STRUCTURE AND SPECTRAL PROPERTIES OF β-CARBOLINES. PART 7.[1] THE PICTET-SPENGLER REACTION OF TRYPTAMINES WITH *N*-BENZYL-4-PIPERIDONE

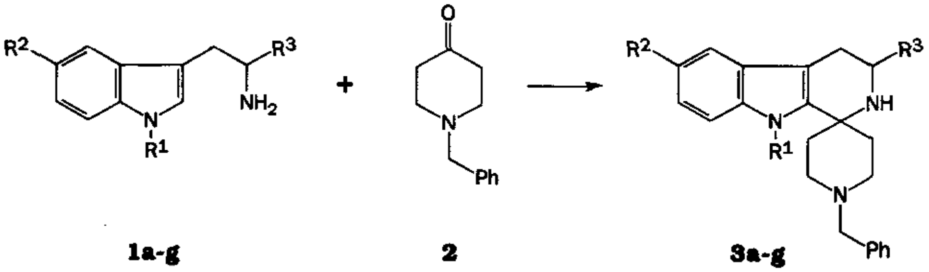
Maria J. Mokrosz,[a] Piotr Kowalski,[b] Andrzej J. Bojarski,[a] and Jerzy L. Mokrosz*[a]

[a]Department of Medicinal Chemistry, Institute of Pharmacology, Polish Academy of Sciences, 12 Smętna Street, 31-343 Kraków, Poland
[b]Institute of Organic Chemistry and Technology, Cracow Technical University, 24 Warszawska Street, 31-155 Kraków, Poland

Abstract - The Pictet-Spengler reaction of substituted tryptamines (**1b**-**1g**) with *N*-benzyl-4-piperidone afforded spiro derivatives (**3b**-**3g**) with a yield of 11-76%. A charge sensitivity analysis (CSA) of the protonated form of Schiff bases (**8**) indicated that the intramolecular electrophilic attack at position 3 is favorable in relation to that at position 2.

Our systematic studies on the structure-activity relationship of the central nervous system agents indicate that many 1,2,3,4-tetrahydro-β-carboline derivatives show an interesting *in vivo* activity, e.g. an antidepressant or an anxiolytic one.[2] Recently we have shown that even simple 2-alkyl-1,2,3,4-tetrahydro-β-carbolines have a significant affinity for the 5-HT_{1A} and 5-HT_2 subpopulation of serotonine receptors.[3] On the other hand, we have also reported that spiro-β-carboline (**3a**) is an important and convenient substrate for the synthesis of rigid, heterocyclic systems which may serve as model structures in a search for topographical relations of the above-mentioned serotonine receptors.[1,4]

In view of these, this paper describes the synthesis of fuctionalized spiro[piperidine-4',1-(1,2,3,4-tetrahydro-β-carbolines)] (**3b-3g**), which can be obtained by the Pictet-Spengler reaction between tryptamines (**1b-1g**) and *N*-benzyl-4-piperidone (**2**).



Scheme 1

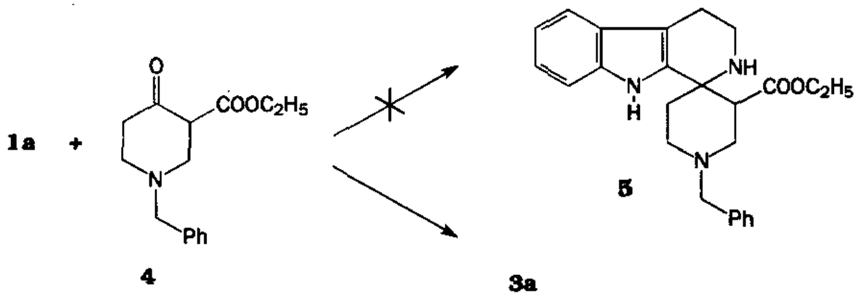
General procedure: A mixture of tryptamine hydrochloride (**1a-g**, 3 mmol), *N*-benzyl-4-piperidone (**2**, 0.76 g, 3.75 mmol), 36% HCl (0.5 ml) and *n*-butanol (20 ml) was refluxed for 5 h and left overnight at room temperature. Then the solvent was evaporated, the residue was treated with acetone-ethanol (2:1, 40 ml), and the crystalline product was filtered off. The product was recrystallized from ethanol.

