Synthesis of New Derivatives of β-Carboline-hydantoin

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Reaction of tetrahydro-β-carboline-3-carboxylic acids **4a-c** with alkyl and phenyl isocyanates in acetone provide the corresponding 2,5-disubstituted 1,3-dioxo-6*H*-1,2,3,5,11,11a-hexahydroimidazo[1,5-*b*]-β-carbolines **2a-r**.

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The studies by Braestrup *et al.* [1-3], which suggested that ethyl β-carboline-3-carboxylate binds with high affinity at the so-called benzodiazepine receptors in the central nervous system, created considerable interest in biogenically active β-carbolines [4,6] and tetrahydro-β-carbolines [4-6].

On the other hand, in the course of work directed toward the synthesis and biological properties of new tryptophan derivatives [7-11], we have described the preparation of a series of hydantoins **1** [7,10,11].

The above considerations might become an important basis for the design of a new type of compounds **2**, combining tetrahydro-β-carboline and hydantoin rings.

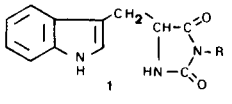


Figure 1

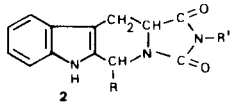
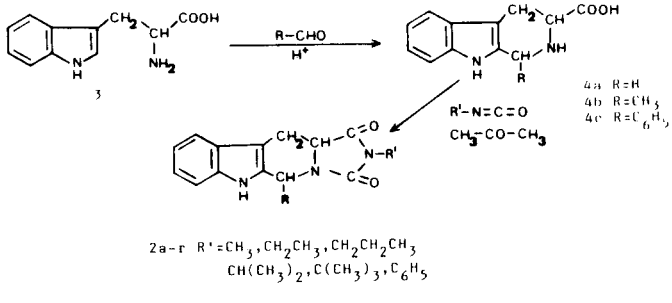


Figure 2

This paper describes the synthesis and physical properties of a series of 2,5-disubstituted 1,3-dioxo-6*H*-1,2,3,5,-11,11a-hexahydroimidazo[1,5-*b*]-β-carbolines **2**.

The route used for the preparation of the compounds **2**, is summarized in Scheme 1.

Scheme 1



The tetrahydro-β-carboline-3-carboxylic acids **4a-c** were obtained by a Pictet-Splengler condensation between L-tryptophan and the appropriate aldehyde in acidic media according to the literature reported procedures [12-15]. Cyclization with acetaldehyde [13-14] and benzaldehyde [15] provided the corresponding separable mixture of the *cis* and *trans* isomers. The stereochemistry of the isomers of **4b** has been reported in the literature [13,16]. The stereochemistry in **4c** was assigned on the basis of their ^{13}C nmr spectra [17,18].

The treatment of (-)-(3*S*)-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid **4a** with alkyl and phenyl isocyanates in acetone gave the corresponding 2-substituted 1,3-dioxo-6*H*-1,2,3,5,11,11a-hexahydroimidazo[1,5-*b*]-β-carbolines **2a-f**. Similarly, the 2,5-disubstituted β-carbolines **2g-r** were isolated by the reactions of (-)-(1*S*,3*S*)-1-methyl- and *cis*-1-phenyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acids **4b,c** with the corresponding alkyl or phenyl isocyanates.

The structural assignment of **2** was established on the basis of elemental analysis and spectral data. The signal assignments of ^{13}C nmr spectra were based on the literature [18,19] reported data (Table 1).

EXPERIMENTAL

Melting points were determined on a Büchi apparatus in open capillaries and are uncorrected. The ir spectra were determined on a Perkin-Elmer 781 spectrophotometer. The ^1H and ^{13}C nmr spectra were recorded on a Varian T-60A (60 MHz) and Varian FT-80A spectrometers, respectively. The elemental analyses were performed by "Centro Nacional de Química Orgánica", Madrid.

(-)-(3*S*)-1,2,3,4-Tetrahydro-β-carboline-3-carboxylic Acid [12-14] (**4a**), (-)-(1*S*,3*S*)-1-Methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid [13-14] (**4b**) and *cis*-1-Phenyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid [15] (**4c**).

