INTRAMOLECULAR MANNICH REACTION OF 2-OXOTRYPTAMINES WITH ACETONE YIELDING SPIRO[INDOLE-3,3′-PYRROLIDIN]-2-ONES

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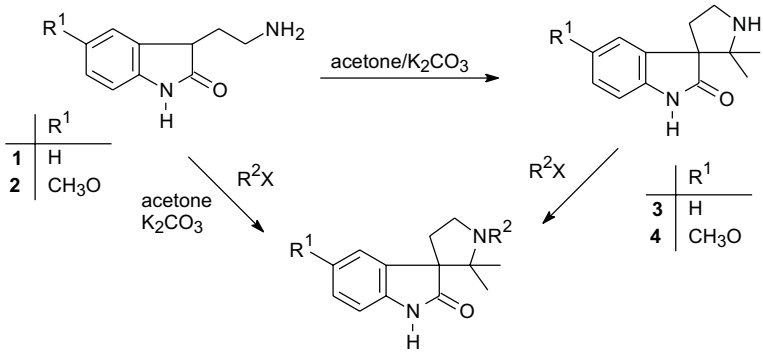
Dedicated to the memory of the late Professor Miroslav Protiva.

2-Oxotryptamines undergo intramolecular Mannich-type cyclization with acetone to give 2′,2′-dimethylspiro[indole-3,3′-pyrrolidin]-2-ones. In presence of an alkylating reagent, this reaction gives the corresponding 1′-substituted products.

Key words: Intramolecular Mannich reaction; Spirocyclic compounds; Indoles; Pyrrolidines; Cyclizations; Alkaloids.

3-Substituted indolin-2-ones are regarded physiologically active compounds with potential selectivity toward different receptor tyrosine kinases[1] and serotonines. In an attempt to synthesize new 3-substituted indolin-2-ones for pharmacological screening 2-oxotryptamine (**1**) and 5-methoxy-2-oxotryptamine (**2**) – obtained by DMSO/HCl oxidation[2] of tryptamine and 5-methoxytryptamine, respectively – were alkylated with various alkyl halogenides in acetone in the presence of K_2CO_3. Surprisingly enough, ^{1}H NMR spectroscopic studies of the compounds, thus obtained in rather high yields as the only products, unambiguously proved that instead of the expected mono- or dialkylation, an intramolecular Mannich-type reaction took place with the participation of acetone and, consequently, various *N*-alkylated 2′,2′-dimethylspiro[indole-3,3′-pyrrolidin]-2-ones (**5**–**23**) were obtained.

The intramolecular cyclization could be performed without alkylating agent and K_2CO_3; in this case, *N*-unsubstituted spiro compounds **3** and **4** were isolated which, upon subsequent alkylation, could be transformed into the *N*-alkyl derivatives **5**–**23**.



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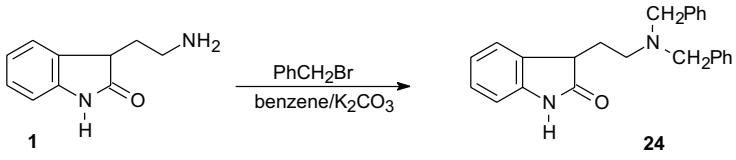
Starting material	Alkyl halogenide	Product		
		No	R^1	R^2
1 or **3**	$Ph–CH_2–Br$	**5**	H	$Ph–CH_2–$
2 or **4**	$Ph–CH_2–Br$	**6**	CH_3O	$Ph–CH_2–$
1 or **3**	$CH_2=CH–CH_2Br$	**7**	H	$CH_2=CH–CH_2–$
2 or **4**	$CH_2=CH–CH_2Br$	**8**	CH_3O	$CH_2=CH–CH_2–$
1 or **3**	$I–CH_2CONH_2$	**9**	H	$–CH_2CONH_2$
2 or **4**	$I–CH_2CONH_2$	**10**	CH_3O	$–CH_2CONH_2$
1 or **3**	CH_3I	**11**	H	CH_3
2 or **4**	CH_3I	**12**	CH_3O	CH_3
1 or **3**	C_2H_5I	**13**	H	C_2H_5
2 or **4**	C_2H_5I	**14**	CH_3O	C_2H_5
1 or **3**	$Ph–CH_2CH_2CH_2Br$	**15**	H	$Ph–CH_2CH_2CH_2–$
1 or **3**	$Ph–CH_2CH_2Br$	**16**	H	$Ph–CH_2CH_2–$
1 or **3**	$CH_2=CH–CH_2CH_2Br$	**17**	H	$CH_2=CH–CH_2CH_2–$
1 or **3**	$CH_2=C(CH_3)CH_2Cl$	**18**	H	$CH_2=C(CH_3)CH_2–$
1 or **3**	$C_6H_{13}I$	**19**	H	$CH_3CH_2CH_2CH_2CH_2CH_2–$
1 or **3**	$HOCH_2CH_2CH_2Br$	**20**	H	$HOCH_2CH_2CH_2–$
1 or **3**	$BrCH_2CH_2CH_2CO_2Et$	**21**	H	$–CH_2CH_2CH_2CO_2Et$
1 or **3**	$ClCH_2CO_2CH_3$	**22**	H	$–CH_2CO_2CH_3$
2 or **4**	$BrCH_2CO_2C_2H_5$	**23**	CH_3O	$–CH_2CO_2C_2H_5$

As in the original reaction in the presence of alkyl halogenides not even traces of *N*-alkylated oxotryptamines could be detected, ΔG^* of the cyclization is supposedly much lower than that of the *N*-alkylation; thus cyclization is followed by alkylation of the spiro compound.

