Structure and Spectral Properties of β-Carbolines, I:

^{13}C-NMR and Mass Spectra of Decahydro-5H-pyrido[1',2';5,1]-imidazo[3,4-a]-β-carbolines

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^{13}C-NMR and the electron impact mass spectra of the β-carboline derivatives **1** - **18** were examined. The structure of the possible diastereomers is discussed. A quantitative relationship between the relative intensity of ions a in the mass spectra of **1** - **18** and the structure of substituents R was found.

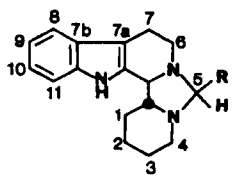
Struktur und spektroskopische Eigenschaften von β-Carbolinen, 1. Mitt.:
^{13}C-NMR-Spektren und Massenspektren der Dekahydro-5H-pyrido[1',2';5,1]-imidazo[3,4-a]-β-carboline

Die ^{13}C-NMR-Spektren und Massenspektren der Carbolinderivate **1** - **18** wurden untersucht. Die Struktur der möglichen Diastereomeren wird diskutiert. In den Massenspektren wurde eine quantitative Korrelation zwischen den relativen Intensitäten der Fragmentionen **a** und den Substituenten R gefunden.

The β-carbolines are an important group of compounds with a broad spectrum of activity towards the central nervous system (CNS)[1,2]. Hitherto the attention of our group has been focussed on the synthesis of 3,4-dihydro- and 1,2,3,4-tetrahydro-β-carbolines as potential CNS agents[3-12]. Some of these compounds showed a significant analgesic[13], sedative[10,13], antidepressant[9,13] or anticonvulsant[8,11] activity in animal tests. It was also demonstrated that the toxicity and specific activity of the investigated β-carbolines depend on their structure, i.e. the mode of substitution and the kind of substituents[8-11,13].

The purpose of the forthcoming series of papers is to get a more systematic insight into the structure and some physico-chemical properties of compounds with the β-carboline moiety built-in.

In this paper we discuss the influence of different alkyl and aryl substituents R at position 5 on the ^{13}C-NMR and electron impact mass spectra of (±)-threo-5-(substituted)-1,2,3,4,4a,4b,5a,5b,6,7-decahydro-5H-pyrido[1',2';5,1]-imidazo[3,4-a]-β-carbolines **1** - **18** (Table 1). One of these compounds, **6**, displayed an anticonvulsant action, comparable with that of phenytoin, in a preliminary pharmacological screening[8].



1 - 18

The ^{13}C-NMR chemical shifts of the skeleton carbon atoms of compounds **1** - **18** are listed in Tables 2 and 3. The data were assigned by an analysis of the signal multiplicity, obtained from proton coupled spectra, and by a correlation with the spectra of tetrahydro-β-carboline and its 1,2- and 1,3-disubstituted derivatives[17-19]. The chemical shifts of the substituent (R) carbon atom which are not included in the tables were found at their typical ranges[20]. The signals of the indol moiety carbon atoms 7a - 12a of compounds **1** - **18** are in a very narrow range ($0.3 \leq \delta \leq 2.9$ ppm) and are slightly shifted downfield (by ca. 0 - 2.8 ppm) in comparison with those for tetrahydro-β-carboline[16]. The C-1 - C-3

Table 1: Substituent constants and $^{1}\chi^{v}$ indices for compounds **1** - **18**

No.	R	$\sigma^{*a)}$	$\sigma^{b)}$	$^{1}\chi^{v}$
1	H	0.49		7.992
2	methyl	0.00		8.454
3	ethyl	-0.10		8.992
4	propyl	-0.12		9.492
5	isopropyl	-0.19		9.364
6	phenyl	0.60	0.00	10.076
7	2-chlorophenyl	1.05		10.484
8	3-chlorophenyl	0.98	0.37	10.478
9	4-chlorophenyl	0.87	0.24	10.478
10	2-nitrophenyl	1.14		10.581
11	3-nitrophenyl	1.21	0.71	10.575
12	4-nitrophenyl	1.26	0.78	10.575
13	4-(diethylamino)phenyl		-0.53	11.659
14	2-pyridyl			c)
15	3-pyridyl		0.73	9.926
16	4-pyridyl		0.83	9.926
17	2,3-dimethoxyphenyl			c)
18	2,4-dimehtoxyphenyl			c)

[a)] inductive substituent constants for the whole substituent taken from ref.[14,15].
[b)] *Hammett* constants for substituents in the phenyl ring taken from ref.[16].
[c)] $^{1}\chi^{v}$ not calculated because of lack of polar constants.