Table 1

Synthesis and structure of compounds (**3a-g**, **6** and **7**).[5]

Substrate	Product	R^1	R^2	R^3	mp (°C)	Yield (%)
1a	**3a**	H	H	H	260-261	90
1b	**3b**	CH_3	H	H	241-243	34
1c	**3c**	H	OCH_3	H	259-261	54
1d	**3d**	CH_3	OCH_3	H	216-218	24
1e	**3e**	H	OCH_3	CH_3	216-218	54
1f	**3f**	H	Cl	H	250-252	76
1g	**3g**	H	NO_2	H	258-260	11
1a	**6**	H	H	H	126-128	24
6	**3a**	H	H	H	260-261	51
1a	**7**	H	H	H	oil	43

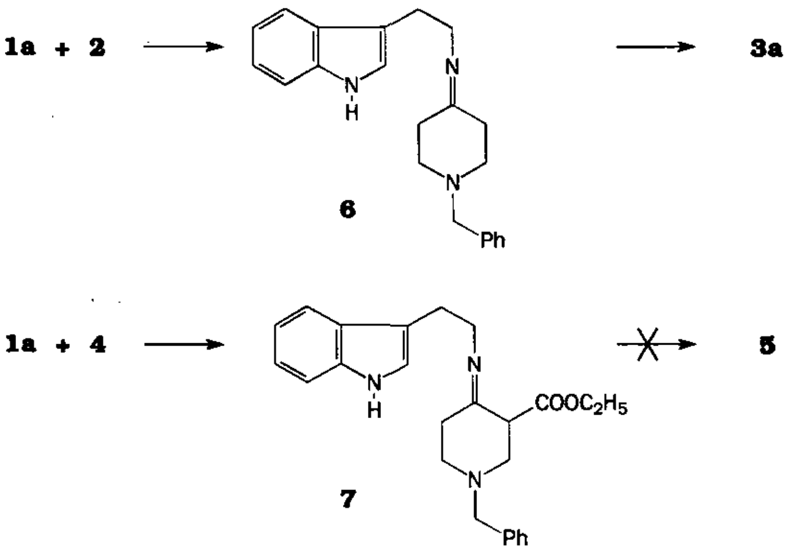
The reaction carried out in the boiling n-butanol in the presence of 36% HCl afforded spiro derivatives (**3a-g**), with a strongly differentiated yield ranging from 90 to 11% (Scheme 1, Table 1). Only derivatives (**3a**) and (**3f**) were obtained with a high yield of 90 and 76%, respectively. However, this should be attributed to a shift in the reaction equilibrium[6] due to precipitation of **3a** and **3f** upon heating, rather than to the R^2 substituent effect. On the other hand, the reaction of **1a** with piperidone (**4**) did not produce the expected product (**5**); only **3a** was isolated with a 6% yield after heating for 60 h (Scheme 2). A carboethoxy group of piperidone (**4**) underwent hydrolysis and decarboxylation during the reaction to yield **2**. Indeed, when the reaction between **1a** and **4** was carried out in the presence of 20% HCl using a Dean-Stark trap, the yield of the product (**3a**) increased, up to 68%.



Scheme 2

It has been well documented that the Schiff base is a stable intermediate in the Pictet-Spengler reaction.[7] In a reaction with tryptamine (**1a**), both *N*-benzyl-4-piperidone (**2**) and its 3-carboethoxy derivative (**4**) formed Schiff bases (**6**) and (**7**), respectively. The intermediate **6** cyclized smoothly in the presence of a gaseous HCl to give **3a** with a yield of 51%, whereas **7** did not react under the same conditions (Scheme 3).

