CARBOLINES.

VII.* 1-METHYL-4-HETARYLMETHYL-β-CARBOLINES

T. M. Efremova, K. I. Kuchkova,
and A. A. Semenov

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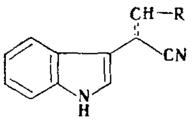
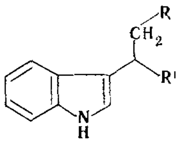
Unsaturated nitriles, which were reduced in two steps to tryptamines, were obtained by reaction of 3-indolylacetonitrile with heterocyclic aldehydes. Substituted β-carbolines were synthesized by cyclization of the acetyl derivatives of the tryptamines and subsequent photochemical dehydrogenation.

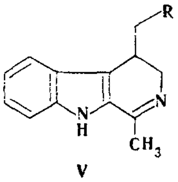
In a study of the relationship between the structure and physiological properties in a number of 4-substituted β-carbolines, we found it necessary to synthesize those derivatives of this heterocyclic system in which the substituent would contain a ring or branching one methylene group away from the carboline ring. In the present communication we describe a method for the solution of this synthetic problem as applied to arylmethyl- and hetarylmethyl-β-carbolines in which the key step is crotonic condensation of the appropriate aldehydes with 3-indolylacetonitrile. (This sort of reaction is known for 2-indolylacetonitrile [2,3].) The condensation proceeds by refluxing in methanol in the presence of triethylbenzylammonium methoxide with the formation of unsaturated cyano compounds (Ia-i). The double bond in these substances is resistant to the action of most reducing agents but adds hydrogen on treatment with sodium amalgam.



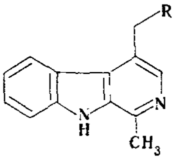
I



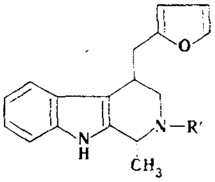
II–IV



V



VI



VII, VIII

II $R'=CN$; III $R'=CH_2NH_2$; IV $R'=CH_2NHCOCH_3$; VII $R'=H$; VIII $R'=COCH_3$

Saturated nitriles II were then reduced with lithium aluninium hydride (IIa,b, i) or Raney nickel with hydrazine hydrate [4] to give substituted tryptamines (III). They were acetylated and cyclized to dihydro-β-carbolines V by treatment with phos-

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*See [1] for the preceding communication.

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TABLE 1. 2-(3-Indolyl)-3-hetaryl-2-propenenitriles (I)

Compound	3-Hetaryl (or aryl)	mp, °C*	Reaction time	Empirical Formula	Found, %			Calc., %			Yield %
					C	H	N	C	H	N	
Ia	Phenyl	114—115	10	$C_{17}H_{12}N_2$	83,8	5,1	11,2	83,6	5,0	11,5	73
Ib	2-Pyridyl	158—160	2	$C_{16}H_{11}N_3$	78,0	4,8	17,0	78,4	4,5	17,1	47
Ic	3-Pyridyl	194—196	1	$C_{16}H_{11}N_3$	78,1	4,6	16,8	78,4	4,5	17,1	67
Id	4-Pyridyl	232—234	1	$C_{16}H_{11}N_3$	78,6	4,9	17,2	78,4	4,5	17,1	39
Ie	1-Methyl-2-imidazolyl	244—246	4	$C_{15}H_{12}N_4$	72,5	4,8	22,1	72,6	4,9	22,6	70
If	1-Benzyl-2-imidazolyl	274	6	$C_{21}H_{16}N_4$	77,9	5,0	17,5	77,8	5,0	17,3	85
Ig	2-Furyl	130—132	10	$C_{15}H_{10}N_2O$	76,9	4,3	12,0	76,9	4,3	12,0	68
Ih	1-Methyl-2-pyrryl	164—166	10	$C_{16}H_{13}N_3$	77,5	5,4	17,4	77,7	5,3	17,4	87
Ii	4-Methyl-2-thiazolyl	184—185	2	$C_{15}H_{11}N_3S$	68,1	4,4	15,8	67,9	4,2	15,8	33

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*Compounds Ia,G were crystallized from iso-$C_5H_{11}OH$, Ib was crystallized from ethylacetate, Ic,d,h,i were crystallized from CH_3OH, Ie was crystallized from DMFA + CH_3OH, and If crystallized from DMFA.

phorus pentachloride in nitrobenzene [5]. This method was used to obtain 3,4-dihydro-β-carbolines (Va-f,i). We were unable to cyclize amides IVg-h by this method. Furan derivative IIIg was then treated with acetaldehyde in formic acid, and an unstable tetrahydro-β-carboline (VII), which was characterized as acetyl derivative VIII, was obtained. Under similar conditions, pyrrole analog IIIh gave only resinification products.

