STRUCTURE AND SPECTRAL PROPERTIES OF β-CARBOLINES. PART 6.[1] REGIOSELECTIVITY OF CYCLOCONDESATION OF SPIRO[PIPERIDINE-m',1-(1,2,3,4-TETRAHYDRO-β-CARBOLINES)] WITH ALDEHYDES

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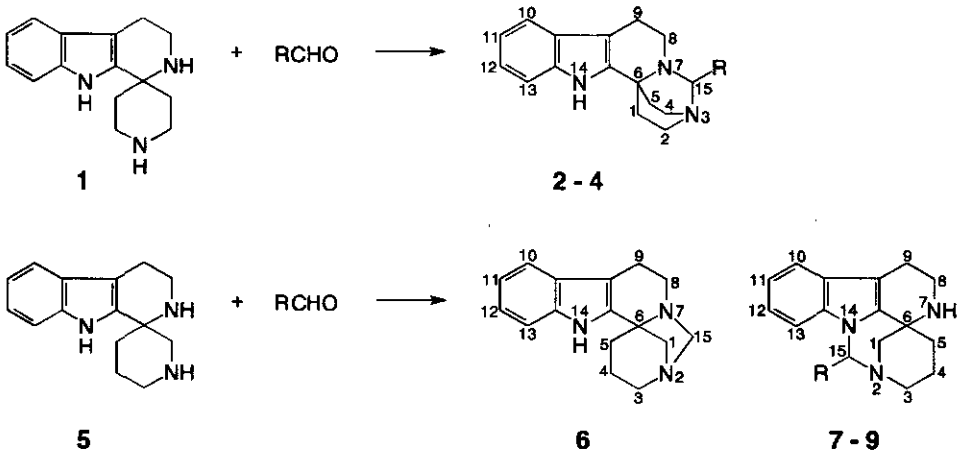
Abstract - Cyclocondensation of spiro derivatives of 1,2,3,4-tetrahydro-β-carbolines (**1**) and (**5**) with aldehydes was found to be a regioselective process. The structure of individual new ring systems, i.e. N-3,7 (**2-4**), N-2,7 (**6**) and N-2,14 (**7-9**) cyclocondensation products, was determined using ^{1}H nmr techniques.

In our previous papers we reported on the synthesis of new ring systems which contain a 1,2,3,4-tetrahydro-β-carboline skeleton.[1,2] In order to expand our interest in preparing rigid systems which may serve as model ligands of the well defined geometry of serotonine receptors,[3] we decided to explore the reaction of two spirans (**1**) and (**5**) with aldehydes.
A cyclocondensation of **1** with paraformaldehyde, benzaldehyde or o-chlorobenzaldehyde in an aprotic medium yielded bicyclic compounds (**2**), (**3**) and (**4**), respectively, as the only product of the reaction. A reaction of spiran (**5**) with paraformaldehyde under the same conditions resulted in a mixture of two isomers (**6**) and (**7**) (Scheme 1). A cyclocondensation at the N-2,7 atoms (**6**) occurred with a low yield, whereas a competitive

process which involved the N-2,14 atoms furnished isomer (**7**) as a major product. However, a reaction of **5** with aromatic aldehydes gave only the N-2,14 condensation products (**8**) and (**9**) (Table 1).



R: H (**2**, **7**); C_6H_5 (**3**, **8**); 2-Cl-C_6H_4 (**4**, **9**)

Scheme 1. *General procedure:* A solution of **1** or **5** (240 mg, 1 mmol) and paraformaldehyde (2 mmol) or the appropriate aromatic aldehyde (1.1 mmol) in benzene (10 ml) was refluxed for 2-3 h. The reaction mixture was evaporated to dryness, and the residue was recrystallized from ethyl acetate (**2**), benzene (**3**), methanol (**4**), ethanol (**6**), ethanol/n-hexane (**7**), ether (**8**) or ether/n-hexane (**9**). The mixture of **6** and **7** was separated by a silica gel chromatography with chloroform/ethanol/triethylamine (7:2:1) as a mobile phase.

^{1}H Nmr spectra of the aromatic region and chemical shifts of the C-15 methylene bridge protons (Table 2) have a strong diagnostic value for the structure determination of the investigated compounds. ^{1}H Chemical shifts were assigned by correlation with the spectra of spirans (**1**) and (**5**),[1] and on the grounds of 1D nOe and 2D COSY experiments. The most spectacular difference in the spectra of **2-4** and **6-9** is the presence of the 14-NH resonance. The signal that is characteristic for structures (**2-4**) and (**6**) disappeared in spectra of **7-9** (Table 2). The 15-H_2 signals in compounds (**7-9**) were shifted downfield by

0.71-1.75 ppm, in relation to the position of those signals in structures (**2-4**) and (**6**), as a result of a deshielding effect of the indole nucleus.

