A Versatile, Unexpected, One-Pot Regioselective Synthesis of a New Class of 1,3-Diazepinoindolones by Reaction of Pyranoindolones with Monosubstituted Ureas

Despina Livadiotou, Constantinos A. Tsoleridis,* Julia Stephanidou-Stephanatou*

Department of Chemistry, Laboratory of Organic Chemistry, Aristotle University of Thessaloniki, 54124 Thessaloniki, Macedonia, Greece
Fax +30(2310)997679; E-mail: tsolerid@chem.auth.gr; E-mail: ioulia@chem.auth.gr

Received 11 March 2009; revised 24 April 2009

Abstract: The regioselective one-pot synthesis of a new class of 4,6-dihydro[1,3]diazepino[5,6-*b*]indol-3(2*H*)-ones, in very good yields, via reaction of pyranoindolones with monosubstituted ureas is described. Reaction of *N*,*N*′-disubstituted ureas with pyranoindolones, under similar conditions, gave the corresponding β-carbolinones. The reaction mechanisms leading to both types of product are discussed and the structures are confirmed by spectroscopic techniques.

Key words: bisnucleophiles, carbenes, diazepinoindolones, pyranoindolones, substituted ureas, one-pot reaction

Previously, we have studied the reaction of pyranoindolones with bisnucleophiles such as methyl-, phenyl- and benzoylhydrazine. In the case of methylhydrazine, diazepinoindole derivatives were isolated,[1] but with phenyl- or benzoylhydrazine, β-carbolinones were the only reaction products.[2]

In the light of these results and in continuation of our research on the synthesis of compounds containing an indole ring, we decided to extend our research to the reaction of pyranoindolones with other ambident nucleophiles, such as substituted ureas, since to our knowledge, no analogous reactions have been reported in the literature. In fact, after a thorough search, the only similar reaction that could be found was that between 2-pyranones and urea, which was used to generate ammonia.[3] Pyranoindolones are interesting in that they possess an electrophilic center at C-1 (an enol carbon) in addition to a strong solvent effect;[1,2] this renders their study even more challenging. Moreover, it is known that medium-sized indolofused azacycles constitute structural arrangements in many natural and synthetic bioactive compounds.[4,5] In the present work we describe a one-pot method for the synthesis of a new class of 1,3-diazepinoindolones in very good yields.

Initially, pyranoindolones **1a**–**d** were reacted with three molar equivalents of *N*-methylurea in refluxing bromobenzene to give 1,3-diazepinoindolones **3a**–**d** in excellent yields (90–93%, Scheme 1 and Table 1), instead of the expected β-carbolinones **5** or 1,2-diazepinoindolones **6**. Analogous reactions occurred with *N*-benzylurea to give compounds **3e–h** which were also isolated in very good yields (89–92%). However, when unsubstituted urea was used, a mixture of various unidentified products was formed.

The reaction was also studied using a disubstituted urea. Thus, reaction of pyranoindolones **1c**,**d** with three molar equivalents of *N*,*N*′-dimethylurea (**2c**) in bromobenzene at reflux gave β-carbolinones **4** in yields of 60–61%, instead of the corresponding 1,3-diazepinoindolones **3** (Scheme 1, Table 1). The reaction proceeded analogously at lower temperatures (refluxing xylenes), although slightly longer reaction times were necessary (Table 1).

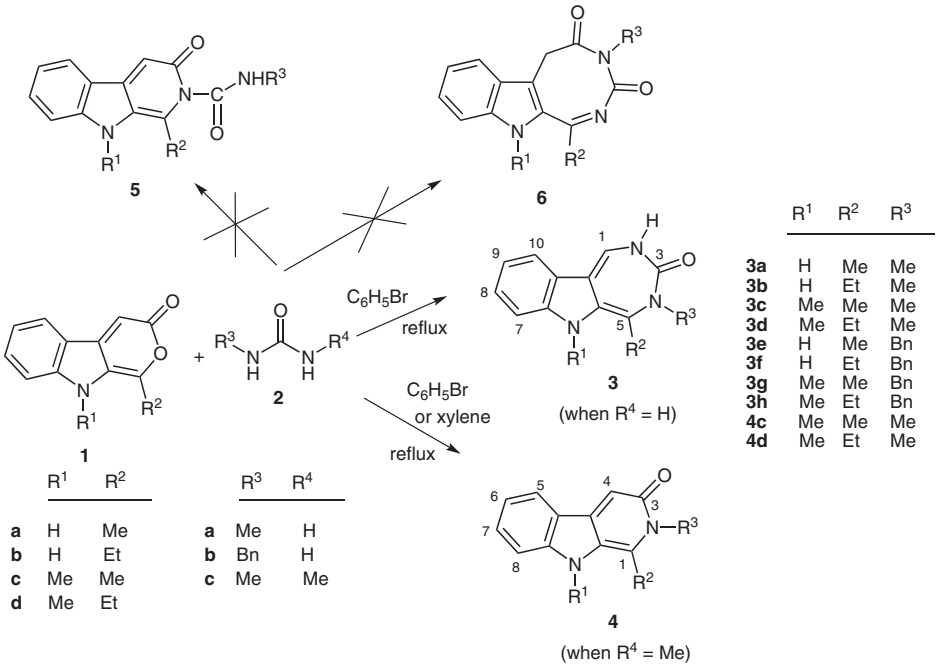
Table 1 Reaction Conditions and Products

