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SYNTHESIS AND TRANSFORMATIONS OF 2,2-DIMETHYL-4-CHLOROMETHYL-1,2,3,4-TETRAHYDRO-γ-CARBOLINE

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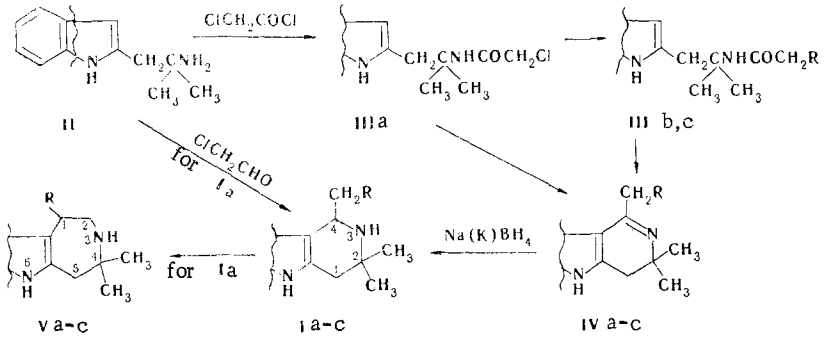
The synthesis of 2,2-dimethyl-4-chloromethyl-1,2-dihydro- and -1,2,3,4-tetrahydro-γ-carbolines was developed, and it is shown that the latter undergo rearrangement processes to give 4,4-dimethyl-, 1-piperidino-4,4-dimethyl-, and 1-morpholino-4,4-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles, respectively, under the influence of nucleophilic reagents, viz., sodium borohydride, piperidine, and morpholine.

Compounds that contain a 1-amino-2-chloroethane fragment may undergo various rearrangement processes [1-7] leading in a number of cases to interesting reaction products under the influence of nucleophilic reagents. For example, the first representative of tranquilizers of the benzo-1,4-diazepine series, viz., chlorodiazepoxide (Librium), was synthesized from 2-chloromethyl-4-phenyl-6-chloro-3-oxide [sic] by reaction with methylamine [6], while 1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles were obtained by reduction of 1-chloromethyl-1,2,3,4-tetrahydro-β-carbolines with sodium borohydride [7].

In this connection we developed the synthesis of 2,2-dimethyl-4-chloromethyl-1,2,3,4-tetrahydro-γ-carboline (Ia) on the basis of the quite accessible 2-(2-aminoisobutyl)indole (II) [8] and studied some transformations of chloride Ia. Compound Ia was obtained via two methods: 1) via the Pictet—Spengler reaction from chloroacetaldehyde and isotryptamine derivative II; 2) by conversion of II to its chloroacetyl derivative Bischler—Napieralski cyclization of amide IIIa to 2,2-dimethyl-4-chloromethyl-1,2-dihydro-γ-carboline (IVa), and careful reduction of the latter with sodium borohydride. Chloride Ia is unstable in the base form, and it was therefore isolated and characterized in the form of the hydrochloride.

The reaction of chloride Ia with sodium borohydride concludes with the formation of 4,4-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-e]indole (Va). The isomeric product of "normal" reductive dechlorination, viz., 2,2,4-trimethyl-1,2,3,4-tetrahydro-γ-carboline [8], could not be detected in the reaction mixture.



I, IV a R = Cl; V a R = H; I, III-V b R = piperidino; c R = morpholino

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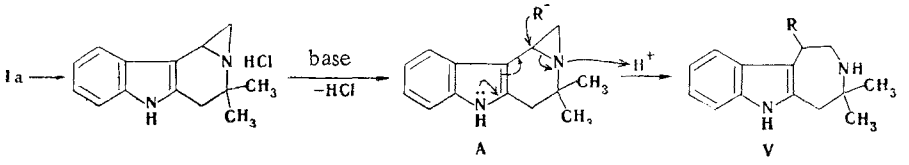
Compound Va is also obtained by the rather vigorous reaction of chloromethyldihydrocarboline IVa with sodium borohydride. If chloride Ia is treated with piperidine or morpholine, 1-piperidino- or 1-morpholinohexahydroazepinoindole (Vb or Vc) is formed as a result of a rearrangement process and replacement of the chlorine atom by an amino group. In order to confirm their structure we synthesized the isomeric 2,2-dimethyl-4-piperidino(or morpholino)methyl-1,2,3,4-tetrahydro-γ-carbolines (Ib, c), i.e., the possible products of "normal" replacement of the chlorine atom in chloride Ia by an amino group. For this, chloride IIIa was converted to amino amides IIIb, c, which were then cyclized to dihydrocarbolines IVb, c; reduction of IVb, c with sodium borohydride led to Ib, c.

