Synthesis and Stereochemistry of New Trihydrodiazabicyclo-[3.m.n]alkano[4',5':1,2]pyrido[3,4-*b*]indole Ring System [1]

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The classical Pictet-Spengler reaction of tryptamine with the isomeric *N*-benzylpiperidones **3a**, **3b** and *N*-benzylpyrrolidone **3c** yielded the spiro derivatives of 1,2,3,4-tetrahydro-β-carboline **5a**, **5b** and **5c**. Cyclocondensation of the spirotetrahydrocarboline with chloroacetic chloride and the subsequent reductive debenzylation afforded the new ring systems of trihydrodiazabicyclo[3.m.n]alkano[4',5':1,2]pyrido[3,4-*b*]indoles **8a**, **8b**, and **8c**. The structures of the bicyclic systems **8a**, **8b**, and **8c** were determined by using both, high-resolution ^1H and ^{13}C nmr techniques and force field and MNDO calculations.

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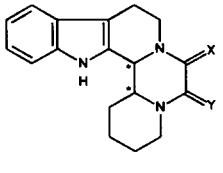
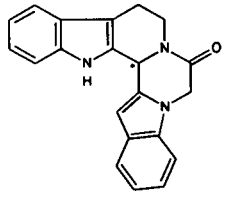
Recently we have found that even simple 2-*n*-butyl and 2-*n*-hexyl derivatives of 1,2,3,4-tetrahydro-β-carboline and its 9-methyl analog show a high affinity (at a nanomolar level) for the central serotonin neuroreceptors of the 5-HT_{1A} and 5-HT_2 type [2]. We explained this phenomena using the steric model of the 5-HT_{1A} site, derived from topography of (+)-LSD molecule. We also found that the pharmacological profile of 7-[2-(1-phenyl-4-piperazinyl)-ethyl] derivative of **4a** resembles that of buspirone, which is a well known anxiolytic agent [3]. Having searched for new model compounds of the well established geometry, with the β-carboline moiety built into a fused ring system, we previously reported on a simple and effective synthesis of compounds **1** [4] and **2** [1]. We also studied in detail the structure of individual diastereomers of compounds **1a**, **1b**, **1c**, and then the conformation of the decahydrodipyridopyrazino (**1**) and tetrahydropyridopyrazino (**2**) skeletons [1,3].



1a - c



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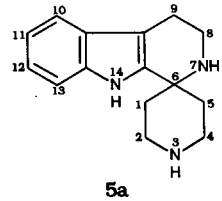
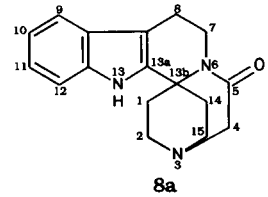
a; X=O, Y=H_2
b; X=H_2, Y=O
c; X=Y=H_2

Results and Discussion.

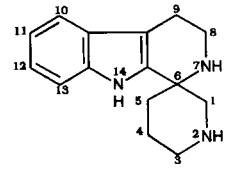
In order to extend our study we synthesized the three spiro derivatives of 1,2,3,4-tetrahydro-β-carboline **5a**, **5b**, **5c**, and the new heterocyclic systems the trihydrodiazabicyclo[3.m.n]alkano[4',5':1,2]pyrido[3,4-*b*]indol-5(6*H*)-ones **8a** and **8c**, and -indol-6(7*H*)-one **8b**.



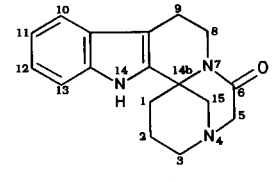
5a



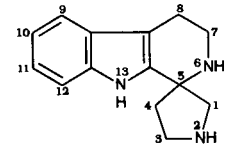
8a



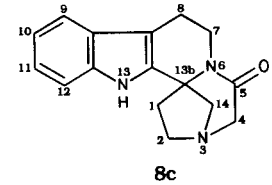
5b



8b



5c

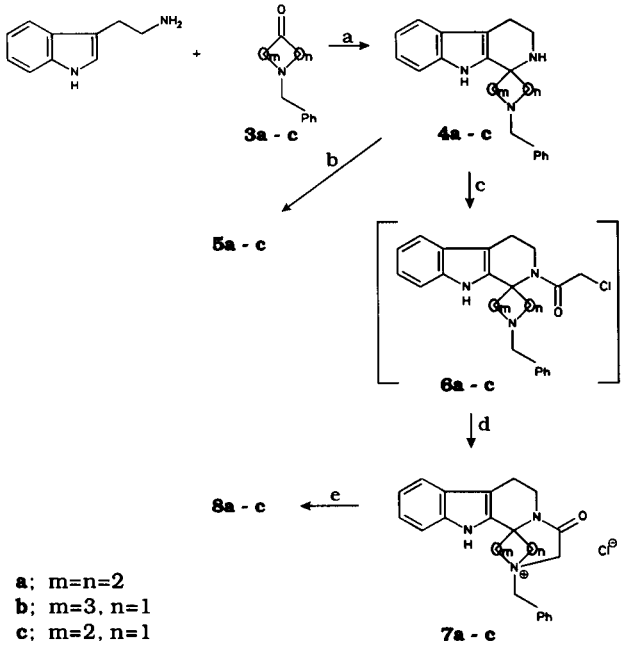


8c

The bicyclic systems **8a**, **8b**, **8c** were obtained following a simple and efficient three-step procedure (Scheme 1). The spiro derivatives **4a**, **4b**, **4c** were synthesized by the classical Pictet-Spengler reaction between tryptamine and the appropriate *N*-benzylpiperidones (**3a**, **3b**) or *N*-benzylpyrrolidone-3 (**3c**). The reaction furnished hydrochlorides of **4a**, **4b** and **4c** in a high 84-90% and a moderate 47% yield, respectively. The products were pure enough for the next synthetic steps. Reaction of **4a**, **4b** or **4c** with chloroacetic chloride in a two-phase medium (chloroform/water), in the presence of potassium carbonate at room temperature, led to chloroacetamides **6a**, **6b** or **6c**, which underwent partial cyclization to the bicyclic derivatives **7a**, **7b** or **7c** during crystallization from ethanol. Only derivative **6a** was stable enough to go through the isolation and purification processes. Briefly, the mixtures of crude products