It is generally accepted that the Pictet-Spengler condensation involves the intermediacy of the imminium ion (**8**), and that the electrophilic character of the C=N bond of this intermediate explains differences in the reactivity.[7b,8] Two likely pathways may operate in the reaction, in which the imminium intermediate (**8**) is attacked either at C-3, followed by rearrangement of spiroindolenine(**9**)to **10**, or directly at C-2 (Scheme 4).[7] Although the spiroindolenine mechanism is regarded as a central step of the Pictet-Spengler condensation,[6-9] it has also been shown that the cyclization may occur by a direct attack of the indole ring at position 2.[10]



Scheme 3

A mixture of tryptamine (**1a**) (3.7 g, 23 mmol) and **2** or **4** (23 mmol) in an anhydrous benzene (90 ml) was refluxed under a Dean-Stark trap for 2 h. Then the solvent was evaporated and the product was recrystallized from ethanol. A solution of **6** (3.3 g, 10 mmol) in *n*-butanol (25 ml) was saturated with a gaseous HCl for 30 min. Then the reaction mixture was refluxed for 3 h and left overnight at room temperature to give **3a**.

It has been shown that the Pictet-Spengler cyclization is controlled by its kinetics and/or thermodynamics.[6] We have assumed that the observed yield of formation of **3** is the result of the thermodynamic control of the reaction, except of derivatives (**3a**) and (**3f**) which precipitated during the reaction (Table 1). Therefore, heats of formation of particular intermediates (**8-10**), which are involved in the Pictet-Spengler reaction, were calculated by a MNDO method[11] (Table 2). The results of calculations indicate that there exists a good qualitative correlation between the ΔH^{o} values of **8** and **10**, and the observed yield of the reaction for **3b-3e** and **3g**: the higher difference $\Delta(\Delta H^{o})_{8\text{-}10}$, the lower yield of the cyclization.

Table 2

Heats of formation of intermediates (**8**-**10**)

Compound	ΔH° [kcal/mol]			$\Delta(\Delta H^\circ)$ [kcal/mol]	
	8	**9**	**10**	**8 - 9**	**8 - 10**
a	234.4	251.2	249.4	-16.8	-15.0
b	235.0	250.9	252.8	-15.9	-17.8
c	194.9	210.7	210.6	-15.8	-15.7
d	195.1	209.9	214.0	-14.8	-18.9
e	191.6	208.4	208.2	-16.8	-16.6
f	228.1	247.6	246.4	-19.5	-18.3
g	252.1	227.0	276.0	-24.9	-23.9

In order to analyze the reaction pathways and the most sensitive centers of the indole ring towards the electrophilic attack, net atomic charges of the imminium intermediate (**8**) were calculated by a MNDO method,[11] and a charge sensitivity analysis (CSA) including its basic concepts such as hardness/softness, the Fukui function (FF) and a negative chemical potential was performed.

The theory and usefulness of CSA to predict a site and a path selectivities in chemical processes have been already shown.[12] The information about reactivity may be extracted from *atoms-in-molecule* (AIM) rigid chemical potentials and hardness tensor. The first quantity is defined as the first partial derivative of the system electronic energy (E) with respect to a population of AIM (eq. 1, where $N = \{N_1, N_2, ..., N_m\}$), whereas the latter one as the respective second partial derivative (eq. 2), where m denotes number of atoms in the system.

