New Tetracyclic Compounds Containing the β-Carboline Moiety

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Oxidation of 1-methyl-3-methoxycarbonyl-β-carboline with selenium dioxide gave 1-formyl-3-methoxycarbonyl-β-carboline **II**. Compound **II** reacted with acetic or propionic anhydride to give easily the 2-methoxycarbonyl-6*H*-indolo[3,2,1-*d*,*e*][1,5]naphthyridin-6-ones **III**; reaction of **II** with some primary amines led to the formation of the Schiff bases **IV**, which were reduced to the 1-aminomethyl-3-methoxycarbonyl-β-carbolines **V** with sodium borohydride.

Cyclization of **V** with aqueous formaldehyde led to the pyrimido[3,4,5-*lm*]pyrido[3,4-*b*]indoles **VI**.

Analogously, cyclization with formaldehyde, acetone or 1,1'-carbonyldiimidazole of the 3-aminomethyl-1,2,3,4-tetrahydro-β-carbolines **VIII**, obtained by reaction of 3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline **VII** with amines followed by lithium aluminium hydride reduction of the resulting amides, gave the imidazo[1',5'-1,6]pyrido[3,4-*b*]indoles **IX** and **X**.

Dieckmann cyclization of 3-methoxycarbonyl-2-[(3-ethoxycarbonyl)-1-propyl]-1,2,3,4-tetrahydro-β-carboline **XI** led to a 1:1 mixture of the β-ketoesters **XII** and **XIII**, which underwent deethoxycarbonylation to 5,6,8,9,10,11,11a,12-octahydroindolo[3,2-*b*]quinolizin-11-one **XIV**.

Finally, the polyphosphoric acid (or esters) catalyzed cyclization of the *N*-acyl derivatives **XVI** of 3-hydrazinocarbonyl-β-carboline **XV** led smoothly to the 3-(1,3,4-oxadiazol-2-yl)-β-carbolines **XVII**.

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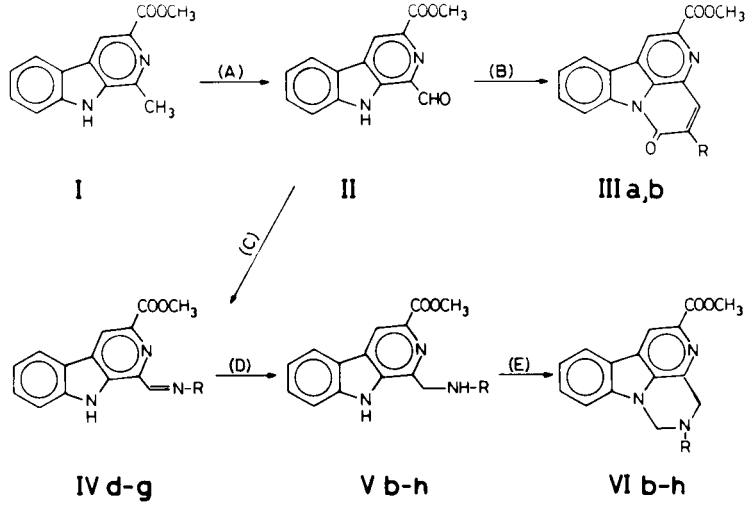
The synthesis of compounds containing the structural framework of β-carboline is of great importance in connection with their occurrence in a number of physiologically active indole alkaloids and with the recent discovery of the potent affinity of several 3-substituted β-carbolines for benzodiazepine receptors [1-4].

As a part of our interest in the study of β-carboline derivatives, in the present paper we describe the synthesis of some indolo[3,2,1-*de*][1,5]naphthyridines **III**, pyrimido-[3,4,5-*lm*]pyrido[3,4-*b*]indoles **VI**, imidazo[1',5'-1,6]pyrido-[3,4-*b*]indoles **IX** and **X**, indolo[3,2-*b*]quinolizines **XII**, **XIII**, **XIV**, and 3-(1,3,4-oxadiazol-2-yl)-β-carbolines

Scheme 1



(A): SeO_2 ; (B): $(R-CO)_2O$; (C): $R-NH_2$; (D): $NaBH_4$; (E): CH_2O.

	R
a	H
b	$-CH_3$
c	$-C_2H_5$
d	$-nC_4H_9$

	R
e	$-CH_2-C_6H_5$
f	$-(CH_2)_2-C_6H_5$
g	$-(CH_2)_2-CH_2OH$
h	$-(CH_2)_2-N(C_2H_5)_2$

XVII, to test their abilities to bind to brain benzodiazepine receptors.

The synthetic pathway to compounds **III** and **VI**, illustrated in the Scheme 1, started from 1-formyl-3-methoxycarbonyl-β-carboline **II**, prepared in 68% yield by selenium dioxide oxidation of the 1-methyl derivative of 3-methoxycarbonyl-β-carboline **I**. Compound **II** has been previously obtained in our laboratories, in lower yield, by selenium dioxide oxidation of 1-benzyl-1-methyl-3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline [5].

When refluxed for 5 hours in acetic or propionic anhydride in the presence of pyridine, compound **II** was found to give easily the 2-methoxycarbonyl-6*H*-indolo-[3,2,1-*de*][1,5]naphthyridin-6-ones **III**.

