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SYNTHESIS AND SPECTRAL FEATURES OF NEW 1-ALKYL-5-(INDOL-2(3)-YL)PYRROLIDIN-2-ONES

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The mass spectrometric behavior of 1-alkyl-5-(1H-indol-2-yl)pyrrolidin-2-ones and 1-alkyl-5-(1H-indol-3-yl)pyrrolidin-2-ones was studied and the fragmentation of these compounds was established. The product of N-methylindole reaction with 1-benzyl-5-hydroxypyrrolidin-2-one was shown to be 1-benzyl-5-(1-methylindol-3-yl)pyrrolidin-2-one.

Keywords: 5-hydroxypyrrolidin-2-ones, indoles, amidoalkylation, mass spectrometry.

In previous work [1], we reported the synthesis of new 1-alkyl-5-(1*H*-indolyl)pyrrolidin-2-ones **1** and **2**, and found that these compounds do not undergo the Plancher rearrangement during their formation.

However, in a continuation of this research, we found that the ^{1}H NMR signal at 6.88 ppm, which belongs to the indole system pyrrole ring proton in the product obtained from *N*-methylindole (**3e**) and 1-benzyl-5-hydroxypyrrolidin-2-one (**4a**), appears almost exactly in the middle between the signals for H-3 (6.45 ppm) and H-2 (7.26 ppm) in unsubstituted indole [2]. Thus, the spectrum does not permit us to establish the substitution pattern of the indole system, i.e., to clearly distinguish between the structures **1d** and **2b** (Table 1).

In order to resolve this problem, we investigated the mass spectrometric behavior of compounds **1a**-**g** and **2a**.

Compounds **1a**-**g** and **2a** were prepared from the indoles **3a**-**f** and 1-alkyl-5-hydroxypyrrolidin-2-ones **4a** and **4b** according to our published procedure [1].

The proposed schemes for electron impact fragmentation of indoles **1a**-**g** and **2a** are given in Figures 1-3. The numbering sequence of the fragment ions and the quantitative characteristics of this fragmentation are given in Tables 2 and 3.

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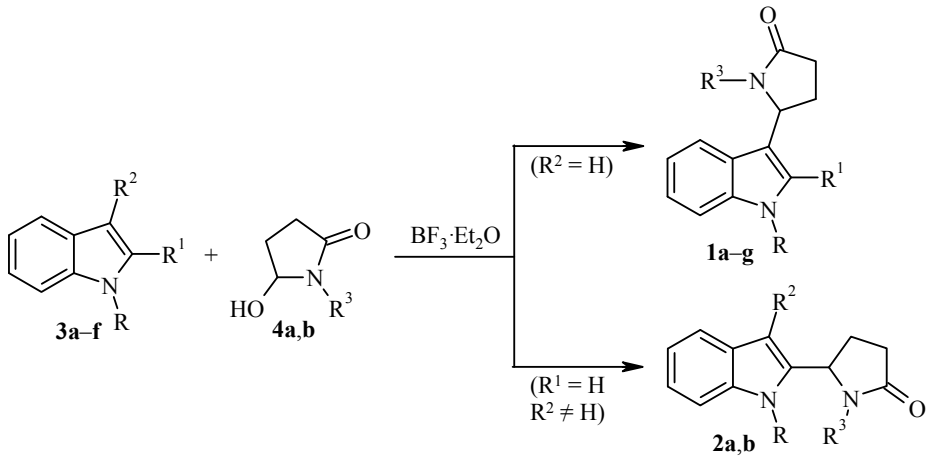

