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Synthesis of Imidazo[1′,5′:1,2]pyrido [3,4-*b*]indole Derivatives

Magdolna Solymár, Márta Palkó, Tamás Martinek, and **Ferenc Fülöp***

Institute of Pharmaceutical Chemistry, University of Szeged, H-6701 Szeged, Hungary

Summary. The reactions of 1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid and its ethyl ester with alkyl and aryl isothiocyanates under mild conditions resulted in the corresponding thiohydantoin-fused tetrahydro-β-carbolines. Treatment of the ethyl ester with isocyanates furnished ethyl 2-alkyl- or arylcarbamoyl-1,2,3,4-tetrahydro-β-carboline-1-carboxylates which were transformed to hydantoin-fused tetrahydro-β-carbolines. The structures of the thiohydantoin compounds, involving two conformers and the presence of keto-enol tautomerism, were determined by NMR spectroscopy.

Keywords. β-Carbolines; Hydantoins; Thiohydantoins; Keto-enol tautomerism.

Introduction

The β-carboline structure is present in important natural compounds, and its derivatives exert various pharmacological effects on the benzodiazepine receptors in the mammalian nervous system [1–4]. It is also found as a structural element of compounds exerting anticancer potential, analgesic activity, or oxytocin antagonism [5]. In 1994, in a programme with the goal of developing new drugs affecting the central nervous system, *Lopez-Rodriguez et al.* have studied the ring-closure possibilities of the 1,2,3,4-tetrahydro-β-carboline skeleton through the reaction of 1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid (**1**) with alkyl and aryl isocyanates under vigorous conditions (refluxing for 40 h in acetone or *DMSO*). In their case the corresponding hydantoin analogues have been formed [6]. Some further derivatives of the 4-ring hydantoins exert pharmacological effects on α_1-adrenoreceptors [7]. However, the synthesis of thiohydantoin derivatives remained unsolved under the circumstances applied: in the reactions of **1** and isothiocyanates, decarboxylation took place, and open-chain thiourea derivatives have been isolated instead of the desired thiohydantoins [6].

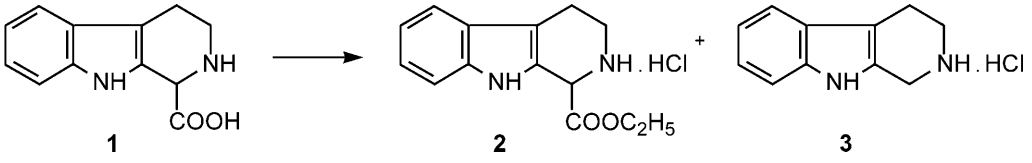
Our present aim is to attempt the synthesis of thiohydantoin-fused imidazo [1′,5′:1,2]pyrido[3,4-*b*]indole derivatives under mild conditions based on the results of similar ring closures [8–13], starting from ethyl 1,2,3,4-tetrahydro-β-carboline-1-carboxylate (**2**).