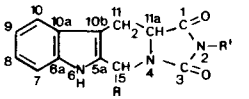
Compounds **4a-c** were obtained according to the literature methods.

General Procedure for the Reaction of **4a-c** with Alkyl and Phenyl Isocyanates.

Alkyl or phenyl isocyanate (0.009 mole) in 30 ml of dry acetone was added to a suspension of tetrahydro-β-carboline-3-carboxylic acid **4** (0.009 mole) in 20 ml of acetone. The reaction mixture was refluxed for 40 hours. Compounds **4a-c** were removed by filtration and the solvent was evaporated to dryness. The residue solidified on trituration with ethanol.

Table 1

^{13}C NMR (δ, ppm) [a] of 2,5-Disubstituted 1,3-Dioxo-6*H*-1,2,3,5,11,11a-hexahydroimidazo[1,5-*b*]-β-carbolines **2a-r**



Compound	R	R'	C_1	C_3	C_{6a}	C5*a*	C_{10a}	C_8	C_9	C_{10}	C_7	C_{10b}	C_{11a}	C_5	C_{11}	R				R'			
2a	H	CH_3	172.9	155.0	136.4	129.7	126.3	121.3	118.8	117.8	111.2	104.9	54.9	37.6	22.4	—	—	—	—	24.4	—	—	—
2b	H	CH_3CH_2	172.7	154.8	136.5	129.8	126.4	121.4	118.9	117.9	111.3	104.9	54.8	37.5	22.6	—	—	—	—	33.1	13.5	—	—
2c	H	$CH_3CH_2CH_2$	172.9	154.9	136.5	129.8	126.3	121.2	118.9	117.8	111.2	104.9	54.9	37.5	22.3	—	—	—	—	39.7	21.1	11.2	—
2d	H	$(CH_3)_2CH$	172.7	154.5	136.3	129.7	126.3	121.3	118.8	117.8	111.2	104.8	54.2	37.4	22.6	—	—	—	—	42.7	19.6	19.5	—
2e	H	$(CH_3)_3C$	173.6	155.3	136.3	129.8	126.3	121.2	118.7	117.7	111.1	104.7	53.9	37.3	22.8	—	—	—	—	56.7	28.4	—	—
2f	H	C_6H_5	171.9	153.8	136.5	129.6	126.3	121.4	118.9	117.9	111.3	105.5	54.8	37.8	22.5	—	—	—	—	132.2	128.9	128.0	126.9
2g	CH_3	CH_3	171.6	155.2	136.3	135.7	126.0	121.2	118.8	117.9	111.1	104.8	57.5	48.1	21.8	20.3	—	—	—	24.1	—	—	—
2h	CH_3	CH_3CH_2	172.8	155.0	136.2	135.9	126.0	121.2	118.9	118.0	111.1	104.9	57.0	48.0	22.0	20.1	—	—	—	32.5	13.3	—	—
2i	CH_3	$CH_3CH_2CH_2$	171.8	155.2	136.5	136.0	126.2	121.4	118.9	118.1	111.3	104.9	57.5	48.3	22.2	20.4	—	—	—	39.6	21.3	11.3	—
2j	CH_3	$(CH_3)_2CH$	171.4	154.8	136.2	135.8	126.0	121.2	118.7	117.9	111.1	104.7	56.9	48.1	21.9	20.1	—	—	—	42.4	19.6	19.4	—
2k	CH_3	$(CH_3)_3C$	172.3	155.8	136.3	136.0	126.1	121.2	118.8	117.9	111.2	104.8	56.8 or 56.7	48.1	22.2	20.5	—	—	—	56.8 or 56.7	28.6	—	—
2l	CH_3	C_6H_5	170.7	154.1	136.4	135.7	126.1	121.4	118.9	118.3	111.2	104.9	57.6	48.4	22.0	20.4	—	—	—	132.1	128.8	127.9	126.9
2m	C_6H_5	CH_3	171.7	154.3	136.8	134.7	125.9	121.4	118.9	118.1	111.3	105.1	55.8	57.8	21.8	140.7	128.2	127.9	127.5	24.1	—	—	—
2n	C_6H_5	CH_3CH_2	171.6	154.1	136.7	134.8	126.0	121.5	118.9	118.2	111.4	105.1	55.8	56.7	21.8	140.8	128.5	128.3	127.5	32.8	13.7	—	—
2o	C_6H_5	$CH_3CH_2CH_2$	172.1	154.4	136.9	135.0	126.1	121.7	119.1	118.4	111.5	105.1	55.9	57.7	22.1	141.0	128.5	127.5	—	39.8	21.2	11.2	—
2p	C_6H_5	$(CH_3)_2CH$	171.6	154.0	136.7	134.8	125.9	121.9	118.8	118.2	111.3	105.1	55.7	57.2	21.8	140.9	128.9	127.3	—	42.7	19.7	19.4	—
2q	C_6H_5	$(CH_3)_3C$	172.5	154.9	136.7	135.0	126.0	121.4	118.8	118.2	111.3	105.1	55.7	56.9 or 56.7	22.1	141.3	128.3	127.1	—	56.9 or 56.7	28.5	—	—
2r	C_6H_5	C_6H_5	170.7	153.3	136.8	134.7	126.0	121.5	118.9	118.3	111.4	105.1	56.0	57.7	21.9	140.7	132.0	128.7	128.3	127.8	127.4	127.1	126.6