When 3,4-dihydro-β-carboline Va is heated with palladium black in ethylene glycol, it is dehydrogenated to VIa. However, the remaining dihydro compounds could not be dehydrogenated in this way, probably because of poisoning of the catalyst by the reaction products. 1,4-Dimethyl-3,4-dihydro-β-carboline is dehydrogenated by the action of maganese dioxide in refluxing acetone, but this method could not be extended to dihydro-β-carbolines with heterocyclic substituents. Photochemical dehydrogenation [6] proved to be the most general and fully preparative method. Specifically, β-carbolines VI were formed when acid solutions of dihydrocarbolines V were irradiated with a mercury lamp in the presence of air oxygen. The synthesis proceeds well without purification of the intermediate II, III, and IV.

EXPERIMENTAL

The melting points were determined with a Köffler block and were not corrected. The UV spectra of alcohol solutions were recorded with a Specord UV-vis spectrophotometer. The IR spectra of mineral-oil suspensions were recorded with a UR-10 spectrometer. The IR and mass-spectral data confirm the proposed structures.

2-(3-Indolyl)-3-phenyl-2-propenenitrile (Ia). A 1-g (6.3 mmole) sample of 3-indolylacetonitrile and 0.7 g (6.3 mmole) of benzaldehyde were added to a solution of triethylbenzylammonium methoxide prepared from 0.15 g (6.5 mmole) of sodium and 1.48 g (6.5 mmole) of triethylbenzylammonium chloride in 22.5 ml of anhydrous methanol, and the mixture was refluxed for 10 h, after which it was poured into water. The aqueous mixture was extracted with water, and the extract was washed with water, dried with magnesium sulfate, and evaporated to dryness. The residue was crystallized from isoamyl alcohol.

The other unsaturated nitriles (I) were similarly obtained (Table 1).

2(3-Indolyl)-3-phenylpropionitrile (IIa). A 3.21-g sample of nitrile was dissolved in 64 ml of alcohol, and 3.2 sodium amalgam was added in several portions while monitoring the course of the reduction by thin-layer chromotography (TLC) on aluminum oxide [acetone—chloroform (1:9)]. After 5 h 40-50 g of the amalgam had been consumed,

TABLE 2. 2-(3-Indolyl)-3-hetarylpropionitriles (II)

Compound	3-Hetaryl (or aryl)	mp, °C*	Empirical formula	Found, %			Calc., %			Yield, %
				C	H	N	C	H	N	
IIa	Phenyl†	150—151	$C_{17}H_{14}N_2\cdot$ $\cdot C_6H_3O_7N_3$	57,9	3,7	14,9	58,1	3,6	14,9	100‡
IIb	2-Pyridyl	92	$C_{16}H_{13}N_3$	77,8	5,6	16,9	77,7	5,3	17,0	79
IIc	3-Pyridyl	136—138	$C_{16}H_{13}N_3$	77,4	5,4	16,8	77,7	5,3	17,0	69
IId	4-Pyridyl	142—144	$C_{16}H_{13}N_3$	77,5	5,6	16,9	77,7	5,3	17,0	78
IIe	1-Methyl-4-pyrazolyl	142	$C_{15}H_{14}N_4$	71,7	5,4	22,4	78,0	5,4	22,4	83

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*Compound IIa was crystallized from CH_3OH, IIb,d were crystallized from iso-C_3H_7OH, IIc was crystallized from $CH_3CO_2C_2H_5$, and IIe was crystallized from trichlorethylene.

†These are the data for the picrate.

‡ This is the yield of crude chromatographically-pure nitrile.

TABLE 3. Picrates of Amines III

Compound	Hetaryl (aryl)	mp, °C*	Empirical Formula	Found, %			Calc., %			Reduction method
				C	H	N	C	H	N	
IIIa	Phenyl	206—210	$C_{12}H_{18}N_2\cdot C_6H_3N_3O_7$	57,6	4,5	14,7	57,6	4,4	14,6	$LiAlH_4$
IIIb	2-Pyridyl	220—222	$C_{16}H_{17}N_3\cdot 2C_6H_3N_3O_7$	47,5	3,6	17,6	47,4	3,6	17,8	$Ni+N_2H_4$
IIIc	3-Pyridyl	203—205	$C_{16}H_{17}N_3\cdot 2C_6H_3N_3O_7$	47,4	3,4	17,6	47,4	3,3	17,8	$Ni+N_2H_4$
IIId	4-Pyridyl	140—141	$C_{16}H_{17}N_3\cdot 2C_6H_3N_3O_7$	47,7	3,3	18,0	47,4	3,3	17,8	$Ni+N_2H_4$
IIIe	1-Methyl-2-imidazolyl	194—195	$C_{15}H_{18}N_4\cdot 2C_6H_3N_3O_7$	45,5	3,3	20,0	45,5	3,4	19,7	$Ni+N_2H_4$
IIIf	1-Benzyl-2-imidazolyl	158—160	$C_{21}H_{22}N_4\cdot 2C_6H_3N_3O_7$	50,2	3,7	17,5	50,3	3,6	17,8	$Ni+N_2H_4$
IIIg	2-Furyl*	204—206	$C_{15}H_{16}N_2O\cdot C_6H_3N_3O_7$	53,7	4,1	15,0	53,8	4,1	14,9	$Ni+N_2H_4$
IIIi	4-Methyl-2-thiazolyl	105—107	$C_{15}H_{17}N_3S\cdot 2C_6H_3N_3O_7\cdot$ $\cdot CH_3OH$	44,4	3,6	16.6	44,2	3,6	16,6	$LiAlH_4$

