INDOLE DERIVATIVES

XXVI. A New Synthesis of 1,2,3,4-Tetrahydro-γ-carbolines and a Study of Their Reduction*

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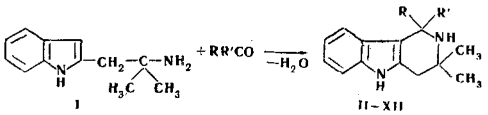
A new method for the synthesis of alkyl-substituted tetrahydro-γ-carbolines has been developed which involves the cyclodehydration of 2-(2'-aminoisobutyl)indole and 2-(2'aminoethyl)indole with various aldehydes and ketones. The reduction with amalgamated zinc in hydrochloric acid of 2, 2-dimethyl-, 4, 4-dimethyl-, and 2, 2-dimethyl-4-phenyl-1, 2, 3, 4-tetrahydro-γ-carbolines has been studied. The structure of the compounds obtained on reduction has been demonstrated.

In a study of the reduction of a whole series of polyalkylated tetrahydro-γ-carbolines, we have shown [1, 2] that it takes place anomalously with the cleavage of the piperidine ring and leads to indolines of the class of 2,3-dihydro-α-tryptamine, which are readily dehydrogenated to the corresponding α-tryptamines. Thanks to this reaction, 2-(2'-aminoisobutyl)indole (I) has become a fairly accessible compound. The widely used method of the cyclodehydration of 3-(2'-aminoethyl)indoles with aldehydes [3,4], leading to 1,2,3,4-tetrahydro-β-carbolines is well known. However, this method has not been applied to the 2-(2'-aminoalkyl)indoles, although this route appears extremely attractive for the preparation of 1,2,3,4-tetrahydro-γ-carbolines. In view of this, we have studied the reaction of aldehydes and ketones with 2-(2'-aminoisobutyl)indole and have obtained the corresponding 1,2,3,4-tetrahydro-γ-carbolines (II–XII). In the preparation of II–VI, the reaction between I and various aldehydes was carried out in an acetate buffer at pH 4.7 and at room temperature.



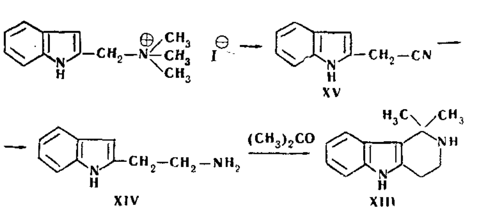
I

II–XII

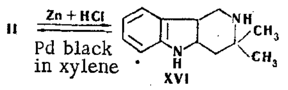
II – X R'=H
II R=H
III R=CH_3
IV R=C_2H_5
V R=C_6H_5
VI R=CH=CH—C_6H_5
VII R=C_6H_4OH-4
VIII R=$C_6H_4OCH_3$-4
IX R=$C_6H_3(O_2CH_2)$-3,4
X R=$C_6H_4N(CH_3)_2$-4
XI R=R'=CH_3
XII R=CH_3; R'=C_2H_5

The synthesis of compounds VII–XII was carried out by treating the hydrochloride of I at room temperature or at boiling point with the appropriate aldehydes and ketones in an aqueous alcoholic benzene medium in the presence of catalytic amounts of hydrochloric acid. In all cases the yields were high.

