REDUCTION OF 1,2,3,4-TETRAHYDRO-γ-CARBOLINES WITH ALKALI METAL BOROHYDRIDES IN TRIFLUOROACETIC ACID*

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A preparative method for the synthesis of 9-(2,2,2-trifluoroethyl)-1,2,3,4,4a,9a-hexahydro-γ-carbolines by the action of alkali metal borohydrides in trifluoroacetic acid on 1,2,3,4-tetrahydro-γ-carbolines was developed. The indicated trifluoroethyl derivatives can also be obtained by reaction of the same reagents with 1,2,3,4,4a,9a-hexahydro-γ-carbolines, which are intermediates in the overall reduction—trifluoroethylation process.

The use of $NaBH_4$ in the presence of carboxylic acids for the reduction of compounds with an indole structure leads to the formation of 1-alkylindolines. The corresponding indolines are also formed on passing to CF_3COOH, but alkylation of the nitrogen atom either does not occur or takes place to only a small extent (up to ~7%) [2].

We have shown that the reduction of 1,2,3,4-tetrahydro-γ-carbolines (I-IX) with KBH_4 (or $NaBH_4$) in CF_3COOH may lead to both the corresponding 1,2,3,4,4a,9a-hexahydro-γ-carbolines (X-XVI) and products of trifluoroethylation of the indole nitrogen atom (XVII-XXIII), depending on the molar ratio of the components. Hexahydrocarbolines X-XVI can be obtained in rather pure form in up to 85% yields if the course of the reaction is monitored by thin-layer chromatography (TLC) and gas–liquid chromatography (GLC) and the process is stopped at the step involving the reduction of the double bond of the indole system. Compounds X-XIV are converted to N-trifluoroethylhexahydrocarbolines by the action of the indicated reagents; this was demonstrated in the case of alkylation of hexahydrocarboline X to N-trifluoroethyl derivative XVII.

It should be noted that the use of the KBH_4—CF_3COOH system is particularly valuable in the case of the reduction of tetrahydrocarbolines with polyalkylated piperidine rings (of the VI, VII, and XXIV type), since the literature does not contain other methods for their conversion to the corresponding hexahydro derivatives: The action of zinc in hydrochloric acid is accompanied by destruction of the piperidine ring [3].

The UV spectra of ordinary indolines and X-XVI are similar to one another. The IR spectrum of X contains stretching vibrations of an NH group (3400 cm^{-1}), but these bands are absent in the spectrum of XVII. A multiplet signal of the 9a-H proton with a chemical shift of ~3.7 ppm appears in the PMR spectrum of X (or XI); signals of protons of an NCH_2CF_3 group in the form of quartets with J ~ 10 Hz are observed in the PMR spectra of XVII, XIX, and XX at 3.5 ppm (as a consequence of spin–spin coupling with three magnetically equivalent ^{19}F nuclei with a spin of 1/2), while multiplets of 9a-H protons are observed at ~3.3 ppm, and the number of aromatic protons does not change during the reaction. The molecular weights of XVII, XVIII, and XX were determined by mass spectroscopy (M^+ 284, 304, and 288, respectively).

An analysis of the data obtained by TLC and GLC and from the PMR spectra makes it possible to conclude that the hexahydro-γ-carbolines formed in the reaction are configurationally homogeneous and evidently have cis-fused rings; this is confirmed by the identical character of X and a sample obtained by reduction of tetrahydrocarboline I with zinc and hydrochloric acid [4]. It follows from this that the stereochemical specificity of the reduction of

*See [1] for a preliminary communication.

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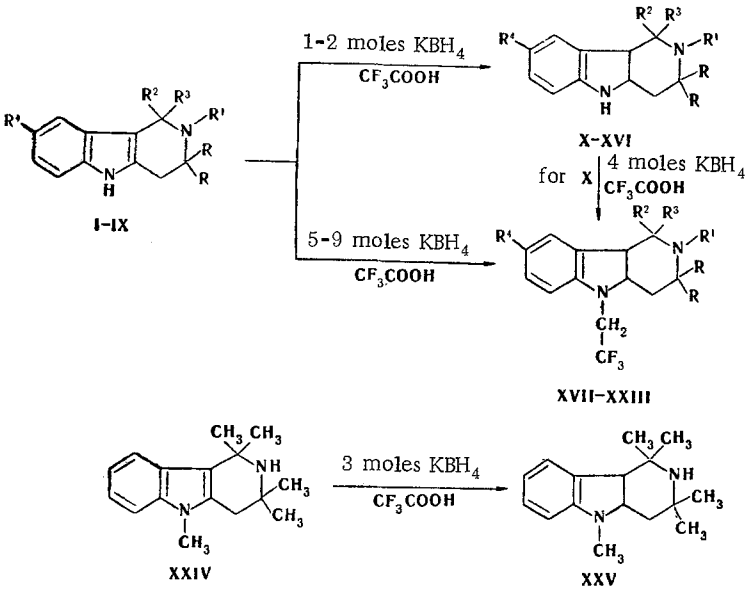
1,2,3,4-tetrahydro-γ-carbolines with alkali metal borohydrides in CF_3COOH differs from that observed in the reduction with diborane, in which trans-1,2,3,4,4a,9a-hexahydro-γ-carbolines are formed [5].