6 and **7** were refluxed in butanol for 30 minutes to complete the reaction. The quaternary salts **7a**, **7b** or **7c** were formed with a 51-72% overall yield. A reductive debenzylation of **4a**, **4b** or **4c** and **7a**, **7b** or **7c** with hydrogen and palladium supported on charcoal as catalyst in an autoclave afforded the spiro derivatives **5a**, **5b** or **5c** and the bicyclic systems **8a**, **8b** or **8c**, respectively, with a high yield of 71-92%.

Scheme 1. Conditions: [a] H^+/BuOH, Δ; [b] H_2, Pd/C; [c] $ClCH_2COCl$, K_2CO_3, $CHCl_3/H_2O$; [d] BuOH, Δ; [e] H_2, Pd/C.



The ^{13}C nmr chemical shifts for compounds **5** and **8** were assigned by correlation with the spectra of other tetrahydro-β-carbolines [5], octahydroindolo[2,3-*a*]quinolizines [6], quinolizidine [7], substituted piperidines and pyrrolidines [8], and the ring systems **1a**, **1b** and **1c** [4]. The signals of both the indole moiety and carbon atoms of the saturated heterocyclic ring systems were found at their typical values. Resonance signals of C-6 (**8b**) and C-5 (**8c**) carbonyl atoms are shifted upfield by 4.6 and 7.1 ppm, respectively, in relation to C-5 for compound **8a**. The observed strong upfield shifts may arise not only from an additional steric strain, but also from a decreased conjugation within the amide fragment, which can be realized by twisting the amide bond in a solution [8,9].

The ^1H nmr spectra of spirans **5a**, **5b** and **5c** are in good agreement with their structures, and the observed coupling constants of 3'- and 4'-piperidine protons have values typical of a chair conformation of these rings. We reported previously that a strong intramolecular hydrogen bond exists between 2'-N and 9-N atoms of 1-(2-piperidyl)-1,2,3,4-tetrahydro-β-carboline [10]. A similar strong intramolecular hydrogen bond exists between 1'-N and 2-N atoms of 1-indol-2-yl-1,2,3,4-tetrahydro-β-carboline [1]. We also showed that in both cases the indole NH nitrogen shows a donor character. Moreover, it is obvious that the NH proton signal position of the indole ring depends on formation of a hydrogen bond with the solvent and on the solvation state, as well [11,12]. The indole NH signals broaden and appear at δ 8.06, 9.67 and 8.60 for spirans **5a**, **5b** and **5c**, respectively. On the other hand, the same NH signals for the respective bicyclic compounds **8a**, **8b** and **8c** become sharp and appear at δ 7.78, 8.00 and 8.32, respectively. The latter resonances are within the typical range characteristic for derivatives of 1,2,3,4-tetrahydro-β-carboline, in which intramolecular hydrogen bond does not exist [1,4,6,10]. The indole NH signal for spirans **5a** and **5c** is shifted downfield by 0.28 ppm, in relation to compounds **8a** and **8c**, respectively. The observed downfield shift should be attributed to changes in the solvation state of the appropriate spirans and bicyclic compounds rather than to formation of the intramolecular hydrogen bond. The 14-NH signal of spiran **5b** is distinctly shifted downfield (by 1.67 ppm), in comparison with the same signal position observed for bicyclic system **8b**. All these results clearly suggest that the intramolecular hydrogen bond may exist only in the case of spiran **5b**, due to a favorable steric arrangement of the 14-N and 2-N atoms. In fact, the distance between appropriate nitrogen atoms has the smallest value in spiran **5b**, being equal to 3.22 Å. However, this pivotal distance in spirans **5a** and **5c** equals 3.58 Å and 4.12 Å, respectively, as measured from the MNDO minimized structures. Moreover, the electron lone pair of the pyrrolidine or piperidine nitrogen atoms in **5a** and **5c** has a less favorable or even opposite orientation in comparison with that observed for spiran **5b**.

Structures of the new ring systems **8a**, **8b** and **8c** were

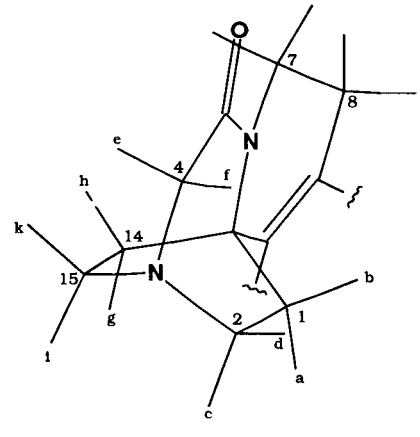


Figure 1. The calculated (MNDO) conformation of the 3,6-diazabicyclo[3.2.2]nonano[4',5':1,2]pyrido fragment of **8a**.

defined on the basis of ^1H and ^{13}C nmr spectra, one-dimensional nuclear Overhauser enhancement (1D nOe) measurements (Table 1) and proton-proton two-dimensional correlation spectroscopy (2D COSY) experiments (Tables 2, 3, 5). Moreover, the structures of compounds **8a**, **8b** and **8c** were built using the SYBYL package, and their geometry was optimized by the force field method at the first approximation level, and then by the MNDO method. The results are shown in Figures 1, 2 and 3.