1 a R = H, R^1 = Me, R^3 = Bn; **b** R = H, R^1 = Ph, R^3 = Bn; **c** R = Me, R^1 = Ph, R^3 = Bn;
d R = Me, R^1 = H, R^3 = Bn; **e** R = R^1 = Me, R^3 = *s*-Bu; **f** R = H, R^1 = Ph, R^3 = *s*-Bu;
g R = Me, R^1 = Ph, R^3 = *s*-Bu; **2 a** R = H, R^2 = Me, R^3 = Bn; **b** R = Me, R^2 = H, R^3 = Bn;
3 a R = R^2 = H, R^1 = Me; **b** R = R^2 = H, R^1 = Ph; **c** R = R^1 = H, R^2 = Me;
d R = Me, R^1 = Ph, R^2 = H; **e** R = Me, R^1 = R^2 = H; **f** R = R^1 = Me, R^2 = H;
4 a R^3 = Bn, **b** R^3 = *s*-Bu

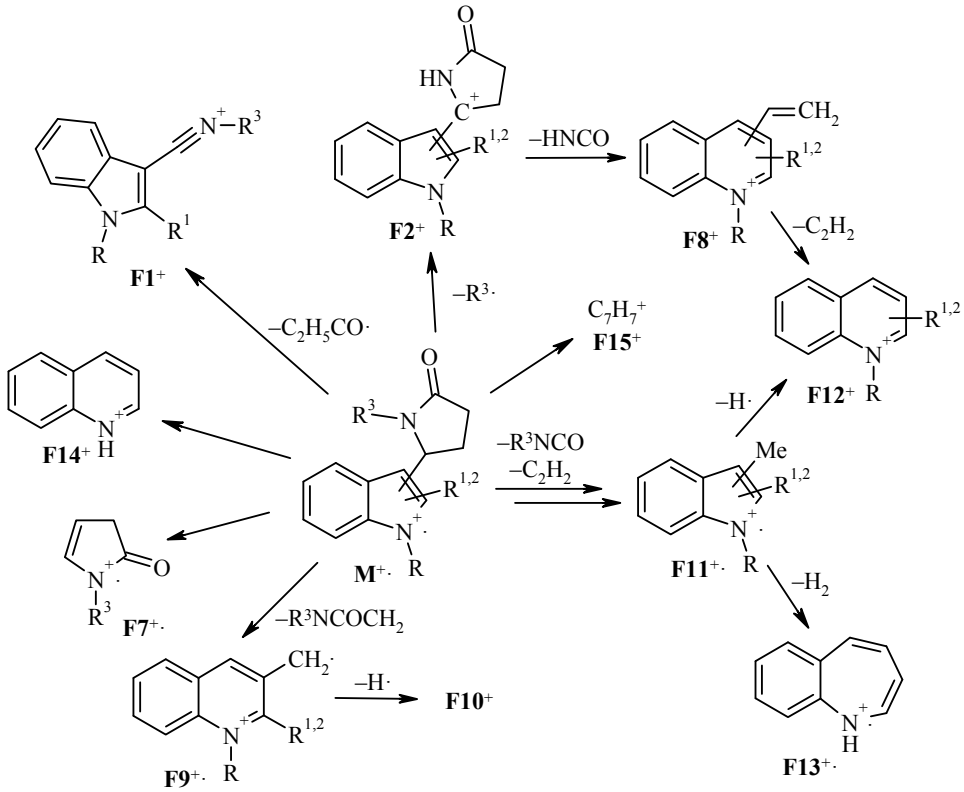

Fig. 1. Proposed scheme for the general mass spectral fragmentation pathways of indoles **1a-g** and **2a**.

The mass spectral fragmentation of indoles **1e-g** differs from the fragmentation of indoles **1a-d** by greater diversity, where the additional fragmentation directions are shown in Figure 2. These features are attributed to the significant difference in the stability of *sec*-butyl and benzyl fragments. The quantitative characteristics of the additional fragmentation directions for indoles **1e-g** are given in Table 3.