The following mechanism of formation of V by the action of nucleophilic reagents on chloride Ia can be proposed:



When sodium borohydride is used, the nucleophile is the hydride ion, and this corresponds to a reduction reaction. It is apparent from the scheme that the C_3—C_4 bond (in accordance with the numbering in the carboline system), being the most polarized bond in the aziridine fragment of the intermediate (A), undergoes cleavage under the influence of a nucleophilic particle.

Thus the synthesis of chloromethyl derivative Ia and a study of its properties make it possible to obtain new types of compounds with azepinoindole structures.

In view of the fact that among derivatives of γ-carbolines and azepinoindoles one finds substances with pronounced physiological activity, compounds of the I, IV, and V type were studied by standard methods (20-50 mg/kg in mice) of screening of psychotropic substances. Compounds IVa and Vb, c depress the orientational-exploratory behavior of animals, affect phenamine stereotypy, and potentiate the convulsive effect of picrotoxin; the greatest activity is displayed by IVa (LD_{50} 75 mg/kg), which also gives rise to a weak analgesic effect and disrupts the coordination of movements in animals but does not have cataleptogenic activity.

EXPERIMENTAL

The PMR spectra of solutions of the compounds in $CDCl_3$ or d_5-pyridine were recorded with Varian T-60 and Varian HA-100D (in the case of Vb) spectrometers. The individuality of the substances obtained was monitored by means of thin-layer chromatography (TLC) on activity IV Al_2O_3 with elution with chloroform–ether.

2-(2-Chloroacetamidoisobutyl)indole (IIIa). A 6-g (53 mmole) sample of chloroacetyl chloride was added dropwise with cooling and stirring to a solution of 5 g (26 mmole) of amine II in 100 ml of benzene in the presence of 2.5 g of sodium hydroxide in 10 ml of water and the mixture was stirred for another hour at ~20°C. The benzene layer was separated, and the solvent was removed by distillation to give 6.3 g of chloroamide IIIa.

2-(2-Piperidino- and -morpholinoacetamidoisobutyl)indoles (IIIb, c). A mixture of 6 mmole of amide IIIa and 19 mmole of piperidine or morpholine in 24 ml of absolute benzene was refluxed for 1-2 h, after which the precipitated piperidine or morpholine hydrochloride was removed by filtration of the hot mixture. Amino amides IIIb, c were isolated from the filtrate by cooling.

2,2-Dimethyl-4-chloromethyl-1,2-dihydro-γ-carboline (IVa) Hydrochloride. A) An 18-g (0.16 mole) sample of chloroacetyl chloride was added dropwise to a heated solution of 10 g (53 mmole) of amine II in 175 ml of benzene in the presence of 5 g of sodium hydroxide in 10 ml of water (the reaction mixture became warmer), and the mixture was maintained at ~20°C for 1 h. The precipitated substance was removed by filtration and dissolved in alcohol, and a solution of hydrogen chloride in alcohol was added to precipitate 11.6 g of the hydrochloride of carbinol IVa.

B) A 0.25-ml sample of a 21% solution of hydrogen chloride in absolute alcohol was added to a solution of 0.2 g (0.75 mmole) of IIIa in 5 ml of absolute benzene. After 15 min, 0.1 g of the precipitated hydrochloride of IVa was separated.

TABLE 1. Characteristics of the Synthesized Compounds (I, III-V)