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Table 2: ^{13}C Chemical shift ranges of the skeleton carbon atoms 1 - 4 and 6 - 12a for compounds **1** - **18**

Carbon atom	δ (ppm)[a]	Carbon atom	δ (ppm)
1	28.4 - 29.4	7b	126.8 - 128.4
2	22.6 - 24.4	8	117.9 - 118.3
3	24.7 - 26.1	9	119.0 - 119.8
4	43.2 - 50.7	10	121.3 - 122.0
6	46.6 - 51.0	11	110.6 - 111.0
7	18.2 - 23.5	11a	135.4 - 136.3
7a	108.7 - 109.9	12a	132.7 - 135.6

[a] Downfield from TMS, in $CDCl_3$ solution.

Table 3: Ratio of (±)-A/(±)-**B** diastereomers and δ(^{13}C) chemical shifts (in ppm) of 4b-, 5- and 5b-carbon atoms

No.	Ratio[a]	δ (ppm)		
	(±)-A/(±)-**B**	4b	5b	5
1		59.1	77.7	67.6
2B	0/100	58.7	70.0	77.8(76.7)[b]
3A/3B	30/70	60.8/59.9	57.8/67.3	77.2/85.8(86.1)[b]
4A/4B	30/70	60.8/59.9	57.8/67.2	77.2/84.9(83.6)[b]
5B	0/100	61.0	65.0	91.1(94.4)[b]
6A/6B	40/60	63.3/59.3	62.4/70.7	82.7/85.6
7A/7B	95/5	62.4/59.5	63.2/70.2	77.2/80.1
8B	0/100	59.3	70.5	85.2
9B	0/100	59.3	70.6	84.9
10A	100/0	62.3	63.4	75.8
11A	100/0	62.5	63.0	81.7
12A	100/0	62.4	63.1	81.5
13B	0/100	58.9	70.8	85.2
14B	0/100	59.7	70.2	86.8
15B	0/100	59.5	70.6	83.4
16B	0/100	59.6	70.4	84.8
17B	0/100	59.3	70.4	77.5
18B	0/100	59.0	70.2	76.5

[a] Ratio determined from ^{13}C-NMR spectrum.
[b] Chemical shifts for a (±)-**B** diastereomer calculated from eq. (2).

chemical shifts are also in narrow ranges and, as can be expected, the C-4, C-6, and C-7 resonances are more differentiated due to the effects of the substituents at position 5 (Table 2). The C-4b, C-5, and C-5b resonances of the imidazolidine ring are of the highest diagnostic value for the structural determination of **1** - **18** (Table 3).

Condensation of one of the diastereomers of 1-(2-piperidyl)-1,2,3,4-tetrahydro-β-carboline[6] with various aldehydes yields the cyclic aminals **1** - **18**, as described[8,11]. The compounds obtained in this reaction should have H-4b and H-5b atoms fixed in trans position; moreover, two diastereomers should exist due to a new asymmetric center at position 5 (Fig. 1).

The dihedral angle between H_{4b}-C_{4b}-C_{5b}-H_{5b} atoms should be within a range of $150° \leq \varphi \leq 180°$, as shown by an analysis of *Dreiding* models. In the ^1H-NMR spectra of compounds **1** - **4**, **6**, **7** and **9** the H-5b signal appeared at δ = 3.9 - 4.3 ppm as a doublet and the vicinal coupling constant

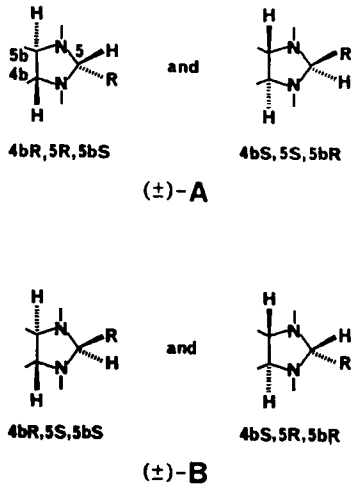


Fig. 1: Two pairs of possible enantiomers (±)-**A** and (±)-**B** of the imidazoline ring of **1** - **18**.