Several syntheses of compound **IIIa** (R = H) are reported in the literature [6-9]; the sequence here reported represents, however, a novel and simple approach to prepare the still unknown 5-methyl derivative **IIIb**.

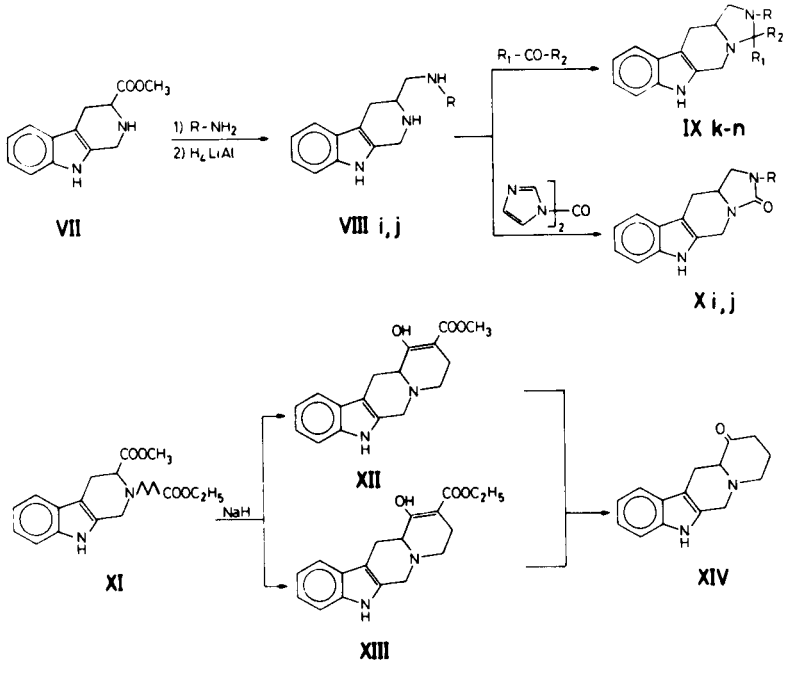
The condensation of the aldehyde **II** with various amines in methanol, followed by reduction with sodium borohydride of the resulting Schiff bases **IV** (compounds **IVb,c,h** were not isolated from the reaction mixture) provided good to excellent yields of the 1-aminomethyl-3-methoxycarbonyl-β-carbolines **V**. Cyclization of the latter with formaldehyde in the presence of an excess of ethyldiisopropylamine in refluxing methanol for 1 hour, led finally to compounds **VI**.

The starting material for the syntheses of the tetracyclic compounds **IX**, **X** and **XIV**, summarized in Scheme 2, was the 3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline **VII** [4]. When allowed to react at 80° for 20 hours with benzylamine or 2-phenylethylamine used as solvents, **VII** gave the corresponding amides (precipitated by diethyl ether addition to the cooled reaction mixture) which were, in turn, reduced by lithium aluminium hydride in refluxing dioxane to give the related amines **VIII** in 83% and 68% yield respectively.

The treatment of compounds **VIII** with formaldehyde, acetone or 1,1'-carbonyldiimidazole offered a direct and excellent method for the synthesis of the cyclized products **IX** and **X**.

Condensation of **VII** with ethyl 4-bromobutyrate led the diester **XI**, whose Dieckmann cyclization gave a 84% yield of 1:1 mixture of the β-ketoesters **XII** and **XIII**, easily separated by silica gel column chromatography. Compound **XII** was formed from **XIII** by sodium methoxide catalyzed transesterification. Moreover, ir and nmr spectra showed these compounds to be completely enolized either in the solid phase or in solution. The indolo-[3,2-*b*]quinolizin-11-one **XIV** was finally obtained by

Scheme 2

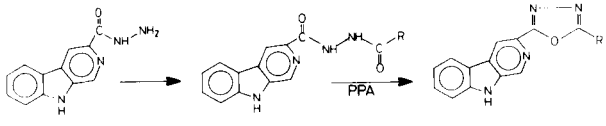


	R	R_1	R_2
i	$-CH_2-C_6H_5$		
j	$-(CH_2)_2-C_6H_5$		
k	$-CH_2-C_6H_5$	H	H
l	$-(CH_2)_2-C_6H_5$	H	H
m	$-CH_2-C_6H_5$	$-CH_3$	$-CH_3$
n	$-(CH_2)_2-C_6H_5$	$-CH_3$	$-CH_3$

heating the crude mixture of the β-ketoesters **XII** and **XIII** in dimethyl sulfoxide in the presence of sodium chloride.

In Scheme 3 the synthesis of 3-(1,3,4-oxadiazol-2-yl)-β-carbolines **XVII**, readily achieved starting from hydrazinocarbonyl-β-carboline **XV** [11], is reported.

Scheme 3



XV XVI a,b,c XVII a,b,c

a: R=H; b: R= -CH3; c: R= -C6H5

The reaction of **XV** with refluxing formic acid, with acetic anhydride at room temperature or with benzoyl chloride in boiling pyridine, afforded respectively the acyl derivatives **XVIa, XVIb** and **XVIc**, which were easily cyclized to the desired oxadiazoles **XVII** by treatment with polyphosphoric esters in anhydrous chloroform at room temperature, **XVIIa**, or with polyphosphoric acid at 100-110°, **XVIIb,c**.