Substrate	Urea	Solvent	Time (h)	Product	Yield (%)
1a	**2a**	PhBr	1	**3a**	90
1b	**2a**	PhBr	2	**3b**	91
1c	**2a**	PhBr	3.5	**3c**	91
1d	**2a**	PhBr	3	**3d**	93
1a	**2b**	PhBr	3	**3e**	89
1b	**2b**	PhBr	4.5	**3f**	91
1c	**2b**	PhBr	3.5	**3g**	92
1d	**2b**	PhBr	8	**3h**	91
1c	**2c**	PhBr	5	**4c**	60
1c	**2c**	$C_6H_4Me_2$	6	**4c**	63
1d	**2c**	PhBr	3	**4d**	61
1d	**2c**	$C_6H_4Me_2$	5	**4d**	57

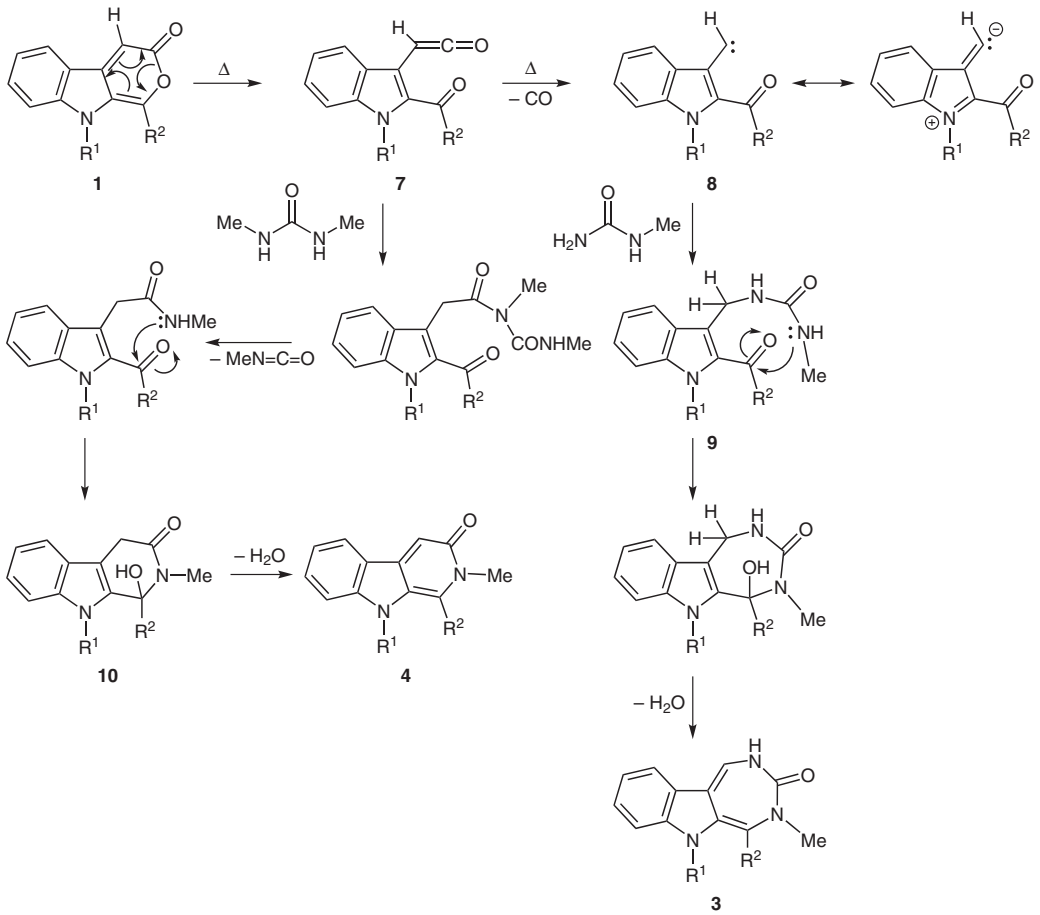
Concerning the reaction mechanism, attack of the less hindered unsubstituted NH_2 group of the urea[6] on C-1, the reactive electrophilic center, of the pyranoindolone would be expected, as was observed in the case of other ambident nucleophiles.[1,2] However, the isolation of products **3** led to the conclusion that the reaction followed a different pathway (Scheme 2), most probably as a result of the weak nucleophilic character of the urea nitrogens. According to the proposed mechanism the reaction is initiated by electrocyclic ring-opening of the pyrone ring of **1** leading to the formation of a vinylogous acylketene inter-