with H-4b was J_{vic} = 8.2 - 9.2 Hz. The dihedral angle values calculated from the above coupling constants and *Karplus* equation (1)[21], are φ = 161° - 177° and are placed within the predicted range. This means that H-4b and H-5b atoms accupy axial or pseudo-axial positions.

$$J_{vic} = 9.5 \cos^2 \varphi - 0.28 \quad \text{when } 90° < \varphi < 180° \tag{1}$$

The ^{13}C-NMR spectra indicate that compounds **3**, **4**, **6**, and **7** exist as a mixture of diastereomers (±)-**A** and (±)-**B**. The assignment of C-4b, C-5, and C-5b resonances to particular diastereomers is based on steric relation in the imidazolidine ring. In diastereomer (±)-**A** the substituent R is in a cis-position to H-5b, while in (±)-**B** the substituent R is in a trans-position to this H (Fig. 1). An increased 5,5b-interaction for (±)-**A** diastereomers (**3**, **4**, **6**, and **7**) causes the C-5b C-atom to resonate upfield of its respective position in (±)-**B** diastereomers because of the compression effect[20,22]. Contrarily, the steric interaction between the R-substituent and H-4b for (±)-**A** (trans) is weaker than that for (±)-**B** (cis), and the C-4b signal of (±)-**B** diastereomers is shifted upfield in relation to that of (±)-**A** (Table 3). The observed effect of alkyl substituents on the C-5 chemical shift in a (±)-**B** diastereomer is also characteristic. The chemical shifts of C-5 atom were calculated from eq. (2) using the incremental system developed for alkanes[29]. As shown in Table 3 the calculated values are in a good agreement with the observed ones.

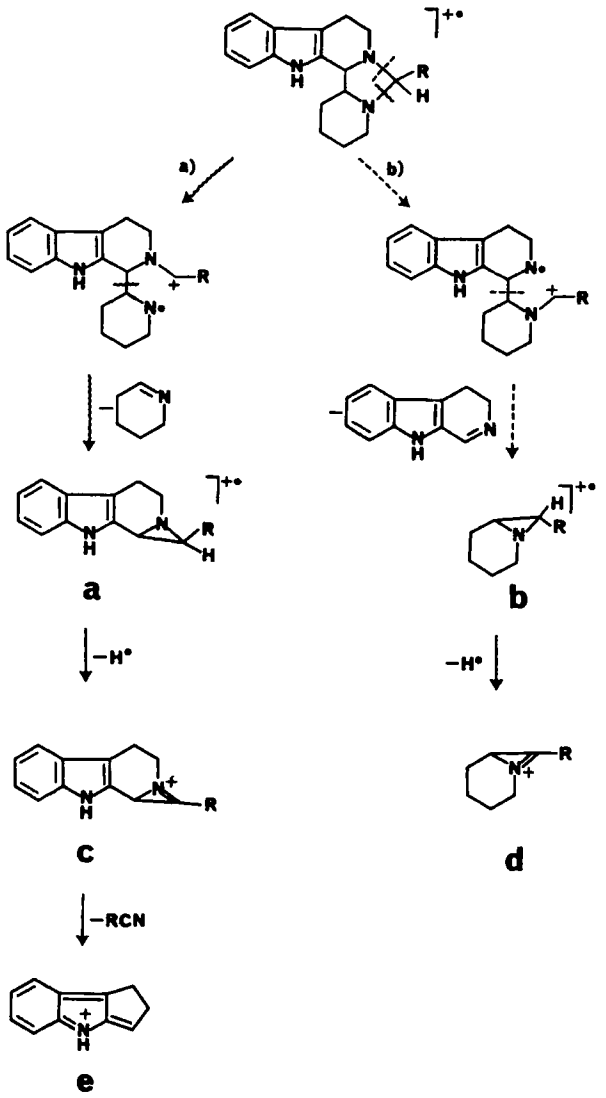
$$\delta_{C\text{-}5} = 67.6 + \Sigma_l A_l n_{kl} + S_{kl} \tag{2}$$

where A_l is the additive parameter for shifts caused by *n* carbon atoms at position *l* relative to observed carbon (*k*), S_{kl} is the steric correction term for branched alkanes.