I, X, XVII $R=R^2=R^3=H$, $R^1=R^4=CH_3$; II, XI, XVIII $R=R^2=R^3=H$, $R^1=CH_3$, $R^4=Cl$; III, XII, XIX $R=R^2=R^3=H$, $R^1=CH_3$, $R^4=Br$; IV, XX $R=R^2=R^3=H$, $R^1=CH_3$, $R^4=F$; V, XXI $R=R^2=R^3=H$, $R^1=CH_3$, $R^4=COOC_2H_5$; VI, XIII, XXII $R=R^2=R^3=CH_3$, $R^1=R^4=H$; VII, XIV, XXIII $R=R^2=R^3=R^4=CH_3$, $R^1=H$; VIII, XV $R=CH_3$, $R^1=R^2=R^4=H$, $R^3=C_6H_5$; IX, XVI $R=CH_3$, $R^1=R^2=R^3=R^4=H$

Thus we have developed a preparative method for the synthesis of the previously unknown 9-(2,2,2-trifluoroethyl)-1,2,3,4,4a,9a-hexahydro-γ-carbolines by the action of alkali metal borohydrides in trifluoroacetic acid on 1,2,3,4-tetrahydro- or 1,2,3,4,4a,9a-hexahydro-γ-carbolines. Compounds of the XVII-XXIII type may serve as starting compounds for the preparation of various γ-carboline derivatives.

EXPERIMENTAL

The UV spectra of solutions of the compounds in alcohol (c 10^{-4}-10^{-5} M, d 1 cm) were recorded with a Perkin-Elmer 402 spectrophotometer. The IR spectra of solutions in chloroform (c 0.1 M, d 0.17) were recorded with a Perkin-Elmer 457 spectrometer. The PMR spectra were recorded with a Varian T-60 spectrometer. Gas-chromatographic analysis was carried out with a Tsvet chromatograph; the liquid phase was SE-30, the length of the column was 30 m, the carrier gas was nitrogen, and the temperature was 180°C. The mass spectra were obtained with an MKh-1303 mass spectrometer with a system for direct introduction of the samples into the ion source at an ionizing voltage of 50 or 30 eV (the ionization-chamber temperature was 150°C).

2,2-R_2-3-R^1-4-R^2-4-R^3-6-R^4-1,2,3,4,4a,9a-hexahydro-γ-carbolines (X-XVI, XXV). A 1.1-2.5-mmole sample of KBH_4 was added in small portions to 1 mmole of tetrahydrocarboline II (one can also use its hydrochloride) in 25 ml of CF_3COOH, and the mixture was then poured into ice water. The aqueous mixture was made alkaline with cooling with 50% KOH solution, 75 ml of ether was added, and the mixture was stirred for 15 min. The ether solution was separated, and the aqueous solution was extracted with ether. The combined organic solution was washed with water, dried with $MgSO_4$, and evaporated. The residue was dissolved in chloroform, and the dihydrochloride of XI was isolated by the addition of an alcohol solution of hydrogen chloride.

Hexahydrocarbolines X, XII-XVI, and XXV were similarly obtained from bases I and III and the hydrochlorides of VI-IX and XXIV.

Data for X-XVI and XXV are given in Table 1.

2,2-R_2-3-R^1-4-R^2-4-R^3-6-R^4-9-(2,2,2-trifluoroethyl)-1,2,3,4,4a,9a-hexahydro-γ-carbolines (XVII-XXIII). An 84-mmole sample of KBH_4 was added in small portions to 12.3 mmole of tetrahydrocarboline IV (one can also use its hydrochloride) in 55 ml of CF_3COOH, after which the

TABLE 1. 2,2-R_2-3-R^1-4-R^2-4-R^3-6-R^4-1,2,3,4,4a,9a-hexahydro-γ-carbolines (X-XVI, XXV)

Compound	mp, °C	Found, %				Empirical formula	Calculated, %				Yield, %
		C	H	Cl	N		C	H	Cl	N	
X·2HCl	274—276 (dec.)[a]										80
XI·2HCl	245—246[a]	48,7	5,8	35,7	9,4	$C_{12}H_{17}Cl_3N_2$	48,7	5,8	36,0	9,5	60
XII·2HCl	229—231[a]			44,5[b]	8,4	$C_{12}H_{17}BrCl_2N_2$			44,3[b]	8,2	69
XII	81—82[c]	54,2	5,7		10,5	$C_{12}H_{15}BrN_2$	53,9	5,6		10,5	
XIII·2HCl	242—244 [6][d]										
XIV·2HCl	242—243[e]	60,3	8,4	22,4	8,8	$C_{16}H_{26}Cl_2N_2$	60,5	8,3	22,3	8,8	66
XIV	66—67,5[f]	78,5	9,9		11,6	$C_{16}H_{24}N_2$	78,6	9,9		11,5	
XV·2HCl	246—247[g]			20,0	8,1	$C_{19}H_{24}Cl_2N_2$			20,2	8,0	86
XV	101—102[h]	81,8	8,0		10,1	$C_{19}H_{22}N_2$	81,9	7,9		10,0	
XVI	225—226 [3][g]										
XXV	277—278 [7][e]										

[a]From alcohol—water. [b]Br + Cl. [c]From hexane. [d]From alcohol. [e]From alcohol—methanol. [f]From petroleum ether; bp 134-135°C (1.5 mm). [g]From methanol. [h]From petroleum ether.

