Stereospecificity in the Reaction of Tetrahydro-β-carboline-3-carboxylic Acids with Isocyanates and Isothiocyanates. Kinetic vs Thermodynamic Control

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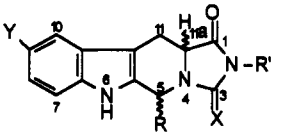
Benzodiazepines possessing anxiolytic, anticonvulsant, sedative-hypnotic, and myorelaxant effects are among the most widely prescribed drugs in medicine. It is now generally accepted that these compounds produce their pharmacological actions by binding to specific sites on the GABA receptor complex.[1–5] Only a small number of ligands chemically different from the benzodiazepines bind to the benzodiazepine receptor (BzR) with high affinity.[6–9] A case in point is the group of β-carbolines, where some derivatives[10–16] have been related to the endogenous ligand of the benzodiazepine receptor. Depending upon their intrinsic activity profiles, β-carbolines are classified as agonists, inverse agonists, antagonists, and partial agonists, making the β-carboline structure an important basis for the design of new benzodiazepine-related drugs.

In the course of a program to design new drugs acting on the central nervous system (CNS), we were interested in the synthesis of a new type of compounds **1** and **2** combining tetrahydro-β-carboline and hydantoin or thiohydantoin skeletons. In a previous paper[17] we reported the preparation of the molecules **1** (X = O) from isocyanates and 1-substituted-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid **3**, obtained by Pictet–Spengler condensation. Nevertheless, no stereochemical control of the reaction has been studied until now.



1 X = O
2 X = S

In keeping with our interest in the central role that the stereochemical control could play in the pharmacological profile of this type of compounds, we report here a detailed study of the stereochemistry in the reaction of **3** with isocyanates and isothiocyanates.

Initially we chose to investigate the reaction of *cis*-1-substituted-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acids **3** with isocyanates in refluxing acetone[17] and acetone/DMSO. Both conditions provided the (±)-*cis* diastereomer **1**. The stereochemistry of **1** was identified by ^{13}C NMR at C5 and C11a using the method of Cook et al.[18] With this in mind, it could be expected that the treatment of **3** with isothiocyanates could provide the *cis* isomer of β-carboline–thiohydantoin rings. However when we carried out this reaction the *trans* diastereomer **2** was isolated as the only product.

The stereochemical assignment of **2a–f** was based on a detailed study of their ^{13}C NMR data and of related compounds (Tables 1 and 2). Thus, by examination of the chemical shifts for carbon atoms C5 and C11a of compounds of the types **1g–i**[17] and **2g–i**, which do not exhibit *cis–trans* isomerism (R = H), it can be observed that the signals for these carbons in the thiohydantoin system were downfield (ΔC5, 4.4; ΔC11a, 3–3.5 ppm) relative to those of hydantoin (Table 2). Conversely, a *cis–trans* configurational change causes an upfield shift[18] (ΔC5, 2–4 ; ΔC11a, 3–4 ppm). Therefore, if the isolated isomer had been the *cis*, this compensation would not have been observed (Table 1).

The stereochemistry of **2** (*trans* by ^{13}C NMR) was corroborated by an X-ray structure analysis (Figure 1). With respect to the selected plane defined by C5–N1–C16, the atoms C23 and H5 are located at a distance of −1.44 and −0.81 Å, respectively, both on the same side of this plane.

It was eventually demonstrated that the *cis* isomer **1e** [R = Ph, R′ = Et; ^{13}C NMR ($CDCl_3$) δ 56.6 (C11a), 57.9 (C5)] could be completely converted into the *trans* isomer **1e′** [^{13}C NMR ($CDCl_3$) δ 51.9 (C11a), 53.1 (C5)] on heating in refluxing acetonitrile in the presence of sodium carbonate. The *trans* isomer remained unaffected when treated under analogous conditions. Apparently, the *trans* diastereomer is formed under thermodynamic control, while the *cis* isomer is regulated by kinetic control.