* Corresponding author. E-mail: fulop@pharma.szote.u-szeged.hu

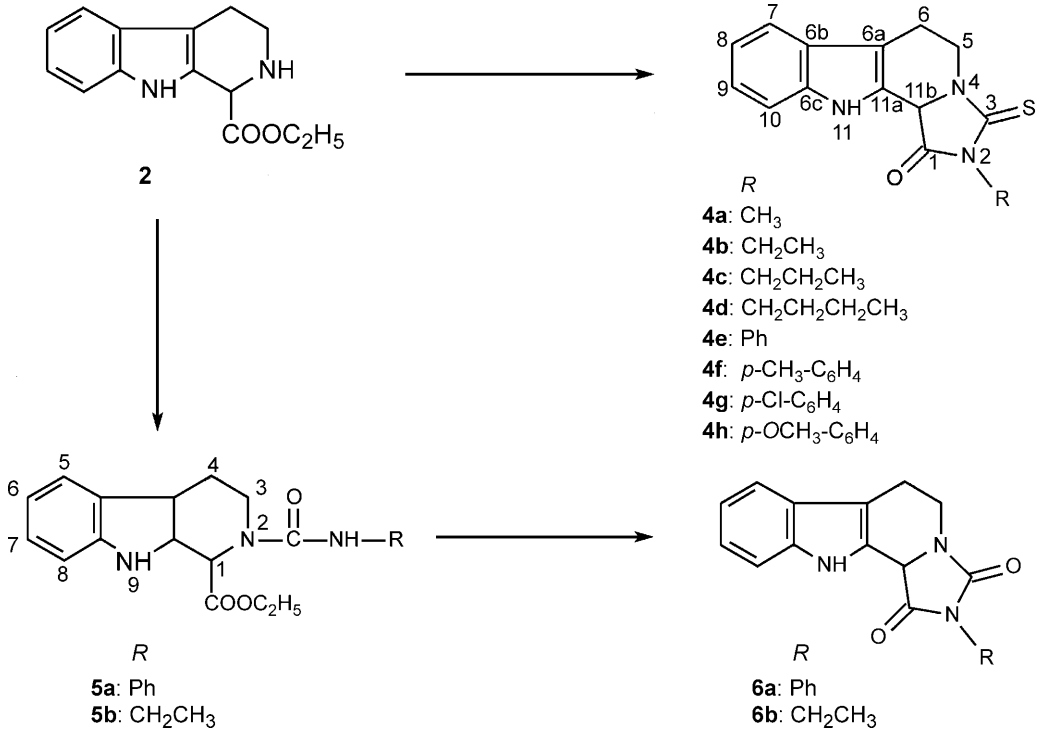
Results and Discussion

1,2,3,4-Tetrahydro-β-carboline-1-carboxylic acid (**1**) was obtained from tryptamine hydrochloride and glyoxylic acid [14]. Racemic **1** was esterified by two methods (Scheme 1): refluxing in ethanol with thionyl chloride (method A) or reaction with dry hydrogen chloride gas in ethanol (method B) [14]. Both methods resulted besides **2** in a by-product, the hydrochloride of 1,2,3,4-tetrahydronorharmane (**3**) as a consequence of decarboxylation. This side-product could be filtered off from the hot ethanolic solutions. Method A gave **2** in a somewhat higher yield (A: 76%, B: 57%).

When the ester base **2** was combined with alkyl and aryl isothiocyanates at room temperature in methanol, the corresponding target thiohydantoins **4** could be filtered off from the reaction mixtures after stirring overnight (Scheme 2). Generally, the yields were fair to good (41–74%), except in the case of **4d** where it was only 16%. No decarboxylation was observed during the reactions, and no



Scheme 1



Scheme 2

intermediates or by-products could be isolated from the residues. From the reactions of **1** and isothiocyanates under the same conditions, but with sodium methylate as the catalyst, the thiohydantoins **4** were obtained in rather low yields.

In the reactions of **2** and ethyl and phenyl isocyanates under similarly mild conditions, the corresponding urea derivatives **5** were formed as crystalline products. These were cyclized by refluxing in ethanol for one day under hydrochloric acid catalysis. Hydantoin compounds **6a** and **6b** were formed in 56 and 37% yield; and no other products could be isolated.

The low solubility and susceptibility to degradation of **4a**–**h** made the proof of the thiohydantoin structure by NMR spectroscopy difficult. Hydantoin derivatives can undergo keto-enol tautomerism [6]. In addition, the saturated nitrogen containing heterocycles tend to populate more than one low-energy conformation in solution due to the relative ease of nitrogen inversion [15]. Bearing in mind the above possible processes, the observed line broadening in pyridine-d_5 at 300 K was not surprising. In order to slow down the chemical exchange we decreased the temperature to 243 K. At this temperature two exchanging species were observed. The results of ^{1}H and ^{13}C resonance assignment by means of COSY, HSQC, and HMBC for **4b** as an example demonstrated that the two species have the same spin connectivity and similar chemical shifts. Concerning the constitution, the missing H-11b signal and the chemical shift values for C-11b (71.25 and 67.96 ppm) pointed to the predominance of the enol form for both species; however, the presence of the keto form cannot be excluded. In addition to the arguments described above, the ^{13}C chemical shifts relating to C-1 (170.06 and 169.03 ppm) are between the values for the possible enol (*ca.* 90 ppm) and keto (*ca.* 220 ppm) forms. The chemical shifts of C-11b (71.25 and 67.96 ppm) are also

Table 1. ^{1}H and ^{13}C NMR data of the conformers **4bA** and **4bB** dissolved in pyridine-d_5