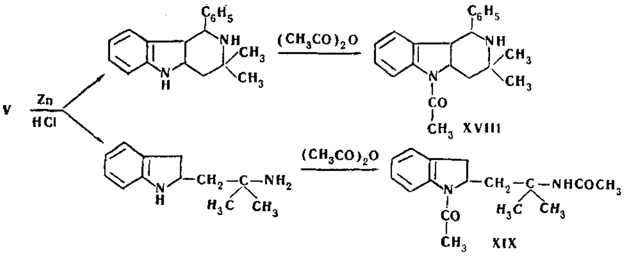
Continuing our investigation of the nature of the reduction of polyalkylated 1,2,3,4-tetrahydro-γ-carbolines as a function of their structure [1,2], we have followed the influence of substituents in positions 2 and 4 on this process. As examples of compounds with such substituents we took substances II, V, and 4,4-dimethyl-1,2,3,4-tetrahydro-γ-carboline (XIII). The latter was synthesized by condensing 2-(2'-aminoethyl)indole (XIV) with acetone. Compound XIV was synthesized by the method of Skinner and Parkhurst [5] from 2-(2'-dimethylaminomethyl)indole with some modifications: we obtained 2-cyanomethylindole (XV) in a yield of 50% by boiling the methiodide with potassium cyanide in dimethylformamide for 1 hr. In working by Skinner and Parkhurst's method [5] (18 hours' boiling in methanol) we were able to obtain the nitrile in a yield of only 15–20%. Compound XV was reduced with lithium aluminum hydride in ether to XIV.



On being boiled with acetone, the hydrochloride of the amine XIV gave the tetrahydro-γ-carboline XIII with a yield of 54%. The 1,2,3,4-tetrahydro-γ-carbolines II, XIII, and V were reduced with zinc dust in hydrochloric acid with the addition of mercuric chloride.



From a chromatographic study of the reaction mixture after the reduction of II it was found that it contained a single substance. Its structure as 2,2-dimethyl-1,2,3,4,4a,9a-hexahydro-γ-carboline (XVI) was by its dehydrogenation over Pd black in boiling xylene to compound II. The reduction of XIII under the same conditions gave as the sole reaction product 4,4-dimethyl-1,2,3,4,4a,9a-hexahydro-γ-carboline (XVII), the structure of which was shown by its dehydrogenation over Pd black to XIII.



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*For part XXV, see [2].

4-R-2,2-Dimethyl-1,2,3,4-tetrahydro-γ-carbolines

Compound	R	Mp, °C*	Empirical formula	Found, %			Calculated, %			Yield, % (method of synthesis)	Hydrochlorides					
											mp, °C	empirical formula	found, %		calculated, %	
				C	H	N	C	H	N				N	Cl	N	Cl
II*	H	193—194.5	$C_{13}H_{16}N_2$	77.90 77.87	8.24 8.17	14.23 14.22	77.95	8.05	13.99	90 (A)	204—205 from ethanol	$C_{13}H_{16}N_2 \cdot HCl$	11.44 11.47	14.70 14.70	11.83	14.97
III	CH_3	157—159	$C_{14}H_{18}N_2$	78.76 78.66	8.72 8.64	13.13 13.26	78.46	8.46	13.07	74 (B)						
IV	C_2H_5	124—125.5	$C_{15}H_{20}N_2$	79.13 78.90	8.75 8.87	12.25 12.18	78.90	8.83	12.27	92 (A)	221—222	$C_{15}H_{20}N_2 \cdot HCl$	10.65 10.41	13.08 13.25	10.54	13.39
V	C_6H_5	114—115	$C_{19}H_{20}N_2$	82.92 82.66	7.42 7.57	9.86 9.83	82.57	7.29	10.13	94 (B)	243—244	$C_{19}H_{20}N_2 \cdot HCl$		11.54 11.30		11.33
VI	$CH=CH$ C_6H_5	163—164	$C_{21}H_{22}N_2$	83.17 83.17	7.40 7.47	9.45 9.38	83.40	7.33	9.26	90 (B)	192—193	$C_{21}H_{22}N_2 \cdot HCl$	8.47	10.32 10.31	8.27	10.46

*Compound II was recrystallized from benzene and III-VI from a mixture of benzene and petroleum ether.