These results have been confirmed by AM1 quantum mechanical calculations[19] included in the MOPAC[20] program. Isomer **1e** (*cis*) showed a heat of formation of 41.59 kcal/mol and isomer **1e′** (*trans*) a heat of formation of 38.37 kcal/mol. The difference in energy (3.22 kcal/mol) reveals that the *trans* isomer is more stable than the *cis* and in the equilibrium the ratio of *cis* to *trans* is 0.4:99.6. The calculated heat of formation is also higher for the *cis*

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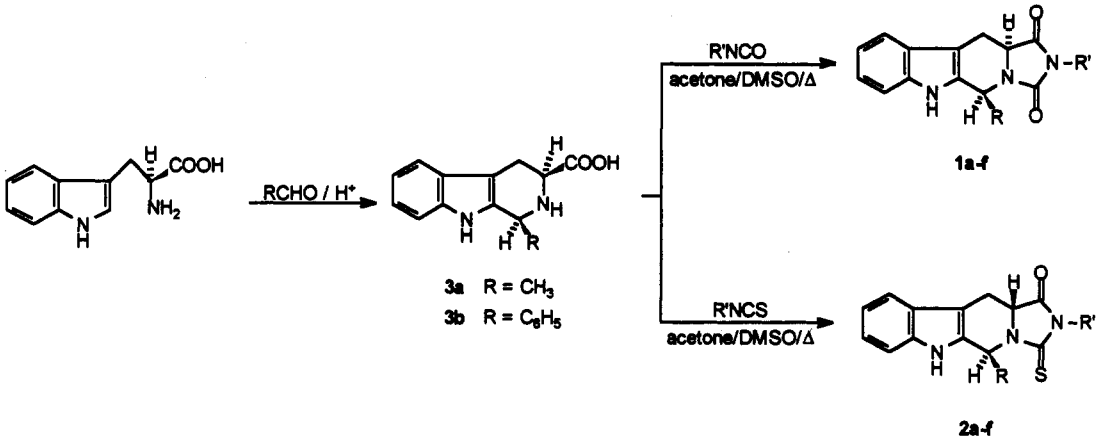
Scheme 1



1-2	a	b	c	d	e	f
R	Me	Me	Me	Ph	Ph	Ph
R′	Me	Et	Ph	Me	Et	Ph

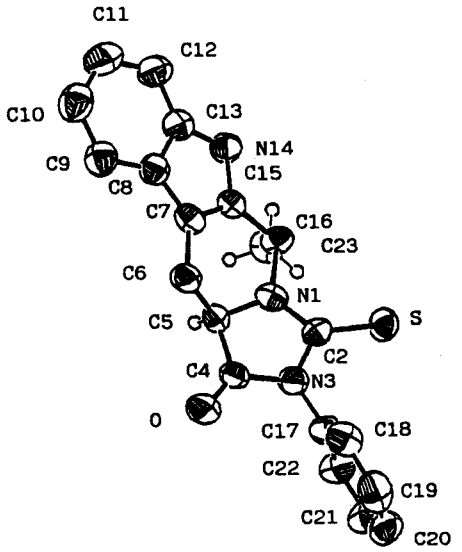
Table 1. ^{13}C NMR Signals for C5 and C11a (DMSO-d_6) of 1 and 2a–f

	1a	1b	1c	1d	1e	1f	2a	2b	2c	2d[a]	2e[a]	2f[a]
C5	48.1	48.0	48.4	57.8	56.7	57.7	48.4	48.4	48.7	55.8	55.6	56.0
C11a	57.5	57.0	57.6	55.8	55.8	56.0	55.4	55.3	55.7	55.4	55.1	55.4

[a] The signals for carbon atoms are interchangeable.

Table 2. ^{13}C NMR for C5 and C11a (DMSO-d_6)

	1 (R = H)			2 (R = H)			
	g: R′ = Me	h: R′ = Et	i: R′ = Ph		g: R′ = Me	h: R′ = Et	i: R′ = Ph
C5	37.6	37.5	37.8	C5	42.0	41.9	42.2
C11a	54.9	54.8	54.8	C11a	57.8	57.8	58.2



TORSION ANGLES

	MEASURED	CALCULATED	
		TRANS	CIS
$C_2N_1C_{16}C_{23}$	89.8	100.6	39.0
$C_5N_1C_{16}C_{23}$	88.8	101.2	129.0

Figure 1. Crystal structure of compound 2c (R = Me, R′ = Ph). Measured (X-ray) and calculated (AM1) torsion angles with crystallographic numbering system.

isomer of 2c compared to the *trans* isomer ($\Delta H_{cis} - \Delta H_{trans}$ = 3.35 kcal/mol). This indicates that in this case only the thermodynamically controlled product is obtained irrespective of the reaction conditions.

In summary, we have investigated the stereospecificity in the reaction of tetrahydro-β-carboline-3-carboxylic acid with isocyanates and isothiocyanates. This reaction provides easy access to compounds of current interest due to their potential biological applications.