	4bA δ/ppm		**4bB** δ/ppm	
	^{1}H	^{13}C	^{1}H	^{13}C
1	–	170.06	–	169.03
3	–	182.8	–	184.74
5	2.52, 4.98	40.46	3.88, 5.44	42.62
6	2.44, 2.84	20.21	2.76, 2.93	19.94
6a	–	112.45	–	111.65
6b	–	125.85	–	126.21
6c	–	138.24	–	138.30
7	6.96	112.23	7.35	120.17
8	7.05	123.36	7.74	119.64
9	7.17	119.18	7.43	112.8
10	7.51	118.92	7.33	123.48
11	12.4	–	13.41	–
11a	–	121.94	–	122.75
11b	–[b]	71.25[a]	–[b]	67.96[a]

[a] δ values between those for the enol (80 ppm) and keto (56 ppm) forms (C-11b) [5]; [b] the methine proton at C-11b is missing because of the suggested keto-enol tautomerism and HD exchange

average values in both species between the chemical shifts found in the literature [6] for the enol (80 ppm) and keto (56 ppm) forms. These observations, together with the missing H-11b, suggest a rapid acid-catalyzed equilibrium between the two tautomeric forms in both conformers. From these data we may conclude that the NMR signals belong to two exchanging conformational isomers which are predominantly the enol forms of the thiohydantoin derivatives. The two conformers are designated by **4bA** and **4bB**; the chemical shifts given in Table 1.

In $CDCl_3$ solutions of **4**, broadened signals were obtained which would also suggest the possibility of a conformational equilibrium. The compounds **4** were satisfactorily soluble in *DMSO*-d_6, where characteristic but still slightly broadened signals appeared. The geometry of the two conformations could not be established, but the conformational equilibrium is obviously due to nitrogen inversion [15].

Conclusions

It was proven that 2-substituted 5,6,11,11b-tetrahydro-1-oxo-1*H*-imidazo[1′,5′:1,2] pyrido[3,4-*b*]indole-3-thiones **4** can be prepared under mild conditions from 1,2,3,4-tetrahydro-β-carboline-1-carboxylic acid (**1**) and its ethyl ester **2**. The structures of the thiohydantoin compounds, involving two conformers and the presence of keto-enol tautomerism, were determined by NMR spectroscopy.

Experimental

Melting points were determined with a Kofler apparatus at a heating rate of 4°C/min; the values are not corrected. ^{1}H NMR spectra were recorded in 5 mm tubes in the appropriate solvents on a Bruker DRX 400 instrument at 400 MHz. IR spectra were measured in KBr disks on a Perkin Elmer Paragon 1000PC FT-IR spectrometer. Analytical data were obtained by a Heraeus apparatus; they were in favourable agreement with the calculated values. The cyanates and isothiocyanates used were commercial products (Aldrich, Fluka). Yields in parentheses refer to reactions starting from **1**.

Ethyl 1,2,3,4-tetrahydro-β-carboline-1-carboxylate (**2**)

Method A: Absolute EtOH (18 cm^3) was cooled below -10°C. $SOCl_2$ (1.59 cm^3, 21.8 mmol) was added dropwise, the temperature being kept below -10°C. Then, **1** (4.3 g, 19.8 mmol) was added to the mixture, which was first stirred for 0.5 h at 0°C and then for 3 h at room temperature, and finally refluxed for 1 h.

Method B [14]: A suspension of 7.33 g dried and well-powdered **1** (33.8 mmol) in 150 cm^3 absolute EtOH was saturated with dry HCl gas under stirring, and the mixture was then refluxed for 2 h.

The crystalline product was filtered off from the hot solution in both cases and was identified as 1,2,3,4-tetrahydronorharmane (**3**; A: 1.28 g, 6.1 mmol, 18%; B: 2.45 g, 11.7 mmol, 35%). EtOH was evaporated under reduced pressure, and diethyl ether was added to promote crystallization. From the hydrochloride, the free base was obtained by treatment with aqueous NaOH and extraction with $CHCl_3$ followed by drying (Na_2SO_4) and evaporation. The product was purified by column chromatography on silica gel with a mixture of toluene: MeOH = 4:1 as the eluent. Method A resulted in a yield of 76% **2**, whereas method B gave a yield of 57%.

Yellowish needles; m.p.: 107–110°C (Et_2O; Ref. [14]: m.p.: 110–111°C); IR (KBr): $\bar{\nu} = 3363$, 1715, 1252 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.25$ (t, $J = 7.05$ Hz, CH_3), 2.54–2.63 (m, H-6a,b),

2.95–3.05 (m, H-5a), 3.06–3.16 (m, H-5b), 4.08–4.23 (m, CH_2), 4.67 (s, H-11b), 6.95 (t, $J = 7.30$ Hz, H-8), 7.04 (t, $J = 7.30$ Hz, H-9), 7.33 (d, $J = 7.8$ Hz, H-7), 7.39 (d, $J = 7.8$ Hz, H-10), 10.64 (s, H-11) ppm.