The nmr and ir spectra of the prepared new compounds are in agreement with the proposed structures; nmr data of the most significant compounds are reported in the Experimental.

Standard pharmacological studies of some of these compounds will be published elsewhere.

EXPERIMENTAL

Melting points were determined on a Kofler hot stage apparatus and are uncorrected. The ^{1}H-nmr spectra were recorded on a Varian T-60 and a Bruker 400 MHz spectrometers with TMS as internal standard. Chemical shifts are given in δ units. Abbreviations are as follows: d = doublet; m = multiplet; s = singlet; bs = broad singlet; at = apparent triplet; dd = doublet of doublets. The ir spectra were obtained with a Perkin-Elmer 580 double beam spectrophotometer (nujol). Sodium sulfate was used to dry organic solutions.

3-Methoxycarbonyl-1-methyl-β-carboline **I** [10], 3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline **VII** [4] and 3-hydrazinocarbonyl-β-carboline **XV** [11] were prepared as reported.

1-Formyl-3-methoxycarbonyl-β-carboline **II**.

To a stirred solution of 3-methoxycarbonyl-1-methyl-β-carboline **I** (2 g, 0.008 mole) in dioxane (40 ml) selenium dioxide (2 g) was added and the reaction mixture was allowed to reflux for 2 hours. The hot suspension was filtered through Celite and the solvent was evaporated. The crude product was crystallized from 1-propanol, yield 1.4 g (69%), mp 244-246°; ^{1}H-nmr (hexadeuterodimethylsulfoxide): δ 12.33 (bs, 1H, N*H*), 10.05 (s, 1H, C*H*O), 9.07 (s, 1H, H_4), 8.40 (d, 1H, H_8), 7.57 (m, 3H, H_5, H_6, H_7), 3.97 (s, 3H, COOCH_3); ir (nujol): cm^{-1} 1735 (ester), 1690 (aryl aldehyde).

Anal. Calcd. for $C_{14}H_{10}N_2O_3$: C, 66.13; H, 3.96; N, 11.02. Found: C, 66.00; H, 4.07; N, 10.87.

Compound II Oxime, Semicarbazone and Dimethylacetale.

These compounds had the following melting points: oxime, mp 260-262° (methanol); semicarbazone: mp 238-240° (aqueous dimethylformamide); dimethylacetal, mp 126-127° (aqueous methanol). The latter derivative resulted by a 4 hours refluxing of **II** in methanolic hydrogen chloride.

2-Methoxycarbonyl-6*H*-indolo[3,2,1-*de*][1,5]naphthyridin-6-one **IIIa**.

2-Methoxycarbonyl-5-methyl-6*H*-indole[3,2,1-*de*][1,5]naphthyridin-6-one **IIIb**.

Compound **II** (1.0 g, 0.004 mole) was boiling in acetic or propionic anhydride (10 ml) and pyridine (1 ml) for 3 hours to give respectively **IIIa** and **IIIb**.

Compound **IIIa**, after evaporation of dryness of the reaction mixture was directly crystallized from 1-propanol, yield 0.8 g (72%), mp 248-250° (lit[6] mp 249-250°).

Anal. Calcd. for $C_{16}H_{10}N_2O_3$: C, 69.06; H, 3.62; N, 10.07. Found: C, 69.18; H, 3.40; N, 10.19.

Compound **IIIb** was obtained by addition of methanol (20 ml) to the cooled reaction mixture; the resulting precipitate was collected and purified by silica gel column chromatography (ethyl acetate-*n*-hexane 1:1). Compound **IIIb** was crystallized from 1-propanol, yield 0.8 g (68%), mp 253-255°; ^{1}H-nmr (deuteriochloroform): δ 8.70 (s, 1H, H_1), 8.53 (d, 1H, H_8), 8.06 (d, 1H, H_{11}), 7.93 (s, 1H, H_4), 7.57 (m, 2H, H_9, H_{10}), 4.07 (s, 3H, COOCH_3), 2.37 (s, 3H, C5-CH_3); ir (nujol): cm^{-1} 1710 (ester), 1670 (amide).

Anal. Calcd. for $C_{17}H_{12}N_2O_3$: C, 69.85; H, 4.14; N, 9.59. Found: C, 69.54; H, 4.21; N, 9.29.

3-Methoxycarbonyl-1-methylaminomethyl-β-carboline **Vb**.

To a stirred suspension of **II** (1.5 g, 0.006 mole) in methanol (30 ml), kept at 0°, methylamine (1 ml) was added; the reaction mixture was stirred at room temperature for about 1 hour, until the starting material had disappeared (tlc monitored). Sodium borohydride (1.6 g, 0.04 mole) was then added in small portions while stirring at 0-5° and the mixture stirred for 2 hours at room temperature. Water (100 ml) was added, the mixture extracted with ethyl acetate (3 x 50 ml) and the organic layer separated. Removal of the solvent gave an oil which was crystallized from methanol, yield 1.5 g (84%), mp 147-149°.

Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.90; H, 5.61; N, 15.61. Found: C, 67.08; H, 5.55; N, 15.49.

1-Ethylaminomethyl-3-methoxycarbonyl-β-carboline **Vc**.