Table 1. Physicochemical Data and Analyses of Compounds (**2-4**) and (**6-9**).

No.	mp (°C)	Yield (%)	Analysis (%), Calcd (Found) C	H	N	M^+ (%)[a]
2	218-220	74	70.82[b] (70.74)	7.80[b] (8.02)	15.48[b] (15.50)	253 (100)
3	195-197 (decomp.)	86	80.21 (80.62)	7.04 (6.97)	12.76 (12.49)	329 (99)
4	220 (decomp.)	44	72.62 (72.51)	6.09 (5.97)	11.55 (11.42)	365 (31)
6	153-156	12	75.85 (75.72)	7.56 (7.44)	16.59 (16.26)	253 (20)
7	133-139 (decomp.)	82	75.85 (75.98)	7.56 (7.66)	16.59 (16.84)	253 (12)
8	168-170	53	80.21 (79.86)	7.04 (7.05)	12.76 (12.44)	329 (32)
9	146-148	36	72.61 (72.49)	6.09 (6.28)	11.55 (11.36)	365 (2)

[a]Electron impact mass spectra at 70 eV. [b]Analysis for monohydrate.

The aromatic 13-H resonance in **2-4** and **6** is insensitive to the C-15 substituents, whereas the same proton in compounds (**8**) and (**9**) is shielded by the C-15 aromatic substituents and its signal is shifted upfield by 0.39 and 0.81 ppm, respectively, in relation to **7**. A similar effect was observed for the 11-H resonance signal. Moreover, the shielding effect of the indole ring system reflects in a significant upfield shift of the 2'-H and 3'-H resonances in **8** and **9** in comparison with **3** and **4** (Table 2).

The 1D nOe difference measurements were also found useful for the structure determination. Irradiation of the 14-NH signal of **2** resulted in an increased intensity of

the 1- and 5-H^{ax} signal, whereas irradiation of the 15-H_2 signal caused enhancement of the 7-H_2 resonance intesity. Contrariwise, irradiation of each of the 15-H_2 doublets in compound (**7**) increased the same 13-H resonance signal.

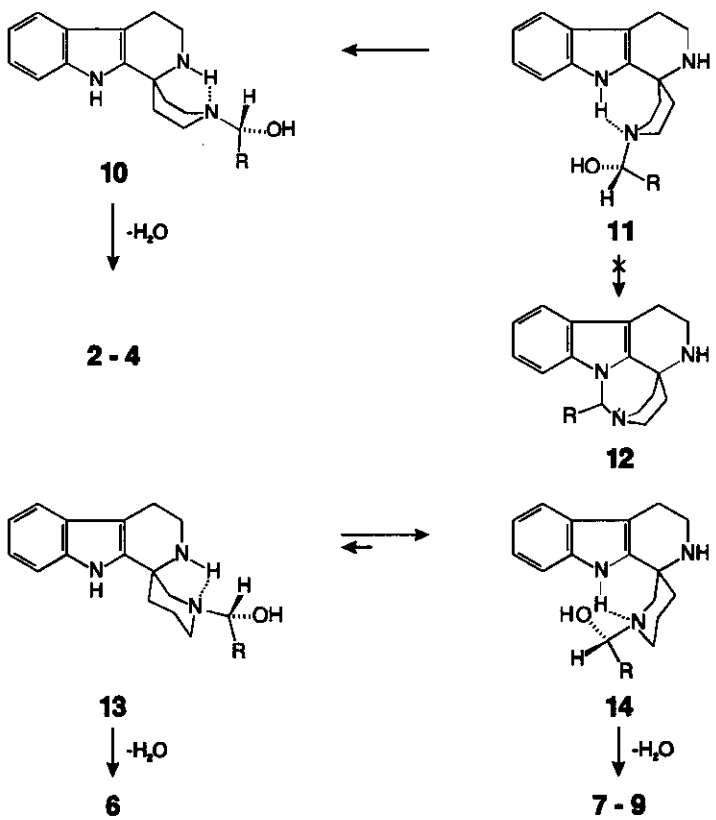
Table 2. ^{1}H Chemical Shifts (Aromatic Region and Methylene Bridge) of Compounds (**2-4**) and (**6-9**).[4]