TABLE 1. ^{1}H NMR Spectra of the Indoles Synthesized

Com-pound	Chemical shifts, δ, ppm (*J*, Hz)
1a	2.06 (3H, s, CH_3); 2.20–2.39 (2H, m, 4'-CH_2); 2.58-2.67 (1H, m) and 2.70-2.78 (1H, m, 3'-CH_2); 3.41 (1H, d, *J* = 14.5) and 5.13 (1H, d, *J* = 14.5, PhC$\underline{H}_2$N); 4.69 (1H, br. t, *J* = 7.3, 5'-CH); 7.04 (2H, d, *J* = 7.5, H-2,6 Ph); 7.09 (1H, t, *J* = 7.0, H Ar); 7.18 (1H, t, *J* = 7.6, H Ar); 7.22-7.30 (3H, m, H Ar); 7.34 (1H, d, *J* = 8.1, H Ar); 7.44 (1H, br. d, *J* = 7.5, H Ar); 7.96 (1H, br. s, NH)
1b	2.30-2.45 (2H, m, 4'-CH_2); 2.57-2.66 (1H, m) and 2.69-2.80 (1H, m, 3'-CH_2); 3.48 (1H, d, *J* = 14.6) and 5.12 (1H, d, *J* = 14.6, PhC$\underline{H}_2$N); 4.89 (1H, t, *J* = 7.9, 5'-CH); 6.89-6.94 (2H, m, H Ar); 7.06-7.18 (6H, m, H Ar); 7.26-7.30 (1H, m, H Ar); 7.32-7.36 (3H, m, H Ar); 7.46 (1H, d, *J* = 8.1, H Ar); 7.58 (1H, d, *J* = 7.9, H Ar); 8.21 (1H, br. s, NH)
1c	2.25-2.36 (2H, m, 4'-CH_2); 2.48-2.60 (1H, m) and 2.60-2.73 (1H, m, 3'-CH_2); 3.54 (1H, d, *J* = 14.7) and 5.11 (1H, d, *J* = 14.7, PhC$\underline{H}_2$N); 3.58 (0.3H, s) and 3.59 (2.7H, s, NCH_3); 4.53 (1H, t, *J* = 7.8, 5'-CH); 6.92-6.96 (2H, m, H Ar); 6.97-7.21 (5.4H, m, H Ar); 7.25-7.44 (5.6H, m, H Ar); 7.57 (1H, d, *J* = 8.0, H Ar)
1d	2.15-2.24 (1H, m) and 2.36-2.45 (1H, m, 4'-CH_2); 2.53-2.61 (1H, m) and 2.67-2.75 (1H, m, 3'-CH_2); 3.62 (1H, d, *J* = 14.6) and 5.08 (1H, d, *J* = 14.6, PhC$\underline{H}_2$N); 3.79 (2.7H, s) and 3.80 (0.3H, s, NCH_3); 4.79 (1H, dd, *J* = 8.0, *J* = 6.3, 5'-CH); 6.88 (1H, s, H-2); 7.10-7.14 (3H, m, H Ar); 7.23-7.32 (4H, m, H Ar); 7.36 (1H, d, *J* = 8.2, H-4(7)); 7.47 (1H, d, *J* = 8.0, H-7(4))