Compound **Vc** was prepared from **II** and ethylamine under the same conditions described for **Vb**. The intermediate, not isolated Schiff base, was immediately reduced by sodium borohydride to give **Vc** in 80% yield, mp 80-81° (methanol).

Anal. Calcd. for $C_{16}H_{17}N_3O_2$: C, 67.82; H, 6.05; N, 14.83. Found: C, 67.76; H, 6.02; N, 14.61.

1-Butylaminomethyl-3-methoxycarbonyl-β-carboline Dihydrochloride. **Vd**.

a) A mixture of **II** (1.5 g, 0.006 mole) and *n*-butylamine (1.1 g, 0.015 mole) in methanol (50 ml) was first heated for a few minutes at 40°, then stirred at room temperature for 1 hour. **IVd** was obtained as a crystalline solid whose separation was enhanced by dilution of the reaction mother liquor with ethyl ether, yield 1.5 g

(81%), mp 86-87° (methanol).

Anal. Calcd. for $C_{18}H_{19}N_3O_2$: C, 69.88; H, 6.19; N, 13.58. Found: C, 70.05; H, 6.10; N, 13.32.

b) A solution of **IVd** (1.4 g, 0.0045 mole) in methanol (50 ml), cooled at 0-5°, was treated under stirring with sodium borohydride (1.6 g, 0.04 mole) in small portions. The mixture was allowed to react for 2 hours at room temperature, water (150 ml) was added and the suspension extracted with ethyl acetate (3 x 50 ml). The combined organic layers, after evaporation gave **Vd** as a viscous residue which was purified as the dihydrochloride from ethanolic hydrogen chloride-ethyl ether and by crystallization from methanol, yield 1.4 g (81%), mp 224-226°.

Anal. Calcd. for $C_{18}H_{23}Cl_2N_3O_2$: C, 59.38; H, 6.03; N, 10.93. Found: C, 59.27; H, 6.23; N, 11.03.

1-Benzylamino-3-methoxycarbonyl-β-carboline Dihydrochloride. **Ve.**

Compound **Ve** dihydrochloride was prepared in 2 steps, as described for **Vd** dihydrochloride. The intermediate Schiff base **IVe**, resulting from the reaction of **II** with benzylamine, was first separated from the reaction methanolic mother liquor by dilution with ethyl ether, then crystallized from methanol, yield 78%, mp 110-112°.

Anal. Calcd. for $C_{21}H_{17}N_3O_2$: C, 73.45; H, 4.99; N, 12.24. Found: C, 73.62; H, 5.14; N, 12.08.

Compound **Ve** dihydrochloride, obtained by reduction of **IVe** (see **Vd**) was crystallized from methanol, yield 92%, mp 235-237°.

Anal. Calcd. for $C_{21}H_{21}Cl_2N_3O_2$: C, 60.29; H, 4.94; N, 10.04. Found: C, 60.07; H, 5.14; N, 9.82.

3-Methoxycarbonyl-1-(2-phenylethyl)aminomethyl-β-carboline Dihydrochloride **Vf.**

Compound **Vf** was obtained as the dihydrochloride in the same manner described for **Vd** dihydrochloride.

The reaction of **II** with β-phenylethylamine gave the Schiff base **IVf** in 75% yield, mp 190-191° (methanol-ethyl ether).

Anal. Calcd. for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 74.00; H, 5.46; N, 11.94.

Compound **Vf** dihydrochloride was obtained in a yield of 87%, mp 232-234° (ethanol).

Anal. Calcd. for $C_{22}H_{23}Cl_2N_3O_2$: C, 61.11; H, 5.36; N, 9.72. Found: C, 61.28; H, 5.38; N, 9.90.

1-(3-Hydroxypropyl)aminomethyl-3-methoxycarbonyl-β-carboline Dihydrochloride **Vg.**

Compound **Vg** was prepared from **II** and 3-amino-1-propanol under the same aforementioned conditions.

Compound **IVg** under yield 86%, mp 196-198° (methanol-ethyl ether).

Anal. Calcd. for $C_{17}H_{17}N_3O_3$: C, 65.58; H, 5.50; N, 13.50. Found: C, 65.69; H, 5.30; N, 13.28.

Compound **Vg** dihydrochloride under yield of 96%, mp 239-241° (ethanol-ethyl ether).

Anal. Calcd. for $C_{17}H_{21}Cl_2N_3O_3$: C, 52.85; H, 5.48; N, 10.88. Found: C, 53.02; H, 5.64; N, 10.96.

1-(*N,N*-β-Diethylaminoethyl)aminomethyl-3-methoxycarbonyl-β-carboline Trihydrochloride **Vh.**

Compound **Vh** was prepared from **II** and *N,N*-β-diethylaminoethylamine in the same manner described for **Vd**, but, in this case, the intermediate Schiff base was not isolated.

Compound **Vh** was obtained as the trihydrochloride, yield 80%, mp 212-213° (1-butanol).

Anal. Calcd. for $C_{20}H_{29}Cl_3N_4O_2$: C, 51.78; H, 6.26; N, 12.08. Found: C, 51.65; H, 6.32; N, 11.96.