SYNTHESIS 2009, No. 15, pp 2579–2583
Advanced online publication: 26.06.2009
DOI: 10.1055/s-0029-1216868; Art ID: P04009SS

mediate **7**. Subsequent decarbonylation of **7**, in refluxing bromobenzene, leads to the formation of carbene **8** which is stabilized by the indole nitrogen. The carbene then inserts[7] into the N–H bond of the urea to form intermediate **9** which undergoes cyclization and elimination of water to yield product **3**.



Scheme 1 Reactions of pyranoindolones **1** with monosubstituted ureas **2a**,**b** to afford 1,3-diazepinoindolones **3**, and with *N*,*N*′-dimethylurea (**2c**) to give β-carbolinones **4**



Scheme 2 Plausible mechanisms for the formation of compounds **3** and **4**

The formation of β-carbolinones **4** most probably occurs via attack of the NH group of the disubstituted urea **2c** on the intermediate ketene **7**. Subsequent abstraction of methyl isocyanate followed by ring-closure to give **10** and elimination of water leads to compounds **4** (Scheme 2).

The assignment of the molecular structures of novel compounds **3** and **4** was based on rigorous spectroscopic analysis including IR and NMR spectroscopy [^{1}H, ^{13}C, correlation spectroscopy (COSY), nuclear Overhauser exchange spectroscopy (NOESY), heteronuclear chemical-shift correlation (HETCOR) and correlation through long-range coupling (COLOC)], mass spectrometry and elemental analysis. As an example, the structural assignment of 1,3-diazepinoindole **3c** is described. The elemental analysis and mass spectrum established that one molecule of pyranoindolone **1c** had reacted with one molecule of *N*-methylurea with the loss of a molecule of formic acid. This was also confirmed from the ^{13}C NMR spectrum where 14 different signals were observed. Moreover, in the IR spectrum, the N–H and carbonyl absorptions were identified at 3451, 3400, 3195 (N–H), and 1685 and 1659 (NC=O) cm^{-1}, respectively. The presence and positions of the four indole-aromatic protons were proven unequivocally from their ^{1}H NMR splitting patterns and long-range correlations (COLOC). The long-range C–H correlation spectra were optimized for J = 10 Hz, with aromatic protons showing ^3J correlations, and protons on saturated carbons demonstrating COLOC via ^2J and ^3J couplings. Consequently, the C5-methyl group protons showed correlations with the carbon at 128.1 ppm (C5) and with the quaternary carbon at 127.8 ppm (C5a) whereas the indole *N*-methyl protons correlated with the same quaternary carbon (C5a) and with the quaternary carbon at 147.7 ppm (C6a). The N4-methyl protons correlated with the carbon at 128.1 ppm (C5) and the carbonyl carbon at 161.5 ppm (C3), thus confirming its position. Finally, proton H1 correlated with carbon C5a and the quaternary carbon at 120.6 ppm (C10a) which established the complete carbon skeleton of product **3c** (Figure 1).

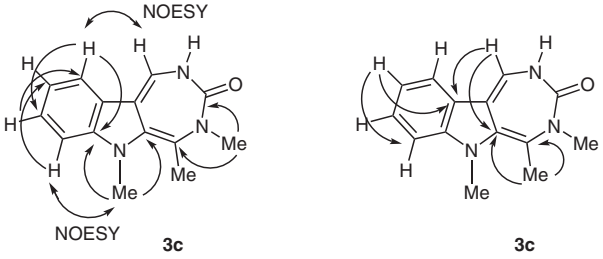


Figure 1 Correlations (COLOC) between the protons and carbons (*via* $^2J_{C-H}$ and $^3J_{C-H}$) in compound **3c**. NOESY correlations were observed between protons H7 and 6-Me and between H1 and H10. Benzylic-type coupling (J = 0.6 Hz) between protons H1 and 5-Me were also observed

For compounds **3e**–**h** the benzylic protons appear as broad signals which are indicative of rotational restriction about this group. In compound **3h**, the correlation (COLOC) between proton H10 at 7.89 ppm and the quaternary carbon at 139.7 ppm (C10b) confirms their positions three bonds apart. The structures of compounds **4c**,**d** were easily elucidated by analogy with the β-carbolinones discussed in our previous work.[2]

In conclusion, we have developed a direct method for the synthesis of a new class of 1,3-diazepinoindoles via reaction of pyranoindolones with bisnucleophiles. Full assignment of the ^{1}H and ^{13}C NMR chemical shifts of the products has been achieved unambiguously. Although some [1,3]diazepino[4,5-*b*]indol-6-ones have been reported in the literature,[8] our procedure constitutes the first example of the synthesis of [1,3]diazepino[5,6-*b*]indol-3-ones. While bis-diazepinones have demonstrated promising biological activity[8,9] further investigations are complicated by the lack of efficient methods for their preparation. Work in this area is continuing in our laboratory using other bisnucleophiles, and we will report our results in due course.