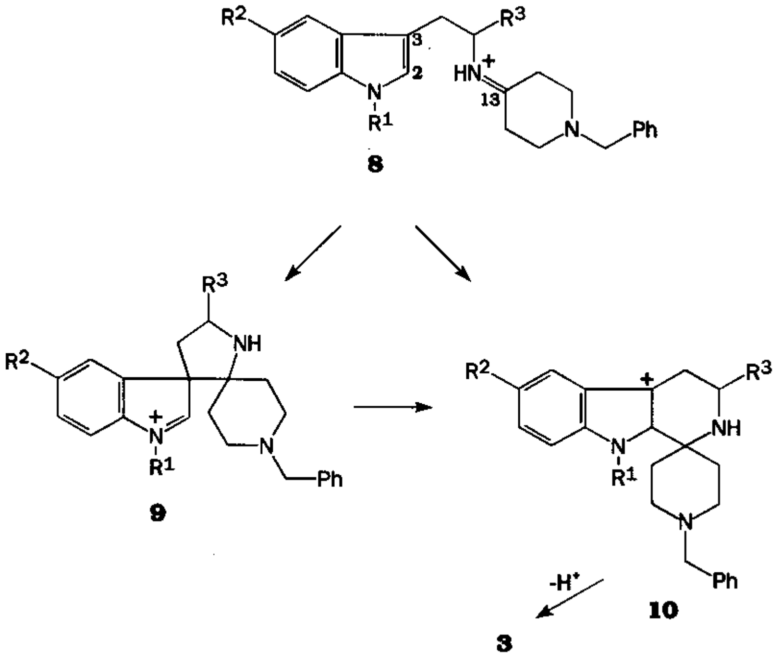
$$\underset{\sim}{\mu} = \{\mu_1, \mu_2, ..., \mu_m\} = \partial E(\underset{\sim}{N})/\partial \underset{\sim}{N} \qquad (1)$$

$$\underset{\approx}{\eta} = \partial^2 E(\underset{\sim}{N})/\partial \underset{\sim}{N}^2 = \partial \underset{\sim}{\mu}(N)/\partial \underset{\sim}{N} \qquad (2)$$

Both quantities are interpolated to the actual valence states, characterized by AIM charges, and they correspond to a system (M) composed of mutually closed atoms. This means that there is no flow of electrons between atoms (eq. 3).

$$M = (i\,|\,j\,|\,\ldots\,) \tag{3}$$

Removing the barrier on the charge flow, one can obtain a hierarchy of relaxed quantities.



Scheme 4

Such relaxed parameters contain information about "real" chemical processes, and better describe the site and path phenomena. The FF indices are convenient parameters in discussing the charge rearrangement during a chemical process. The FF index (eq. 4) describes a change in the electron population of the *i*-th AIM per global perturbation in the number of electrons (dN).

$$FF_i = \partial N_i / \partial N \tag{4}$$

The sign of the index is responsible for a local donor/acceptor behavior. Hence, when the whole molecule acts as a base, atoms with positive indices have a local donor character, whereas these with negative ones have local acceptor properties. The highest sensitive AIM on the electrophilic attack has the smallest charge, but the highest chemical potential and FF index. Significant hardnesses permit a discussion of the relative contribution of different energy components (charge transfer and electrostatic) to the overall stabilization energy, according to the *hard-soft-acid-base* (HSAB) principle and its partition on AIM.

Table 3

Net atomic charges (n.c.), the relaxed chemical potentials (μ) and hardness, and Fukui function indices (FF) of intermediates (**8a-g**).

Compd.	Atom no.	n.c. [a.u.]	μ [a.u.]	Hardness [a.u.]	FF
8a	2	0.077	-0.354	0.182	0.005
	3	-0.232	-0.337	0.153	0.036
	13	0.276	-0.382	0.218	-0.005
8b	2	0.085	-0.352	0.178	0.000
	3	-0.237	-0.332	0.147	0.038
	13	0.272	-0.378	0.212	-0.003
8c	2	0.084	-0.349	0.176	0.005
	3	-0.236	-0.330	0.145	0.038
	13	0.273	-0.376	0.210	-0.003
8d	2	0.090	-0.350	0.175	0.000
	3	-0.238	-0.330	0.143	0.035
	13	0.275	-0.377	0.208	-0.004
8e	2	0.079	-0.349	0.175	0.004
	3	-0.234	-0.330	0.145	0.034
	13	0.275	-0.379	0.210	-0.005
8f	2	0.084	-0.351	0.177	0.005
	3	-0.229	-0.335	0.148	0.036
	13	0.274	-0.379	0.211	-0.003
8g	2	0.091	-0.339	0.175	0.006
	3	-0.219	-0.325	0.146	0.031
	13	0.279	-0.369	0.208	-0.003