All of the compounds **V** hydrochloride showed the following ^1H nmr spectral data (hexadeuteriodimethylsulfoxide): δ 12.9 (bs, 1H, N*H*), 9.7 (bs, 2H, NH_2^+R), 8.9 (s, 1H, H_4), 8.4 (d, 1H, H_8), 7.5 (m, 3H, H_5, H_6, H_7), 4.85 (bs, 2H, CH_2NH$_2^+$R), 3.95 (s, 3H, COOCH_3).

2-Methyl-5-Methoxycarbonyl-2,3-dihydro-1*H*-pyrimido[3,4,5-*lm*]-pyrido[3,4-*b*]indole **VIb.**

To a solution of **Vb** (1.0 g, 0.0037 mole) in ethanol (30 ml), aqueous 40% formaldehyde (0.3 ml, 0.0044 mole) was added and the mixture was kept at reflux for 1 hour. The solvent was then removed under reduced pressure and the residue crystallized from ethyl acetate, yield 0.8 g (77%), mp 170-172°.

Anal. Calcd. for $C_{16}H_{15}N_3O_2$: C, 68.31; H, 5.38; N, 14.94. Found: C, 68.19; H, 5.38; N, 14.81.

2-Ethyl-5-methoxycarbonyl-2,3-dihydro-1*H*-pyrimido[3,4,5-*lm*]-pyrido[3,4-*b*]indole **VIc.**

Compound **VIc** was likewise prepared from **Vc**, yield 85%, mp 141-143° (aqueous 80% methanol).

Anal. Calcd. for $C_{17}H_{17}N_3O_2$: C, 69.13; H, 5.80; N, 14.23. Found: C, 69.19; H, 5.83; N, 14.19.

2-Butyl-5-methoxycarbonyl-2,3-dihydro-1*H*-pyrimido[3,4,5-*lm*]-pyrido[3,4-*b*]indole **VId.**

Compound **Vd** dihydrochloride (1 g, 0.0026 mole), dissolved in ethanol (30 ml) containing *N*-diisopropylethylamine (1 ml), was refluxed with aqueous 40% formaldehyde (0.3 ml, 0.0044 mole) for 1 hour. Removal of the solvent under reduced pressure gave a residue which was crystallized from aqueous 80% methanol, yield 0.75 g (80%), mp 53-55°.

Anal. Calcd. for $C_{19}H_{21}N_3O_2.2H_2O$: C, 63.51; H, 6.96; N, 11.69. Found: C, 63.59; H, 6.76; N, 11.68.

2-Benzyl-5-methoxycarbonyl-2,3-dihydro-1*H*-pyrimido[3,4,5-*lm*]-pyrido[3,4-*b*]indole **VIe.**

Compound **VIe** was prepared from **Ve** dihydrochloride under the same conditions described for **VId**, yield 96%, mp 208-209° (ethanol).

Anal. Calcd. for $C_{22}H_{19}N_3O_2$: C, 73.93; H, 5.36; N, 11.76. Found: C, 73.96; H, 5.58; N, 11.61.

2-(β-Phenylethyl)-5-methoxycarbonyl-2,3-dihydro-1*H*-pyrimido-[3,4,5-*lm*]pyrido[3,4-*b*]indole **VIf.**

Compound **VIf** was likewise obtained from **Vf** dihydrochloride, yield 77%, mp 88-90° (ethanol).

Anal. Calcd. for $C_{23}H_{21}N_3O_2$: C, 74.37; H, 5.70; N, 11.31. Found: C, 74.21; H, 5.60; N, 11.20.

2-(3-Hydroxypropyl)-5-methoxycarbonyl-2,3-dihydro-1*H*-pyrimido[3,4,5-*lm*]pyrido[3,4-*b*]indole **VIg.**

Compound **VIg** was obtained from **Vg** dihydrochloride in 85% yield, mp 136-138° (aqueous methanol).

Anal. Calcd. for $C_{18}H_{19}N_3O_3.H_2O$: C, 62.96; H, 6.16; N, 12.24. Found: C, 62.98; H, 6.27; N, 11.95.

2-(*N,N*-β-Diethylaminoethyl)-5-methoxycarbonyl-2,3-dihydro-1*H*-pyrimido[3,4,5-*lm*]pyrido[3,4-*b*]indole **VIh.**

Compound **VIh** was prepared as the hydrochloride from **Vh** trihydrochloride in 80% yield, mp 194-196° (2-propanol).

Anal. Calcd. for $C_{21}H_{27}ClN_4O_2$: C, 62.60; H, 6.75; N, 13.91. Found: C, 62.57; H, 6.62; N, 13.76.

All of the compounds **VI** showed the following ^1H nmr spectral features (hexadeuteriodimethylsulfoxide): δ 8.70 (s, 1H, H_6), 8.40 (d, 1H, H_{10}), 7.50 (m, 3H, H_7, H_8, H_9), 5.50 (bs, 2H, H_1), 4.40-4.20 (bs, 2H, H_3), 3.90 (s, 3H, $COOCH_3$).

3-Benzylaminocarbonyl-1,2,3,4-tetrahydro-β-carboline.

A solution of 3-methoxycarbonyl-1,2,3,4-tetrahydro-β-carboline **VII** (2.0 g, 0.0087 mole) in benzylamine (10 ml) was heated at 80° for 20 hours. After cooling, ethyl ether (100 ml) was added and the obtained amide filtered and crystallized from methanol, yield 2.2 g (83%), mp 250-253°.