As expected, dialkylation of 2-oxotryptamines could be finally performed using benzene as a solvent instead of acetone.



Intramolecular cyclization of 2-oxotryptamine with aldehydes resulting in diastereomeric mixtures of 2′-substituted spiro[indole-3,3′-pyrrolidin]-2-ones is widely used[3]; the method was frequently utilized for the synthesis of various oxindol alkaloids (*e.g.* in the aspidosperma and strychnos series), similar reaction with ketones, however, has not yet been published. Therefore present broader application of the well known method opens up the possibility to synthesize 2′,2′-disubstituted spiro[indole-3,3′-pyrrolidin]-2-ones which could not be prepared up to now *via* any other way.

Both pharmacological interests on new oxindole compounds and investigation of the stereochemical aspects of the reaction with asymmetric ketones comparing with those with aldehydes justify further study on the scope and limitation as well as on stereochemical outcome of this Pictet–Spengler type oxindole ring closure. This work is in progress.

EXPERIMENTAL

NMR spectra were taken on a Varian VXR 400 instrument at room temperature, chemical shifts being reported relative to δ_{TMS} 0.00 ppm. IR spectra were measured on a Nicolet 205 FT-IR spectrometer. For TLC analysis, MN Polygram SIL G/UV_{254} sheets and for column chromatography Kieselgel 60 (0.063–0.200) adsorbent were used. Melting points were measured on a Boetius hot-stage apparatus; they are uncorrected.

2′,2′-Dimethylspiro[indole-3,3′-pyrrolidin]-2-ones **3** and **4**

To a solution of 2-oxotryptamine hydrochloride (**1** or **2**; 10 mmol) in acetone (60 ml), an aqueous solution of crystalline sodium acetate (1.4 g in 8 ml water) was added, and the mixture, stirred magnetically, was refluxed for 3 h. The mixture was then evaporated, the residue was dissolved in ice–water (30 ml), its pH was set to 8–9 with ammonia and the solution was extracted with chloroform (3 × 10 ml). The organic layer was dried ($MgSO_4$)

and evaporated. Crystallization of the residue gave the title compounds as base or hydrochloride, respectively.

2′,2′-Dimethylspiro[indole-3,3′-pyrrolidin]-2-one (**3**). Colourless crystals, yield 1.15 g (53%). M.p. 162–164 °C (acetone). Analysis: calculated: 72.19% C, 7.46% H, 12.95% N; found: 72.31% C, 7.55% H, 12.80% N. IR (KBr): 1 704 (5-membered lactam). ^{1}H NMR ($CDCl_3$): 1.14 + 1.25 2 × s, 2 × 3 H (2 × 2′-CH_3); 2.32 t, 2 H, J = 7.4 (4′-H_2); 3.1 brs, 1 H (N1′-H); 3.2–3.34 m, 2 H (5′-H_2); 6.92 d, 1 H (7-H); 7.03 ddd, 1 H (5-H); 7.22 ddd, 1 H (6-H); 7.26 d, 1 H (4-H); 9.04 brs, 1 H (indoline NH).

5-Methoxy-2′,2′-dimethylspiro[indole-3,3′-pyrrolidin]-2-one (**4**). The residue after evaporation was acidified (HCl–methanol). Hydrochloride: colourless crystals, yield 1.77 g (72%). M.p. 222–225 °C (MeOH–Et_2O). Analysis: calculated: 59.47% C, 6.42% H, 12.54% Cl, 9.91% N; found: 59.27% C, 6.46% H, 12.19% Cl, 10.01% N. IR (KBr): 1 711 (5-membered lactam), 3 304 ($^+NH_2$). ^{1}H NMR ($CDCl_3$): 1.13 + 1.46 2 × s, 2 × 3 H (2 × 2′-CH_3); 2.24 + 2.6 2 × m, 2 × 1 H (4′-H_2); 3.4–3.55 m, 2 H (5′-H_2); 3.7 s, 3 H (OCH_3); 6.83 m, 2 H (6-H + 7-H); 7.03 ddd, 1 H (5-H); 7.02 d, 1 H (4-H); 8.68 + 7.26 2 × brs, 2 × 1 H ($^+$N1′-H_2); 10.75 brs, 1 H (indoline NH).

1′-Alkyl-2′,2′-dimethylspiro[indole-3,3′-pyrrolidin]-2-ones (**5–23**). *General Method*

A) From 2-Oxotryptamines (**1** or **2**) by One-Pot Cyclization and Alkylation

To a solution of 2-oxotryptamine (**1** or **2**; 10 mmol), freshly prepared from its hydrochloride, in anhydrous acetone (100 ml), finely powdered anhydrous K_2CO_3 (2.5 g), anhydrous NaI (0.5 g) and an alkyl halogenide (11 mmol) was added. The magnetically stirred suspension was then refluxed under argon for 3–30 h. (With volatile alkyl halogenides the reaction was carried out at room temperature and more alkyl halogenide was used.) The progress of the reaction could be checked by TLC. After completion, the mixture was evaporated *in vacuo* and the residue was taken up in chloroform–water. The organic phase was dried ($MgSO_4$), evaporated and the residue cystallized (in some cases purification by column chromatography was necessary).