The piperidine ring of the bicyclic system **8a** exists in the boat conformation, and the 1,4-diazepane ring adopts a half-chair conformation (Figure 1). In such an arrangement the 4-H_2 atoms are homotopic, and irradiation of their singlet signal results in an increased intensity of both b,h and d,k signals, as indicated by 1D nOe difference measurements (Table 1). The 2D correlation spectrum of **8a** is also clear (Table 2) and fully consistent with the structure shown in Figure 1. However, the typical long range (1,4 W-shape) correlations between e-c and f-i atoms offer the most accurate diagnosis for the structure determination. The symmetry of the bicyclic fragment also results in homotopic relation between the 7- and 8-H_2 protons that appear as simple triplets in the ^1H nmr spectra.

Table 1

Results of proton-proton 1D nOe experiments

Compound	Irradiated protons	nOe observed (%)
8a	4-H_2	1-H_b and 14-H_h (1), 2-H_d and 15-H_k (3)
8b	3-$H_{e,f}$	1-H_a (0.5), 2-H_c (2.5), 2-H_d (1.5), 5-H_g and 15-H_i (3.5)
	5-H_h	5-H_g (23), 15-H_k (3.5)
8c	1-H_b	1-H_a (16.5), 2-H_d (3)
	4-H_f	4-H_e (21), 14-H_h (3.5)

Table 2

Results of proton-proton 2D COSY experiments, measured for **8a** (diazabicyclo[3.2.2]nonano[4',5':1,2]pyrido fragment)

Protons	Observed correlations
1-H_a and 14-H_g	1-H_b and 14-H_h, 2-H_c and 15-H_i, 2-H_d and 15-H_k
1-H_b and 14-H_h	1-H_a and 14-H_g, 2-H_c and 15-H_i, 2-H_d and 15-H_k
2-H_c and 15-H_i	1-H_a and 14-H_g, 1-H_b and 14-H_h, 2-H_d and 15-H_k
2-H_d and 15-H_k	1-H_a and 14-H_g, 1-H_b and 14-H_h, 2-H_c and 15-H_i
4-H_2	2-H_c and 15-H_i [a]
7-H_2	8-H_2
8-H_2	7-H_2

[a] Long range (1,4) correlation between e-c and/or f-i.

Conformation of the bicyclic system **8b** is shown in Figure 2. The piperidine ring has a chair conformation, in which the electron lone pair of the N-4 atom occupies an equatorial position, whereas the 6-oxopiperazine ring exists in a half-chair conformation, as suggested by the MNDO calculations. The results of the 1D nOe and 2D COSY experiments are fully consistent with the above findings (Tables 1 and 4). The 1D nOe measurements indicate that the H-atoms a and i occupy an axial position on the piperidine ring. The cross correlations are also typical of the conformation shown in Figure 2.

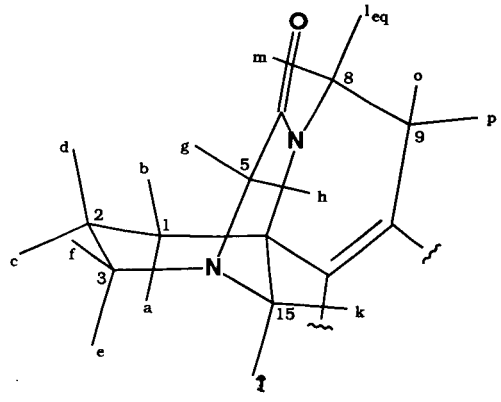


Figure 2. The calculated (MNDO) conformation of the 4,7-diazabicyclo[3.3.1]nonano[4',5':1,2]pyrido fragment of **8b**.

Table 3

Results of proton-proton 2D COSY experiments, measured for **8b** (diazabicyclo[3.3.1]nonano[4',5':1,2]pyrido fragment)

Protons	Observed correlations
1-H_a	1-H_b, 2-H_c, 2-H_d
1-H_b	1-H_a, 2-H_c, 2-H_d, 15-H_k [a]
2-H_c	1-H_a, 1-H_b, 2-H_d, 3-$H_{e,f}$
2-H_d	1-H_a, 1-H_b, 2-H_c, 3-$H_{e,f}$
3-$H_{e,f}$	2-H_c, 2-H_d, 15-H_k [b]
5-H_g	5-H_h, 15-H_i [a]
5-H_h	5-H_g
8-H^{ax} and 9-H_2	8-H^{eq}
8-H^{eq}	8-H^{ax} and 9-H_2
15-H_i	5-H_g [a], 15-H_k
15-H_k	1-H_b [a], 3-H_f [a], 15-H_i

[a] Long range (1,4) correlation. [b] Long range f-k correlation.