[a] DMSO-d_6.

2-Methyl-1,3-dioxo-6*H*-1,2,3,5,11,11a-hexahydroimidazo[1,5-*b*]-β-carboline (**2a**).

This compound was obtained in a yield of 23%, mp 246-248° (ethanol); ir (potassium bromide): ν 3300 (NH), 1765 (C=O), 1700 (N-CO-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.3-2.7 (m, 2H, CH_2), 2.9 (s, 3H, CH_3), 4.0-5.0 (m, 3H, CH, CH_2-N), 6.7-7.3 (m, 4H, ArH), 10.6 (s, 1H, NH).

Anal. Calcd. for $C_{14}H_{13}N_3O_2$: C, 65.88; H, 5.10; N, 16.47. Found: C, 65.56; H, 5.38; N, 16.19.

2-Ethyl-1,3-dioxo-6*H*-1,2,3,5,11,11a-hexahydroimida[1,5-*b*]-β-carboline (**2b**).

The residue was purified by silica gel column chromatography (ethyl acetate) as an oil, yield 18%; ir (potassium bromide): ν 3020 (NH), 1770 (C=O), 1705 (N-CO-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.1 (t, 3H, CH_3), 2.3-2.8 (m, 2H, CH_2), 3.3 (q, 2H, CH_2-ethyl), 3.9-4.9 (m, 3H, CH, CH_2-N), 6.4-7.3 (m, 4H, ArH), 10.6 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.91; H, 5.57; N, 15.61. Found: C, 66.78; H, 5.64; N, 15.70.

2-*n*-Propyl-1,3-dioxo-6*H*-1,2,3,5,11,11a-hexahydroimidazo[1,5-*b*]-β-carboline (**2c**).

The residue was purified with silica gel column chromatography (ethyl acetate) as an oil, yield 20%; ir (potassium bromide): ν 3360 (NH), 1770 (C=O), 1710 (N-CO-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.9 (t, 3H, CH_3), 1.2-1.9 (m, 2 H, CH_2-propyl), 2.4-2.8 (m, 2H, CH_2), 3.5 (t, 2H, N-CH_2-propyl), 4.2-5.2 (m, 3H, CH, CH_2-N), 6.8-7.6 (m, 4H, ArH), 10.9 (s, 1H, NH).

Anal. Calcd. for $C_{16}H_{17}N_3O_2$: C, 67.84; H, 6.01; N, 14.84. Found: C, 67.59; H, 5.94; N, 14.67.

2-Isopropyl-1,3-dioxo-6*H*-1,2,3,5,11,11a-hexahydroimidazo-[1,5-*b*]-β-carboline (**2d**).