The reduction of 2,2-dimethyl-4-phenyl-1,2,3,4-tetrahydro-γ-carboline (V) gave an oil which, on chromatography in a thin layer of alumina, gave two spots. The oil was acetylated with acetic anhydride and the reaction product was chromatographed on alumina of activity grade ~4. Elution with benzene gave two substances, one of which corresponded by analysis to 9-acetyl-2,2-dimethyl-4-phenyl-1,2,3,4,4a,9a-hexahydro-γ-carboline (XVIII) and the second to 1-acetyl-2-(2'-acetylaminoisobutyl)indoline. The latter compound has the same R_f value as and gives no depression of the melting point with the 1-acetyl-2-(2'-acetylaminoisobutyl)indoline that we synthesized previously [1].

EXPERIMENTAL

2,2-Dimethyl-4-R-1,2,3,4-tetrahydro-γ-carbolines (II-VI). A) To a solution of 0.01 mole of the hydrochloride I in 75 ml of acetate buffer with pH 4.7 was added 0.01 mole of aldehyde, and the mixture was left at room temperature in the dark for a day, after which potassium carbonate solution was added and the precipitate was filtered off and recrystallized. B) The operations were similar to method A, but after a day the precipitate of hydrochloride was filtered off, dissolved in water, and treated with potassium carbonate to give the product in the form of the free base (table).

2,2-Dimethyl-4-(p-hydroxyphenyl)-1,2,3,4-tetrahydro-γ-carboline (VII). A solution of 1 g (4.4 mmole) of the hydrochloride of I and 0.65 g (5.3 mmole) of p-hydroxybenzaldehyde in 13 ml of ethanol containing one drop of concentrated HCl was boiled for 10 min the precipitate that deposited was filtered off. This gave 1 g of the hydrochloride of VII (70%), mp 226.5-227° C (from ethanol). Found, %: N 8.40, 8.53; Cl 10.60, 10.59. Calculated for $C_{19}H_{20}N_2O \cdot HCl$, %: N 8.52; Cl 10.78. Base, mp 218-219° C (from ethanol). Found, %: C 78.29, 78.10; H 6.92, 6.94; N 9.54, 9.31. Calculated for $C_{19}H_{20}N_2O$, %: C 78.04; H 6.89; N 9.58.

2,2-Dimethyl-4-(p-methoxyphenyl)-1,2,3,4-tetrahydro-γ-carboline (VIII). A solution of 1 g (4.4 mmole) of the hydrochloride of I and 0.72 g (5.3 mmole) of p-methoxybenzaldehyde in 13 ml of ethanol containing one drop of concentrated HCl was boiled for 6 hr. On cooling, a precipitate of the hydrochloride of VIII deposited, weight 1.56 g (100%), mp 197-198° C (from a mixture of ethanol and ether). Found, %: N 8.08, 8.01; Cl 10.57, 10.44. Calculated for $C_{20}H_{22}N_2O \cdot HCl$, %: N 8.17; Cl 10.34.

2,2-Dimethyl-4-(3',4'-methylenedioxyphenyl)-1,2,3,4-tetrahydro-γ-carboline (IX). A mixture of 1 g (4.4 mmole) of the hydrochloride of I, 0.71 g (4.7 mmole) of heliotropin, 13 ml of ethanol, 0.3 ml of water, one drop of concentrated HCl, and 5 ml of benzene was boiled, with the azeotropic distillation of the water. The substance that separated after cooling was filtered off, weight 1.35 g (80%), mp 217-218° C (from ethanol). Found, %: N 7.71, 7.84; Cl 9.90, 9.75. Calculated for $C_{20}H_{20}N_2O_2 \cdot HCl$, %: N 7.85; Cl 9.93.