Experimental Section

Solvents were purified and dried prior to use by distillation from an appropriate drying agent. Analytical thin-layer chromatography (TLC) was performed on precoated TLC plates (silica gel 60 F_{254}, layer thickness 0.2 mm). Column chromatography was performed with silica gel 60 (70–230 mesh).

Melting points were determined using a capillary melting point apparatus and are uncorrected. NMR spectra were obtained in DMSO-d_6 unless otherwise specified and chemical shifts are reported in ppm downfield relative to tetramethylsilane.

(−)-(1S,3S)-1-Methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid (3a) was prepared according to the literature[21] method.

(±)-*cis*-1-Phenyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic Acid (3b). Distilled benzaldehyde (4.9 mL, 48 mmol) was added to 5.02 g (24 mmol) of L-tryptophan dissolved in 40 mL of 0.1 N H_2SO_4, and the mixture was refluxed under N_2 for 6.30 h. The precipitated product was collected by filtration, washed with water (4 × 15 mL), and dried to yield 4.6 g (65%) of **3b** as a white solid: mp 228–230 °C (EtOH); $[\alpha]_D$ = −2° (c = 1, CF_3-COOH); IR (KBr) 3460, 3280, 2940, 1640, 1570 cm^{-1}; ^1H NMR δ 2.95 (t, 1H, J = 12.9 Hz), 3.04 (dd, 1H, J = 15.3, 2.7 Hz), 3.53 (dd, 1H, J = 11.4, 4.2 Hz), 5.26 (s, 1H), 6.93–7.02 (m, 2H), 7.16 (d, 1H, J = 7.2 Hz), 7.32–7.44 (m, 6H), 10.33 (s, 1H); ^{13}C NMR δ 24.1, 57.2, 57.7, 108.0, 111.5, 118.0, 118.8, 121.3, 126.3, 128.5,

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128.8, 129.8, 132.3, 136.8, 138.3, 171.9. Anal. Calcd for $C_{18}H_{16}N_2O_2$: C, 73.95; H, 5.52; N, 9.58. Found: C, 73.84; H, 5.46; N, 9.32.

General Preparation of Substrates 1 and 2. The corresponding isocyanate or isothiocyanate (9 mmol) was added to a suspension of **3** (9 mmol) in 35 mL of dry acetone and 15 mL of dry DMSO. The reaction mixture was refluxed to complete dissolution. The solvent was evaporated to dryness and the crude product was purified by column chromatography (silica gel, ethyl acetate/hexane 9:1).

***cis*-2,5-Disubstituted-5,6,11,11a-tetrahydro-1*H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*]indole-1,3(2*H*)-diones 1a–d,f.** The physical and spectroscopic data are agreement with that reported previously.[17]

***cis*-2-Ethyl-5-phenyl-5,6,11,11a-tetrahydro-1*H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*]indole-1,3(2*H*)-dione (1e):** mp 234–236 °C (lit.[17] mp 232–234 °C); IR (KBr) 3360, 1765, 1710 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.15 (t, 3H, J = 7.0 Hz), 3.02 (dd, 1H, J = 15.0, 11.4 Hz), 3.32–3.60 (m, 3H), 4.32 (dd, 1H, J = 11.4, 4.4 Hz), 5.69 (s, 1H), 7.12–7.56 (m, 9H), 7.83 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.4, 22.4, 33.6, 56.6, 58.0, 106.8, 111.2, 118.4, 120.0, 122.6, 126.1, 127.8, 128.5, 128.7, 133.5, 136.7, 138.8, 154.6, 171.5.

***trans*-2-Ethyl-5-phenyl-5,6,11,11a-tetrahydro-1*H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*]indole-1,3(2*H*)-dione (1e′).** A solution of **1e** (1.04 g, 3 mmol) and potassium carbonate (0.56 g, 4 mmol) in acetonitrile (17 mL) was refluxed for 2 h. The precipitate was removed by filtration and the filtrate was evaporated. The resulting oil was crystallized from ethanol to give 0.96 g (93%) of **1e′**: mp 245–246 °C; IR (KBr) 3360, 1770, 1710 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.19 (t, 3H, J = 7.0 Hz), 2.84 (dd, 1H, J = 15.2, 11.1 Hz), 3.41–3.60 (m, 3H), 4.22 (dd, 1H, J = 11.0, 5.4 Hz), 6.23 (s, 1H), 7.15–7.30 (m, 8H), 7.54 (d, 1H, J = 7.8 Hz), 8.15 (s, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.5, 23.3, 33.7, 51.9, 53.1, 107.8, 111.2, 118.4, 120.0, 122.8, 126.1, 128.1, 128.8, 129.0, 130.4, 136.6, 139.2, 154.7, 172.7. Anal. Calcd for $C_{21}H_{19}N_3O_2$: C, 73.04; H, 5.51; N, 12.17. Found: C, 73.33; H, 5.74; N, 12.25.