When the chemical shifts of C-4b, C-5, and C-5b atoms were collated, it became apparent that the structure of a (±)-**A** diastereomer should be ascribed to derivatives **10** -

12, while the structure of a (±)-**B** diastereomer to derivatives **2**, **5**, **8**, **9**, and **13** - **18**. Formation of the (±)-**B** diastereomer is preferred in most cases. However, there is not apparent relationship between formation of particular diastereomers and the steric hindrance introduced by substituents at position 5. Thus, it seems that the reaction is both thermodynamically and kinetically controlled.

The electron impact mass spectra of derivatives **1** - **18** were examined[8,11], the characteristic fragmentation patterns are shown in Scheme 1. Initial fragmentation occurs by cleavage of the C-N bonds (pathway (a) or (b)) of the imidazolidine ring. Further cleavage of the C-C bond yields the complementary fragments **a** and **b**. Ion **a** is the base peak for most of the investigated compounds (except **5** and **10**, Table 4); it decomposes by loss of H· and a subsequent elimination of RCN yielding ion **e** (as indicated by metastable ions). The observed fragmentation pattern is consistent with that of substituted tetrahydro-β-carbolines[23].



Scheme 1: Main fragmentation pathways of $M^{+\cdot}$ (**1** - **18**).

Some electron impact induced fragmentation processes can be described quantitatively in terms of ion structure[24-26]. One of the possible fragmentation pathways of compounds **1** - **18**, formation of ion **a** from the molecular ion, can also be described quantitatively as a function of the structure of the substituent. Their structure was described by means of sets of polar constants (σ^* or σ) and a set of the first order molecular connectivity indices ($^1\chi^v$) (Table 1), which can be regarded as steric descriptors of a molecule[27]. For the purpose of correlation analysis compounds **1** - **18** were divided into two subsets: in the first subset the polar effect of the substituents is described by the σ^* inductive constants, and for the second one by the σ *Hammett* constants.

For **1** - **12**:

$$\log a/M = 4.753 + 0.554\,\sigma^* - 0.302\,^1\chi^v \quad (3)$$
$$n = 12,\ r = 0.950,\ s = 0.077,\ C.L. = 99.9\%$$

and for **6**, **8**, **9**, **11** - **13**, **15**, **16**:

$$\log a/M = 0.993 + 0.416\,\sigma - 0.091\,^1\chi^v \quad (4)$$
$$n = 8,\ r = 0.933,\ s = 0.076,\ C.L. = 99.9\%$$

where *r* is the correlation coefficient, *s* is the standard error and *C.L.* is the confidence level for *r*, evaluated by *Student's* test.

The correlations shown in equations (3) and (4) are good and highly significant and indicate that the formation of the most characteristic fragments (**a**) is linearily dependent on the structure of the substituents of the investigated compounds.

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Experimental Part

Materials and apparatus: syntheses of the investigated compounds are described: **2** - **4** and **6**[8] and **7** - **9** and **13** -**18**[11].-Uncorrected m.p.s.: *Boetius* apparatus (VEB Analytik, Dresden).- Elemetal analyses: Institute of Organic Chemistry, PAS, Warsaw.- ^{13}C-NMR spectra: Bruker 300 75.47 MHz.- ^{1}H-NMR spectra: Bruker 300, 300 MHz, in $CDCl_3$ solution, TMS as intern. standard.- Mass spectra: LBK 9005. Temp. ion source: 100 - 120 °C, trap current was 60 μA, electron energy: 70 eV. The samples were introduced using a direct insertion probe.

Preparation of compounds **1**, **5** *and* **10** - **12**

To a solution of 0.255 g (0.001 mol) of (±)-erythro-1-(2-piperidyl)-1,2,3,4-tetrahydro-β-carboline[6] in 10 ml of benzene 0.002 mol of an appropriate aldehyde was added. The mixture was refluxed for 1 h, then the solvent was evaporated under reduced pressure and the residue was recrystallized.

(±)-threo-1,2,3,4,4a,4b,5a,5b,6,7-Decahydro-5H-pyrido-[1',2';5,1]-imidazo[3,4-a]-β-carboline (**1**)

Colouress crystals from benzene, 0.21 g (79%), m.p. 98-100°C.- $C_{17}H_{21}N_3 \cdot H_2O$ (285.4) Calcd. C 71.5 H 8.1 N 14.7 Found C 71.5 H 8.6 N 14.4.