Melting points were measured using a Kofler hot-stage apparatus and are uncorrected. Column chromatography was carried out using Merck silica gel (0.063–0.200 mm). TLC was performed on precoated silica gel glass plates containing a fluorescent indicator (Macherey–Nagel UV$_{254}$, 0.25 mm) using PE–EtOAc (3:1). PE refers to the fraction boiling between 60–80 °C. NMR spectra were recorded at r.t. on a Bruker AM 300 spectrometer at 300 MHz (^{1}H) and 75 MHz (^{13}C), respectively, using $CDCl_3$ as the solvent . In the case of insoluble products, 5–20% of DMSO-d_6 was added to the $CDCl_3$ solution. CD_3OD was used as solvent in the case **3k**. ^{1}H NMR chemical shifts are expressed in δ values (ppm) relative to TMS (0.00 ppm) as internal standard. ^{13}C NMR spectra are expressed in δ values (ppm) relative to the $CDCl_3$ solvent signal at 77.05 ppm, and at 49.0 ppm in the case of CD_3OD. Coupling constants ^nJ are reported in Hz. IR spectra were recorded on a Perkin-Elmer 1600 series FTIR spectrometer and are reported in wavenumbers (cm^{-1}). Low-resolution electron impact mass spectra were recorded using a 6890N GC–MS system (Agilent Technology); LC-MS (ESI, 1.65 eV) spectra were recorded on an LCMS-2010 EV instrument (Shimadzu). Elemental analyses were recorded using a Perkin-Elmer 2400-II CHN analyzer.

4,6-Dihydro[1,3]diazepino[5,6-*b*]indol-3(2*H*)-ones (3a–h); General Procedure

To a refluxing solution of pyranoindolone **1** (1.5 mmol) in bromobenzene (15 mL) was added monosubstituted urea **2a**,**b** (4.5 mmol) and heating was continued until **1** was consumed. The reaction mixture was allowed to cool (5–10 °C) and the precipitated product was filtered off, washed with Et_2O (15 mL) and recrystallized from EtOH. If crystallization was not possible the solvent was removed by distillation and the residue was purified by column chromatography on silica gel using PE–EtOAc (5:1) as eluent, slowly increasing the polarity up to 1:5 to give the products.

4,5-Dimethyl-4,6-dihydro[1,3]diazepino[5,6-*b*]indol-3(2*H*)-one (3a)

Yellow crystals; yield: 0.204 g (90%); mp >350 °C (EtOH).

IR (KBr): 3407, 3371, 3276, 3171 (NH), 1686, 1670 (NC=O) cm^{-1}.

^{1}H NMR ($CDCl_3$ containing DMSO-d_6): δ = 2.63 (s, 3 H, 5-Me), 3.71 (s, 3 H, 4-Me), 5.72 (br s, 1 H, H2), 6.99 (s, 1 H, H1), 7.08 (ddd, J = 1.0, 7.2, 8.0 Hz, 1 H, H9), 7.28 (dd, J = 1.0, 8.0 Hz, 1 H, H7), 7.45 (ddd, J = 1.0, 7.2, 8.0 Hz, 1 H, H8), 7.88 (dd, J = 1.0, 8.0 Hz, 1 H, H10), 9.04 (br s, 1 H, H6).

^{13}C NMR ($CDCl_3$, containing DMSO-d_6): δ = 15.8 (5-Me), 32.0 (4-Me), 102.5 (C1), 111.1 (C7), 119.0 (C9), 121.0 (C10a), 122.9 (C10), 125.9 (C5a), 129.1 (C5), 130.1 (C8), 138.1 (C10b), 145.1 (C6a), 161.5 (C3).

LC-MS (ESI, 1.65 eV): *m*/*z* (%) = 267 (100) [M + 1+ K^+].

Anal. Calcd for $C_{13}H_{13}N_3O$: C, 68.70; H, 5.77; N, 18.49. Found: C, 68.85; H, 5.83, N, 18.57.

5-Ethyl-4-methyl-4,6-dihydro[1,3]diazepino[5,6-*b*]indol-3(2*H*)-one (3b)

Yellow crystals; yield: 0.219 g (91%); mp 149–150 °C (EtOH).