The results of calculations indicate that substituents R^1, R^2 and R^3 of the intermediate (**8**) have a negligible effect on the electron population of the analyzed atoms (C-2, C-3 and C-13) and their CSA parameters (Table 3). The calculated net atomic charges (by the MNDO method) clearly differentiate between C-2 and C-3 atoms and let us conclude that the intramolecular electrophilic attack at position 3 of the indole ring system is highly preferable in relation to that at position 2. Although the relaxed chemical potentials and Fukui function indices do not clearly differentiate between C-2 and C-3 atoms, the presented data indicate that the electrophilic attack at position 3 seems to be still more favorable than that at position 2. Contrariwise, the hardness values of the analyzed atoms indicate that position 2 should be more susceptible to the electrophilic attack than position 3 (Table 1). Therefore from the presented analysis it may be concluded that the Pictet-Spengler reaction involves a spiroindolenine mechanism rather than a direct C-2 attack. However, the latter mechanism cannot be excluded.

REFERENCES AND NOTES

1. Part 6: M. J. Mokrosz, M. H. Paluchowska, S. Misztal, and J. L. Mokrosz, *Heterocycles*, preceding paper.
2. P. Bartyzel, S. Misztal, E. Tatarczyńska, and E. Chojnacka-Wójcik, *Pol. J. Pharmacol. Pharm.*, 1989, **41**, 495; J. Boksa, S. Misztal, E. Chojnacka-Wójcik, L. Gastoł-Lewińska, A. Gródecka, and J. L. Mokrosz, *Pharmazie*, 1992, **47**, 254.
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. S. Misztal, M. H. Paluchowska, M. J. Mokrosz, P. Bartyzel, and J. L. Mokrosz, *J. Heterocycl. Chem.*, in press.
5. Compound **3b**; *Anal.* Calcd for $C_{23}H_{27}N_3 \cdot 2HCl$: C, 66.02; H, 6.99; N, 10.04. Found: C, 65.88; H, 6.87; N, 10.18; ms: m/z 345 (M^+, 41%), 211 (65), 197 (24), 146 (45), 91 (100).

   Compound **3c**; *Anal.* Calcd for $C_{23}H_{27}N_3O \cdot 2HCl \cdot 2H_2O$: C, 61.06; H, 6.90; N, 9.28. Found: C, 61.36; H, 6.98; N, 9.02; ms: m/z 361 (M^+, 66%), 227 (35), 214 (35), 91 (100).

   Compound **3d**; *Anal.* Calcd for $C_{24}H_{29}N_3O \cdot 2HCl$: C, 64.28; H, 6.97; N, 9.37. Found: C, 64.50; H, 7.12; N, 9.12; ms: m/z 375 (M^+, 48%), 241 (86), 146 (54), 91 (100).

   Compound **3e**; *Anal.* Calcd for $C_{24}H_{29}N_3O \cdot 2HCl \cdot H_2O$: C, 61.80; H, 7.13; N, 9.01.

Found: C, 61.50; H, 7.33; N, 9.05; ms: m/z 375 (M^+, 30%), 240 (100), 146 (41), 91 (77).

Compound **3f**; *Anal.* Calcd for $C_{22}H_{24}ClN_3 \cdot 2HCl \cdot H_2O$: C, 57.86; H, 6.18; N, 9.20. Found: C, 57.68; H, 6.40; N, 9.06; ms: m/z 365 (M^+, 28%), 367 (M^+, 9), 230 (38), 146 (42), 91 (100).