1′-Benzyl-2′,2′-dimethylspiro[indole-3,3′-pyrrolidin]-2-one (**5**). Reaction time 7 h. Yield 1.5 g (49%). TLC: hexane–ethyl acetate 2 : 1 (R_F 0.35), m.p. 176–178 °C (ethyl acetate). Analysis: calculated: 78.40% C, 7.24% H, 9.14% N; found: 78.32% C, 7.19% H, 9.20% N. IR (KBr): 1 710 (5-membered lactam), 3 180 (NH), ^{1}H NMR ($CDCl_3$): 0.84 + 1.24 2 × s, 2 × 3 H, 2 × 2′-CH_3); 1.88 + 2.49 2 × ddd, 2 × 1 H, J_{gem} = 12.7, J_{vic} = 9.4 + 4.5 and 10.5 + 5.2, respectively (4′-H_2); 2.72 + 3.05 2 × ddd, 2 × 1 H, J_{gem} = 9.1, J_{vic} = 10.5 + 4.5 and 9.4 + 5.2, respectively (5′-H_2); 3.38 + 3.92 2 × d, 2 × 1 H, J_{gem} = 12.8 (N-CH_2-Ph); 6.88 d, 1 H (7-H); 7.04 ddd, 1 H (5-H); 7.19 ddd, 1 H (6-H); 7.25–7.45 m, 5 H (arom. benzyl); 7.51 d, 1 H (4-H); 8.40 brs, 1 H (NH).

1′-Benzyl-5-methoxy-2′,2′-dimethylspiro[indole-3,3′-pyrrolidin]-2-one (**6**). Reaction time 5 h. Yield 2.1 g (63%). TLC: hexane–ethyl acetate 2 : 1 (R_F 0.3), m.p. 191–193 °C (ethyl acetate). Analysis: calculated: 74.97% C, 7.19% H, 8.33% N; found: 75.07% C, 7.19% H, 8.21% N. IR (KBr): 1 704 (5-membered lactam), 3 183 (NH). ^{1}H NMR ($CDCl_3$): 0.86 + 1.24 2 × s, 2 × 3 H, 2 × 2′-CH_3); 1.86 + 2.49 2 × ddd, 2 × 1 H, J_{gem} = 12.5, J_{vic} = 9.3 + 4.5 and 10.5 + 5.3, respectively (4′-H_2); 2.70 + 3.05 2 × ddd, 2 × 1 H, J_{gem} = 9.1, J_{vic} = 10.5 + 4.5 and 9.3 + 5.3, respectively (5′-H_2); 3.35 + 3.94 2 × d, 2 × 1 H, J_{gem} = 12.8 (N-CH_2-Ph); 3.80 s, 3 H (OCH_3);

6.74 dd, 1 H, *J* = 8.3 + 2.5 (6-H); 6.78 d, *J* = 8.3 (7-H); 7.18 d, *J* = 2.5 (4-H); 7.23–7.45 m, 5 H (arom. benzyl); 8.22 brs, 1 H (NH).

1′-Allyl-2′,2′-dimethylspiro[indole-3,3′-pyrrolidin]-2-one (**7**). Reaction time 10 h. Yield 1.1 g (43%). TLC: CH_2Cl_2–methanol 9 : 1 (R_F 0.43), m.p. 153–155 °C (ethanol). Analysis: calculated: 74.97% C, 7.86% H, 10.93% N; found: 74.90% C, 7.78% H, 10.75% N. IR (KBr): 1 702 (5-membered lactam), 3 194 (NH). ^{1}H NMR ($CDCl_3$): 0.72 + 1.13 2 × s, 2 × 3 H, 2 × 2′-CH_3); 1.92 + 2.47 2 × ddd, 2 × 1 H, J_{gem} = 12.7, J_{vic} = 9.5 + 4.5 and 10.6 + 5.3, respectively (4′-H_2); 2.71 + 3.28 2 × ddd, 2 × 1 H, J_{gem} = 9.1, J_{vic} = 10.6 + 4.5 and 9.5 + 5.3 (5′-H_2); 2.91 + 3.34 2 × dddd, 2 × 1 H, J_{gem} = 13.3, J_{vic} = 7.5 and 4.5, respectively, J_{allyl} = 1.2 + 0.8 and 1.9 + 1.9, respectively (N1′-CH_2); 5.1 + 5.27 2 × ddd, 2 × 1 H, J_{gem} = 1.9, J_{vic} = 10.0 and 17.0, respectively, J_{allyl} = 1.9 + 0.8 and 1.9 + 1.2, respectively (CH=C**H**$_2$); 5.93 dddd, 1 H, J = 17.0 + 10.0 + 7.5 + 4.5 (C**H**=CH_2); 6.87 d, 1 H (7-H); 7.00 dd, 1 H (5-H); 7.18 dd, 1 H (6-H); 7.52 d, 1 H (4-H); 8.48 brs, 1 H (NH).