***trans*-2,5-Dimethyl-1-oxo-5,6,11,11a-tetrahydro-1*H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*]indole-3(2*H*)-thione (2a):** yield (85%); mp 240 °C (dec) (EtOH); IR (KBr) 3350, 1740, 1480 cm^{-1}; ^{1}H NMR δ 1.59 (d, 3H, J = 6.7 Hz), 2.76 (dd, 1H, J = 14.8, 11.1 Hz), 3.18 (s, 3H), 3.26 (dd, 1H, J = 14.8, 5.6 Hz), 4.73 (dd, 1H, J = 10.8, 5.6 Hz), 5.70 (q, 1H, J = 6.6 Hz), 7.01 (t, 1H, J = 7.9 Hz), 7.11 (td, 1H, J = 7.9, 1.2 Hz), 7.36 (d, 1H, J = 7.3 Hz), 7.46 (d, 1H, J = 7.6 Hz), 11.14 (s, 1H); ^{13}C NMR δ 19.0, 22.5, 27.4, 48.4, 55.4, 104.0, 111.2, 118.1, 118.9, 121.5, 125.9, 134.1, 136.4, 173.3, 179.8. Anal. Calcd for $C_{15}H_{15}N_3OS$: C, 63.13; H, 5.30; N, 14.72; S, 11.21. Found: C, 63.23; H, 5.46; N, 14.66; S, 11.16.

***trans*-2-Ethyl-5-methyl-1-oxo-5,6,11,11a-tetrahydro-1*H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*]indole-3(2*H*)-thione (2b):** yield (96%); mp 222 °C (dec) (EtOH); IR (KBr) 3320, 1740, 1470 cm^{-1}; ^{1}H NMR δ 1.17 (t, 3H, J = 7.1 Hz), 1.59 (d, 3H, J = 6.6 Hz), 2.77 (dd, 1H, J =13.9, 11.5 Hz), 3.28 (dd, 1H, J = 14.9, 5.6 Hz), 3.80 (q, 2H, J = 6.9 Hz), 4.80 (dd, 1H, J = 11.0, 5.6 Hz), 5.70 (q, 1H, J = 6.6 Hz), 7.01 (t, 1H, J = 7.3 Hz), 7.10 (t, 1H, J = 7.3 Hz), 7.35 (d, 1H, J = 7.8 Hz), 7.48 (d, 1H, J = 7.8 Hz), 10.80 (s, 1H); ^{13}C NMR δ 12.9, 19.0, 22.6, 35.7, 48.4, 55.3, 103.9, 111.2, 118.0, 118.9, 121.5, 125.9, 134.1, 136.4, 173.0, 179.2. Anal. Calcd for $C_{16}H_{17}N_3OS$: C, 64.18; H, 5.72; N, 14.03; S, 10.71. Found: C, 64.03; H, 5.77; N, 14.02; S, 11.00.

***trans*-5-Methyl-1-oxo-2-phenyl-5,6,11,11a-tetrahydro-1*H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*]indole-3(2*H*)-thione (2c):** yield (90%); mp 240 °C (dec) (EtOH); IR (KBr) 3370, 1740, 1600, 1500, 1470 cm^{-1}; ^{1}H NMR δ 1.65 (d, 3H, J = 6.6 Hz), 3.04 (dd, 1H, J = 14.8, 11.0 Hz), 3.34 (dd, 1H, J = 14.8, 5.8 Hz), 4.99 (dd, 1H, J = 11.0, 5.8 Hz), 5.76 (q, 1H, J = 6.6 Hz), 7.03 (td, 1H, J = 7.5, 1.1 Hz), 7.13 (td, 1H, J = 7.5, 1.2 Hz), 7.36–7.54 (m, 7H), 10.72 (s, 1H); ^{13}C NMR δ 19.0, 22.8, 48.7, 55.8, 104.1, 111.3, 118.2, 119.0, 121.7, 125.9, 128.8, 129.0, 129.2 133.5, 134.1, 136.4, 172.9, 179.5. Anal. Calcd for $C_{20}H_{17}N_3OS$: C, 69.13; H, 4.93; N, 12.09; S, 9.23. Found: C, 69.08; H, 5.03; N, 12.10; S, 9.12.

