (1982).

[9] N. R. Oakley and B. J. Jones, *Neuropharmacology*, **21**, 587 (1982).

[10] C. Braestrup and M. Nielsen, *J. Neurochem.*, **37**, 333 (1981).

[11] F. J. Ehlert, W. R. Roeske and H. I. Yamamura, *Life Sci.*, **29**, 235 (1981).

[12] J. D. Hirsch, R. L. Kochman and P. R. Sumner, *Mol. Pharmacol.*, **21**, 618 (1982).

[13] G. Neef, U. Eder, R. Schmiechen, A. Huth, D. Rahtz, D. Seidelmann, W. Kehr, D. Palenschat and C. T. Braestrup, Schering A. G., European Patent 54,507 (1982); *Chem. Abstr.*, **98**, 16663c (1983).

[14a] G. Berti and A. Da Settimo, *Gazz. Chim. Ital.*, **90**, 525 (1960); [b] J. B. Hester, *J. Org. Chem.*, **29**, 1158 (1964).

[15] G. Cavallini and F. Ravenna, *Farmaco, Ed. Sci.*, **13**, 105 (1958).

[16] H. L. Atkins, D. R. Christman, J. S. Fowler, W. Hauser, R. M. Hoyte, J. F. Klopper, S. S. Lin and A. P. Wolf, *J. Nucl. Med.*, **13**, 713 (1972).

[17] L. Goodman, R. R. Spencer, G. Casini, O. P. Crews and E. J. Reist, *J. Med. Chem.*, **8**, 251 (1965).

[18] J. Degraw and L. Goodman, *J. Org. Chem.*, **27**, 1395 (1962).

[19] K. P. Lippke, W. G. Schunack, W. Wenning and W. E. Mueller, *J. Med. Chem.*, **26**, 499 (1983).

[20] M. Massotti, D. Lucantoni, M. G. Caporali, L. Mele and F. Gatta, *J. Pharmacol. Exp. Ther.*, **234**, 274 (1985).

[21] M. Julia and J.-Y. Lallemand, *Bull. Soc. Chim. France*, 2058 (1973).

[22] J. Le Men and M. C. Fan, *Bull. Soc. Chim. France*, 1866 (1959).

[23] K. N. F. Shaw and C. Nolan, *J. Org. Chem.*, **22**, 1668 (1957).

[24] P. Bouchet, C. Coquelet, G. Joncheray and J. Elguero, *Synth. Commun.*, **4**, 57 (1974).

[25] J. I. Degraw, V. H. Brown and W. A. Skinner, *J. Med. Chem.*, **9**, 140 (1966).

[26] F. Ravenna, *Experientia*, **14**, 273 (1958).

[27] G. Berti, A. Da Settimo, R. De Fazi and G. De Caro, *Farmaco, Ed. Sci.*, **19**, 411 (1964).

[28] J. P. Saxena, *Indian J. Chem.*, **4**, 148 (1966).

[29] G. Neef, U. Eder, A. Huth, D. Rahtz, R. Schmiechen and D. Seidelmann, *Heterocycles*, **20**, 1295 (1983).

[30] T. Neilson, H. C. S. Wood and A. G. Wylie, *J. Chem. Soc.*, 371 (1962).

[31] B. C. McKusick and O. W. Webster, *Org. Synth.*, **41**, 102 (1961).

[32] J. C. Sheehan and D.-D. H. Yang, *J. Am. Chem. Soc.*, **80**, 1154 (1958).

[33] Y. Kanaoka, E. Sato, O. Yonemitsu and Y. Ban, *Tetrahedron Letters*, 2419 (1964).

[34] A. P. Krapcho, *Synthesis*, 805 and 893 (1982) and the literature cited therein.