1′-Allyl-5-methoxy-2′,2′-dimethylspiro[oxindole-3,3′-pyrrolidine] (**8**). Reaction time 4 h. Purification by column chromatography (CH_2Cl_2–methanol 9 : 1). Yield: 1.1 g (37%). TLC: toluene–diethylamine 9 : 1 (R_F 0.4), m.p. 105–106 °C (hexane). Analysis: calculated: 71.30% C, 7.74% H, 9.78% N; found: 71.12% C, 7.59% H, 9.91% N. IR (KBr): 1 703 (5-membered lactam), 3 191 (NH). ^{1}H NMR ($CDCl_3$): 0.73 + 1.13 2 × s, 2 × 3 H, 2 × 2′-CH_3); 1.90 + 2.46 2 × ddd, 2 × 1 H, J_{gem} = 12.8, J_{vic} = 9.4 + 4.5 and 10.6 + 5.3, respectively (4′-H_2); 2.69 + 3.29 2 × ddd, 2 × 1 H, J_{gem} = 9.4, J_{vic} = 10.6 + 4.5 and 9.4 + 5.3, respectively (5′-H_2); 2.89 + 3.36 2 × dddd, 2 × 1 H, J_{gem} = 13.5, J_{vic} = 7.5 and 4.5, respectively, J_{allyl} = 1.3 + 1.0 and 1.9 + 1.8, respectively (N1′-CH_2); 3.79 s, 3 H (OCH_3); 5.09 + 5.26 2 × dddd, 2 × 1 H, J_{gem} = 1.8, J_{vic} = 10.2 and 17.0, respectively, J_{allyl} = 1.8 + 1.0 and 1.9 + 1.3, respectively (CH=C**H**$_2$); 5.92 dddd, 1 H, *J* = 17.0 + 10.2 + 7.5 + 4.5 (C**H**=CH_2); 6.73 dd, 1 H, *J* = 8.3 + 2.5 (6-H); 6.75 d, 1 H, *J* = 8.3 (7-H); 7.20 d, 1 H, *J* = 2.5 (4-H); 8.14 brs, 1 H (NH).

(2′,2′-Dimethyl-2-oxospiro[indole-3,3′-pyrrolidin]-1′-yl)acetamide (**9**). Reaction time 1.5 h. Yield 1.8 g (66%). TLC: acetone (R_F 0.46), m.p. 129–132 °C (ethyl acetate). Analysis: calculated: 65.21% C, 7.01% H, 15.37% N; found: 65.08% C, 7.09% H, 15.19% N. IR (KBr): 1 660 (amide), 1 700 (5-membered lactam), 3 200 (NH), 3 321 (amide NH_2). ^{1}H NMR ($CDCl_3$): 0.92 + 1.07 2 × s, 2 × 3 H, (2 × 2′-CH_3); 2.22 m, 2 H (4′-H_2); 2.89 + 3.37 2 × m, 2 × 1 H (5′-H_2); 2.99 + 3.37 2 × d, 2 × 1 H, J_{gem} = 17.2 (CH_2CO); 6.44 + 8.72 2 × brd, 2 × 1 H, J_{gem} = 4.5 ($CONH_2$); 6.92 d, 1 H (7-H); 6.99 dd, 1 H (5-H); 7.20 dd, 1 H (6-H); 7.21 dd, 1 H (4-H); 10.23 brs, 1 H (NH).

(5-Methoxy-2′,2′-dimethyl-2-oxospiro[indole-3,3′-pyrrolidin]-1′-yl)acetamide (**10**). Reaction time 3 h. Yield 1.7 g (56%). TLC: CH_2Cl_2–methanol 9 : 1 (R_F 0.32), m.p. 211–212 °C (ethyl acetate). Analysis: calculated: 63.35% C, 6.98% H, 13.85% N; found: 63.51% C, 7.06% H, 13.70% N. IR (KBr): 1 674 (amide CO), 1 690 and 1 700 (5-membered lactam), 3 180 (NH), 3 319 (amide NH_2). ^{1}H NMR ($CDCl_3$): 0.94 + 1.10 2 × s, 2 × 3 H (2 × 2′-CH_3); 2.15 - 2.30 m, 2 H (4′-H_2); 2.84 + 3.41 2 × m, 2 × 1 H (5′-H_2); 2.98 + 3.42 2 × d, 2 × 1 H, J_{gem} = 17.3 (CH_2CO); 3.79 s, 3 H (OCH_3); 6.76 dd, 1 H, *J* = 8.4 + 2.5 (6-H); 6.83 d, 1 H, *J* = 2.5 (4-H); 6.86 d, 1 H, *J* = 8.4 (7-H); 7.41 + 8.78 2 × brd, 2 × 1 H, J_{gem} = 4.5 ($CONH_2$); 10.53 brs, 1 H (NH).

1′,2′,2′-Trimethylspiro[indole-3,3′-pyrrolidin]-2-one (**11**). Reaction time 12 h at room temperature. Yield 1.57 g (69%). TLC: toluene–diethylamine 9 : 1 (R_F 0.41), m.p. 132–134 °C (hexane). Analysis: calculated: 73.01% C, 7.88% H, 12.16% N; found: 72.86% C, 7.69% H, 12.00% N. IR (KBr): 1 703 (5-membered lactam), 3 179 (NH). ^{1}H NMR ($CDCl_3$): 0.75 + 1.07 2 × s, 2 × 3 H (2 × 2′-CH_3); 1.98 + 2.43 2 × ddd, 2 × 1 H, J_{gem} = 13.0, J_{vic} = 9.5 + 4.6 and 10.3 + 5.3,

respectively (4′-H_2); 2.31 s, 3 H (1′-CH_3); 2.93 + 3.12 2 × ddd, 2 × 1 H, J_{gem} = 9.0, J_{vic} = 10.3 + 4.6 and 9.5 + 5.3, respectively (5′-H_2); 6.85 d, 1 H (7-H); 6.98 dd, 1 H (5-H); 7.17 dd, 1 H (6-H); 7.40 d, 1 H, (4-H); 8.44 brs, 1 H (NH).