Compound	mp,[a] °C	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	Cl	N		C	H	Cl	N	
Ia·HCl	211 (dec.)	59,1	6,3	24,6	9,7	$C_{14}H_{18}Cl_2N_2$	58,9	6,3	24,8	9,8	90[b]
Ib	198—199	76,4	9,1		14,2	$C_{19}H_{27}N_3$[c]	76,5	9,2		14,1	74
Ib·2HCl	182—183			17,5	10,4	$C_{19}H_{29}Cl_2N_3$			17,8	10,7	
Ic	210—211,5	72,3	8,4		14,0	$C_{18}H_{25}N_3O$[d]	72,2	8,4		14,0	86
Ic·2HCl	181—182			18,3	10,7	$C_{18}H_{27}ClN_3O$			18,2	10,7	
IIIa	116,5—118	63,5	6,4	13,3	10,6	$C_{14}H_{17}ClN_2O$	63,5	6,4	13,4	10,6	90
IIIb	162—163	72,6	8,7		13,7	$C_{19}H_{27}N_3O$	72,8	8,7		13,5	100
IIIb·HCl	118—120			9,9		$C_{19}H_{28}ClN_3O$			10,1		
IIIc	189—191	68,8	8,0		13,1	$C_{18}H_{25}N_3O_2$	68,2	7,5		12,6	78
IIIc·HCl	105—106			9,5		$C_{18}H_{26}ClN_3O_2$			9,6		
IVa·HCl	>300	59,5	5,6	24,8	9,8	$C_{14}H_{16}Cl_2N_2$	59,4	5,7	25,0	9,8	77[e]
IVb	78—79	75,2	8,3		14,1	$C_{19}H_{25}N_3 \cdot 1/2\,H_2O$	75,0	8,6		13,8	95
IVb·2HCl	215—216			19,3	11,1	$C_{19}H_{27}Cl_2N_3$			19,3	11,4	100
IVc	210—211,5	72,3	8,4		14,1	$C_{18}H_{25}N_3O$	72,2	8,4		14,0	
IVc·2HCl	181—182			18,3	10,7	$C_{18}H_{27}Cl_2N_3O$			18,2	10,7	
Va	126—128	78,6	8,4		12,8	$C_{14}H_{18}N_2$[f]	78,4	8,4		13,0	
Va·HCl	263—264			14,1		$C_{14}H_{19}ClN_2$			14,1		24[g]
Vb	131—132	76,6	9,1		14,2	$C_{19}H_{27}N_3$[c]	76,5	9,1		14,1	70
Vb·2HCl	167—168			19,0	11,4	$C_{19}H_{29}Cl_2N_3$			19,1	11,3	
Vc	146—148	72,3	8,6		14,0	$C_{18}H_{25}N_3O$[d]	72,2	8,4		14,0	87
Vc·2HCl	157—158			17,9		$C_{18}H_{27}Cl_2N_3O$			18,1		

[a]The compounds were recrystallized: Ib, c, IIIb, c, IVb, c, and Vb, c from benzene, IIIa from heptane, Va from heptane–benzene, the hydrochlorides of Ia, c, IVb, c, and Va, b, c from alcohol, and the hydrochloride of IVa from alcohol–benzene. [b]The yield was 63% by method B. [c]M 297.43 (297 by mass spectrometry). [d]M 299.42 (299 by mass spectrometry). [e]The yield was 50% by method B. [f]M 214.30 (214 by mass spectrometry). [g]The yield was 39% by method B.

2-2-Dimethyl-4-piperidino- and -morpholinomethyl-1,2-dihydro-γ-carboline (IVb, c) Dihydrochlorides. A solution of 1.6 mmole of the corresponding amino amide IIIb, c in 15 ml of a 30% solution of hydrogen chloride in alcohol and 15 ml of absolute benzene was refluxed for 1 h, after which the benzene layer was separated, and the precipitate was triturated with absolute ether to give the crystalline hydrochlorides of IVb, c.

2,2-Dimethyl-4-chloromethyl-1,2,3,4-tetrahydro-γ-carboline (Ia) Hydrochloride. A) A solution of 0.3 g (1.1 mole) of chloride IVa and 0.1 g (2.6 mmole) of sodium borohydride in 7 ml of alcohol was stirred at ~20°C for 1 h, after 20 ml of water was added, and the precipitate was removed by filtration and dissolved in ether. The ether solution was dried with magnesium sulfate and treated with a solution of hydrogen chloride in ether to precipitate 0.3 g of the hydrochloride of Ia.

B) A mixture of 5 g (22 mmole) of amine II and 1.8 g (26 mmole) of chloroacetaldehyde in 125 ml of an acetate buffer with pH 4.7 was allowed to stand at 20°C for 3 days, after which it was made alkaline with potassium carbonate and extracted with ether. The ether solution was dried with magnesium sulfate and treated with a solution of hydrogen chloride in ether to precipitate 4.6 g of the hydrochloride of Ia.