Table 4

Vicinal coupling constants (J^{vic}) of the 8-H_i and 7-H_i atoms, and calculated and measured torsion angles (ϕ) for compounds **8b** and **8c**, respectively

Compound (atom)	δ	J^{vic} (Hz)	ϕ (°) Calcd. [a]	ϕ (°) Measured [b]
8b (8-H_i)	5.11	2.8 (1-p)	52	50
		1.5 (1-o)	62	76
8c (7-H_i)	5.00	4.2 (i-l)	43	41
		1.9 (i-m)	59	75

[a] Calculated from the observed J^{vic} using equation (1) [13]. [b] Measured from the minimized geometry of **8b** and **8c**.

Protons of the ethylene bridge C_8–C_9 of compound **8b** are diastereotopic. The resonance of the 8-H_1 atom is shifted downfield up to δ 5.11. The position of this signal indicates that the 8-H_i atom is ecliptic with the C-6 carbonyl group. The calculated and measured values of the torsion angles for the ethylene bridge H-atoms are compared in Table 4 [13].

The calculated conformation of compound **8c**, by means of the MNDO method (Figure 3), is in a good agreement with the results of both 1D nOe and 2D COSY experiments (Tables 1, 4 and 5). The pyrrolidine ring has an envelope conformation and the lone electron pair at the C-3 atom is placed in the ring plane. The hydrogen atoms of the C_7–C_8 ethylene bridge are diastereotopic and the torsion angles are shown in Table 4. The 7-H_i signal is distinctly shifted downfield (δ 5.00). On the other hand, the ^{13}C resonance signal of the C-5 carbonyl atom is shifted upfield by 7.1 ppm in relation to the C-5 signal position observed for compound **8a**. Therefore, it seems to be obvious that the C_7–H_i bond should be almost coplanar with the carbonyl bond, whereas the amide bond cannot be planar. Hence the 5-oxopiperazine ring should adopt a boat conformation in the solution rather than a half-chair one, which predominates in the isolated state.

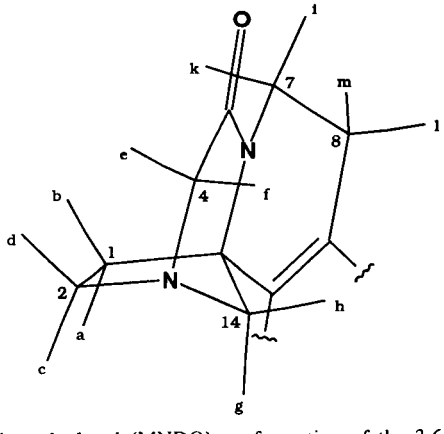


Figure 3. The calculated (MNDO) conformation of the 3,6-diazabicyclo[3.2.1]octano[4',5':1,2]pyrido fragment of **8c**.

Table 5

Results of proton-proton 2D COSY experiments, measured for **8c** (diazabicyclo[3.2.1]octano[4',5':1,2]pyrido fragment)

Protons	Observed correlations
1-H_a	1-H_b, 2-H_c, 2-H_d
1-H_b	1-H_a, 2-H_c, 2-H_d, 14-H_h [a]
2-H_c	1-H_a, 1-H_b, 2-H_d, 4-H_f [a]
2-H_d	1-H_a, 1H_b, 2-H_c, 14-H_h [a]
4-H_e	4-H_f, 14-H_g [a]
4-H_f	2-H_c [a], 4-H_e
7-H^{ax} and 8-H_2	7-H^{eq}
7-H^{eq}	7-H^{ax} and 8-H_2
14-H_h	1-H_b [a], 2-H_d [a], 14-H_g
14-H_g	4-H_e [a], 14-H_h

[a] Long range (1,4) correlation.

EXPERIMENTAL

All melting points are uncorrected and were determined on Böetius apparatus. Microanalyses were performed in the Institute of Organic Chemistry, Polish Academy of Sciences, Warszawa. The ^{13}C nmr spectra were obtained at 125 MHz on a Bruker 500 NMR spectrometer, referred to deuteriochloroform (δ = 77.0). The ^1H nmr spectra, one-dimensional nuclear Overhauser enhancement measurements and two-dimensional proton-proton correlation spectra obtained using double quantum filtered technique were taken at 500 MHz with the same spectrometer in deuteriochloroform solution with tetramethylsilane as an internal standard.

Commercially available reagent grade solvents and reagents were used without further purification. Analytical tlc was performed on DC-Alufolien silica gel 60 F_{254} (Merck) and spots were visualized with uv light. Room temperature refers to 17-21°.

Molecular modelling experiments, force field and MNDO calculations were conducted using the SYBYL 5.51 software package (Tripos), installed on ESV 10/33 workstation.

General Procedure for the Condensation of Tryptamine with *N*-Benzylpiperidones **3a** and **3b** or *N*-Benzylpyrrolidone-3 **3c**.

A mixture of tryptamine hydrochloride (7.9 g, 40 mmoles), *N*-benzyl-3-, *N*-benzyl-4-piperidone (**3a, 3b**) (7.9 g, 40 mmoles) or *N*-benzylpyrrolidone-3 (**3c**) (9.3 g, 53 mmoles), 36% hydrochloric acid (7.1 ml) in *n*-butanol (150 ml) was refluxed for 3 hours. Then 100 ml of solvents were distilled off, and the reaction mixture was cooled down. In case of compound **4c**, the reaction mixture was evaporated to dryness. The oily residue was dissolved in 100 ml of hot methanol and cooled down. The precipitate was filtered off, washed with acetone (10 ml) and recrystallized from methanol to give **4a**, **4b** and **4c** in 90, 84 and 47% yield, respectively.