5-Methoxy-1′,2′,2′-trimethylspiro[indole-3,3′-pyrrolidin]-2-one (**12**). Reaction time 12 h at room temperature. Yield 1.1 g (42%). TLC: toluene–diethylamine 9 : 1 (R_F 0.38), m.p. 123–125 °C (hexane). Analysis: calculated: 69.20% C, 7.74% H, 10.76% H; found: 69.11% C, 7.79% H, 10.58% N. IR ($CHCl_3$): 1 706 (5-membered lactam). ^{1}H NMR ($CDCl_3$): 0.75 + 1.07 2 × s, 2 × 3 H (2 × 2′-CH_3); 1.95 + 2.43 2 × m, 2 × 1 H (4′-H_2); 2.29 s, 3 H (1′-CH_3); 2.88 + 3.13 2 × m, 2 × 1 H (5′–H_2); 3.79 s, 3 H (OCH_3); 6.70 dd, 1 H (6-H); 6.77 d, 1 H (7-H); 7.08 d, 1 H (4-H); 8.36 brs, 1 H (NH).

1′-Ethyl-2′,2′-dimethylspiro[indole-3,3′-pyrrolidin]-2-one (**13**). Reaction time 5 h. Purification by column chromatography (toluene–diethylamine 9 : 1). Yield 1.5 g (62%). TLC: toluene–diethylamine 9 : 1 (R_F 0.48), m.p. 157–160 °C (ethyl acetate). Analysis: calculated: 73.74% C, 8.25% H, 11.46% N; found: 74.02% C, 8.31% H, 11.38% H. IR (KBr): 1 713 (5-membered lactam), 3 178 (NH). ^{1}H NMR ($CDCl_3$): 0.68 + 1.11 2 × s, 2 × 3 H (2 × 2′-CH_3); 1.16 dd, 3 H ($CH_2C\mathbf{H}_3$); 1.91 + 2.47 2 × ddd, 2 × 1 H, J_{gem} = 12.6, J_{vic} = 9.5 + 4.5 and 10.5 + 5.3, respectively (4′-H_2); 2.36 + 2.65 2 × m, 2 × 1 H ($C\mathbf{H}_2CH_3$); 2.68 + 3.36 2 × ddd, 2 × 1 H, J_{gem} = 9.0, J_{vic} = 10.5 + 4.5 and 9.5 + 5.3, respectively (5′-H_2); 6.86 dd, 1 H (7-H); 6.99 ddd, 1 H (5-H); 7.17 ddd, 1 H (6-H); 7.52 dd, 1 H (4-H); 8.42 brs, 1 H (NH). ^{13}C NMR ($CDCl_3$): 14.72 + 15.74 + 22.16 (2 × 2′-CH_3 + $CH_2\mathbf{C}H_3$); 31.86 (C4′); 41.39* ($\mathbf{C}H_2CH_3$); 48.18* (C5′); 60.55 (C2′); 66.21 (C3); 108.89 (C7); 122.01 (C5); 125.83 (C4); 127.29 (C6); 135.05 (C3a); 140.01 (C7a); 180.42 (C2).

1′-Ethyl-5-methoxy-2′,2′-dimethylspiro[indole-3,3′-pyrrolidin]-2-one (**14**). Reaction time 8 h. Yield 1.8 g (66%). TLC: toluene–diethylamine 9 : 1 (R_F 0.35), m.p. 142–144 °C (diethyl ether–hexane). Analysis: calculated: 70.05% C, 8.08% H, 10.21% N; found: 69.93% C, 8.21% H, 10.07% N. IR (KBr): 1 703 (5-membered lactam), 3 203 (NH). ^{1}H NMR ($CDCl_3$): 0.70 + 1.11 2 × s, 2 × 3 H (2 × 2′-CH_3); 1.16 dd, 3 H, J = 7.2 + 6.8 ($CH_2C\mathbf{H}_3$); 1.89 + 2.48 2 × ddd, 2 × 1 H, J_{gem} = 12.8, J_{vic} = 9.5 + 4.5 and 10.7 + 5.3, respectively (4′-H_2); 2.35 + 2.66 2 × dq 2 × 1 H, J_{gem} = 11.5, J_{vic} = 6.8 and 7.2 ($C\mathbf{H}_2CH_3$); 2.67 + 3.36 2 × ddd, 2 × 1 H, J_{gem} = 8.9, J_{vic} = 10.7 + 4.5 and 9.5 + 5.3, respectively (5′-H_2); 3.78 s, 3 H (OCH_3); 6.71 dd, 1 H, J = 8.5 + 2.6 (6-H); 6.75 d, 1 H, J = 8.5 (7-H); 7.22 d, 1 H, J = 2.6 (4-H); 8.26 brs, 1 H (NH).