1e	0.68-0.84 (3.8H, m), 1.10-1.20 (1.7H) and 1.46-1.57 (0.5H, m, C$\underline{H}_3$CH$_2$CHC$\underline{H}_3$); 1.59-1.75 (2H, m, CH$_3$C$\underline{H}_2$CH); 2.16-2.47 (2H, m, 4'-CH_2); 2.42 (3H, s, 2-CH_3); 2.47-2.61 (1H, m) and 2.62-2.79 (1H, m, 3'-CH_2); 3.36-3.46 (0.47H, m) and 3.81-3.90 (0.53H, m, CHN); 3.68 (1.67H, s) and 3.69 (1.33H, s, NCH_3); 4.92-5.03 (1H, m, 5'-CH); 7.02-7.12 (1H, m, H Ar); 7.14-7.21 (1H, m, H Ar); 7.24-7.31 (1H, m, H Ar); 7.48 (0.47H, d, *J* = 7.5, H Ar); 7.52 (0.53H, d, *J* = 7.9, H Ar)
1f	0.58-0.65 (3H, m, C$\underline{H}_3$CH$_2$); 0.67 (1.5H, d, *J* = 6.9) and 0.99 (1.5H, d, *J* = 6.9, CHC$\underline{H}_3$); 1.08-1.18 (0.5H, m), 1.25-1.38 (1H, m) and 1.50-1.60 (0.5H, m, CH$_3$C$\underline{H}_2$CH); 2.31-2.62 (3H, m, 4'-CH_2, 3'-CH_A); 2.68-2.87 (1H, m, 3'-CH_B); 3.32-3.41 (0.5H, m) and 3.77-3.86 (0.5H, m, CHN); 5.07-5.12 (1H, m, 5'-CH); 7.13 (1H, tdd, *J* = 7.5, *J* = 3.1, *J* = 0.9, H Ar); 7.21-7.26 (1H, m, H Ar); 7.38-7.56 (6H, m, H Ar); 7.59 (0.5H, br. d, *J* = 8.0, *J* = 7.9) and 7.63 (0.5H, br. d, *J* = 8.0, *J* = 7.9, H Ar); 8.28 (0.5H, br. s) and 8.31 (0.5H, br. s, NH)
1g	0.57-0.63 (3H, m, C$\underline{H}_3$CH$_2$); 0.71 (1.42H, d, *J* = 6.9) and 1.01 (1.58H, d, *J* = 6.9, CHC$\underline{H}_3$); 1.13-1.23 (0.60H, m), 1.31-1.38 (1H, m) and 1.55-1.62 (0.40H, m, CH$_3$C$\underline{H}_2$CH); 2.27-2.56 (3H, m, 4'-CH_2, 3'-CH_A); 2.58-2.85 (1H, m, 3'-CH_B); 3.27-3.35 (0.53H, m) and 3.74-3.83 (0.47H, m, CHN); 3.58 (1.42H, s) and 3.59 (1.58H, s, NCH_3); 4.75 (1H, t, *J* = 7.7, 5'-CH); 7.15 (1H, tdd, *J* = 7.5, *J* = 2.1, *J* = 1.0, H Ar); 7.24-7.30 (1H, m, H Ar); 7.31-7.39 (3H, m, H Ar); 7.47-7.57 (3H, m, H Ar); 7.60 (0.47H, s) and 7.65 (0.53H, br. d, *J* = 8.0, H Ar)
2a	2.09 (3H, s, CH_3); 2.14-2.25 (1H, m) and 2.37-2.46 (1H, m, 4'-CH_2); 2.56-2.65 (1H, m) and 2.69-2.76 (1H, m, 3'-CH_2); 3.49 (1H, d, *J* = 14.5) and 5.08 (1H, d, *J* = 14.5, PhC$\underline{H}_2$N); 4.79 (1H, t, *J* = 7.6, 5'-CH); 7.10-7.16 (3H, m, H Ar); 7.21 (1H, d. t, *J* = 7.6, *J* = 1.2, H Ar); 7.25-7.33 (3H, m, H Ar); 7.37 (1H, d, *J* = 8.1, H Ar); 7.55 (1H, br. d, *J* = 7.8, H Ar); 8.96 (1H, br. s, NH)