2,2-Dimethyl-4-(p-dimethylaminophenyl)-1,2,3,4-tetrahydro-γ-carboline (X). A mixture of 1 g (4.4 mmole) of the hydrochloride of I, 0.79 g (5.3 mmole) of p-dimethylaminobenzaldehyde, 50 ml of ethanol, and one drop of concentrated HCl was left at room temperature for a week. Then it was poured into water and potassium carbonate was added, to give 1.3 g (80%) of a substance with mp 191-192° C (from benzene). Found, %: C 78.92, 79.02; H 7.97, 7.90; N 12.80, 12.79. Calculated for $C_{21}H_{25}N_3$, %: C 78.95; H 7.88; N 13.15. Dihydrochloride (hydrate) mp 196-197° C (from ethanol). Found, %: N 9.82, 9.98; Cl 17.38, 17.16. Calculated for $C_{21}H_{25}N_3 \cdot 2HCl \cdot H_2O$, %: N 10.24; Cl 17.28.

2,2,4,4-Tetramethyl-1,2,3,4-tetrahydro-γ-carboline (XI). To 0.5 g (2.2 mmole) of the hydrochloride of I in 5 ml of ethanol were added 3.96 g (0.068 mole) of acetone and one drop of concentrated HCl, and the mixture was boiled for 5 min, after which the precipitate that had deposited was filtered off. Weight 0.5 g (85%), mp 246-246.5° C (from ethanol). Base: mp 143-145° C, giving no depression with the substance obtained previously [6].

4-Ethyl-2,2,4-trimethyl-1,2,3,4-tetrahydro-γ-carboline (XII). To 0.5 g (2.2 mmole) of the hydrochloride of I in 5 ml of ethanol were added 3.96 g (0.055 mole) of ethyl methyl ketone and three drops of concentrated HCl, the mixture was boiled for 3 hours, and the precipitate that deposited was filtered off. Weight 0.61 g (100%), mp 227-228° C (from a mixture of ethanol and ether). Found, %: Cl 12.54. Calculated for $C_{16}H_{22}N_2 \cdot HCl$, %: 12.70. Base: mp 111-112° C (from n-heptane). Found, %: C 79.26, 79.23; H 9.14, 9.21; N 11.84. Calculated for $C_{16}H_{22}N_2$, %: C 79.28; H 9.15; N 11.56.

2-Cyanomethylindole (XV). A mixture of 65 g (0.2 mole) of 2-dimethylaminomethylindole methiodide [5] and 20 g of potassium cyanide in 360 ml of dimethylformamide was boiled under nitrogen for 50 min. The solution was cooled and poured into ice water and extracted with ether, and the extract was dried with magnesium sulfate. The ether was distilled off and the substance was crystallized from ether to give 16.2 g of product. By chromatography on a column of alumina with benzene elution, the mother liquor yielded another 2.2 g. Yield 18.4 g (57%), mp 96-98° C [5].

2-(2'-Aminoethyl)indole (XIV). With stirring, 4.4 g (0.028 mole) of XV in 70 ml of absolute ether was added to 4 g (0.1 mole) of lithium aluminum hydride in 160 ml of absolute ether. The reaction mixture was boiled for 3 hr and was left overnight. With cooling, it was decomposed with water and then with 10% caustic soda solution. It was extracted with ether, the extract was dried with magnesium sulfate, and the ether was distilled off to give 2 g (50%) of a product with mp 98–100° C (100–101° C).

4, 4-Dimethyl-1, 2, 3, 4-tetrahydro-γ-carboline (XIII). A mixture of 0.65 g (2.2 mmole) of the hydrochloride of **XIV**, 7 ml of ethanol, 5.6 g (0.095 mole) of acetone, and three drops of concentrated HCl was boiled for 3 hr and the precipitate of hydrochloride was filtered off to give 0.4 g (57%) of a substance with mp 257–258° C (from ethanol). Found, %: N 11.70, 11.65; Cl 15.14, 15.05. Calculated for $C_{13}H_{16}N_2 \cdot HCl$, %: N 11.83; Cl 14.97. Base, mp 170–171° C (from benzene). Found, %: N 13.96, 13.88. Calculated for $C_{13}H_{16}N_2$, %: N 13.98.