The residue was purified with silica gel column chromatography (ethyl acetate) as an oil, yield 15%; ir (potassium bromide): ν 3340 (NH), 1765 (C=O), 1700 (N-CO-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.3 (d, 6H, $2CH_3$), 2.3-3.4 (m, 3H, CH_2, CH-isopropyl), 4.0-5.0 (m, 3H, CH, CH_2-N), 6.7-7.4 (m, 4H, ArH), 10.7 (s, 1H, NH).

Anal. Calcd. for $C_{16}H_{17}N_3O_2$: C, 67.84; H, 6.01; N, 14.84. Found: C, 67.66; H, 6.20; N, 14.92.

2-*t*-Butyl-1,3-dioxo-6*H*-1,2,3,5,11,11a-hexahydroimidazo[1,5-*b*]-β-carboline (**2e**).

This compound was obtained in a yield of 15%, mp 208-210° (ethanol); ir (potassium bromide): ν 3320 (NH), 1760 (C=O), 1700 (N-CO-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.6 (s, 9H, $3CH_3$), 2.5-2.8 (m, 2H, CH_2), 4.0-5.0 (m, 3H, CH, CH_2-N), 6.7-7.4 (m, 4H, ArH), 10.7 (s, 1H, NH).

Anal. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.69; H, 6.40; N, 14.14. Found: C, 68.42; H, 6.78; N, 14.04.

2-Phenyl-1,3-dioxo-6*H*-1,2,3,5,11,11a-hexahydroimidazo[1,5-*b*]-β-carboline (**2f**).

This compound was obtained in a yield of 31%, mp 236-238° (ethanol); ir (potassium bromide): ν 3330 (NH), 1760 (C=O), 1700 (N-CO-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.3-2.9 (m, 2H, CH_2), 4.1-5.0 (m, 3H, CH, CH_2-N), 6.7-7.4 (m, 9H, ArH), 10.7 (s, 1H, NH).

Anal. Calcd. for $C_{19}H_{15}N_3O_2$: C, 71.92; H, 4.73; N, 13.25. Found: C, 71.68; H, 4.84; N, 12.91.

2,5-Dimethyl-1,3-dioxo-6*H*-1,2,3,5,11,11a-hexahydroimidazo-[1,5-*b*]-β-carboline (**2g**).

This compound was obtained in a yield of 28%, mp 250-252° (ethanol); ir (potassium bromide): ν 3310 (NH), 1760 (C=O), 1690 (N-CO-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.8 (d, 3H, CH_3), 2.4-2.7 (m, 2H, CH_2), 2.9 (s, 3H, N-CH_3), 4.2 (m, 1H, CH), 4.9 (q, 1H, CH-methyl), 6.8-7.5 (m, 4H, ArH), 10.6 (s, 1H, NH).

Anal. Calcd. for $C_{15}H_{15}N_3O_2$: C, 66.91; H, 5.58; N, 15.61. Found: C, 67.22; H, 5.90; N, 15.30.

2-Ethyl-5-methyl-1,3-dioxo-6*H*-1,2,3,5,11,11a-hexahydroimidazo-[1,5-*b*]-β-carboline (**2h**).

This compound was obtained in a yield of 39%, mp 232-234° (ethanol); ir (potassium bromide): ν 3320 (NH), 1760 (C=O), 1690 (N-CO-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.1 (t, 3H, CH_3-ethyl), 1.9 (d, 3H, CH_3), 2.3-2.8 (m, 2H, CH_2), 3.4 (q, 2H, CH_2-ethyl), 4.3 (m, 1H, CH), 4.9 (q, 1H, CH-methyl), 6.8-7.6 (m, 4H, ArH), 10.9 (s, 1H, NH).

Anal. Calcd. for $C_{16}H_{17}N_3O_2$: C, 67.84; H, 6.01; N, 14.84. Found: C, 67.85; H, 5.81; N, 14.68.

5-Methyl-2-*n*-propyl-1,3-dioxo-6*H*-1,2,3,5,11,11a-hexahydroimidazo[1,5-*b*]-β-carboline (**2i**).

