DRUG SYNTHESIS METHODS AND MANUFACTURING TECHNOLOGY

SYNTHESIS OF 3-ALKYL- AND 3,9-DIALKYL-1,2,3,4-TETRAHYDRO-γ-CARBOLINES

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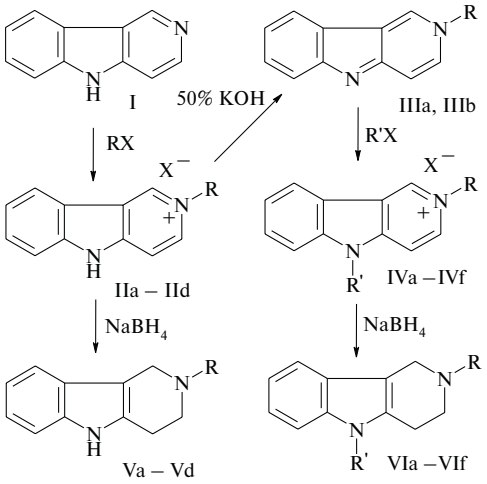
The derivatives of tetrahydro-γ-carbolines exhibit a broad spectrum of pharmacological properties [1]. Examples of highly effective drugs widely used in medicine are offered by 3-methyl-9-benzyl-1,2,3,4-tetrahydro-γ-carboline naphthalene-1,5-disulfonate (diazoline) [2] and 9-[2-(2-methylpyrid-5-yl)ethyl]-3,6-dimethyl-1,2,3,4-tetrahydro-γ-carboline dihydrochloride (dimebone) [3].

Tetrahydro-γ-carbolines are usually synthesized by the Fischer method employing the condensation of phenylhydrazine derivatives with N-methyl-γ-piperidone [4]. The resulting 3-methyl-1,2,3,4-tetrahydro-γ-carbolines are used as intermediate compounds in the synthesis of biologically active substances [5].

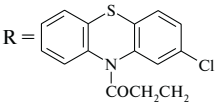
Using γ-carboline as the initial compound, we planned to obtain a series of N-alkyl(benzyl)tetrahydro derivatives from monoquaternary salts by analogy with the synthesis of substituted spinaceamine and 2-azaspinaceamine [6, 7] and pyridyl-N-alkyltetrahydroharmines [8].

The initial γ-carboline (I) was synthesized using the Graebe – Ullmann reaction proceeding from 1-phenyl-1,2,3-triazolo[4,5-c]pyridine [9]. The reactions of compound I with alkyl halides yielded monoquaternary salts (IIa – IId), which were reduced by sodium borohydride to obtain 3-alkyl(arylalkyl)-1,2,3,4-tetrahydro-γ-carbolines (Va – Vd) with a yield of 60 – 91% (Table 1).

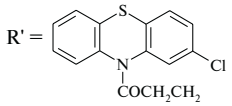
The proposed structures of quaternary salts IIa – IId and the corresponding reduction products Va – Vd were confirmed by the ^{1}H NMR data (Tables 2 and 3). For example, the reduction of 3-methyl-γ-carbolinium iodide IIa [10] leads to 3-methyl 1,2,3,4-tetrahydro-γ-carboline (Va), previously synthesized by the Fischer method [11, 12].



II, III, V, R = CH_3 (a); R = $C_6H_5CH_2$ (b); R = CH_2CH_2OH (c);

R =  (d)

IV, VI, R = R' = CH_3 (a); R = CH_3, R' = CH_2CH_2OH (b); R = CH_3,

R' =  (c)

R = $CH_2C_6H_5$, R' = CH_3 (d); R = R' = $CH_2C_6H_5$ (e);
R = $CH_2C_6H_5$, R' = CH_2CH_2OH (f)

X = I (IIa, IVa, IVd); Cl (IIb – IId, IVb, IVc, IVe, IVl)

In the ^{1}H NMR spectrum of salt IIa, the signals from pyridine protons H-1, H-2, and H-4 are observed in the region of aromatic shifts. In contrast, the ^{1}H NMR spectrum of compound Va displays three groups of signals due to methylene protons in positions 1, 2, 4 (Tables 2 and 3).

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As is known, the interaction of 3-methyl-γ-carbolinium iodide IIa [10] with a concentrated alkali solution leads to the formation of an anhydrobase possessing the structure of compound IIIa [13]. Under analogous conditions, 3-benzyl-γ-carboliniumiodide IIb [10] yielded anhydrobase IIIb, with the structure confirmed by the ^{1}H NMR data.