2,2-Dimethyl-4-piperidino- and morpholinomethyl-1,2,3,4-tetrahydro-γ-carbolines (Ib, c). A 0.2-g (3.7 mmole) sample of potassium borohydride was added in portions in the course of an hour to a solution of 1.7 mmole of the corresponding dihydrocarboline IVb, c in 10 ml of alcohol and 2.5 ml of water, and the mixture was then diluted with water, made alkaline with potassium carbonate, and extracted with ether. The ether solution was dried with magnesium sulfate and evaporated to give Ib, c.

4,4-Dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (Va) Hydrochloride. A) A suspension of 6.8 g (23.8 mmole) of the hydrochloride of Ia in 125 ml of diglyme was added to 8 g (0.21 mole) of sodium borohydride in 100 ml of diglyme at 50°C, and the mixture was heated at 80°C for 30 h. The diglyme was removed by vacuum distillation, and the residue was treated with water. The aqueous mixture was made alkaline with potassium carbonate and extracted with ether. The usual workup gave 1.2 g of the hydrochloride of Va.

B) A 5-g (17.6 mmole) sample of the hydrochloride of IVa in 115 ml of diglyme was added to 5.7 g (0.15 mole) of sodium borohydride in 76 ml of diglyme at 50°C, and the mixture was heated at 80°C for 18 h. It was then worked up as described above to give 1.7 g of the hydrochloride of Va, which was identical to the sample synthesized by method A.

1-Piperidino-4,4-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (Vb). A mixture of 1 g (3.5 mmole) of the hydrochloride of Ia and 3.4 g of piperidine in 25 ml of absolute benzene was refluxed for 21 h, after which the benzene solution was washed with water and dried with magnesium sulfate, and the solvent was removed by vacuum distillation to give 0.6 g of Vb.

1-Morpholino-4,4-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indole (Vc). A mixture of 2.2 g (7.7 mmole) of the hydrochloride of Ia and 8 g of morpholine in 60 ml of benzene was refluxed for 17 h, after which Vc was obtained as in the preparation of Vb.

Data for all of the substances obtained are presented in Table 1 (the bases were obtained from the hydrochlorides or the hydrochlorides were obtained from the bases by the usual methods).

PMR spectra, ppm: Ia (base), 1.1 and 1.3 [two s, 6H, 3-CH_3)$_2$], 1.8 (s, 3-H), 2.5 (center of two doublets of an AB system, 1-H_2, ^2J = 16 Hz), 3.8 (doublet of doublets of one of the 4-CH_2Cl protons, ^2J = 12 Hz, $^3J_2$ = 8 Hz), 4.1-4.6 (unresolved signals of the 4-H and one of the 4-CH_2Cl protons), and 8.1 (9-H); Ib, 1.1 and 1.3 [two s, 6H, 2-$(CH_3)_2$], 1.5 and 2.5 (two groups of signals of the protons of the piperidine ring), 2.2-3.4 (unresolved signals of 1-H_2 and 4-CH_2Cl), 4.4 (m, 4-H), and 8.9 (9-H); Ic, 1.1 and 1.3 [two s, 2-$(CH_3)_2$], 2.5 and 3.7 (two groups of signals of the protons of the morpholine ring), 4.3 (m, 4-H), and 8.8 (9-H); IVa (base), 1.4 [s, 2-$(CH_3)_2$], 2.8 (s, 1-H_2), 4.5 (s, 4-CH_2), and 8.2 (9-H); IVb, 1.2 [s, 2-$(CH_3)_2$], 1.5 and 2.4 (piperidine ring), 2.7 (s, 1-H_2), 3.6 (s, 4-CH_2), 8.4 (9-H); Va, 1.1 [s, 4-$(CH_3)_2$], 1.5 (3-H, vanishes upon deuteration), 2.8 (s, 5-H_2), 2.7-3.2 (1-H_2, 2-H_2), 7.8 (6-H, vanishes upon deuteration); Vb, 0.9 and 1.1 [two s, 4-$(CH_3)_2$], 1.3 and 2.45 (piperidine ring), 2.63 (d, 5-H, ^2J = 15 Hz), and 3.1 (q, 2-H, ^2J = 15 Hz, $^3J_2$ = 3 Hz), 3.3 (d, 5-H', ^2J = 15 Hz), 3.33 (q, 2-H', ^2J = 15 Hz, $^3J_2$ = 5.5 Hz), 3.56 (q, 1-H, ^3J = 5.5 Hz, $^3J_2$ = 3 Hz), and 3.7 (broad signal, 3-H + H_2O in the solvent; the chemical shift changes as the temperature is raised).

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