This compound was obtained in a yield of 33%, mp 208-210° (ethanol); ir (potassium bromide): ν 3320 (NH), 1760 (C=O), 1690 (N-CO-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.9 (t, 3H, CH_3-propyl), 1.2-1.8 (m, 2H, CH_2-propyl), 1.9 (d, 3H, CH_3), 2.3-2.7 (m, 2H, CH_2), 3.4 (t, 2H, N-CH_2-propyl), 4.1 (m, 1H, CH), 4.9 (q, 1H, CH-methyl), 6.8-7.6 (m, 4H, ArH), 10.8 (s, 1H, NH).

Anal. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.69; H, 6.40; N, 14.14. Found: C, 68.66;, H, 6.70; N, 14.05.

2-Isopropyl-5-methyl-1,3-dioxo-6*H*-1,2,3,5,11,11a-hexahydroimidazo[1,5-*b*]-β-carboline (**2j**).

This compound was obtained in a yield of 25%, mp 194-196° (ethanol); ir (potassium bromide): ν 3370 (NH), 1770 (C=O), 1700 (N-CO-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.3 (d, 6H, CH_3-isopropyl), 1.8 (d, 3H, CH_3), 2.3-3.7 (m, 3H, CH_2, CH-isopropyl), 4.2 (m, 1H, CH), 4.9 (q, 1H, CH-methyl), 6.8-7.6 (m, 4H, ArH), 11.0 (s, 1H, NH).

Anal. Calcd. for $C_{17}H_{19}N_3O_2$: C, 68.69; H, 6.40; N, 14.14. Found: C, 68.35; H, 6.57; N, 13.80.

2-*t*-Butyl-5-methyl-1,3-dioxo-6*H*-1,2,3,5,11,11a-hexahydroimidazo-[1,5-*b*]-β-carboline (**2k**).

This compound was obtained in a yield of 26%, mp 190-192° (ethanol); ir (potassium bromide): ν 3330 (NH), 1760 (C=O), 1700 (N-CO-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.6 (s, 9H, $3CH_3$), 1.9 (d, 3H, CH_3), 2.4-2.7 (m, 2H, CH_2), 4.1 (m, 1H, CH), 4.8 (q, 1H, CH-methyl), 6.8-7.5 (m, 4H, ArH), 10.9 (s, 1H, NH).

Anal. Calcd. for $C_{18}H_{21}N_3O_2$: C, 69.45; H, 6.75; N, 13.50. Found: C, 69.15; H, 6.85; N, 13.35.

5-Methyl-2-phenyl-1,3-dioxo-6*H*-1,2,3,5,11,11a-hexahydroimidazo-[1,5-*b*]-β-carboline (**2l**).

This compound was obtained in a yield of 35%, mp 240-242° (ethanol); ir (potassium bromide): ν 3360 (NH), 1760 (C=O), 1705 (N-CO-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.9 (d, 3H, CH_3), 2.4-2.7 (m, 2H, CH_2), 4.4 (m, 1H, CH), 4.9 (q, 1H, CH-methyl), 6.7-7.5 (m, 9H, ArH), 10.8 (s, 1H, NH).

Anal. Calcd. for $C_{20}H_{17}N_3O_2$: C, 72.51; H, 5.14; N, 12.69. Found: C, 72.68; H, 5.21; N, 12.59.

2-Methyl-5-phenyl-1,3-dioxo-6*H*-1,2,3,5,11,11a-hexahydroimidazo[1,5-*b*]-β-carboline (**2m**).

This compound was obtained in a yield of 75% mp 254-256° (ethanol); ir (potassium bromide): ν 3350 (NH), 1765 (C=O), 1700 (N-CO-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.5 (s, 3H, CH_3), 2.8-3.3 (m, 2H, CH_2), 4.0 (m, 1H, CH), 5.4 (s, 1H, CH-phenyl), 6.4-7.2 (m, 9H, ArH), 10.1 (s, 1H, NH).

Anal. Calcd. for $C_{20}H_{17}N_3O_2$: C, 72.51; H, 5.14; N, 12.69. Found: C, 72.33; H, 4.94; N, 12.55.

2-Ethyl-5-phenyl-1,3-dioxo-6*H*-1,2,3,5,11,11a-hexahydroimidazo[1,5-*b*]-β-carboline (**2n**).