Heating compound IIIa with methyl iodide in an alcohol medium leads to a high yield of quaternary salt IVa, which is reduced by sodium borohydride to 3,9-dimethyl 1,2,3,4-tetrahydro-γ-carboline (VIa). By the same token, the reduction of quaternary salts IVb – IVf led to tetrahydrobases VIb – VIf (Table 1). The proposed structures of salts IVa – IVf and the corresponding reduction products VIa – VIf correspond to the observed ^{1}H NMR spectra (Tables 2 and 3). For example, the spectrum of compound VIa displays, in comparison with the spectrum of the initial salt IVa, additional signals from protons of the methylene groups 1-CH_2, 2-CH_2, and 4-CH_2.

As is known, the group of 10-aminoalkyl derivatives of phenothiazine contains a number of highly effective drugs [14, 15]. With a view to study the pharmacological activity of these compounds, we have synthesized with good yields the derivatives of 1,2,3,4-tetrahydro-γ-carboline (Vd, VIc) containing nitrogen atoms of the pyrrole and tetrahydropyridine fragments bound to 2-chlorophenothiazine.

Thus, we have developed a new approach to the synthesis of 1,2,3,4-tetrahydro-γ-carboline derivatives which allows compounds with various alkyl and arylalkyl substituents at nitrogen atoms of both pyrrole and tetrahydropyridine fragments.

EXPERIMENTAL PART

The course of reactions was monitored and the purity of products was checked by TLC on Silufol UV-254 plates eluted in ethanol and developed by exposure to iodine vapors or UV radiation. The data of elemental analyses of the products agree with the results of analytical calculations according to the empirical formulas. The yields and melting temperatures of the synthesized compounds are listed in Table 1.

The ^{1}H NMR spectra were measured on a Tesla BS-467C spectrometer (working frequency, 60 MHz; solvent, trifluoroacetic acid) and Varian Gemini-200 spectrometer (200 MHz; deuterated methanol and chloroform).

General method for the synthesis of quaternary salts (IIa – IId). A mixture of 10 mmole of base I or IIIa, IIIb and 15 mmole of the corresponding alkyl halide in 15 ml of 2-propanol is heated to boiling for 3 – 3.5 h. Then the excess alkyl halide and solvent are distilled off at a reduced pressure (water-jet pump) and the quaternary salt residue was recrystallized from an appropriate solvent (Table 1).

3-Methyl-γ-carboline (IIIa). To 1.2 g (4.0 mmole) of 3-methyl-γ-carbolinium iodide (IIa) dissolved in 20 ml of hot water was added 20 ml of a 50% aqueous KOH solution. The precipitated light-yellow product was separated by filtration, washed with 5 ml of cold water, and recrystallized from 2-propanol to obtain 0.65 g (93%) of compound IIIa; m.p., 79 – 81°C; $C_{12}H_{10}N_2$; ^{1}H NMR spectrum in $CDCl_3$ (δ, ppm): 3.82 (s, 3H, –N–CH_3), 7.24 – 7.61 (m, 4H, arom. H-5…H-8), 7.89 – 8.04 (m, 3H, arom. H-1, H-2, H-4).

3-Benzyl-γ-carboline (IIIb). Compound IIIb was obtained similarly to IIIa, proceeding from 3-benzyl-γ-carbolinium iodide (IIb). After recrystallization from 2-propanol, the yield of compound IIIa is 71%; m.p., 85 – 87°C; $C_{18}H_{14}N_2$; ^{1}H NMR spectrum in $CDCl_3$ (δ, ppm): 5.26 (s, 3H, –N–CH_3), 7.11 – 7.57 (m, 4H, arom. H-5...H-8), 7.48 (s, 5H, C_6H_5), 7.90 (d, 1H, J 8.0 Hz, H-1), 7.98 (d, 1H, J 8.0 Hz, H-2), 8.36 (s, 1H, H-4).

3-Alkyl-1,2,3,4-tetrahydro-γ-carbolines (Va – Vd) and 3,9-dialkyl-1,2,3,4-tetrahydro-γ-carbolines (VIa – VId). To a solution of 5 mmole of a quaternary salt (IIa – IId, IVa – IVf) in 50 ml of a 70% aqueous ethanol solution was added at room temperature with intensive stirring by portions (over 0.5 – 1 h) 10 mmole of sodium borohydride. When the latter solution was completely added, the stirring was terminated and the mixture was allowed to stand for 16 – 20 h. Then the solvent was evaporated at a reduced pressure (water-jet pump) and the residue was extracted with benzene. The extract was dried over anhydrous alkali, the solvent was distilled off, and the product was recrystallized from an appropriate solvent (Table 1).