IR (KBr): 3421, 3338, 3200 (NH), 1663, 1643 (NC=O), 1614 (NH) cm^{-1}.

^{1}H NMR ($CDCl_3$, containing DMSO-d_6): δ = 1.34 (t, *J* = 7.5 Hz, 3 H, 5-CH_2CH_3), 3.12 (q, *J* = 7.5 Hz, 2 H, 5-CH_2), 3.75 (s, 3 H, 4-Me), 5.50 (br s, 1 H, H2), 6.94 (s, 1 H, H1), 7.05 (dd, *J* = 7.0, 7.5 Hz, 1 H, H9), 7.33 (d, *J* = 8.4 Hz, 1 H, H7), 7.45 (ddd, *J* = 1.0, 7.0, 8.4 Hz, 1 H, H8), 7.87 (dd, *J* = 1.0, 7.5 Hz, 1 H, H10), 10.40 (br s, 1 H, H6).

^{13}C NMR ($CDCl_3$, containing DMSO-d_6): δ = 14.6 (5-CH_2CH_3), 22.0 (5-CH_2), 31.2 (4-Me), 101.2 (C1), 110.8 (C7), 118.0 (C9), 119.9 (C10a), 120.0 (C10), 125.1 (C5a), 129.6 (C8), 132.7 (C5), 137.5 (C10b), 144.8 (C6a), 160.8 (C3).

LC-MS (ESI, 1.65 eV): *m*/*z* (%) = 281 (66) [M + 1+ K^+], 227 (100).

Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.85; H, 6.43; N, 17.59.

4,5,6-Trimethyl-4,6-dihydro[1,3]diazepino[5,6-*b*]indol-3(2*H*)-one (3c)

Yellow crystals; yield: 0.219 g (91%); mp 188–189 °C (EtOH).

IR (KBr): 3451, 3400, 3195 (NH), 1685, 1659 (NC=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.73 (d, *J* = 0.7 Hz, 3 H, 5-Me), 3.66 (s, 3 H, 4-Me), 3.73 (s, 3 H, 6-Me), 6.91 (q, *J* = 0.7 Hz, 1 H, H1), 7.08 (ddd, *J* = 0.8, 7.2, 7.8 Hz, 1 H, H9), 7.12 (dd, *J* = 0.8, 7.9 Hz, 1 H, H7), 7.50 (ddd, *J* = 0.7, 7.2, 7.9 Hz, 1 H, H8), 7.82 (dd, *J* = 0.7, 7.8 Hz, 1 H, H10).

^{13}C NMR ($CDCl_3$): δ = 16.5 (5-Me), 32.1 (4-Me), 34.0 (6-Me), 102.8 (C1), 109.1 (C7), 119.2 (C9), 120.6 (C10a), 122.6 (C10), 127.8 (C5a), 128.1 (C5), 130.5 (C8), 138.8 (C10b), 147.7 (C6a), 161.5 (C3).

MS (EI, 70 eV): *m*/*z* (%) = 242 (80) [M + 1^+], 214 (25), 185 (14), 157 (100).

Anal. Calcd for $C_{14}H_{15}N_3O$: C, 69.69; H, 6.27; N, 17.41. Found: C, 69.78; H, 6.15; N, 17.60.

5-Ethyl-4,6-dimethyl-4,6-dihydro[1,3]diazepino[5,6-*b*]indol-3(2*H*)-one (3d)

Yellow crystals; yield: 0.237 g (93%); mp 145–146 °C (EtOH).

IR (KBr): 3441, 3343, 3300, 3231 (NH), 1759, 1716, 1656 (NC=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.40 (t, *J* = 7.5 Hz, 3 H, 5-CH_2CH_3), 3.18 (q, *J* = 7.5 Hz, 2 H, 5-CH_2), 3.75 (s, 3 H, 4-Me), 3.77 (s, 3 H, 6-Me), 5.10 (br s, 1 H, H2), 7.00 (s, 1 H, H1), 7.10 (dd, *J* = 7.0, 7.5 Hz, 1 H, H9), 7.16 (d, *J* = 8.5 Hz, 1 H, H7), 7.52 (ddd, *J* = 1.0, 7.0, 8.5 Hz, 1 H, H8), 7.87 (dd, *J* = 1.0, 7.5 Hz, 1 H, H10).

^{13}C NMR ($CDCl_3$): δ = 13.9 (5-CH_2CH_3), 20.6 (5-CH_2), 32.7 (4-Me), 34.3 (6-Me), 102.7 (C1), 108.7 (C7), 118.8 (C9), 120.1 (C10a), 122.1 (C10), 126.4 (C5a), 130.2 (C8), 133.1 (C5), 138.7 (C10b), 147.0 (C6a), 161.1 (C3).