Anal. Calcd. for $C_{19}H_{19}N_3O$: C, 74.73; H, 6.27; N, 13.76. Found: C, 74.68; H, 6.23; N, 13.79.

3-Benzylaminomethyl-1,2,3,4-tetrahydro-β-carboline **VIIIi**.

To a warm and well stirred dispersion of lithium aluminium hydride (0.75 g, 0.02 mole) in anhydrous dioxane (100 ml), a solution of 3-benzylaminocarbonyl-1,2,3,4-tetrahydro-β-carboline (2.0 g, 0.0066 mole) in the same solvent (50 ml) was added slowly. The resulting mixture was allowed to reflux for 12 hours, cooled then at 0°, and water (10 ml) carefully added. The precipitated oxides were separated by filtration and washed thoroughly with warm dioxane. The organic solution was concentrated under reduced pressure and the residue crystallized from benzene, yield 1.5 g (78%), mp 132-134°.

Anal. Calcd. for $C_{19}H_{21}N_3$: C, 78.31; H, 7.26; N, 14.42. Found: C, 78.57; H, 7.00; N, 14.29.

3-(2-Phenylethylamino)carbonyl-1,2,3,4-tetrahydro-β-carboline.

This compound was obtained by heating for 8 hours at 90° **VII** (2.0 g, 0.0087 mole) in 2-phenylethylamine (10 ml), dilution of the reaction mixture with ethyl ether gave a crude material which was crystallized from ethyl acetate, yield 2.2 g (80%), mp 189-191°.

Anal. Calcd. for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.15. Found: C, 75.34; H, 6.59; N, 12.98.

3-(2-Phenylethyl)aminomethyl-1,2,3,4-tetrahydro-β-carboline **VIIIj**.

Compound **VIIIj** was likewise prepared in 68% yield by lithium aluminium hydride reduction of 3-(2-phenylethylamino)-carbonyl-1,2,3,4-tetrahydro-β-carboline. Compound **VIIIj** was cristallized from ethyl acetate, mp 168-170° (ethyl acetate).

Anal. Calcd. for $C_{20}H_{23}N_3$: C, 78.65; H, 7.59; N, 13.76. Found: C, 78.67; H, 7.77; N, 13.47.

2-Benzyl-2,3,5,6,11,11a-hexahydro-1H-imidazo[1′,5′:1,6]pyrido-[3,4-*b*]indole **IXk**.

A solution of **VIIIi** (1.0 g, 0.0034 mole) in ethanol (15 ml) was treated with 40% aqueous formaldehyde (1 ml) and the reaction mixture kept for 1 hour at 60°. The obtained precipitate was collected and crystallized from ethanol, yield 0.9 g (84%), mp 237-240°; ^1H nmr (hexadeuteriodimethylsulfoxide): δ 10.70 (s, 1H, N*H*), 7.40-7.20, 7.05-6.90 (m, 9H, aromatics), 3.80 (bs, 2H, $NCH_2C_6H_5$), 3.72 (dd, 2H, H_5), 3.58 (dd, 2H, H_3), 3.25-2.50 (m, 5H, H_1,H_{11},H_{11a}).

Anal. Calcd. for $C_{20}H_{21}N_3$: C, 79.19; H, 6.98; N, 13.85. Found: C, 79.01; H, 7.19; N, 13.58.

2-(2-Phenylethyl)-2,3,5,6,11,11a-hexahydro-1*H*-imidazo[1′,5′:1,6]-pyrido[3,4-*b*]indole **IXl**.

A solution of **VIIIj** (1.0 g, 0.0033 mole) and 40% aqueous formaldehyde (1 ml) in methanol (30 ml) was allowed to reflux for 5 hours. After cooling, the obtained precipitate was collected and crystallized from methanol, yield 0.6 g (60%), mp 193-195°.

Anal. Calcd. for $C_{21}H_{23}N_3$: C, 79.46; H, 7.30; N, 13.24. Found: C, 79.62; H, 7.31; N, 12.98.

2-Benzyl-3,3-dimethyl-2,3,5,6,11,11a-hexahydro-1*H*-imidazo-[1′,5′:1,6]pyrido[3,4-*b*]indole **IXm**.

A suspension of **VIIIi** (1.0 g, 0.0034 mole) in acetone (10 ml) was refluxed for 16 hours. After cooling, the precipitate was collected and recrystallized from methanol, yield 0.9 g (82%), mp 198-200°; ^1H nmr (hexadeuteriodimethylsulfoxide): δ 10.72 (s, 1H, N*H*), 7.40-6.90 (m, 9H, aromatics), 3.78 (dd, 2H, H_5), 3.65 (dd, 2H, $NCH_2C_6H_5$), 3.02 (m, 1H, H_{11a}), 2.78 (m, 2H, H_1), 2.52 (at, 1H, H_{11}), 2.36 (dd, 1H, H_{11}), 1.25 (s, 3H, C_3-CH_3), 1.12 (s, 3H, C_3-CH_3).

Anal. Calcd. for $C_{22}H_{25}N_3$: C, 79.77; H, 7.55; N, 12.69. Found: C, 79.61; H, 7.48; N, 12.52.