2-Substituted 5,6,11,11b-tetrahydro-1-oxo-1H-imidazo[1′,5′:1,2]pyrido[3,4-b]indole-3-thiones (**4a**–**4h**)*; general procedure*

The appropriate isothiocyanate (0.8 mmol) was added to 195 mg (0.8 mmol) **2** dissolved in 40 cm^3 MeOH. The mixture was stirred overnight, and the crystalline product was filtered off and recrystallized. The synthesis was repeated from the acid **1** in every case, the same method being used with the application of 1.6 mmol sodium methylate as catalyst. The analytical data were identical.

2-Methyl-5,6,11,11b-tetrahydro-1-oxo-1H-imidazo[1′,5′:1,2]pyrido[3,4-b]indole-3-thione (**4a**; $C_{14}H_{13}N_3OS$)

Light-pink crystals; m.p.: 195–200°C (EtOH/$CHCl_3$); yield: 66% (16%); IR (KBr): $\bar{\nu} = 3447$, 3399, 3373, 1742, 1728, 1311 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.68$–2.88 (m, H-6a,b), 2.95 (bs, H-5a), 3.21 (s, CH_3), 4.92 (m, H-5b), 7.02 (t, $J = 7.55$ Hz, H-8), 7.15 (t, $J = 7.55$ Hz, H-9), 7.46 (d, $J = 7.55$ Hz, H-7), 7.5 (d, $J = 7.55$ Hz, H-10), 10.52 (s, H-11) ppm.

2-Ethyl-5,6,11,11b-tetrahydro-1-oxo-1H-imidazo[1′,5′:1,2]pyrido[3,4-b]indole-3-thione (**4b**; $C_{15}H_{15}N_3OS$)

White crystals; m.p.: 203–211°C (EtOH/$CHCl_3$); yield: 62% (27%); IR (KBr): $\bar{\nu} = 3460$, 3389, 1742, 1727, 1271 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 1.19$ (t, $J = 7.30$ Hz, CH_3), 2.68–2.85 (m, H-6a,b), 2.91 (bs, H-5a), 3.72–3.91 (m, CH_2), 4.91 (m, H-5b), 7.03 (t, $J = 7.3$ Hz, H-8), 7.16 (t, $J = 7.30$ Hz, H-9), 7.47 (d, $J = 7.8$ Hz, H-7), 7.52 (d, $J = 7.8$ Hz, H-10), 10.49 (s, H-11).

2-Propyl-5,6,11,11b-tetrahydro-1-oxo-1H-imidazo[1′,5′:1,2]pyrido[3,4-b]indole-3-thione (**4c**; $C_{16}H_{17}N_3OS$)

White crystals; m.p.: 188–190°C (EtOH/$CHCl_3$); yield: 41% (19%); IR (KBr): $\bar{\nu} = 3451$, 3389, 1743, 1727 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 0.87$ (t, $J = 7.55$ Hz, CH_3), 1.66 (m, CH_2), 2.63–2.88 (m, H-6a,b), 2.96 (bs, H-5a), 3.61–3.83 (m, CH_2), 4.92 (m, H-5b), 7.48 (d, $J = 8.3$ Hz, H-7), 7.02 (t, $J = 7.3$ Hz, H-8), 7.15 (t, $J = 7.8$, H-9), 7.51 (d, $J = 7.8$, H-10), 8.31 (bs, H-11) ppm.

2-Butyl-5,6,11,11b-tetrahydro-1-oxo-1H-imidazo[1′,5′:1,2]pyrido[3,4-b]indole-3-thione (**4d**; $C_{17}H_{19}N_3OS$)

White crystals; m.p.: 186–188°C (EtOH/$CHCl_3$); yield: 16% (5%); IR (KBr): $\bar{\nu} = 3456$, 3387, 1743, 1724 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 0.90$ (t, $J = 7.30$ Hz, CH_3), 1.23–1.35 (m, CH_2), 1.55–1.69 (m, CH_2), 2.63–2.87 (m, H-6a,b), 2.96 (bs, H-5a), 3.66–3.87 (m, CH_2), 4.91 (m, H-5b), 7.03 (t, $J = 7.55$ Hz, H-8), 7.15 (t, $J = 7.55$, H-9), 7.46 (d, $J = 8.06$ Hz, H-7), 7.52 (d, $J = 8.06$ Hz, H-10), 10.44 (s, H-11) ppm.