Compound **3g**; *Anal.* Calcd for $C_{22}H_{24}N_4O_2 \cdot 2HCl \cdot 2H_2O$: C, 54.43; H, 6.23; N, 11.54. Found: C, 54.68; H, 5.95; N, 11.28; ms: m/z 376 (M^+, 29%), 242 (15), 146 (33), 91 (100).

Compound **6**; *Anal.* Calcd for $C_{22}H_{25}N_3$: C, 79.72; H, 7.60; N, 12.68. Found: C, 79.48; H, 7.66; N, 12.42; ms: m/z 331 (M^+, 10%), 210 (34), 130 (100), 91 (92).

Compound **7**; *Anal.* Calcd for $C_{25}H_{29}N_3O_2$: C, 74.41; H, 7.24; N, 10.41. Found: C, 74.12; H, 6.97; N, 10.11; ms: m/z 330 ($M - COOC_2H_5$, 5%), 317 (41), 226 (100), 197 (69), 134 (59), 91 (81).

6. L. H. Zhang and J. M. Cook, *Heterocycles*, 1988, **27**, 1357; L. Deng, K. Czerwinski, and J. M. Cook, *Tetrahedron Lett.*, 1991, **32**, 175.
7. (a) F. Ungemach and J. M. Cook, *Heterocycles*, 1978, **9**, 1089; (b) D. Soerens, J. Sandrin, F. Ungemach, P. Mokry, G. S. Wu, E. Yamanaka, L. Hutchins, M. DiPierro, and J. M. Cook, *J. Org. Chem.*, 1979, **44**, 535; (c) F. Ungemach, M. DiPierro, R. Weber, and J. M. Cook, *ibid.*, 1981, **46**, 164; (d) M. Jawdosiuk and J. M. Cook, *ibid.*, 1984, **49**, 2699.
8. P. H. H. Hermkens, J. H. van Maarseveen, P. L. H. M. Cobben, H. C. J. Ottenheijm, C. G. Kruse, and H. W. Scheeren, *Tetrahedron*, 1990, **46**, 833.
9. R. Plate, R. H. M. van Hout, H. Behm, and H. J. C. Ottenheijm, *J. Org. Chem.* 1987, **52**, 555; J. Liu, M. Nakagawa, and T. Hino, *Tetrahedron*, 1989, **45**, 7729; J. H. van Maarseveen and H. W. Scheeren, *ibid.*, 1993, **49**, 2325.
10. G. Casnati, A. Dossena, and A. Pochini, *Tetrahedron Lett.*, 1972, 5277; J. J. Liu, M. Nakagawa, K. Ogata, and T. Hino, *Chem. Pharm. Bull.*, 1991, **39**, 1672.
11. The MNDO calculations (full geometry optimization, gradient norm <0.1 kcal/mol/Å) were conducted using the MOPAC-5 program implanted into the SYBYL 5.51 integrated package (Tripos), installed on ESV 10/33 workstation. Conformers with

minimum energy were used. The MNDO geometry and atomic charges were the input data in CSA calculations.

12. H. Lee, W. Yang, and R. G. Parr, *J. Mol. Struct. THEOCHEM*, 1988, **163**, 305; W. Langeaneker, K. Demel, and P. J. Geerlings, *ibid.*, 1991, **234**, 329; L. Komorowski and J. Lipiński, *Chem. Phys.*, 1991, **157**, 45; R. F. Nalewajski and J. Korchowiec, *J. Mol. Catal.*, 1991, **68**, 123; J. Korchowiec and R. F. Nalewajski, *Int. J. Quant. Chem.*, 1992, **44**, 1027; P. Kowalski and J. Korchowiec, *J. Mol. Struct. THEOCHEM*, in press.

Received, 2nd September, 1993