Proton[a]	δ, ppm						
	2	**3**	**4**	**6**	**7**	**8**	**9**
10	7.48	7.51	7.50	7.51	7.44	7.53	7.51
11	7.09	7.11	7.11	7.11	7.04	6.94	6.90
12	7.14	7.16	7.16	7.15	7.09	7.04	7.07
13	7.30	[b]	7.32	7.31	7.17	6.78	6.36
14-NH	7.91	7.65	7.67	7.92			
15	3.88	4.43	4.71	[c]	[d]	6.18	6.23
2'		7.58				[e]	
3'		[b]	8.03			[f]	7.76
4'		[b]	7.30			[f]	7.40
5'		[b]	7.25			[f]	7.31
6'		7.68	7.40			[e]	7.56

[a]Numbering corresponds to that shown in Scheme 1. [b]7.28-7.39, m. [c]3.67 (1H, d, J = 9.3 Hz) and 4.29 (1H, d, J = 9.3 Hz). [d]4.81 (1H, d, J = 11.3 Hz) and 5.00 (1H, d, J = 11.3 Hz). [e]6.43-6.47, m. [f]7.09-7.15, m.

Both MAXIMIN2 and MNDO calculations[5] indicated that the N-2,14 (**7-9**) or N-3,14 (**12**) cyclocondensation products are more stable, by 3.7 - 9.9 kcal/mol, than their N-2,7 (**6**) or N-3,7 (**2-4**) counterparts. On the other hand, the applied conditions of the reaction (benzene, reflux) are characteristic for a kinetic control of the process. There are two basic

nitrogen atoms in spirans (**1**) and (**5**). The determined pK_a values of **1** are equal to 9.69 ± 0.09 and 5.94 ± 0.07 for N-3 and N-7 atoms, respectively.[6] The observed basicity-weakening effect of the N-7 atom in relation to the N-3 one is due to a steric crowding around the N-7 protonation center.[3,7] Therefore it is rational to assume that the N-3 and N-2 nucleophilic centers rather than the N-7 ones in spirans (**1**) and (**5**), respectively, attack the carbonyl group and form hemiaminals as intermediates (Scheme 2).



Scheme 2.

Recently we showed that a strong intramolecular hydrogen bond exists between the 14-NH and 2-N atoms of **5**, due to their favorable steric arrangement.[1] Contrariwise, there is no evidence for an intramolecular hydrogen bond in spiran (**1**).[1] Hence it seems obvious that the intramolecular hydrogen bond should stabilize some conformations of the hemiaminal

intermediates. In fact, among the possible structures of **10**, **11**, **13** and **14**, only **10** and **14** may be significantly stabilized by the intramolecular hydrogen bond which forms the most preferred six-membered ring. In this respect, structure **(13)**, which contains a five-membered ring, is less favorable than **14**. Furthermore, structure **(11)** is definitely unfavorable, since the intramolecular hydrogen bond requires formation of a seven-membered ring. Moreover, an additional steric repulsion between the RCH(OH)-substituent and the indole fragment in **11** may also prevent formation of the N-3,14 hydrogen bond.

Summing up, the above conclusions are fully consistent with the observed regioselectivity of cyclocondensation of **1** and **5** with aldehydes.

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3. A. J. Bojarski, M. T. Cegła, S. Charakchieva-Minol, M. J. Mokrosz, M. Maćkowiak, S. Misztal, and J. L. Mokrosz, *Pharmazie*, 1993, **48**, 289.
4. ^{1}H nmr spectra were measured on a Bruker 500 (500 MHz) instrument in $CDCl_3$ solutions downfield from TMS. ^{1}H Chemical shifts of the diazaspiro[5.5]undecane skeleton are as follow:

   2: δ 1.85 (2H, ddd, J = 12.6, 10.2, and 5.0 Hz, 1- and 5-H^{ax}), 2.02-2.09 (2H, m, 1- and 5-H^{eq}), 2.79-2.84 (4H, m, 8- and 9-H_2), 2.99 (2H, ddd, J = 13.5, 10.2, and 5.3 Hz, 2- and 4-H^{ax}), 3.22 (2H, ddd, J = 13.4, 10.5, and 5.0 Hz, 2- and 4-H^{eq});