This compound was obtained in a yield of 66%, mp 232-234° (ethanol); ir (potassium bromide): ν 3360 (NH), 1765 (C=O), 1710 (N-CO-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.0 (t, 3H, CH_3), 3.0-3.5 (m, 4H, CH_2, CH_2-ethyl), 4.4 (m, 1H, CH), 5.7 (s, 1H, CH-phenyl), 6.7-7.6 (m, 9H, ArH), 10.4 (s, 1H, NH).

Anal. Calcd. for $C_{21}H_{19}N_3O_2$: C, 73.04; H, 5.51; N, 12.17. Found: C, 73.22; H, 5.69; N, 12.18.

5-Phenyl-2-*n*-propyl-1,3-dioxo-6*H*-1,2,3,5,11,11a-hexahydroimidazo[1,5-*b*]-β-carboline (**2o**).

This compound was obtained in a yield of 85%, mp 140-142° (ethanol); ir (potassium bromide): ν 3340 (NH), 1765 (C=O), 1705 (N-CO-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 0.8 (t, 3H, CH_3), 1.3-1.8 (m, 2H, CH_2-propyl), 2.7-3.1 (m, 2H, CH_2), 3.3 (t, 2H, N-CH_2-propyl), 4.5 (m, 1H, CH), 5.8 (s, 1H, CH-phenyl), 6.8-7.6 (m, 9H, ArH), 10.6 (s, 1H, NH).

Anal. Calcd. for $C_{22}H_{21}N_3O_2$: C, 73.54; H, 5.85; N, 11.70. Found: C, 73.62; H, 5.74; N, 11.40.

2-Isopropyl-5-phenyl-1,3-dioxo-6*H*-1,2,3,5,11,11a-hexahydroimidazo[1,5-*b*]-β-carboline (**2p**).

This compound was obtained in a yield of 59%, mp 210-212° (ethanol); ir (potassium bromide): ν 3450 (NH), 1765 (C=O), 1700 (N-CO-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.3 (d, 6H, $2CH_3$), 2.3-3.3 (m, 3H, CH_2, CH-isopropyl), 4.3 (m, 1H, CH), 5.7 (s, 1H, CH-phenyl), 6.7-7.5 (m, 9H, ArH), 10.4 (s, 1H, NH).

Anal. Calcd. for $C_{22}H_{21}N_3O_2$: C, 73.54; H, 5.85; N, 11.70. Found: C, 73.23; H, 5.86; N, 11.40.

2-*t*-Butyl-5-phenyl-1,3-dioxo-6*H*-1,2,3,5,11,11a-hexahydroimidazo-[1,5-*b*]-β-carboline (**2g**).

This compound was obtained in a yield of 46%, mp 233-235° (ethanol); ir (potasium bromide): ν 3450 (NH), 1760 (C=O), 1700 (N-CO-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 1.5 (s, 9H, $3CH_3$), 2.6-3.2 (m, 2H, CH_2), 4.2 (m, 1H, CH), 5.6 (s, 1H, CH-phenyl), 6.6-7.3 (m, 9H, ArH), 10.3 (s, 1H, NH).

Anal. Calcd. for $C_{23}H_{23}N_3O_2$: C, 73.99; H, 6.17; N, 11.26. Found: C, 74.01; H, 6.20; N, 11.25.

2,5-Diphenyl-1,3-dioxo-6*H*-1,2,3,5,11,11a-hexahydroimidazo-[1,5-*b*]-β-carboline (**2r**).

This compound was obtained in a yield of 58%, mp 238-240° (ethanol); ir (potassium bromide): ν 3420 (NH), 1775 (C=O), 1720 (N-CO-N) cm^{-1}; ^1H nmr (DMSO-d_6): δ 2.3-2.6 (m, 2H, CH_2), 4.5 (m, 1H, CH), 5.7 (s, 1H, CH-phenyl), 6.7-7.5 (m, 14H, ArH), 10.4 (s, 1H, NH).

Anal. Calcd. for $C_{25}H_{19}N_3O_2$: C, 76.34; H, 4.83; N, 10.69. Found: C, 76.40; H, 4.81; N, 10.61.

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