TABLE 1. Yields and Physicochemical Characteristics of 3-Alkyl- and 3,9-Dialkyl-1,2,3,4-tetrahydro-γ-carbolinium Halides (IIa – IId, IVa – IVf) and Their Reduction Products (Va – Vd, VIa – VIf)

Target compound	Initial compound	Yield, %	M.p., °C (solvent for crystallization)	Empirical formula
IIa	I	92	232 – 234 (ethanol)	$C_{12}H_{11}IN_2$
IIb	I	86	205 – 208 (2-propanol)	$C_{18}H_{15}ClN_2$
IIc	I	81	237 – 240 (2-propanol)	$C_{13}H_{13}ClN_2O$
IId	I	98	245 – 248 (2-propanol)	$C_{26}H_{19}Cl_2N_3OS$
IVa	IIIa	88	305 – 308 (2-propanol)	$C_{13}H_{13}IN_2$
IVb	IIIa	97	260 – 263 (2-propanol)	$C_{14}H_{15}ClN_2O$
IVc	IIIa	64	230 – 233 (2-propanol)	$C_{27}H_{21}Cl_2N_3OS$
IVd	IIIb	90	202 – 204 (2-propanol)	$C_{19}H_{17}IN_2$
IVe	IIIb	89	238 – 241 (2-propanol)	$C_{25}H_{21}ClN_2$
IVf	IIIb	95	> 250 (ethanol)	$C_{20}H_{19}ClN_2$
Va	IIa	91	168 – 169 (heptane)	$C_{12}H_{14}N_2$
Vb	IIb	88	158 – 160 (heptane)	$C_{18}H_{18}N_2$
Vc	IIc	82	49 – 50 (hexane)	$C_{13}H_{16}N_2$
Vd	IId	60	73 – 74 (benzene)	$C_{26}H_{22}ClN_3OS$
VIa	IVa	86	69 – 70 (hexane)	$C_{13}H_{16}N_2$
VIb	IVb	50	71 – 72 (benzene)	$C_{14}H_{18}N_2O$
VIc	IVc	65	88 – 89 (heptane)	$C_{27}H_{24}ClN_3OS$
VId	IVd	78	89 – 90 (hexane)	$C_{19}H_{20}N_2$
VIe	IVe	83	145 – 147(benzene)	$C_{25}H_{24}N_2$
VIf	IVf	79	47 – 49 (benzene)	$C_{20}H_{22}N_2O$

TABLE 2. ^{1}H NMR Spectra of 3-Alkyl- and 3,9-Dialkyl-1,2,3,4-tetrahydro-γ-carbolinium Halides (IIa – IId, IVa – IVf)*

Compound	^{1}H NMR spectrum (CD_3OD): δ, ppm (J, Hz)					
	H^1, d	H^2, d	H^4, s	N^3-R	N^9-R′	H^5, H^6, H^7, H^8
IIa	8.36, J 7.0	8.57, J 7.0	9.64	4.47 (s, 3H, CH_3)	–	7.38 – 7.49 (m, 2H, H^6, H^7) 7.79 (d, 1H, H^8, J 4.2) 7.94 (d, 1H, H^5, J 7.0)
IIb	6.81, J 7.0	7.87, J 7.0	9.82	5.88 (s, 2H, CH_2); 7.47 – 7.68 m, (C_6H_5)	–	7.47 – 7.68, m, H arom.
IIc	7.53, J 7.0	8.06, J 7.0	8.92	4.06 (t, 2H, β-CH_2); 4.51 (t, 2H, α-CH_2)	–	7.06 – 7.91, m, H arom.
IId	8.14, J 7.0	8.53, J 7.0	9.64	3.80 (t, 2H, β-CH_2); 4.95 (t, 2H, α-CH_2); 7.14 – 7.86 (m, 4H, C_6H_4); 7.92 (d, 1H, H_4, J 7.0); 8.32 (d, 1H, H^3, J 7.0); 8.59 (s, 1H, H^1)	–	7.14 – 7.86, m, H arom.
IVa	8.41, J 7.0	8.64, J 7.0	9.66	4.48 (s, 3H, CH_3)	4.14 (s, 3H, CH_3)	7.62 (d, 1H, H^8, J 7.0) 7.86 (d, 2H, H^7, H^8, J 7.0) 8.10 (d, 1H, H^5, J 7.0)
IVb	8.37, J 7.4	8.60, J 7.4	9.62	4.45 (s, 3H, CH_3)	4.04 (t, 2H, β-CH_2) 4.71 (t, 2H, α-CH_2)	7.52 – 8.2, m, H arom.
IVc	8.27, J 7.0	8.68, J 7.0	9.67	4.51 (s, 3H, CH_3)	3.39 (t, 2H, β CH_3); 4.96 (t, 4H, α-CH_2 β-CH_2); 7.61 – 7.92 (m, 4H, C_6H_4); 8.00 (d, 1H, H^4, J 7.2); 8.44 (d, 1H, H^3, J 7.2); 8.60 (s, 1H, H^1)	7.61 – 7.2, m, H arom.
IVd	7.43, J 7.0	8.12, J 7.0	9.01	5.37 (s, 2H, CH_2); 7.04 (s, 5H, C_6H_5)	3.58 (s, 3H, CH_3)	7.18 – 7.97, m, H arom.
IVe	7.51, J 7.0	8.06, J 7.0	8.96	5.37 (s, 2H, CH_2); 7.06 (s, 5H, C_6H_5)	5.37 (s, 2H, CH_2); 7.06 (s, 5H, C_6H_5)	7.33 – 7.91, m, H arom.
IVf	8.39, J 7.0	8.71, J 7.0	9.84	5.84 (s, 2H, CH_2); 7.46 – 7.58 (m, 5H, C_6H_5)	4.05 (t, 2H, β-CH_2); 4.71 t (2H, α-CH_2)	7.74 – 7.99, m, H arom.