2-(2-Phenylethyl)-3,3-dimethyl-2,3,5,6,11,11a-hexahydro-1*H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*]indole **IXn**.

Compound **IXn** was likewise obtained from **VIIIj** and acetone, yield 75%, mp 192-194° (acetone).

Anal. Calcd. for $C_{23}H_{27}N_3$: C, 79.96; H, 7.88; N, 12.16. Found: C, 80.08; H, 7.96; N, 12.08.

2-Benzyl-3-oxo-2,3,5,6,11,11a-hexahydro-1*H*-imidazo[1′,5′:1,6]-pyrido[3,4-*b*]indole **Xi**.

To a well stirred solution of **VIIIi** (3.0 g, 0.01 mole) in anhydrous tetrahydrofuran (50 ml), 1,1′-carbonyldiimidazole (2.0 g, 0.012 mole) was added. The mixture was stirred at room temperature for 3 hours, then refluxed for 18 hours. The solvent was distilled off under reduced pressure and the residue crystallized from methanol, yield 2.3 g (72%), mp 194-196°; ^1H nmr (hexadeuteriodimethylsulfoxide): δ 10.86 (s, 1H, N*H*), 7.41-7.22, 7.10-6.92 (m, 9H, aromatics), 4.48 (dd, 2H, H_5), 4.36 (s, 2H, $NCH_2C_6H_5$), 3.80 (m, 1H, H_{11a}), 3.50 (at, 1H, H_1), 3.07 (dd, 1H, H_1), 2.92 (dd, 1H, H_{11}), 2.53 (at, 1H, H_{11}); ir (nujol): 1675 cm^{-1} (C=O).

Anal. Calcd. for $C_{20}H_{19}N_3O$: C, 75.68; H, 6.03; N, 13.24. Found: C, 75.57; H, 5.91; N, 13.12.

2-(2-Phenylethyl)-3-oxo-2,3,5,6,11,11a-hexahydro-1*H*-imidazo-[1′,5′:1,6]pyrido[3,4-*b*]indole **Xj**.

Compound **Xj** was prepared from **VIIIj** and *N*,*N*′-carbonyldi-imidazole following the same procedure described for **Xi** and was purified by column chromatography on silica gel, eluting with ethyl acetate. The product **Xj** was crystallized from ethyl acetate, yield 68%, mp 170-172°.

Anal. Calcd. for $C_{21}H_{21}N_3O$: C, 76.10; H, 6.39; N, 12.68. Found: C, 76.02; H, 6.52; N, 12.88.

2-[(3-Ethoxycarbonyl)-1-propyl]-3-methoxycarbonyl-1,2,3,4-tetra-hydro-β-carboline. **XI**.

A mixture of **VII** (7.0 g, 0.03 mole), ethyl 4-bromobutyrate (7.0 g, 0.0033 mole), and potassium carbonate (5.0 g, 0.036 mole) was heated at 100° in an oil bath for 24 hours. The cooled reaction mixture was diluted with water (100 ml), extracted with ethyl

ether and the solvent evaporated. The residue was chromatographed on silica gel column with ethyl acetate-*n*-hexane (1:1) as the eluant to yield 6.5 g (62%) **XI**, as a viscous oil which was used without further purification.

11-Hydroxy-10-methoxycarbonyl-5,6,8,9,11a,12-hexahydro-indolo[3,2-*b*]quinolizine **XII** and 10-Ethoxycarbonyl-11-hydroxy-5,6,8,9,11a,12-hexahydro-indolo[3,2-*b*]quinolizine **XIII**.

Into a well dried flask, under a nitrogen atmosphere, hexane-washed sodium hydride (50% oil dispersion, 1.0 g, 0.02 mole) in anhydrous dimethylformamide (50 ml) was placed and the mixture stirred and ice-cooled. After 5 minutes a solution of the diester **XI** (3.4 g, 0.01 mole) in anhydrous dimethylformamide (50 ml) containing two drops of methanol was added dropwise, over a period of 20 minutes, while the internal temperature was held below 5°. After the addition, the mixture was allowed to warm to room temperature and left while stirring for 20 hours. Water (200 ml) was then added, followed by 10% hydrogen chloride until neutral. The mixture was extracted with chloroform and the solvent evaporated. The resulting residue was chromatographed on silica gel and eluted with chloroform-ethyl acetate (2:1). Compound **XIII** was eluted first, yield 1.2 g, (39%), followed by **XII**, yield 1.4 g, (45%). Compound **XII** was crystallized from benzene, mp 183-185°.

Anal. Calcd. for $C_{17}H_{18}N_2O_3$: C, 68.44; H, 6.08; N, 9.39. Found: C, 68.44; H, 6.09; N, 9.37.

Compound **XIII**, crystallized from benzene, melted at 184-186°.

Anal. Calcd. for $C_{18}H_{20}N_2O_3$: C, 69.21; H, 6.45; N, 8.97. Found: C, 68.97; H, 6.33; N, 8.94.