TABLE 2. Quantitative Characteristics of General Fragmentation Directions of the Indoles Synthesized*

Compound	Mass numbers of ions, *m/z* (I_{rel}, %)																
	$M^{+\cdot}$	**$F1^{+}$**	**$F2^{+}$**	**$F3^{+\cdot}$**	**$F4^{+}$**	**$F5^{+\cdot}$**	**$F6^{+}$**	**$F7^{+\cdot}$**	**$F8^{+}$**	**$F9^{+\cdot}$**	**$F10^{+}$**	**$F11^{+\cdot}$**	**$F12^{+}$**	**$F13^{+\cdot}$**	**$F14^{+}$**	**$F15^{+}$**	Others
1a	304 (100)	247 (6)	213 (20)	—	—	—	—	173 (51)	170 (34)	157 (52)	156 (10)	145 (19)	144 (16)	143 (6)	130 (7)	91 (41)	65 (5)
1b	366 (100)	309 (9)	275 (36)	—	—	—	—	173 (100)	232 (36)	219 (50)	218 (8)	—	206 (15)	—	—	91 (74)	204 (12), 193 (8), 145 (27), 117 (7), 104 (5), 65 (6), 57 (8), 55 (8)
1c	380 (100)	323 (10)	289 (16)	—	—	—	—	173 (100)	232 (22)	233 (26)	—	—	220 (11)	—	—	91 (31)	218 (13), 207 (5), 204 (5), 190 (6), 145 (24), 117 (5)
1d	304 (100)	247 (13)	213 (29)	—	—	—	—	173 (31)	170 (29)	157 (71)	156 (6)	145 (13)	144 (21)	143 (5)	130 (5)	91 (40)	171 (25), 117 (6), 115 (5), 77 (5), 65 (5)
1e	284 (100)	—	—	—	—	—	—	139 (61)	184 (89)	171 (22)	170 (12)	—	158 (17)	—	—	—	169 (10), 168 (9), 144 (7), 128 (6), 124 (5), 83 (6), 82 (8), 56 (10)
1f	332 (100)	—	—	—	—	—	—	139 (38)	232 (65)	219 (20)	218 (14)	—	206 (14)	—	—	—	230 (10), 204 (12), 151 (7), 108 (6)
1g	346 (100)	—	—	—	—	—	—	139 (74)	246 (66)	233 (19)	—	—	220 (16)	—	—	—	218 (17), 204 (7), 158 (7), 124 (6)
2a	304 (100)	247 (3)	213 (11)	199 (49)	198 (15)	197 (12)	184 (7)	—	170 (18)	157 (18)	156 (13)	145 (5)	144 (11)	143 (4)	130 (11)	91 (52)	106 (7)

*The values of the mass numbers of ions with a relative intensity of at least 5%.