2′,2′-Dimethyl-1-(3-phenylpropyl)spiro[indole-3,3′-pyrrolidin]-2-one (**15**). Reaction time 3 h. Yield 1.2 g (36%). TLC: $CHCl_3$–methanol 4 : 1 (R_F 0.62), m.p. 148–149 °C (diethyl ether). Analysis: calculated: 79.01% C, 7.86% H, 8.38% N; found: 78.86% C, 7.81% H, 8.27% N. IR ($CHCl_3$): 1 710 (5-membered lactam), 3 179 (NH). ^{1}H NMR ($CDCl_3$): 0.67 + 1.11 2 × s, 2 × 3 H (2 × 2′-CH_3); 1.87 m, 2 H (N-$CH_2C\mathbf{H}_2$); 1.94 + 2.50 2 × ddd, 2 × 1 H, J_{gem} = 12.8, J_{vic} = 9.4 + 4.5 and 10.6 + 5.4, respectively (4′-H_2); 2.41 + 2.61 2 × ddd, 2 × 1 H, J_{gem} = 11.4, J_{vic} = 5.6 + 5.4 and 7.8 + 7.8, respectively (CH_2Ph); 2.67 + 2.81 2 × dt 2 × 1 H, J_{gem} = 13.7, J_{vic} = 7.5 and 8.0, respectively (N1′-$C\mathbf{H}_2CH_2$); 2.73 + 3.38 2 × ddd, 2 × 1 H, J_{gem} = 9.0, J_{vic} = 10.6 + 4.5 and 9.4 + 5.4, respectively (5′-H_2); 6.85 dd, 1 H (7-H); 7.00 dd, 1 H (5-H); 7.17 dd, 1 H (6-H); 7.15–7.30 m, 5 H (Ph); 7.54 d, 1 H (4-H); 8.24 brs, 1 H (NH).

2′,2′-Dimethyl-1′-(2-phenylethyl)spiro[indole-3,3′-pyrrolidin]-2-one (**16**). Reaction time 4 h. Yield 1.4 g (44%). TLC: $CHCl_3$–methanol 4 : 1 (R_F 0.33), m.p. 146–148 °C (methanol). Analysis: calculated: 78.71% C, 7.55% H, 8.74% N; found: 78.57% C, 7.42% H, 8.71% N. IR (KBr): 1 708 (5-membered lactam), 3 180 (NH). ^{1}H NMR ($CDCl_3$): 0.60 + 1.11 2 × s, 2 × 3 H (2 × 2′-CH_3); 1.87 + 2.48 2 × ddd, 2 × 1 H, J_{gem} = 12.7, J_{vic} = 9.3 + 4.3 and 10.6 + 5.4, respectively (4′-H_2); 2.58–3.00 m, 5 H (5′-H_A + CH_2-CH_2-Ph); 3.38 ddd, 1 H, J_{gem} = 8.8, J_{vic} = 9.3 +

5.4 (5′-H_B); 6.80 m, 2 H (5-H + 7-H); 6.98 dd, 1 H (4-H); 7.10 ddd, 1 H (4-H); 7.20–7.40 m, 5 H (Ph); 8.26 brs, 1 H (NH).

1′-(But-3-enyl)-2′,2′-dimethylspiro[indole-3,3′-pyrrolidin]-2-one (**17**). Reaction time 17 h. Yield 0.95g (37%). TLC: toluene–diethylamine 9 : 1 (R_F 0.42), m.p. 119–120 °C (diethyl ether). Analysis: calculated: 75.52% C, 8.20% H, 10.36% N; found: 75.72% C, 8.29% H, 10.16% N. IR (KBr): 1 642 (weak; C=C), 1 704 (5-membered lactam), 3 179 (NH). ^{1}H NMR ($CDCl_3$): 0.68 + 1.12 2 × s, 2 × 3 H (2 × 2′-CH_3); 1.91 + 2.49 2 × ddd, 2 × 1 H, J_{gem} = 12.7, J_{vic} = 9.3 + 4.4 and 10.7 + 5.4, respectively (4′-H_2); 2.23–2.38 m, 2 H (N-CH_2C**H**$_2$); 2.43 + 2.68 2 × ddd, 2 × 1 H, J_{gem} = 11.5, J_{vic} = 7.5 + 4.5 and 8.2 + 7.8, respectively (N-CH_2); 2.71 + 3.36 2 × ddd, 2 × 1 H, J_{gem} = 8.9, J_{vic} = 10.7 + 4.4 and 9.3 + 5.4, respectively (5′-H_2); 5.05 + 5.12 2 × dddd, 2 × 1 H, J_{gem} = 2.2, J_{vic} = 10.2 and 17.0, J_{allyl} = 1.4 + 1.0 and 1.6 + 1.4, respectively (CH=C**H**$_2$); 5.90 dddd, 1 H, J = 17.0 + 10.2 + 6.8 + 6.6 (C**H**=CH_2); 6.84 d, 1 H (7-H); 6.98 dd, 1 H (5-H); 7.17 dd, 1 H (6-H); 7.52 d, 1 H (4-H); 8.32 brs, 1 H (NH).

2′,2′-Dimethyl-1′-(2-methylprop-2-enyl)spiro[indole-3,3′-pyrrolidin]-2-one (**18**). Reaction time 5 h. Yield 1.8 g (67%). TLC: toluene–diethylamine 9 : 1 (R_F 0.43), m.p. 169–170 °C (diethyl ether–hexane). Analysis: calculated: 75.52% C, 8.20% H, 10.36% N; found: 75.38% C, 8.09% H, 10.25% N. IR (KBr): 1 640 (weak; C=C), 1 701 (5-membered lactam), 3 180 (NH). ^{1}H NMR ($CDCl_3$): 0.72 + 1.14 2 × s, 2 × 3 H (2 × 2′-CH_3); 1.83 brs, 3 H (C**H**$_3$-C=CH_2); 1.91 + 2.48 2 × ddd, 2 × 1 H, J_{gem} = 12.8, J_{vic} = 9.4 + 4.5 and 10.7 + 5.3, respectively (4′-H_2); 2.66 + 3.19 2 × ddd, 2 × 1 H, J_{gem} = 9.4, J_{vic} = 10.7 + 4.5 and 9.4 + 5.3, respectively (5′-H_2); 2.85 + 3.18 2 × brd, 2 × 1 H, J_{gem} = 12.7 (N-C**H**$_2$-C=CH_2); 4.84 + 4.97 2 × m, 2 × 1 H (C=C**H**$_2$); 6.85 d, 1 H (7-H); 7.00 dd, 1 H (5-H); 7.18 dd, 1 H (6-H); 7.48 d, 1 H (4-H); 8.26 brs, 1 H (NH).