2, 2-Dimethyl-1, 2, 3, 4, 4a, 9a-hexahydro-γ-carboline (XVI). In 20 ml of ethanol in the presence of 0.02 g of mercuric chloride, 5 g (0.025 mole) of **II** was reduced with 36 g (0.55 g-atom) of zinc dust in 115 ml of concentrated HCl with boiling for 10 hr. The zinc dust was added in 6 g portions and the acid was added gradually. Then, with cooling and stirring, the reaction mixture was made strongly alkaline with 40% caustic soda. The oil that separated out was extracted with ether and the extract was dried with magnesium sulfate. After the ether had been distilled off, 3.4 g of an oily product was obtained which was chromatographed on a column of alumina of activity grade ~4 with elution by benzene. This yielded 0.4 g (8%) of a substance with mp 193–194° C, giving no depression of the melting point with the starting material, and 2.4 g (48%) of **XVI**, mp 68–70° C (from petroleum ether). Found, %: C 77.01, 77.15; H 9.08, 9.11; N 13.98, 14.05. Calculated for $C_{13}H_{18}N_2$, %: C 77.18; H 8.96; N 13.84. **Dihydrochloride,** mp 225–226° C (from methanol). Found, %: N 10.33, 10.14; Cl 25.79, 25.67. Calculated for $C_{13}H_{18}N_2 \cdot 2HCl$, %: N 10.18; Cl 25.76.

2, 2-Dimethyl-1, 2, 3, 4-tetrahydro-γ-carboline (II). 0.6 g (3 mmole) of **XVI** was boiled in xylene over Pd black for 2 hr; 0.3 g (50%) of **II**, mp 193–194° C, was obtained.

4, 4-Dimethyl-1, 2, 3, 4, 4a, 9a-hexahydro-γ-carboline (XVII). As described above, 2.6 g (0.013 mole) of **XIII** in 10 ml of water was reduced with 18 g of zinc dust and 60 ml of concentrated HCl in the presence of 0.01 g of mercuric chloride. From the ether was isolated 1.5 g (58%) of an oily product which crystallized on standing, mp 104–105.5° C (from n-heptane). Found, %: C 76.90, 76.93; H 9.00, 8.83; N 13.87, 13.93. Calculated for $C_{13}H_{18}N_2$, %: C 77.18; H 8.96; N 13.84. **Dihydrochloride,** mp 226–227° C (from ethanol). Found, %: C 56.45, 56.45; H 7.64, 7.56; N 10.41, 10.23. Calculated for $C_{13}H_{18}N_2 \cdot 2HCl$, %: C 56.72; H 7.32; N 10.18.

9-Acetyl-2, 2-dimethyl-4-phenyl-1, 2, 3, 4, 4a, 9a-hexahydro-γ-carboline (XVIII) and 1-acetyl-2-(2'-acetylaminoisobutyl)indoline (XIX). As described above, 8.9 g (0.032 mole) of V in 45 ml of ethanol was reduced with 35 g of zinc dust and 108 ml of concentrated HCl in the presence of 0.03 g of mercuric chloride. This yielded 3 g of an oily substance giving two spots on a thin-layer chromatogram. Three grams of this mixture was boiled in 10 ml of benzene and 5.4 ml of acetic anhydride for 1 hr, after which it was made alkaline with potassium carbonate and extracted with ether. The ether was distilled off and the residue was chromatographed on a column of alumina of activity grade 4, being eluted with benzene, to give 0.7 g (7%) of **XVIII**, mp 166–167° C (from a mixture of benzene and petroleum ether). Found, %: C 78.65, 78.93; H 7.51, 7.51; N 8.81, 9.03. Calculated for $C_{21}H_{24}N_2O$, %: C 78.71; H 7.54; N 8.74. Also obtained was 1.7 g (19%) of XIX, mp 142–143° C, giving no depression of the melting point with the substance obtained previously [1].

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