   3: δ 1.76 (1H, ddd, J = 13.4, 10.2, and 3.2 Hz, 1-H^{ax}), 1.89-1.93 (2H, m, 5-H_2), 2.25 (1H, ddd, J = 13.4, 10.3, and 3.1 Hz, 1-H^{eq}), 2.62-2.75 (3H, m, 4-H^{ax} and 9-H_2), 2.84 (1H, td, J = 11.3 and 3.4 Hz, 8-H), 2.90-2.98 (2H, m, 4- and 8-H), 3.15 (1H, ddd, J = 13.4, 10.2, and 3.1 Hz, 2-H^{ax}), 3.47 (1H, ddd, J = 13.4, 10.3, and 3.2 Hz, 2-H^{eq});

4: δ 1.77 (1H, ddd, J = 13.4, 10.1, and 2.9 Hz, 1-H^{ax}), 1.92-1.96 (2H, m, 5-H_2), 2.26-2.34 (1H, m, 1-H^{eq}), 2.55-2.90 (5H, m, 4-H^{ax}, 8- and 9-H_2), 2.93-3.00 (1H, m, 4-H^{eq}), 3.12 (1H, ddd, J = 13.4, 10.0, and 7.8 Hz, 2-H^{ax}), 3.47-3.54 (1H, m, 2-H^{eq});

6: δ 1.55-1.65 (2H, m, 5-H_2), 1.87 (1H, td, J = 12.6 and 5.6 Hz,4-H^{ax}), 2.02-2.13 (1H, m, 4-H^{eq}), 2.68 (1H, td, J = 10.6 and 3.4 Hz, 8-H), 2.77 (1H, ddd, J = 15.3, 3.3, and 2.3 Hz, 9-H), 2.80-2.93 (3H, m, 1-, 3-, and 9-H), 2.99 (1H, dd, J = 13.7 and 6.0 Hz, 3-H), 3.05 (1H, d, J = 11.1 Hz, 1-H), 3.13 (1H, ddd, J = 10.5, 4.4, and 2.2 Hz, 8-H);

7: δ 1.54-1.61 (2H, m, 4-H^{eq} and 5-H^{ax}), 1.69-1.80 (1H, m, 4-H^{ax}), 1.97 (1H, bs, 7-NH), 2.35 (1H, bd, J = 14.0 Hz, 5-H^{eq}),2.61 (1H, dd, J = 12.6 and 1.2 Hz, 1-$H^{endo\text{-}15}$), 2.65 (1H, ddd, J = 15.7, 5.5, and 1.4 Hz, 9-H), 2.74 (1H, ddd, J = 15.7, 10.7, and 6.5 Hz, 9-H), 2.99 (1H, d, J = 12.4 Hz, 1-$H^{egzo\text{-}15}$), 3.04 (1H, td, J = 13.9 and 3.9 Hz, 3-H^{ax}), 3.18-3.24 (2H, m, 3-H^{eq} and 8-H), 3.37 (1H, ddd, J = 13.6, 10.7, and 5.6 Hz, 8-H);

8: δ 1.60-1.70 (3H, m, 4-H^{eq}, 5-H^{ax} and 7-NH), 1.74-1.85 (1H, m, 4-H^{ax}), 2.42-2.48 (1H, m, 5-H^{eq}), 2.74 (1H, d, J = 12.8 Hz, 1-$H^{egzo\text{-}15}$), 2.80 (1H, ddd, J = 15.8, 5.2, and 1.0 Hz, 9-H), 2.91 (1H, bd, J = 12.8 Hz, 1-$H^{endo\text{-}15}$), 2.95 (1H, ddd, J = 15.8, 10.8, and 7.0 Hz, 9-H), 3.28 (1H, td, J = 13.8 and 4.0 Hz, 3-H^{ax}), 3.34 (1H, ddd, J = 13.7, 7.0, and 1.0 Hz, 8-H), 3.52-3.61 (2H, m, 3-H^{eq} and 8-H);

9: δ 1.52 (1H, bd, J = 13.0 Hz, 5-H^{ax}), 1.64-1.72 (2H, m, 4-H^{eq} and 7-NH), 1.75-1.85 (1H, m, 4-H^{ax}), 2.50-2.55 (1H, m, 5-H^{eq}), 2.69-2.89 (5H, m, 1-H, 3- and 9-H_2), 3.27 (1H, d, J = 12.4 Hz, 1-H), 3.33 (1H, ddd, J = 13.7, 4.7, and 1.4 Hz, 8-H), 3.50 (1H, ddd, J = 13.7, 10.7, and 5.9 8-H);

5. The force field and the MNDO calculations were conducted using the SYBYL 5.51 integrated package (Tripos), installed on ESV 10/33 workstation.
6. Ionization constants were determined by a potentiometric titration of **1·2HCl** at 20 ± 0.5 °C.
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Received, 11th August, 1993