A suspension of dihydrochloride **4a**, **4b** or **4c** (0.5 g) in chloroform (30 ml) was treated with an excess of 25% ammonia until the precipitate dissolved. The organic layer was separated and dried over anhydrous magnesium sulphate. The inorganic salt was filtered off. The filtrate was evaporated to dryness and the residue was crystallized to give the appropriate free base of **4a**, **4b** or **4c**.

Spiro[*N*-benzylpiperidine-4',1-(1,2,3,4-tetrahydro-β-carboline)] Dihydrochloride (**4a**).

This compound was obtained as colorless crystals, mp 260-261° dec (lit [3] 259-264° from ethylene glycol); tlc: R_f 0.80 (ethanol/25% ammonia [9:1]).

Anal. Calcd. for $C_{22}H_{25}N_3 \cdot 2HCl \cdot 0.5H_2O$: C, 63.92; H, 6.83; N, 10.17. Found: C, 64.12; H, 6.92; N, 10.07.

Free base of **4a** was obtained as colorless crystals (methanol/-water [4:1]), mp 75-77°.

Spiro[*N*-benzylpiperidine-3',1-(1,2,3,4-tetrahydro-β-carboline)] Dihydrochloride (**4b**).

This compound was obtained as colorless crystals, mp 208-211°; tlc: R_f 0.80 (ethanol/25% ammonia [9:1]).

Anal. Calcd. for $C_{22}H_{25}N_3 \cdot 2HCl$: C, 65.34; H, 6.73; N, 10.39. Found: C, 64.95; H, 6.70; N, 10.45.

Free base of **4b** was obtained as colorless crystals (chloroform/-methanol [9:1]), mp 255-258° decomposition.

Spiro[*N*-benzylpyrrolidine-3',1-(1,2,3,4-tetrahydro-β-carboline)] Dihydrochloride (**4c**).

This compound was obtained as colorless crystals, mp 250-253°; tlc: R_f 0.80 (ethanol/25% ammonia [9:1]).

Anal. Calcd. for $C_{21}H_{23}N_3 \cdot 2HCl$: C, 64.62; H, 6.46; N, 10.76. Found: C, 64.69; H, 6.54; N, 10.58.

Free base of **4c** was obtained as colorless crystals (benzene/hexane [1:1]), mp 78-81°.

General Procedure for the Preparation of Quaternary Salts **7a**, **7b**, **7c**.

To a vigorously stirred suspension of dihydrochlorides of **4a**, **4b** or **4c** (12 mmoles) in chloroform (80 ml) and 20% aqueous solution of potassium carbonate (80 ml) chloroacetyl chloride (2.85 g, 2 ml, 25 mmoles) was added dropwise. The reaction mixture was stirred at room temperature for one hour then the organic layer was separated, washed with water until neutral and dried over anhydrous magnesium sulphate. The solvent was evaporated to give spiro[*N*-benzylpiperidine-4′,1-(2-chloroacetamido-1,2,3,4-tetrahydro-β-carboline)] (**6a**) as colorless crystals (methanol), mp 206-209° (lit [3] mp 212-215° from acetone). The crude products **6a**, **6b** or **6c** were refluxed without purification in *n*-butanol (50 ml) for 40 minutes. After cooling the reaction mixture was kept in refrigerator overnight. Then the precipitate was filtered off and recrystallized to give **7a**, **7b** and **7c** in 72, 58 and 51% yield, respectively.

3-Benzyl-7,8,13-trihydro-3-azonium-6-azabicyclo[3.2.2]nonano-[4′,5′:1,2]pyrido[3,4-*b*]indol-5(6*H*)-one Chloride (**7a**).

This compound was obtained as colorless microcrystals, mp 334-337° (methanol).

Anal. Calcd. for $C_{24}H_{26}ClN_3O \cdot 0.75CH_3OH$: C, 68.82; H, 6.77; N, 9.73. Found: C, 68.74; H, 6.88; N, 9.84.

4-Benzyl-8,9,14-trihydro-4-azonium-7-azabicyclo[3.3.1]nonano-[4′,5′:1,2]pyrido[3,4-*b*]indol-6(7*H*)-one Chloride (**7b**).

This compound was obtained as colorless microcrystals, mp 218-220° (ethanol/hexane [4:1]).

Anal. Calcd. for $C_{24}H_{26}ClN_3O \cdot H_2O$: C, 67.67; H, 6.63; N, 9.87. Found: C, 67.30; H, 6.77; N, 10.04.

3-Benzyl-7,8,13-trihydro-3-azonium-6-azabicyclo[3.2.1]octano-[4′,5′:1,2]pyrido[3,4-*b*]indol-5(6*H*)-one Chloride (**7c**).

This compound was obtained as colorless microcrystals, mp 219-220° (methanol).

Anal. Calcd. for $C_{23}H_{24}ClN_3O \cdot H_2O$: C, 67.06; H, 6.36; N, 10.20. Found: C, 66.81; H, 6.26; N, 10.35.

General Procedure for the Debenzylation of **4** and **7**.

A mixture of *N*-benzyl derivative **4** or **7** (5 mmoles) and palladium supported on charcoal (0.3 g) in methanol (100 ml) and acetic acid (10 ml) was reduced with hydrogen (4 atmospheres) in an autoclave at room temperature for 20 hours. The precipitate was filtered off and treated with hot methanol/water [3:1] mixture (100 ml). The catalyst was filtered off and the combined filtrates were evaporated to dryness. The crystalline hydrochloride salts were recrystallized to give **5a**, **5b** and **5c** or **8a**, **8b** and **8c**. Hydrochlorides of **5** and **8** were transformed into free bases according to the general procedure described for **4**.