***trans*-2-Methyl-1-oxo-5-phenyl-5,6,11,11a-tetrahydro-1*H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*]indole-3(2*H*)-thione (2d):** yield (76%); mp 258 °C (dec) (EtOH); IR (KBr) 3340, 1720, 1470, 1450 cm^{-1}; ^{1}H NMR δ 2.95 (dd, 1H, J = 15.0, 10.9 Hz), 3.14 (s, 3H), 3.46 (dd, 1H, J = 15.1, 6.1 Hz), 4.85 (dd, 1H, J = 10.7, 6.0 Hz), 6.87 (s, 1H), 7.03 (td, 1H, J = 7.8, 1.1 Hz), 7.10 (td, 1H, J = 8.0, 1.2 Hz), 7.29–7.57 (m, 7H), 10.99 (s, 1H); ^{13}C NMR δ 22.9, 27.7, 55.4, 55.8, 105.9, 111.6, 118.5, 119.2, 122.0, 125.8, 128.6, 128.7, 128.8, 131.4, 137.0, 139.0, 173.3, 180.4. Anal. Calcd for $C_{20}H_{17}N_3OS$: C, 69.14; H, 4.93; N, 12.08; S, 9.23. Found: C, 68.94; H, 4.97; N, 12.09; S, 9.50.

***trans*-2-Ethyl-1-oxo-5-phenyl-5,6,11,11a-tetrahydro-1*H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*]indole-3(2*H*)-thione (2e):** yield (65%); mp 206–208 °C (EtOH); IR (KBr) 3330, 1730, 1620, 1460 cm^{-1}; ^{1}H NMR δ 1.29 (t, 3H, J = 7.2 Hz), 3.09 (dd, 1H, J = 15.2, 10.8 Hz), 3.62 (dd, 1H, J = 15.2, 6.3 Hz), 3.93 (q, 2H, J = 7.2 Hz), 5.00 (dd, 1H, J = 10.8, 6.0 Hz), 7.05 (s, 1H), 7.18 (td, 1H, J = 8.0, 1.5 Hz), 7.26 (td, 1H, J = 7.8, 1.5 Hz), 7.44–7.72 (m, 7H), 10.90 (s, 1H); ^{13}C NMR δ 12.9, 22.9, 36.0, 55.2, 55.7, 105.8, 111.5, 118.4, 119.1, 121.9, 125.7, 128.4, 128.5, 128.7, 131.3, 136.9, 138.9, 173.0, 179.7. Anal. Calcd for $C_{21}H_{19}N_3OS$: C, 69.77; H, 5.31; N, 11.63; S, 8.87. Found: C, 69.50; H, 5.49; N, 11.71; S, 8.59.

***trans*-2,5-Diphenyl-1-oxo-5,6,11,11a-tetrahydro-1*H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*]indole-3(2*H*)-thione (2f):** yield (71%); mp 286–288 °C (EtOH); IR (KBr) 3370, 1740, 1600, 1500, 1470 cm^{-1}; ^{1}H NMR δ 3.21 (dd, 1H, J = 14.7, 11.1 Hz), 3.53 (dd, 1H, J = 15.0, 6.0 Hz), 5.05 (dd, 1H, J = 10.8, 6.0 Hz), 6.98 (s, 1H), 7.05 (td, 1H, J = 7.2, 1.2 Hz), 7.13 (td, 1H, J = 7.2, 1.2 Hz), 7.31–7.60 (m, 12H), 11.04 (s, 1H); ^{13}C NMR δ 23.1, 55.4, 56.0, 105.8, 111.5, 118.4, 119.1, 121.9, 125.7, 128.7, 129.1, 131.3, 133.6, 136.9, 138.8, 172.7, 180.0. Anal. Calcd for $C_{25}H_{19}N_3OS$: C, 73.33; H, 4.68; N, 10.26; S, 7.82. Found: C, 73.58; H, 4.67; N, 10.40; S, 7.58.