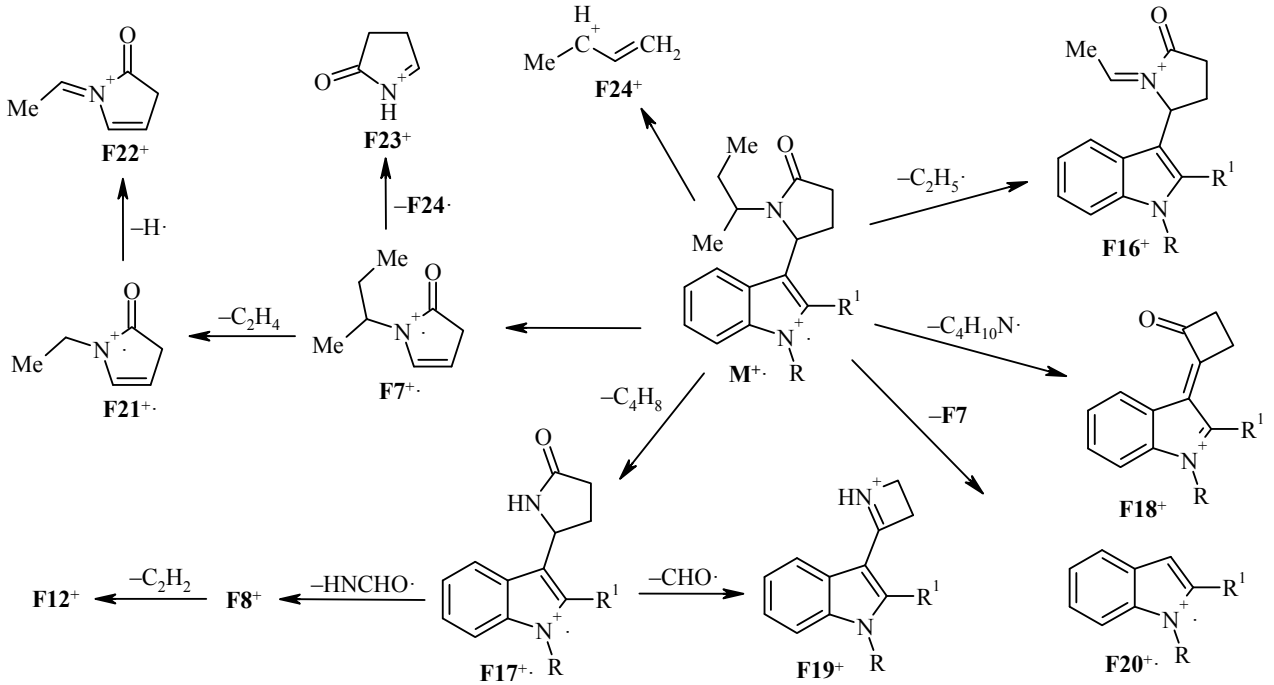

Fig. 2. Proposed scheme for the mass spectral fragmentation pattern of indoles **1e-g** due to the presence of *sec*-butyl group.

The data in Table 2 indicate that the mass spectral behavior of indole **2a** is similar to the behavior of indoles **1a-d**, but there are two significant differences. The most noticeable of them is the presence of fragment ions **F3-F6**, whose formation is outlined in Figure 3. However, as Figure 3 indicates, this feature cannot serve as a criterion for distinguishing between indoles **1d** and **2b**, since it is due not only to localization of the pyrrolidinone fragment at the C-2 position of indole, but also to the absence of a substituent at the indole N-1 atom.

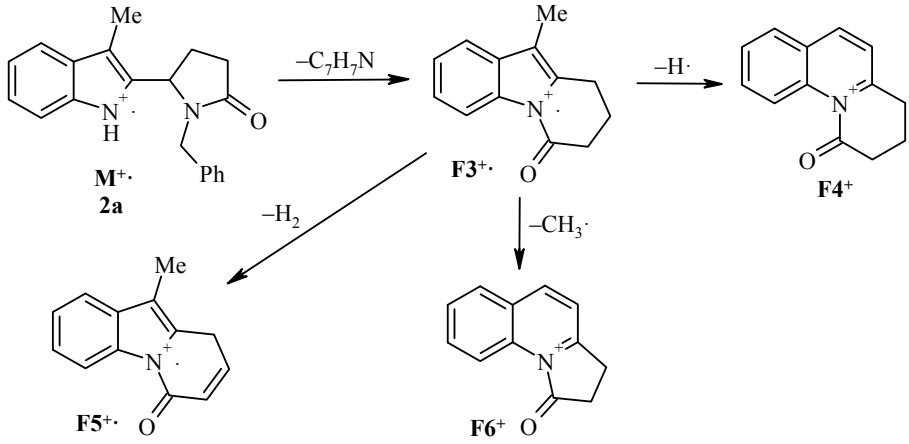

Fig. 3. Additional mass spectral fragmentation patterns of indole **2a.**

The second and most important difference in the mass spectrum of indole **2a** lies in the absence of the peak corresponding to ion **F7**, which is strong in the spectra of all indoles **1a-g** (Table 2). The decomposition direction $\mathbf{M}^{+\cdot} \rightarrow \mathbf{F7}$ may be considered to be the reverse process to the synthesis of indoles **1a-g**. Thus, we may propose that the above-mentioned Plancher type rearrangements [3, 4] are observed when the loss of a

TABLE 3. Quantitative Characteristics of Additional Fragmentation Patterns of Indoles **1e-g***

Compound	Mass numbers of ions, *m/z* (I_{rel}, %)									
	M$^{+\cdot}$	**F16**$^{+}$	**F17**$^{+\cdot}$	**F18**$^{+}$	**F19**$^{+}$	**F20**$^{+\cdot}$	**F21**$^{+\cdot}$	**F22**$^{+}$	**F23**$^{+}$	**F24**$^{+}$
1e	284 (100)	255 (14)	228 (7)	212 (10)	199 (6)	145 (17)	111 (16)	110 (17)	84 (59)	55 (6)
1f	332 (100)	303 (56)	276 (27)	260 (12)	247 (10)	193 (15)	111 (7)	—	84 (38)	55 (7)
1g	346 (100)	317 (31)	290 (21)	274 (7)	261 (10)	207 (24)	111 (13)	110 (22)	84 (51)	55 (6)