Spiro[piperidine-4′,1-(1,2,3,4-tetrahydro-β-carboline)] Hydrochloride (**5a**).

This compound was obtained with 83% yield as colorless crystals, mp 292-293° dec (methanol); tlc: R_f 0.10 (ethanol/25% ammonia [9:1]).

Anal. Calcd. for $C_{15}H_{19}N_3 \cdot HCl \cdot 3H_2O$: C, 54.29; H, 7.90; N, 12.66. Found: C, 54.19; H, 7.94; N, 12.72.

Free base of **5a** was obtained as colorless crystals, mp 252-254° (benzene/methanol [2:1]); ^{1}H nmr: δ 8.06 (br s, 1H, 14-NH), 7.48 (d, 1H, 13-H, J = 7.8 Hz), 7.32 (d, 1H, 10-H, J = 8.0 Hz), 7.15 (t, 1H, 11-H, J = 8.0 Hz), 7.09 (t, 1H, 12-H, J = 7.8 Hz), 3.17 (ddd, 2H, 2- and 4-H^{ax}, J = 13.9, 11.3 and 3.6 Hz), 3.15 (t, 2H, 8-H_2, J = 5.7 Hz), 2.93 (br d, 2H, 2- and 4-H^{eq}, J = 11.3 Hz), 2.71 (t, 2H, 9-H_2, J = 5.7 Hz), 1.98 (ddd, 2H, 1- and 5-H^{ax}, J = 13.6, 12.5, and 4.5 Hz), 1.78 (br d, 2H, 1- and 5-H^{eq}, J = 13.9 Hz), 1.71 (br s, 2H, 3- and 7-NH); ^{13}C nmr: δ 140.3 (13a-C), 135.5 (14a-C), 127.4 (9b-C), 121.6 (12-C), 119.3 (11-C), 118.2 (10-C), 110.8 (13-C), 108.5 (9a-C), 51.1 (6-C), 41.8 (2- and 4-C), 39.1 (8-C), 37.1 (1- and 5-C), 23.2 (9-C).

Spiro[piperidine-3′,1-(1,2,3,4-tetrahydro-β-carboline)] Hydrochloride (**5b**).

This compound was obtained with 83% yield as colorless crystals, mp 218-220° (methanol); tlc: R_f 0.10 (ethanol/25% ammonia [9:1]).

Anal. Calcd. for $C_{15}H_{19}N_3 \cdot HCl \cdot 2.5H_2O$: C, 55.80; H, 7.80; N, 13.10. Found: C, 56.07; H, 7.84; N, 12.68.

Free base of **5b** was obtained as colorless crystals, mp 91-92° (ethanol/ethyl ether [2:1]); ^{1}H nmr: δ 9.67 (br s, 1H, 14-NH), 7.50 (d, 1H, 13-H, J = 7.8 Hz), 7.35 (d, 1H, 10-H, J = 8.0 Hz), 7.14 (t, 1H, 11-H, J = 8.1 Hz), 7.07 (t, 1H, 12-H, J = 7.9 Hz), 3.30 (ddd, 1H, 8-H_a, J = 13.3, 8.1 [a-d], and 5.4 Hz [a-c]), 3.18 (ddd, 1H, 8-H_b, J = 13.2, 5.5 [b-d], and 4.2 Hz [b-c]), 3.08 (ddd, 1H, 3-H^{ax}, J = 11.3, 8.7, and 4.1 Hz), 2.99 (d, 1H, 1-H, J = 11.1 Hz), 2.82-2.73 (m, 2H, 3-H^{eq} and 9-H_d), 2.71 (ddd, 1H, 9-H_c, J = 15.4, 5.5 [c-a], and 4.2 Hz [c-b]), 2.27-2.20 (m, 1H, 4-H), 1.84-1.69 (m, 4H, 4-H, 5-H^{eq}, 2- and 7-NH), 1.59 (ddd, 1H, 5-H^{ax}, J = 12.8, 10.9, and 4.5 Hz); ^{13}C nmr: δ 140.0 (13a-C), 135.2 (14a-C), 127.1 (9b-C), 121.1 (12-C), 118.9 (11-C), 118.0 (10-C), 110.9 (13-C), 107.0 (9a-C), 57.2 (1-C), 51.1 (6-C), 46.8 (3-C), 39.0 (8-C), 37.3 (5-C), 22.9 (9-C), 22.6 (4-C).

Spiro[pyrrolidine-3′,1-(1,2,3,4-tetrahydro-β-carboline)] Dihydrochloride (**5c**).

This compound was obtained with 72% yield as colorless crystals, mp 209-212° dec (methanol); tlc: R_f 0.10 (ethanol/25% ammonia [9:1]).

Anal. Calcd. for $C_{14}H_{17}N_3 \cdot 2HCl \cdot 0.25H_2O$: C, 55.18; H, 6.45; N, 13.79. Found: C, 55.44; H, 6.72; N, 13.82.