* Compounds IIc and IVd were dissolved in CF_3COOH.

TABLE 3. ^{1}H NMR Spectra of 1,2,3,4-Tetrahydro-γ-carbolines (Va – Vd, VIa – VIf)

Compound	^{1}H NMR spectrum ($CDCl_3$): δ, ppm (J, Hz)					
	1-CH_2	2-CH_2	4-CH_2	N^3-R	N^9-R′	H^5, H^6, H^7, H^8
Va	2.82 t	2.82 t	3.72 s	2.60 (s, 3H, CH_3)	H	7.07 – 7.44 (m, H arom.)
Vb	2.85 t	2.85 t	3.72 s	3.79 (s, 2H, CH_2) 7.03 – 7.09 (m, 5H, C_6H_5)	H	7.23 – 7.43 (m, H arom.)
Vc	2.73 t	2.73 t	3.63 s	2.68 (t, 2H, β-CH_2); 3.71 (t, 2H, α-CH_2)	H	7.06 – 7.29 (m, H arom.)
Vd	2.96 t	2.72 t	3.74 t	5.24 (s, 2H, β-CH_2); 6.06 (t, 2H, α-CH_2); 6.57 – 7.52 (m, 4H, C_6H_4); 8.32 (d, 1H, H^4, J 7.0), 8.56 (d, 1H, H^3, J 7.0); 9.65 (s, 1H, H^1)	H	6.57 – 7.52 (m, H arom.)
VIa	2.89 t	2.89 t	3.75 t	2.60 (s, 3H, CH_3)	3.63 (s, 3H, CH_3)	7.00 – 7.46 (m, H arom.)
VIb	2.76 t	2.76 t	3.60 s	2.51 (s, 3H, CH_3)	3.78 (t, 2H, β-CH_{22}); 4.11 (t, 2H, α-CH_2)	7.09 – 7.43 (m, H arom.)
VIc	2.93 t	2.93 t	3.72 s	2.68 (s, 3H, CH_3)	5.20 (s, 2H, β-CH_2); 5.87 (t, 2H, α-CH_2); 6.56 – 7.45 (m, 4H, C_6H_4); 7.93 (d, 1H, H^4, J 7.0); 8.60 (d, 1H, H^3, J 7.0); 9.58 (s, 1H, H^1)	6.56 – 7.45 (m, H arom.)
VId	2.88 d	2.82 d	3.72 s	3.81 (s, 2H, CH_2); 7.21 – 7.39 (m, 5H, C_6H_5)	3.61 (s, 3H, CH_3)	6.97 – 7.20 (m, H arom.)
VIe	2.86 t	2.73 t	3.78 s	3.78 (s, 2H, CH_3); 7.17 – 7.29 (m, 5H, C_6H_5)	5.21 (s, 2H, CH_2); 7.31 – 7.41 (m, 5H, C_6H_5)	6.98 – 7.09 (m, H arom.)
VIf	2.87 t	2.84 t	3.81 s	3.77 (s, 2H, CH_2); 7.29 – 7.45 (m, 5H, C_6H_5)	2.96 (q, 2H, β-CH_2); 3.81 (s, 2H, α-CH_2)	7.07 – 7.21 (m, H arom.)

γ-Carboline (I). A mixture of 6.8 g (34.7 mmole) 1-phenyl-1,2,3-triazolo[4, 5-c]pyridine [9] and 25.0 g paraffin was heated for 0.5 h at 320°C, after which the temperature was raised to 350°C and the heating was continued for 10 min. Then the reaction mass was cooled and washed with petroleum ether. The residue was dissolved in a 2 N aqueous hydrochloric acid solution, heated with activated charcoal, and neutralized with a 25% aqueous ammonia solution. The precipitated light-grey crystals were separated by filtration and dried to obtain 5.8 g (99%) of γ-carboline (I); m.p., 223 – 225°C (reported m.p., 225°C [9]).

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