MS (EI, 70 eV): *m*/*z* (%) = 254 (100) [M – 1^+].

Anal. Calcd for $C_{15}H_{17}N_3O$: C, 70.56; H, 6.71; N, 16.46. Found: C, 70.67; H, 6.53; N, 16.58.

4-Benzyl-5-methyl-4,6-dihydro[1,3]diazepino[5,6-*b*]indol-3(2*H*)-one (3e)

Yellow crystals; yield: 0.269 g (89%); mp 225–226 °C (EtOH).

IR (KBr): 3420, 3225 (NH), 1710, 1690, 1670, 1650 (NC=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.38 (s, 3 H, 5-Me), 5.38 (s, 2 H, 4-CH_2), 7.00–7.07 (m, 3 H, H1, H7, H4′), 7.11 (dd, *J* = 7.2, 8.0 Hz, 1 H, H9), 7.17–7.30 (m, 4 H, H2′, H3′, H5′, H6′), 7.45 (dd, *J* = 7.2, 8.4 Hz, 1 H, H8), 7.87 (d, *J* = 8.0 Hz, 1 H, H10), 8.27 (br s, 1 H, H6).

^{13}C NMR ($CDCl_3$): δ = 15.5 (5-Me), 47.8 (4-CH_2), 103.0 (C1), 111.4 (C7), 119.6 (C9), 121.2 (C10a), 123.0 (C10), 126.1 (C5a), 126.3 (C2′, C6′), 127.3 (C4′), 128.6 (C5), 128.8 (C3′, C5′), 130.7 (C8), 136.7 (C1′), 138.8 (C10b), 145.3 (C6a), 161.6 (C3).

LC-MS (ESI, 1.65 eV): *m*/*z* (%) = 303 (100) [M^+].

Anal. Calcd for $C_{19}H_{17}N_3O$: C, 75.23; H, 5.65; N, 13.85. Found: C, 75.15; H, 5.53; N, 13.63.

4-Benzyl-5-ethyl-4,6-dihydro[1,3]diazepino[5,6-*b*]indol-3(2*H*)-one (3f)

Yellow crystals; yield: 0.288 g (91%); mp 219–220 °C (EtOH).

IR (KBr): 3430, 3270 (NH), 1690, 1665, 1630 (NC=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.22 (t, *J* = 7.5 Hz, 3 H, 5-CH_2CH_3), 2.84 (q, *J* = 7.5 Hz, 2 H, 5-CH_2), 4.39 (d, *J* = 6.0 Hz, 1 H, H2), 5.58 (br s, 2 H, 4-CH_2), 7.07 (s, 1 H, H1), 7.08–7.14 (m, 3 H, H7, H9, H4′), 7.20–7.30 (m, 4 H, H2′, H3′, H5′, H6′), 7.40 (br s, 1 H, H6), 7.47 (ddd, *J* = 1.1, 7.2, 8.4 Hz, 1 H, H8), 7.90 (dd, *J* = 1.1, 8.0 Hz, 1 H, H10).

^{13}C NMR ($CDCl_3$): δ = 12.9 (5-CH_2CH_3), 22.7 (5-CH_2), 47.3 (4-CH_2), 102.7 (C1), 111.5 (C7), 119.4 (C9), 120.7 (C10a), 122.9 (C10), 125.8 (C5a), 126.0 (C2′, C6′), 127.2 (C4′), 128.7 (C3′, C5′), 130.7 (C8), 133.2 (C5), 137.0 (C1′), 138.7 (C10b), 145.3 (C6a), 161.2 (C3).

LC-MS (ESI, 1.65 eV): *m*/*z* (%) = 357 (100) [M + 1 + K^+].

Anal. Calcd for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24. Found: C, 75.76; H, 6.15; N, 13.48.

4-Benzyl-5,6-dimethyl-4,6-dihydro[1,3]diazepino[5,6-*b*]indol-3(2*H*)-one (3g)

Yellow crystals; yield: 0.291 g (92%); mp 128–130 °C (EtOH).

IR (Nujol®): 3323, 3214 (NH), 1699, 1662 (NC=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.60 (s, 3 H, 5-Me), 3.65 (s, 3 H, 6-Me), 5.44 (br s, 2 H, 4-CH_2), 6.13 (br s, 1 H, 2H), 6.93 (s, 1 H, H1), 7.02–7.11 (m, 4 H, H7, H9, H2′, H6′), 7.18–7.28 (m, 3 H, H3′, H4′, H5′), 7.49 (ddd, *J* = 1.0, 7.0, 7.5 Hz, 1 H, H8), 7.80 (dd, *J* = 1.0, 7.5 Hz, 1 H, 10-H).