Free base of **5c** was obtained as colorless crystals, mp 214-216° (benzene/methanol [2:1]); ^{1}H nmr: δ 8.60 (br s, 1H, 13-NH), 7.48 (d, 1H, 12-H, J = 7.7 Hz), 7.32 (d, 1H, 9-H, J = 8.0 Hz), 7.14 (t, 1H, 10-H, J = 8.0 Hz), 7.08 (t, 1H, 11-H, J = 7.7 Hz), 3.27 (q, 1H, 3-H, J = 8.2 Hz), 3.21-3.14 (m, 1H, 3-H), 3.18 (t, 2H, 7-H_2, J = 5.7 Hz), 3.12 (d, 1H, 1-H, J = 10.3 Hz), 3.03 (d, 1H, 1-H, J = 10.3 Hz), 2.74 (t, 2H, 8-H_2, J = 5.7 Hz), 2.22 (ddd, 1H, 4-H, J = 13.2, 8.6, and 8.5 Hz), 1.97 (ddd, 1H, 4-H, J = 13.1, 8.7, and 8.5 Hz), 1.91 (br s, 2H, 2- and 6-NH); ^{13}C nmr: δ 138.6 (12a-C), 135.6 (13a-C), 127.4 (8b-C), 121.5 (11-C), 119.2 (10-C), 118.0 (9-C), 110.8 (12-C), 108.0 (8a-C), 61.1 (5-C), 59.6 (1-C), 46.2 (3-C), 41.6 (7-C), 40.2 (4-C), 22.8 (8-C).

7,8,13-Trihydro-3,6-diazabicyclo[3.2.2]nonano[4′,5′:1,2]pyrido-[3,4-*b*]indol-5(6*H*)-one Hydrochloride (**8a**).

This compound was obtained with 92% yield as colorless microcrystals, mp 335-338° (ethanol); tlc: R_f 0.31 (methanol).

Anal. Calcd. for $C_{17}H_{19}N_3O$·HCl: C, 64.24; H, 6.34; N, 13.22. Found: C, 63.85; H, 6.69; N, 13.10.

Free base of **8a** was obtained as colorless crystals, mp 335-338° (ethanol); ^{1}H nmr: δ 7.78 (s, 1H, 13-NH), 7.51 (d, 1H, 12-H, J = 7.8 Hz), 7.34 (d, 1H, 9-H, J = 8.0 Hz), 7.20 (t, 1H, 10-H, J = 8.1 Hz), 7.14 (t, 1H, 11-H, J = 7.9 Hz), 4.04 (t, 2H, 7-H_2, J = 5.5 Hz), 3.87 (s, 2H, 4-H_2), 3.20 (ddd, 2H, 2-H_c and 15-H_i, J = 14.7, 8.6, and 6.6 Hz), 3.12 (ddd, 2H, 2-H_d and 15-H_k, J = 14.7, 8.6, and 5.2 Hz), 2.82 (t, 2H, 8-H_2, J = 5.5 Hz), 2.38 (ddd, 2H, 1-H_a and 14-H_h, J = 14.8, 8.7, and 6.7 Hz), 2.22 (ddd, 2H, 1-H_b and 14-H_g, J = 14.7, 8.6, and 5.1 Hz); ^{13}C nmr: δ 174.5 (5-C), 136.4 (12a- or 13a-C), 136.2 (12a- or 13a-C), 126.3 (8b-C), 122.4 (11-C), 120.0 (10-C), 118.5 (9-C), 110.9 (8a- and 12c-C), 62.4 (7-C), 55.0 (13b-C), 46.2 (2- and 15-C), 41.2 (4-C), 34.7 (1- and 14-C), 21.0 (8-C).

8,9,14-Trihydro-4,7-diazabicyclo[3.3.1]nonano[4′,5′:1,2]pyrido-[3,4-*b*]indol-6(7*H*)-one Hydrochloride (**8b**).

This compound was obtained with 71% yield as colorless crystals, mp 272-274° (ethanol); tlc: R_f 0.31 (methanol).

Anal. Calcd. for $C_{17}H_{19}N_3O$·HCl·0.25C_2H_5OH: C, 63.72; H, 6.57; N, 12.74. Found: C, 64.03; H, 6.95; N, 12.86.

Free base of **8b** was obtained as colorless microcrystals, mp 310-311° (ethanol/hexane [4:1]); ^{1}H nmr: δ 8.00 (s, 1H, 14-NH), 7.52 (d, 1H, 13-H, J = 7.8 Hz), 7.34 (d, 1H, 10-H, J = 8.0 Hz), 7.20 (t, 1H, 11-H, J = 8.0 Hz), 7.13 (t, 1H, 12-H, J = 7.9 Hz), 5.11 (ddd, 1H, 8-H^{eq}, J = 13.6, 2.8, and 1.5 Hz), 3.85 (d, 1H, 5-H_h, J = 18.4 Hz), 3.41 (dd, 1H, 15-H_i, J = 13.5 and 1.9 Hz [g-i]), 3.39 (dd, 1H, 5-H_g, J = 18.2 and 1.8 Hz [i-g]), 3.18 (dd, 1H, 15-H_k, J = 13.5 and 2.7 Hz [k-b and k-f]), 3.07 (dddd, 2H, 3-$H_{e,f}$, J = 13.4, 4.2, 3.2, and 2.6 Hz [f-k and f-b]), 2.91-2.79 (m, 3H, 8-H^{ax} and 9-H_2), 2.27 (dddd, 1H, 1-H_b, J = 13.7, 4.3, 2.7 [b-k], and 2.2 Hz), 1.99 (ddd, 1H, 1-H_a, J = 13.7, 8.5, and 4.3 Hz), 1.92-1.87 (m, 1H, 2-H_d), 1.59 (ddd, 1H, 2-H_c, J = 14.0, 4.4, and 2.2 Hz); ^{13}C nmr: δ 169.9 (6-C), 136.2 (13a-C), 134.6 (14a-C), 126.6 (9b-C), 122.4 (12-C), 120.0 (11-C), 118.5 (10-C), 111.0 (13-C), 109.7 (9a-C), 57.3 (8-C), 56.0 (15-C), 53.4 (3-C), 53.2 (14b-C), 35.2 (5-C), 33.6 (1-C), 21.3 (9-C), 17.8 (2-C).