2-Methyl-1-oxo-5,6,11,11a-tetrahydro-1*H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*]indole-3(2*H*)-thione (2g): yield (84%); mp 227–229 °C (EtOH); IR (KBr) 3340, 1740, 1500 cm^{-1}; ^{1}H NMR δ 2.80 (dd, 1H, J = 14.8, 11.1 Hz), 3.17 (s, 3H), 3.27 (dd, 1H, J = 15.0, 5.7 Hz), 4.56–4.65 (m, 2H), 5.41 (d, 1H, J = 16.9 Hz), 7.00 (t, 1H, J = 7.5 Hz), 7.09 (t, 1H, J = 7.6 Hz), 7.36 (d, 1H, J = 7.8 Hz), 7.47 (d, 1H, J = 7.5 Hz), 11.06 (s, 1H); ^{13}C NMR δ 22.3, 27.5, 42.0, 57.9, 104.6, 111.3, 117.9, 118.9, 121.4, 126.0, 129.3, 136.5, 173.2, 180.7. Anal. Calcd for $C_{14}H_{13}N_3OS$: C, 61.97; H, 4.83; N, 15.49; S, 11.82. Found: C, 61.67; H, 4.92; N, 15.16; S, 11.60.

2-Ethyl-1-oxo-5,6,11,11a-tetrahydro-1*H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*]indole-3(2*H*)-thione (2h): yield (84%); mp 196–198 °C (EtOH/H_2O); IR (KBr) 3350, 1720, 1490, 1450 cm^{-1}; ^{1}H NMR δ 1.20 (t, 3H, J = 6.9 Hz), 2.82 (dd, 1H, J = 14.7, 11.1 Hz), 3.32 (dd, 1H, J = 15.0, 5.7 Hz), 3.83 (q, 2H, J = 6.9 Hz), 4.62 (d, 1H, J = 17.1 Hz), 4.69 (dd, 1H, J = 11.1, 5.7 Hz), 5.44 (d, 1H, J = 17.1 Hz), 7.03 (td, 1H, J = 7.2, 1.2 Hz), 7.12 (td, 1H, J = 7.2, 1.2 Hz), 7.39 (d, 1H, J = 7.8 Hz), 7.51 (d, 1H, J = 7.8 Hz), 11.03 (s, 1H); ^{13}C NMR δ 13.0, 22.4, 35.8, 42.0, 57.8, 104.5, 111.3, 117.9, 118.9, 121.5, 126.0, 129.4, 136.5, 172.9, 180.1. Anal. Calcd for $C_{15}H_{15}N_3OS$: C, 63.14; H, 5.30; N, 14.72; S, 11.23. Found: C, 62.85; H, 5.50; N, 14.48; S, 11.18.

1-Oxo-2-phenyl-5,6,11,11a-tetrahydro-1*H*-imidazo[1′,5′:1,6]pyrido[3,4-*b*]indole-3(2*H*)-thione (2i): yield (91%); mp 220 °C (dec) (EtOH); IR (KBr) 3300, 1750, 1600, 1500, 1440 cm^{-1}; ^{1}H NMR δ 3.10 (dd, 1H, J = 14.7, 11.1 Hz), 3.47 (dd, 1H, J = 15.0, 5.7 Hz), 4.63–4.72 (m, 2H), 5.56 (d, 1H, J = 17.1 Hz), 7.16 (t, 1H, J = 7.5 Hz), 7.23 (t, 1H, J = 7.5 Hz), 7.38–7.62 (m, 7H), 11.10 (s, 1H); ^{13}C NMR δ 22.5, 42.3, 58.2, 104.7, 111.3, 118.0, 119.0, 121.5, 126.1, 128.8, 128.9, 129.3, 133.6, 136.5, 172.7, 180.3. Anal. Calcd for $C_{19}H_{15}N_3OS$: C, 68.44; H, 4.53; N, 12.60; S, 9.62. Found: C, 68.19; H, 4.62; N, 12.31; S, 9.90.

X-ray Structural Analysis of 2c ($C_{20}H_{17}N_3OS$); T = 22 °C; monoclinic, space group $P2_1$ with a = 9.144(8) Å, b = 10.282(1) Å, c = 18.765(2) Å, β = 90.22 (3)°; V = 1764(2) Å^3; Z = 4; D_{calcd} = 1.308 g cm^{-3}; μ = 1.86 cm^{-1}; $F(000)$ = 728. The measurements were performed with an Enraf-Nonius CAD4 diffractomer with monochromatic Mo Kα radiation; scan technique $\omega/2\theta$; 3289 unique data; 2164 unique data with $I \geq 2\sigma(I)$; R = 0.042; R_w = 0.040. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge, CB2 1EZ, UK.

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