TABLE 2. 2,2-R_2-3-R^1-4-R^2-4-R^3-6-R^4-9(2,2,2-trifluoroethyl)-1,2,3,4,4a,9a-hexahydro-γ-carbolines (XVII-XXIII)

Compound	mp, °C	Found, %			Empirical formula	Calculated, %			Yield, %
		Cl	F	N		Cl	F	N	
XVII	84—85[a]		20,2	10,2	$C_{15}H_{19}F_3N_2$		20,0	9,9	89
XVII·HCl	225—227[b]	11,0	17,8	9,0	$C_{15}H_{20}ClF_3N_2$	11,0	17,8	8,7	
XVIII	94—96[c]	11,7	19,0	9,1	$C_{14}H_{16}ClF_3N_2$	11,6	18,7	9,2	90
XVIII·HCl	234—236[b]	20,9	16,5	8,1	$C_{14}H_{17}Cl_2F_3N_2$	20,8	16,7	8,2	
XIX	84—85[c]		16,4	8,1	$C_{14}H_{16}BrF_3N_2$[d]		16,3	8,0	89
XIX·HCl	214—216[b]	29,3[e]	14,4	7,1	$C_{14}H_{17}BrClF_3N_2$	29,9[e]	14,8	7,3	
XX	52—53,5[c]		25,9	9,8	$C_{14}H_{16}F_4N_2$		26,3	9,8	89
XX·HCl	230—232[b]	10,9	23,2	8,6	$C_{14}H_{17}ClF_4N_2$	10,9	23,4	8,6	
XXI	94,5—96[c]		16,5	8,1	$C_{17}H_{21}F_3N_2O_2$		16,6	8,2	98
XXI·HCl	223—225[f]	9,3	14,8	7,4	$C_{17}H_{22}ClF_3N_2O_2$	9,4	15,0	7,3	
XXII·HCl	256—257[g]	9,1		7,3	$C_{17}H_{24}ClF_3N_2$	9,4		7,4	73
XXIII·HCl	265—266[h]	10,0		7,8	$C_{18}H_{26}ClF_3N_2$	9,8		7,7	39

[a]From petroleum ether. [b]From isopropyl alcohol. [c]From hexane. [d]Found: Br 23.0%. Calculated: Br 22.9%. [e]Br + Cl. [f]From butanol. [g]From water. [h]From alcohol.

mixture was poured into ice water. The aqueous mixture was made alkaline with cooling with 50% KOH solution and extracted with ether. The ether solution was washed with 5% KOH solution and water, dried with $MgSO_4$, and evaporated to give XX. Compounds XVII-XIX and XXI-XXIII were similarly synthesized.

Data for XVII-XXIII are given in Table 2.

Trifluoroethylation of 3,6-Dimethyl-1,2,3,4,4a,9a-hexahydro-γ-carboline (X). A 3.5-g (69 mmole) sample of KBH_4 was added to 3.3 g (16.3 mmole) of carboline X in 30 ml of CF_3COOH, and the mixture was worked up as indicated above to give 4.1 g (89%) of base XVII with mp 84-85°C (from petroleum ether); no melting-point depression was observed for a mixture with the sample obtained above.

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

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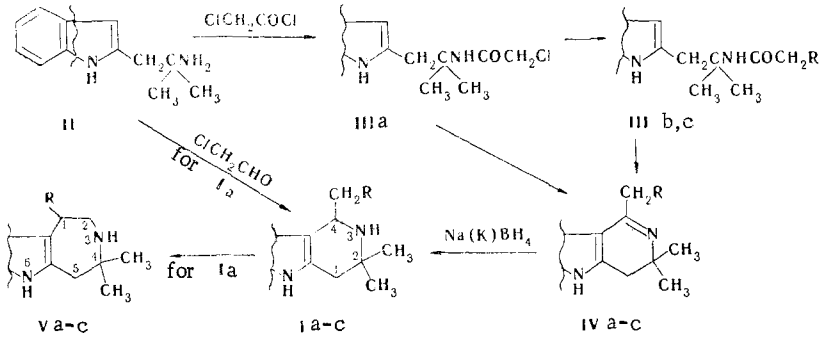
The synthesis of 2,2-dimethyl-4-chloromethyl-1,2-dihydro- and -1,2,3,4-tetrahydro-γ-carbolines was developed, and it is shown that the latter undergo rearrangement processes to give 4,4-dimethyl-, 1-piperidino-4,4-dimethyl-, and 1-morpholino-4,4-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-b]indoles, respectively, 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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