Both compounds showed the following ^{1}H nmr spectral data (deuteriochloroform): δ 12.17 (s, 1H, O*H*), 10.70 (s, 1H, N*H*), 7.50-6.95 (q and m, 4H, aromatics), 3.78 (dd, 2H, H_6), 3.72 (m, 1H, H_{11a}), 3.40-2.10 (m, 6H, H_9, H_8, H_{12}); ir (nujol): 3300 (OH), 1665 (ester enolic form), 1630 (-C=C- enolic form) cm^{-1}.

5,6,8,9,10,11,11a,12-Octahydro-indolo[3,2-*b*]quinolizin-11-one **XIV**.

The crude mixture of **XII** and **XIII**, obtained from the above reaction (2.6 g) was heated under a nitrogen atmosphere at 150° in dimethyl sulfoxide (30 ml) in the presence of sodium chloride (1.0 g) for 20 hours. After cooling, water and chloroform were added and the organic phase separated. The organic layer was thoroughly washed with water, dried and the solvent evaporated. The resulting crude solid was crystallized from methanol, yield 58%, mp 154-156°; ^{1}H nmr (deuteriochloroform): δ 10.72 (s, 1H, N*H*), 7.50-6.90 (q and m, 4H, aromatics), 3.82 (dd, 2H, H_6), 3.58 (m, 1H, H_{11a}), 3.20-1.80 (m, 8H, H_{10}, H_9, H_8, H_{12}); ir (nujol): 1720 cm^{-1} (C=O).

Anal. Calcd. for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 75.00; H, 6.87; N, 11.40.

3-[(*N*-Formyl)hydrazinocarbonyl]-β-carboline **XVIa**.

A solution of **XV** (1.0 g) in 99% formic acid (10 ml) was heated under reflux for 4 hours. The mixture was evaporated to dryness *in vacuo* and the residue washed with saturated aqueous sodium bicarbonate and crystallized from dimethylformamide-ethanol, yield 1.0 g (90%), mp >300°.

Anal. Calcd. for $C_{13}H_{10}N_4O_2$: C, 61.41; H, 3.96; N, 22.04. Found: C, 61.46; H, 4.09; N, 22.11.

3-[(*N*-Acetyl)hydrazinocarbonyl]-β-carboline **XVIb**.

A mixture of **XV** (1.0 g) in acetic anhydride (20 ml) was stirred at room temperature for 2 days. The mixture was diluted with ice water and made alkaline with 10% ammonium hydroxide. The resulting precipitate was collected by filtration, washed with water and crystallized from dimethylformamide-ethanol, yield 0.9 g (7.6%), mp >300°.

Anal. Calcd. for $C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.89. Found: C, 62.40; H, 4.44; N, 20.71.

3-[(*N*-Benzoyl)hydrazinocarbonyl]-β-carboline **XVIc**.

To a suspension of **XV** (1.0 g) in pyridine (20 ml) benzoyl chloride (0.6 ml) was added, and the mixture refluxed for 1 hour. After cooling, the separated solid was collected and crystallized from dimethylformamide, yield 0.8 g (55%), mp >300°.

Anal. Calcd. for $C_{19}H_{14}N_4O_2$: C, 69.08; H, 4.27; N, 16.96. Found: C, 68.98; H, 4.28; N, 17.03.

3-(1,3,4-Oxadiazol-2-yl)-β-carboline **XVIIa**.

To a solution of **XVIa** (1.0 g) in anhydrous chloroform (50 ml), polyphosphoric esters (PPE, 7.0 g) were added. The mixture was stirred at room temperature for 30 hours, then concentrated *in vacuo*. Ice was added to the residue and the solution was made alkaline with 10% ammonium hydroxide. The precipitated solid was collected, washed with water and ethanol, then crystallized from methanol or ethyl acetate, yield 0.45 g (49%), mp 265-268°; ^{1}H nmr (hexadeuteriodimethylsulfoxide): δ 12.10 (s, 1H, N*H*), 9.28 (s, 1H, H_5 oxadiazole), 9.03 (two s, 2H, H_1 and H_4), 8.24 (d, 1H, H_8), 7.65-7.05 (m, 3H, H_5, H_6, H_7).

Anal. Calcd. for $C_{13}H_8N_4O$: C, 66.09; H, 3.41; N, 23.72. Found: C, 65.88; H, 3.40; N, 23.69.

3-(5-Methyl-1,3,4-oxadiazol-2-yl)-β-carboline **XVIIb**.

Compound **XVIb** (1.0 g) was dissolved in polyphosphoric acid (PPA, 10.0 g) and the mixture was heated at 100-110° for 3 hours. After cooling, ice water (100 ml) was added and the mixture elaborated as described for **XVIIa**. Compound **XVIIb** was crystallized from ethanol, yield 0.54 (58%), mp >300°.

Anal. Calcd. for $C_{14}H_{10}N_4O$: C, 67.19; H, 4.03; N, 22.39. Found: C, 66.91; H, 3.91; N, 22.37.

3-(5-Phenyl-1,3,4-oxadiazole-2-yl)-β-carboline **XVIIc**.

Compound **XVIIc** was prepared from **XVIc** and polyphosphoric acid in 64% yield, following the procedure described for **XVIIb**, mp 302-305° (methanol).

Anal. Calcd. for $C_{19}H_{12}N_4O$: C, 73.06; H, 3.87; N, 17.94. Found: C, 72.96; H, 3.74; N, 17.99.

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