2-Phenyl-5,6,11,11b-tetrahydro-1-oxo-1H-imidazo [1′,5′:1,2]pyrido[3,4-b]indole-3-thione (**4e**; $C_{19}H_{15}N_3OS$)

Light-pink crystals; m.p.: 208–214°C (EtOH/$CHCl_3$); yield: 57% (31%); IR (KBr): $\bar{\nu} = 3423$, 3371, 3250, 1754, 1744, 1285 cm^{-1}; ^{1}H NMR (*DMSO*-d_6): $\delta = 2.77$–2.90 (m, H-6a), 2.90–3.02 (m, H-6b),

3.12 (bs, H-5a), 5.12 (bs, H-5b), 7.06 (t, $J = 7.81$, H-8), 7.17 (t, $J = 7.81$, H-9), 7.30–7.37 (m, H-7 and H-10), 7.46–7.58 (m, phenyl), 10.54 (s, H-11) ppm.

2-(p-Tolyl)-5,6,11,11b-tetrahydro-1-oxo-1H-imidazo[1′,5′:1,2]pyrido[3,4-b]indole-3-thione (**4f**; $C_{20}H_{17}N_3OS$)

Light-brown crystals; m.p.: 187–189°C (EtOH/$CHCl_3$); yield: 67% (36%); IR (KBr): $\bar{\nu} = 3442$, 3408, 1752, 1736, 1284 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.35$ (s, CH_3), 2.78–2.88 (m, H-6a), 2.89–3.00 (m, H-6b), 3.10 (s, H-5a), 5.11 (bs, H-5b), 7.05 (t, $J = 7.55$, H-8), 7.12–7.23 (m, H-9, H-7 and H-10), 7.31 (d, $J = 8.06$ Hz, phenyl), 7.52 (d, $J = 7.81$ Hz, phenyl), 10.51 (s, H-11) ppm.

2-(p-Chlorophenyl)-5,6,11,11b-tetrahydro-1-oxo-1H-imidazo[1′,5′:1,2]pyrido[3,4-b]indole-3-thione (**4g**; $C_{19}H_{14}ClN_3OS$)

Light-pink crystals; m.p.: 202–209°C (EtOH/$CHCl_3$); yield: 59% (28%); IR (KBr): $\bar{\nu} = 3419$, 3396, 1745, 1730, 1281, 1253 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.76$–3.01 (m, H-6a,b), 3.08 (bs, H-5a) 5.09 (bs, H-5b), 7.06 (t, $J = 7.55$ Hz, H-8), 7.17 (t, $J = 7.55$ Hz, H-9), 7.39 (d, $J = 8.56$ Hz, phenyl), 7.49–7.56 (m, H-7 and H-10), 7.62 (d, $J = 8.56$ Hz, phenyl), 10.56 (s, H-11) ppm.

2-(p-Methoxyphenyl)-5,6,11,11b-tetrahydro-1-oxo-1H-imidazo[1′,5′:1,2]pyrido[3,4-b]indole-3-thione (**4h**; $C_{20}H_{17}N_3O_2S$)

Light-brown crystals; m.p.: 183–185°C (EtOH/$CHCl_3$); yield: 74% (21%); IR (KBr): $\bar{\nu} = 3363$, 1715, 1252, 1246, 1236 cm^{-1}; ^1H NMR (*DMSO*-d_6): $\delta = 2.73$–3.01 (m, H-6a,b), 3.10 (bs, H-5a), 3.32 (s, OCH_3), 5.10 (bs, H-5b), 6.95–7.09 (m, H-8, H-7 and H-10), 7.16 (t, $J = 7.55$ Hz, H-9), 7.24 (d, $J = 7.81$ Hz, phenyl), 7.53 (d, $J = 7.81$ Hz, phenyl), 10.51 (s, H-11) ppm.

2-Substituted ethyl carbamoyl-1,2,3,4-tetrahydro-β-carboline-1-carboxylates (**5a**,**b**)*; general procedure*

The appropriate isocyanate (0.8 mmol) was added to 195 mg (0.8 mmol) **2** dissolved in 40 cm^3 MeOH. The mixture was stirred overnight, and the crystalline product was filtered off and recrystallized from EtOH and diethyl ether.