^{13}C NMR ($CDCl_3$): δ = 16.3 (5-CH_3), 34.1 (6-CH_3), 47.8 (4-CH_2), 103.5 (C1), 109.1 (C7), 119.3 (C9), 120.7 (C10a), 122.7 (C10), 126.3 (C2′, C6′), 127.2 (C4′), 127.97 (C5a), 128.04 (C5), 128.8 (C3′, C5′), 130.7 (C8), 137.0 (C1′), 139.5 (C10b), 148.0 (C6a), 161.7 (C3).

LC-MS (ESI, 1.65 eV): *m*/*z* (%) = 317 (100) [M^+].

Anal. Calcd for $C_{20}H_{19}N_3O$: C, 75.69; H, 6.03; N, 13.24. Found: C, 75.76; H, 6.15; N, 13.08.

4-Benzyl-5-ethyl-6-methyl-4,6-dihydro[1,3]diazepino[5,6-*b*]indol-3(2*H*)-one (3h)

Yellow crystals; yield: 0.301 g (91%); mp 205–206 °C (EtOH).

IR (KBr): 3383, 3278, 3188 (NH), 1720, 1692, 1654 (NC=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 1.32 (t, *J* = 7.6 Hz, 3 H, 5-CH_2CH_3), 1.80 (br s, 0.5 H, H2), 3.06 (q, *J* = 7.6 Hz, 2 H, 5-CH_2), 3.78 (s, 3 H, 6-Me), 4.38 (br s, 0.5 H, H2), 5.60 (br s, 2 H, 4-CH_2), 7.09 (s, 1 H, H1), 7.06–7.10 (m, 2 H, H2′, H6′), 7.10 (ddd, *J* = 1.0, 7.2, 7.8 Hz, 1 H, H9), 7.17 (dd, *J* = 1.0, 8.3 Hz, 1 H, H7), 7.24 (t, *J* = 6.9 Hz, 1 H,

H4′), 7.22–7.31 (m, 2 H, H3′, H5′), 7.53 (ddd, *J* = 1.2, 7.2, 8.3 Hz, 1 H, H8), 7.89 (dd, *J* = 1.2, 7.8 Hz, 1 H, H10).

^{13}C NMR ($CDCl_3$): δ = 15.0 (5-CH_2CH_3), 21.9 (5-CH_2), 32.7 (6-Me), 47.1 (4-CH_2), 103.8 (C1), 108.9 (C7), 119.2 (C9), 120.5 (C10a), 122.6 (C10), 126.0 (C2′, C6′), 126.9 (C5a), 127.1 (C4′), 128.7 (C3′, C5′), 130.7 (C8), 133.4 (C5), 137.3 (C1′), 139.7 (C10b), 147.5 (C6a), 161.4 (C3).

LC-MS (ESI, 1.65 eV): *m*/*z* (%) = 371 (100) [M + 1 + K^+].

Anal. Calcd for $C_{21}H_{21}N_3O$: C, 76.11; H, 6.39; N, 12.68. Found: C, 76.25; H, 6.19; N, 12.78.

β-Carbolin-3-ones 4c,d; General Procedure

To a refluxing solution of pyranoindolone **1c**,**d** (1.5 mmol) in bromobenzene (15 mL) was added *N*,*N*′-dimethylurea **2c** (4.5 mmol) and heating was continued until **1** was consumed. The reaction mixture was allowed to cool (5–10 °C) and the precipitated product was filtered off, washed with Et_2O (15 mL) and recrystallized from EtOH. If crystallization was not possible the solvent was removed by distillation and the residue was purified by column chromatography on silica gel using EtOAc as eluent, to give products **4c**,**d**.

1,2,9-Trimethyl-2,9-dihydro-3*H*-β-carbolin-3-one (4c)

Yellow crystals; yield: 0.142 g (63%); mp 225–226 °C (EtOH).

IR (KBr): 1663 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$): δ = 2.74 (s, 3 H, 1-Me), 3.65 (s, 3 H, 2-Me), 3.75 (s, 3 H, 9-Me), 6.90 (s, 1 H, H4), 7.09 (dd, *J* = 7.2, 8.0 Hz, 1 H, H6), 7.13 (d, *J* = 8.0 Hz, 1 H, H8), 7.51 (ddd, *J* = 1.3, 7.2, 8.0 Hz, 1 H, H7), 7.80 (dd, *J* = 1.3, 8.0 Hz, 1 H, H5).

^{13}C NMR ($CDCl_3$): δ = 16.5 (1-Me), 32.1 (2-Me), 34.0 (9-Me), 102.8 (C4), 109.1 (C8), 119.2 (C6), 120.6 (C4b), 122.5 (C5), 127.9, 128.0 (C1, C9a), 130.4 (C7), 138.8 (C4a), 147.7 (C8a), 161.5 (C3).