7,8,13-Trihydro-3,6-diazabicyclo[3.2.1]octano[4′,5′:1,2]pyrido[3,4-*b*]indol-5(6*H*)-one Hydrochloride (**8c**).

This compound was obtained with 88% yield as colorless crystals, mp 278-280° dec (methanol/water [2:1]); tlc: R_f 0.31 (methanol).

Anal. Calcd. for $C_{16}H_{17}N_3O$·HCl: C, 63.26; H, 5.97; N, 13.83. Found: C, 63.28; H, 6.24; N, 13.56.

Free base of **8c** was obtained as colorless crystals, mp 296-297° (ethanol); ^{1}H nmr: δ 8.32 (s, 1H, 13-NH), 7.52 (d, 1H, 12-H, J = 7.8 Hz), 7.34 (d, 1H, 9-H, J = 8.0 Hz), 7.21 (t, 1H, 10-H, J = 7.6 Hz), 7.14 (t, 1H, 11-H, J = 7.4 Hz), 5.00 (ddd, 1H, 7-H^{eq}, J = 13.5, 4.2, and 1.9 Hz), 3.86 (d, 1H, 4-H_f, J = 18.0 Hz), 3.51 (ddd, 1H, 2-H_c, J = 12.6, 11.0, and 4.9 Hz), 3.42 (d, 1H, 4-H_e, J = 18.0 Hz), 3.26 (br d, 1H, 14-H_g, J = 18.0 Hz), 3.23 (dd, 1H, 14-H_h, J = 18.0 and 1.3 Hz [h-d]), 3.15 (dddd, 1H, 2-H_d, J = 12.5, 10.9, 5.9, and 1.2 Hz [d-h]), 2.90-2.80 (m, 3H, 7-H^{ax} and 8-H_2), 2.54 (dddd, 1H, 1-H_b, J = 13.5, 10.6, 5.4, and 1.6 Hz [b-h]), 2.31 (ddd, 1H, 1-H_a, J = 13.5, 10.7, and 5.5 Hz); ^{13}C nmr: δ 167.4 (5-C), 136.5 (12a-C), 130.0 (13a-C), 126.7 (8b-C), 122.5 (11-C), 120.0 (10-C), 118.4 (9-C), 111.2 (8a-C), 110.9 (12-C), 63.5 (7-C), 62.4 (13b-C), 61.9 (14-C), 54.7 (2-C), 40.9 (4-C), 36.9 (1-C), 20.9 (8-C).

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REFERENCES AND NOTES

[1] Part **5** of the series, Structure and Spectral Properties of β-Carbolines, For Part **4** see, S. Misztal, Z. Bielecka, and J. L. Mokrosz, *J. Chem. Soc., Perkin Trans. 1*, 1871 (1991).

[2] A. J. Bojarski, M. T. Cegla, S. Charakchieva-Minol, M. J. Mokrosz, M. Maćkowiak, and J. L. Mokrosz, *Pharmazie*, **48**, 289 (1993).

[3] P. Bartyzel, S. Misztal, E. Tatarczyńska, and E. Chojnacka-Wójcik, *Pol. J. Pharmacol. Pharm.*, **41**, 495 (1989).

[4] S. Misztal, M. Dukat, and J. L. Mokrosz, *J. Chem. Soc., Perkin Trans. 1*, 2311 (1990).

[5a] F. Ungemach, D. Soerens, R. Weber, M. DiPierro, O. Campos, P. Mokry, J. M. Cook, and J. V. Silverton, *J. Am. Chem. Soc.*, **102**, 6976 (1980); [b] R. Jokela and M. Lounasmaa, *Tetrahedron*, **43**, 6001 (1987); [c] P. D. Bailey and S. P. Hollinshead, *Heterocycles*, **26**, 389 (1987); [d] M. T. Cegla, B. Duszyńska, S. Misztal, and J. L. Mokrosz, *J. Prakt. Chem.*, **332**, 419 (1990).

[6] M. Lounasmaa and R. Jokela, *Tetrahedron*, **45**, 3975 (1989).

[7] A. R. Stoit and U. K. Pandit, *Tetrahedron*, **45**, 849 (1989).

[8] H. O. Kalinowski, S. Berger, and S. Braun, Carbon-13 NMR Spectroscopy, Wiley, Chichester, New York, Brisbane, Toronto, and Singapore, 1988.

[9] J. L. Mokrosz, *Arch. Pharm. (Weinheim)*, **319**, 1141 (1986).

[10] S. Misztal and M. Dukat, *Heterocycles*, **23**, 2271 (1985).

[11] S. Saito and K. Nukada, *J. Am. Chem. Soc.*, **93**, 1072 (1971).

[12] E. Pretsch, T. Clerc, J. Seibl, and W. Simon, Tables of Spectral Data for Structure Determination of Organic Compounds, Springer-Verlag, Berlin, 1989.

[13] Torsion angles (φ) were estimated from the ^{1}H nmr spectra using a basic equation (1); $J^{vic} = 4.5\cos 2\phi - 0.5\cos\phi + 4.22$ according to: M. Karplus, *J. Am. Chem. Soc.*, **85**, 2870 (1963).