Table 4: Characteristic fragment ions in the EI-Mass spectra of compounds **1** - **18**

No.	m/z (relative intensity, %)					
	$M^{+\cdot}$	a	b	c	d	e
1	267	184	97	183	96	156
	(0.24)	(100)	(6)	(17)	(3)	(26)
2	281	198	111	197	110	156
	(0.66)	(100)	(10)	(9)	(3)	(20)
3	295	212	125	211	124	156
	(1.12)	(100)	(7)	(7)	(4)	(8)
4	309	226	139	225	138	156
	(1.72)	(100)	(6)	(12)	(4)	(7)
5	309	226	139	225	138	156
	(0.18)	(16.40)	(1)	(2)	(1)	(3)
6	343	260	173	259	172	156
	(1.03)	(100)	(5)	(12)	(12)	(19)
7	377	294	207	293	206	156
	(0.65)	(100)	(4)	(9)	(7)	(22)
8	377	294	207	293	206	156
	(0.82)	(100)	(5)	(10)	(9)	(26)
9	377	294	207	293	206	156
	(0.86)	(100)	(6)	(10)	(11)	(27)
10	388	305	218	304	217	156
	(0.45)	(54.93)	(1)	(1)	(1)	(2)
11	388	305	218	304	217	156
	(0.50)	(100)	(2)	(6)	(3)	(19)
12	388	305	218	304	217	156
	(0.45)	(100)	(2)	(6)	(3)	(21)
13	414	331	244	330	243	156
	(1.67)	(100)	(6)	(11)	(11)	(17)
14	344	261	174	260	173	156
	(1.93)	(100)	(6)	(23)	(6)	(6)
15	344	261	174	260	173	156
	(0.75)	(100)	(6)	(17)	(10)	(20)
16	344	261	174	260	173	156
	(0.69)	(100)	(4)	(10)	(6)	(20)
17	403	320	233	319	232	156
	(1.39)	(100)	(3)	(22)	(4)	(11)
18	403	320	233	319	232	156
	(1.55)	(100)	(4)	(14)	(7)	(13)

(±)-threo-5-Isopropyl-1,2,3,4,4a,4b,5a,5b,6,7-decahydro-5H-pyrido-[1',2';5,1]-imidazo[3,4-a]-β-carboline (**5**)

Colourless microcrystals from methanol, 0.14 g (45%), m.p. 64-65°C.- $C_{20}H_{27}N_3$ (309.4) Calcd. C 77.6 H 8.8 N 13.6 Found C 77.3 H 9.2 N 13.3.

(±)-threo-5-(2-Nitrophenyl)-1,2,3,4,4a,4b,5a,5b,6,7-decahydro-5H-pyrido-[1',2';5,1]-imidazo[3,4-a]-β-carboline (**10**)

Pale yellow microcrystals from ethanol: water (3:1), 0.23 g (59%), m.p. 165-166°C.- $C_{23}H_{24}N_4O_2 \cdot C_2H_5OH$ (434.5) Calcd. C 69.1 H 7.0 N 12.9 Found C 69.1 H 7.0 N 12.8.

(±)-threo-5-(3-Nitrophenyl)-1,2,3,4,4a,4b,5a,5b,6,7-decahydro-5H-pyrido-[1',2';5,1]-imidazo[3,4-a]-β-carboline (**11**)

Yellow crystals from ethanol: water (3:1), 0.36 g (93%), m.p. 145-147°C.- $C_{23}H_{24}N_4O_2 \cdot C_2H_5OH$ (434.5) Calcd. C 69.1 H 7.0 N 12.9 Found C 69.3 H 7.0 N 13.1.

(±)-threo-5-(4-Nitrophenyl)-1,2,3,4,4a,4b,5a,5b,6,7-decahydro-5H-pyrido-[1',2';5,1]-imidazo[3,4-a]-β-carboline (**12**)

Pale yellow microcrystals from ethanol:water (3:1), 0.29 g (75%), m.p. 108-110°C.- $C_{23}H_{24}N_4O_2 \cdot C_2H_5OH$ (434.5) Calcd. C 69.1 H 7.0 N 12.9 Found C 69.3 H 7.1 N 12.7.

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