LC-MS (ESI, 1.65 eV): *m*/*z* (%) = 249 (100) [M + Na^+].

Anal. Calcd for $C_{14}H_{14}N_2O$: C, 74.31; H, 6.24; N, 12.38. Found: C, 74.34; H, 6.38; N, 12.45.

1-Ethyl-2,9-dimethyl-2,9-dihydro-3*H*-β-carbolin-3-one (4d)

Yellow crystals; yield: 0.146 g (61%); mp 104–105 °C (EtOH).

IR (KBr): 1634 (C=O) cm^{-1}.

^{1}H NMR ($CDCl_3$, containing DMSO-d_6): δ = 1.43 (t, *J* = 7.5 Hz, 3 H, 1-CH_2CH_3), 3.22 (q, *J* = 7.5 Hz, 2 H, 1-CH_2), 3.78 (s, 3 H, 2-Me), 3.82 (s, 3 H, 9-Me), 6.99 (s, 1 H, H4), 7.11 (dd, *J* = 7.0, 7.5 Hz, 1 H, H6), 7.19 (d, *J* = 8.5 Hz, 1 H, H8), 7.53 (dd, *J* = 7.0, 8.5 Hz, 1 H, H7), 7.87 (d, *J* = 7.5 Hz, 1 H, H5).

^{13}C NMR ($CDCl_3$, containing DMSO-d_6): δ = 14.3 (1-CH_2CH_3), 22.2 (1-CH_2), 29.0 (2-Me), 31.6 (9-Me), 103.1 (C4), 109.0 (C8), 119.3 (C6), 120.5 (C4b), 122.6 (C5), 127.3 (C9a), 130.7 (C7), 133.4 (C1), 139.3 (C4a), 147.6 (C8a), 160.3 (C3).

LC-MS (ESI, 1.65 eV): *m*/*z* (%) = 241 (100) [M + 1^+].

Anal. Calcd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66. Found: C, 74.81; H, 6.58; N, 11.55.

Acknowledgment

The authors thank Professor Philip Kocienski for proposing the mechanism given in Scheme 2.

References and notes

(1) Hatzimimikou, D.; Livadiotou, D.; Tsoleridis, C. A.; Stephanidou-Stephanatou, J. *Synlett* **2008**, 1773.
(2) Livadiotou, D.; Hatzimimikou, D.; Neochoritis, C.; Terzidis, M. A.; Tsoleridis, C. A.; Stephanidou-Stephanatou, J. *Synthesis* **2008**, 3273.
(3) Goel, A.; Singh, F. V.; Sharon, A.; Maulik, P. R. *Synlett* **2005**, 623.
(4) (a) Sundberg, R. J. *Indoles*; Academic Press: New York, **1996**. (b) Joule, J. A. In *Science of Synthesis, Houben-Weyl Methods of Molecular Transformations*, Vol. 10; Thomas, E. J., Ed.; Thieme: Stuttgart, **2000**, 361–652. (c) Rommelspacher, H.; May, T.; Salewsky, B. *Eur. J. Pharmacol.* **1994**, *252*, 51. (d) Kim, H.; Sablin, S. O.; Ramsay, R. R. *Arch. Biochem. Biophys.* **1997**, *337*, 137. (e) Herraiz, T.; Chaparro, C. *Biochem. Biophys. Res. Commun.* **2005**, *326*, 378.
(5) (a) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 73. (b) Somei, M.; Yamada, F. *Nat. Prod. Rep.* **2005**, *22*, 761.
(6) (a) Buscemi, S.; Pace, A.; Piccionello, A. P.; Pibiri, I.; Vivona, N.; Giorgi, G.; Mazzanti, A.; Spinelli, D. *J. Org. Chem.* **2006**, *71*, 8106. (b) Touzot, A.; Soufyane, M.; Berber, H.; Toupet, L.; Mirand, C. *J. Fluorine Chem.* **2004**, *125*, 1299.
(7) Mieusset, J.-L.; Bespokoev, A.; Pacar, M.; Abraham, M.; Arion, V. B.; Brinker, U. H. *J. Org. Chem.* **2008**, *73*, 6551.
(8) Yu, Q.-S.; Greig, N. H.; Holloway, H. W.; Flippen-Anderson, J. L.; Brossi, A. *Med. Chem. Res.* **2000**, *10*, 186.
(9) (a) Shutalev, A. D.; Fesenko, A. A.; Cheshkov, D. A.; Guliguzov, D. V. *Tetrahedron Lett.* **2008**, *49*, 4099. (b) Reisinger, A.; Koch, R.; Wentrup, C. *J. Chem. Soc., Perkin Trans. 1* **1998**, 2247.