*The values of the mass numbers of ions with a relative intensity of at least 5% are shown.

substituent from one indole position and its transfer to another position by any mechanism is facilitated by thermodynamic and kinetic factors. Hence, in our case, the formation of 1-alkyl-5-(indol-3-yl)pyrrolidin-2-ones **1** appears to be under kinetic rather than thermodynamic control, while 1-alkyl-5-(indol-2-yl)pyrrolidin-2-ones **2** are more stable thermodynamically. Since the peak of fragment ion **F7** is lacking only in the spectrum of indole **2a** and is present in the spectra of all other compounds, we may conclude that the product of the reaction of *N*-methylindole (**3e**) with 1-benzyl-5-hydroxypyrrolidin-2-one (**4a**) corresponds specifically to indole **1d**, rather than indole **2b**.

Thus, we conclude that, as in the case of indole itself [1], the pyrrolidinone substituent enters at the C-3 atom in *N*-methylindole.

EXPERIMENTAL

The ^{1}H NMR spectra were recorded on a Bruker Avance-400 spectrometer (400 MHz) in $CDCl_3$ with TMS as internal standard. The electron impact mass spectra at 70 eV were recorded on a VG 70-70E mass spectrometer with direct sample inlet into the ion source. The elemental analysis was carried out on a Carlo Erba ER-20 CHN analyzer. The melting points were determined on an Electrothermal IA9100 instrument with sealed capillaries. The reaction course and purity of the products were monitored by thin layer chromatography on Silufol UV-254 and Merck Silicagel 60 F_{254} precoated silica gel plates. Merck silica gel (0.035-0.070 mm, pore diameter 6 nm, 500 m^2/g) was used for purification of the compounds by column chromatography. Indoles **1a**,**d** and **2a** were obtained according to our previous procedure [1], while the indoles **1b**,**c**,**e-g** were obtained by an analogous procedure from the corresponding indoles and 1-alkyl-5-hydroxypyrrolidin-2-ones.

1-Benzyl-5-(2-phenyl-1*H*-indol-3-yl)pyrrolidin-2-one (1b). Yield 83%; mp 256-258°C (Et_2O). Found, %: C 81.88; H 6.27; N 7.26. $C_{25}H_{22}N_2O$. Calculated, %: C 81.94; H 6.05; N 7.64.

1-Benzyl-5-(1-methyl-2-phenyl-1*H*-indol-3-yl)pyrrolidin-2-one (1c). Yield 82%; mp 167-168°C (hexane). Found, %: C 81.93; H 5.95; N 7.77. $C_{26}H_{24}N_2O$. Calculated, %: C 82.07; H 6.36; N 7.36.

1-*sec*-Butyl-5-(1,2-dimethyl-1*H*-indol-3-yl)pyrrolidin-2-one (1e). Yield 49%; mp 108-109°C (hexane). Found, %: C 75.89; H 8.36; N 10.02. $C_{18}H_{24}N_2O$. Calculated, %: C 76.02; H 8.51; N 9.85.

1-*sec*-Butyl-5-(2-phenyl-1*H*-indol-3-yl)pyrrolidin-2-one (1f). Yield 60%; mp 209-210°C (Et_2O). Found, %: C 79.61; H 7.18; N 8.73. $C_{22}H_{24}N_2O$. Calculated, %: C 79.48; H 7.28; N 8.43.

1-*sec*-Butyl-5-(1-methyl-2-phenyl-1*H*-indol-3-yl)pyrrolidin-2-one (1g). Yield 77%; mp 126-128°C (hexane). Found, %: C 79.88; H 7.32; N 8.11. $C_{23}H_{26}N_2O$. Calculated, %: C 79.73; H 7.56; N 8.09.

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