Ethyl 2-ethylcarbamoyl-1,2,3,4-tetrahydro-β-carboline-1-carboxylate (**5a**; $C_{17}H_{21}N_3O_3$)

Pale-yellow crystals; m.p.: 167–170°C (EtOH/Et_2O); yield: 66%; IR (KBr): $\bar{\nu} = 3338$, 3290, 1726, 1606 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.19$ (t, $J = 7.3$ Hz, CH_3), 1.30 (t, $J = 7.3$ Hz, CH_3, ester), 2.76–2.94 (m, H-6a,b), 3.30–3.39 (m, CH_2), 3.53 (ddd, $J = 4.53$, 11.33, 13.6 Hz, H-5a), 3.92 (ddd, $J = 1.51$, 5.04, 13.6 Hz, H-5b), 4.18–4.31 (m, CH_2, ester), 4.65 (t, $J = 4.5$ Hz, H-11b), 5.93 (s, NH), 7.11 (t, $J = 7.8$ Hz, H-8), 7.2 (t, $J = 7.81$ Hz, H-9), 7.36 (d, $J = 7.8$ Hz, H-7), 7.49 (d, $J = 7.8$ Hz, H-10), 8.28 (s, H-11) ppm.

Ethyl 2-phenylcarbamoyl-1,2,3,4-tetrahydro-β-carboline-1-carboxylate (**5b**; $C_{21}H_{21}N_3O_3$)

Pale-yellow crystals; m.p.: 145–150°C (EtOH/Et_2O); yield: 61%; IR (KBr): $\bar{\nu} = 3386$, 3289, 1723, 1630, 1622 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 1.31$ (t, $J = 7.3$ Hz, CH_3), 2.84–3.03 (m, H-6a,b), 3.67 (ddd, $J = 4.28$, 11.83, 13.6 Hz, H-5a), 4.13 (ddd, $J = 1.02$, 5.04, 13.6 Hz, H-5b), 4.23–4.32 (m, CH_2), 5.99 (bs, H-11b), 6.62 (s, NH), 7.06 (t, $J = 7.55$ Hz, phenyl), 7.13 (t, $J = 7.3$ Hz, H-8), 7.21 (t, $J = 8.06$ Hz, H-9), 7.31 (t, $J = 7.3$ Hz, phenyl), 7.36–7.41 (m, phenyl and H-7), 7.51 (d, $J = 8.06$ Hz, H-10), 8.31 (s, H-11) ppm.

2-Substituted 5,6,11,11b-tetrahydro-1H-imidazo[1′,5′:1,2]pyrido[3,4-b]indole-1,3(2H)-diones (**6a**,**b**)*; general procedure*

The appropriate carbamoyl compounds **5a** or **5b** (50 mg) were refluxed in 25 cm^3 EtOH containing 4% dry HCl for one day. The reaction mixture was evaporated, diethyl ether was added, and the crystalline product was filtered off and recrystallized.

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

Pale-yellow crystals; m.p.: 182–184°C ($EtOH/H_2O$; Ref. [6]: m.p.: 184°C); yield: 56%.

2-Phenyl-5,6,11,11b-tetrahydro-1H-imidazo[1′,5′:1,2]pyrido[3,4-b]indole-1,3(2H)-dione (**6b**; $C_{19}H_{15}N_3O_2$)

Pale-yellow crystals; m.p.: 239–241°C ($EtOH/H_2O$; Ref. [6]: m.p.: 241°C); yield: 37%; IR (KBr): $\bar{\nu} = 3412$, 1772, 1704 cm^{-1}; ^1H NMR ($CDCl_3$): $\delta = 2.89$ (ddd, $J = 1.26$, 4.53, 15.86 Hz, H-6a), 2.99–3.12 (m, H-6b), 3.33 (ddd, $J = 5.04$, 11.58, 13.6 Hz, H-5a), 4.64 (dd, $J = 6.04$, 13.6 Hz, H-5b), 5.39 (t, $J = 1.76$ Hz, H-11b), 7.16 (t, $J = 7.55$ Hz, H-8), 7.25 (t, $J = 7.81$ Hz, H-9), 7.33–7.48 (m, phenyl and H-7), 7.53 (d, $J = 7.8$ Hz, H-10), 8.51 (s, H-11) ppm.

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