1′-Hexyl-2′,2′-dimethylspiro[indole-3,3′-pyrrolidin]-2-one (**19**). Reaction time 30 h. Yield 2.4 g (80%). TLC: toluene–diethylamine 9 : 1 (R_F 0.40), m.p. 113–115 °C (hexane). Analysis: calculated: 75.96% C, 9.39% H, 9.32% N; found: 75.78% C, 9.27% H, 9.24% N. IR (KBr): 1 704 (5-membered lactam), 3 182 (NH). ^{1}H NMR ($CDCl_3$): 0.67 + 1.11 2 × s, 2 × 3 H (2 × 2′-CH_3); 0.92 t, 3 H, J = 7.0 (CH_2-C**H**$_3$); 1.25–1.57 m, 8 H (CH_2-(C**H**$_2$)$_4$-CH_3); 1.91 + 2.48 2 × ddd, 2 × 1 H, J_{gem} = 12.9, J_{vic} = 9.4 + 4.5 and 10.7 + 5.4, respectively (4′-H_2); 2.33 + 2.56 2 × ddd, 2 × 1 H, J_{gem} = 11.5, J_{vic} = 6.5 + 5.5 and 8.0 + 7.8, respectively (1-CH_2); 2.69 + 3.33 2 × ddd, 2 × 1 H, J_{gem} = 9.0, J_{vic} = 10.7 + 4.5 and 9.5 + 5.4, respectively (5′-H_2); 6.84 d, 1 H (7-H); 6.88 dd, 1 H (5-H); 7.16 dd, 1 H (6-H); 7.50 d, 1 H (4-H); 8.20 brs, 1 H (NH).

1′-(*3-Hydroxypropyl)-2′,2′-dimethylspiro[indole-3,3′-pyrrolidin]-2-one* (**20**). Reaction time 3 h. Yield 0.85 g (30%). TLC: $CHCl_3$–methanol 4 : 1 (R_F 0.37), m.p. 177–178 °C (ethyl acetate). Analysis: calculated: 70.05% C, 8.08% H, 10.21% N; found: 69.88% C, 8.02% H, 10.09% N. IR (KBr): 1 708 (5-membered lactam), 3 170 (NH), 3 354 (OH). ^{1}H NMR ($CDCl_3$): 0.97 + 1.00 2 × s, 2 × 3 H (2 × 2′-CH_3); 1.60 + 1.93 2 × m, 2 × 1 H (1′-CH_2C**H**$_2$); 2.13 + 2.25 2 × ddd, 2 × 1 H, J_{gem} = 13.2, J_{vic} = 10.5 + 5.0 and 9.5 + 5.0, respectively (4′-H_2); 2.67–2.85 m, 3 H (5′-H_A + 1′-CH_2); 3.46 ddd, 1 H, J_{gem} = 9.3, J_{vic} = 9.5 + 5.0 (5′-H_B); 3.75–3.85 m, 2 H (C**H**$_2$OH); 5.50 br, 1 H (OH); 6.93 d, 1 H (7-H); 6.97 ddd, 1 H (5-H); 7.18 ddd, 1 H (6-H); 7.21 d, 1 H (4-H); 9.40 brs, 1 H (NH).

Ethyl 4-(2′,2′-dimethyl-2-oxospiro[indole-3,3′-pyrrolidin]-1′-yl)butanoate (**21**). Reaction time 24 h. Purification by column chromatography (toluene–diethylamine 9 : 1). Yield 2.1 g (64%). TLC: toluene–diethylamine 9 : 1 (R_F 0.50), m.p. 91–93 °C (hexane). Analysis: calculated: 69.09% C, 7.93% H, 8.48% N; found: 69.20% C, 8.00% H, 8.29% N. IR (KBr): 1 708 (5-membered lactam), 1 722 (CO), 3 180 (NH). ^{1}H NMR ($CDCl_3$): 0.67 + 1.10 2 × s 2 × 3 H (2 × 2′-CH_2); 1.26 t + 4.14 q, 5 H, J_{vic} = 7.0 ($CO_2C_2H_5$); 1.76–1.97 m, 3 H (1′-CH_2C**H**$_2$ + 4′-H_A); 2.38–2.65 m, 5 H (4′-H_B + 1′-C**H**$_2$$CH_2$C**H**$_2$CO); 2.73 + 3.33 2 × ddd, 2 × 1 H, J_{gem} =

9.0, J_{vic} = 10.6 + 4.5 and 9.5 + 5.4, respectively (5′-H_2); 6.84 d, 1 H (7-H); 7.00 1 H (5-H); 7.17 dd, 1 H (6-H); 7.44 dd, 1 H (4-H); 8.10 brs, 1 H (NH).

Methyl (2′,2′-dimethyl-2-oxospiro[indole-3,3′-pyrrolidin]-1′-yl)acetate (**22**). Reaction time 12 h at room temperature. Yield 2.3 g (80%). TLC: toluene–diethylamine 9 : 1 (R_F 0.43), m.p. 155–157 °C (hexane). Analysis: calculated: 66.55% C, 6.99% H, 9.71% H; found: 66.42% C, 7.11% H, 9.85% N. IR (KBr): 1 710 (5-membered lactam), 1 750 (CO), 3 184 (NH). ^{1}H NMR ($CDCl_3$): 0.72 + 1.15 2 × s, 2 × 3 H (2 × 2′-CH_3); 1.97 + 2.52 2 × ddd, 2 × 1 H (4′-H_2); 2.80 + 3.56 2 × ddd, 2 × 1 H (5′-H_2); 3.18 + 3.53 2 × d, 2 × 1 H (CH_2CO); 3.76 s, 3 H (OCH_3); 6.86 d, 1 H (7-H); 7.02 dd, 1 H (5-H); 7.17 dd, 1 H (6-H); 7.71 d, 1 H (4-H); 8.35 brs, 1 H (NH).

Ethyl 5-methoxy-2′,2′-dimethyl-2-oxospiro[indole-3,3′-pyrrolidin]-1′-yl)acetate (**23**). Reaction time 4 h. Yield 2.4 g (72%). TLC: toluene–diethylamine 9 : 1 (R_F 0.33), m.p. 131–133 °C (hexane). Analysis: calculated: 65.04% C, 7.28% H, 8.43% N; found: 64.88% C, 7.19% H, 8.67% N. IR (KBr): 1 707 (5-membered lactam), 1 742 (CO), 3 180 (NH). ^{1}H NMR ($CDCl_3$): 0.73 + 1.15 2 × s, 2 × 3 H (2 × 2′-CH_3); 1.31 t + 4.21 q, 5 H, J_{vic} = 7.0 (CH_2CH_3); 1.94 + 2.52 2 × ddd, 2 × 1 H, J_{gem} = 12.8, J_{vic} = 9.5 + 4.4 and 10.8 + 5.5, respectively (4′-H_2); 2.77 + 3.54 2 × ddd, 2 × 1 H, J_{gem} = 8.9, J_{vic} = 10.8 + 4.4 and 9.5 + 5.5, respectively (5′-H_2); 3.15 + 3.52 2 × d, 2 × 1 H, J_{gem} = 16.6 (CH_2CO); 3.81 s, 3 H (OCH_3); 6.72 dd, 1 H, J = 8.5 + 2.6 (6-H); 6.75 d, 1 H, J = 8.5 (5-H); 7.50 d, 1 H, J = 2.6 (4-H); 8.18 brs, 1H (NH).

B) By Alkylation of Spiro Compounds **3** and **4**

Performing the reaction in the same way as in method *A* with the exception that spiro[indole-3,3′-pyrrolidin]-2-one **3** or **4** was used as starting material, the same 1′-alkylated spiro compounds **5**–**23** were obtained, which were identical in every respect with those obtained by method *A*. Yields: **5** (76%), **6** (69%), **7** (45%), **8** (54%), **9** (68%), **10** (62%), **11** (91%), **12** (95%), **13** (90%), **14** (86%), **15** (76%), **16** (82%), **17** (52%), **18** (64%), **19** (88%), **20** (55%), **21** (89%), **22** (80%) and **23** (78%).

Alkylation of 2-Oxotryptamines **1** and **2** Without Cyclization

To a solution of 2-oxotryptamine (**1** or **2**; 10 mmol), freshly prepared from its hydro-chloride, in dry benzene (100 ml), finely powdered anhydrous K_2CO_3 (4.17 g, 30 mmol), anhydrous NaI (0.5 g) and an alkyl halogenide (22 mmol) were added. The magnetically stirred suspension was then refluxed under argon for 3–30 h. (With volatile alkyl halogenides, the reaction was carried out at room temperature and more alkyl halogenide was used.) The progress of the reaction could be controlled by TLC. After completion the mixture was evaporated *in vacuo*, the residue was taken up in chloroform–water. The organic phase was dried ($MgSO_4$), evaporated and the residue cystallized. The *N,N-dibenzyl-2-oxotryptamine* (**24**) thus obtained, was isolated as hydrochloride. Yield 2.2 g (56%), m.p. 117–120 °C. TLC: hexane–ethyl acetate 2 : 1 (R_F 0.34). Analysis: calculated: 73.36% C, 6.41% H, 9.02% Cl, 7.13% N; found: 73.11% C, 6.28% H, 9.18% Cl, 7.02% N. IR (KBr): 1 707 (5-membered lactam). ^{1}H NMR (DMSO-d_6 + $CDCl_3$): 2.35 m, 2 H (3-CH_2); 3.09 + 3.18 2 × m, 2 × 1 H (3-$CH_2C\mathbf{H}_2$); 3.44 t, 1 H, J = 6.5 (3-H); 4.29–4.41 m, 4 H, (2 × benzyl C$\mathbf{H}_2$-NH^+); 6.81 d, 1 H (7-H); 6.88 dd, 1 H (5-H); 7.04 d, 1 H (4-H); 7.18 dd, 1 H (6-H); 7.30–7.70 m, 10 H (arom. benzyl); 10.50 brs, 1 H (indoline NH); 11.12 brs, 1 H ($^+$NH).

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