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*The yield of amino after purification through the oxalate was 55%.

†The yield of the dipicrate of the amine was 28%.

the reaction mixture was separated from the mercury and poured into water, and the aqueous mixture was extracted with ether. The extract was dried with sodium sulfate and evaporated to dryness to give 3.4 g of IIa.

Nitriles IIa-e (Table 2) were similarly obtained.

Nitriles IIf-i, which are oily substances from which crystalline derivatives could not be obtained, were used for subsequent syntheses in crude form.

2-(3-Indolyl)-3-phenylpropanes (IIIa). A solution of 3.6 g (14.6 nmole) of nitrile IIa in 40 ml of ether was added with cooling to a stirred suspension of 2.9 g (78.6 mmole) of lithium aluminum hydride in 82 ml of anhydrous ether, and the mixture was refluxed for 3 h. The excess reducing agent was decomposed with ethyl acetate, and the mixture was treated with a solution of potassium sodium tartrate. The ether layer was separated and combined with the ether extracts from the aqueous layer. The combined extracts were dried and evaporated to give 3.5 g of an oily product that was characterized as the picrate.

2-(3-Indolyl)-3-(2-pyridyl)propane (IIIb). A total of 135 ml of 85% hydrazine hydrate was added in the course of 1.5 h to a refluxing solution of 11.1 g of nitrile IIb in 167 ml of isopropyl alcohol in the presence of 9 g of Raney nickel, after which the mixture was refluxed until the reaction was complete. The course of the reaction was monitored by TLC on aluminum oxide [chloroform—methanol (9:1)]. Where necessary, another 30-40 ml of hydrazine hydrate was added. At the end of the reaction the catalyst was separated, and the solution was vacuum evaporated to dryness. A chromatographically pure oily product, which was characterized as the picrate, was obtained

TABLE 4. Salts of Dihydrocarbolines V

Compound	Hetaryl (aryl)	Salt	mp, °C	Empirical formula	Found, %				Calculated, %				Yield, %
					C	H	N	Cl	C	H	N	Cl	
Va	Phenyl	Hydrochloride	204—206	$C_{19}H_{18}N_2 \cdot HCl$	73,0	6,0	8,9	11,4	73,4	6,2	9,0	11,4	54
Vb	2-Pyridyl	Dihydrochloride	161,5	$C_{18}H_{17}N_3 \cdot 2HCl$	62,3	5,7	11,9	20,2	62,1	5,5	12,1	20,4	18
Vc	3-Pyridyl	Dihydrochloride	141—143	$C_{18}H_{17}N_3 \cdot 2HCl \cdot H_2O$	59,2	5,9	11,5	19,3	59,0	5,8	11,5	19,4	46
Vd	4-Pyridyl	Dihydrochloride	181—182	$C_{18}H_{17}N_3 \cdot 2HCl$	61,8	5,9	11,8	20,1	62,1	5,5	12,1	20,4	50
Ve	1-Methyl-4-pyrazolyl	Dihydrochloride	126—127	—	—	—	—	—	—	—	—	—	65
		Perchlorate	228—229	$C_{17}H_{18}N_4 \cdot HClO_4$	54,2	5,2	14,7	9,8	53,9	5,1	14,8	9,4	—
Vf	1-Benzyl-2-imidazolyl	Perchlorate	227—229	—	—	—	—	—	—	—	—	—	14
		Dipicrate	148—150	$C_{23}H_{22}N_4 \cdot 2C_6H_3N_3O_7 \cdot H_2O$	50,7	3,7	16,9		50,6	3,6	16,9		—
Vi	4-Methyl-2-thiazolyl	Picrate	184—186	$C_{17}H_{17}N_3 \cdot C_6H_3N_3O_7$	52,2	4,0	16,0		52,7	3,8	16,0		33

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*Compounds Va,b,d were crystallized from C_2H_5OH, Vc,e were crystallized from iso-$C_5H_{11}OH$, and Ve,f,i were crystallized from CH_3OH.

in quantitative yields. The physical constants of the picrates of amines II are given in Table 3.

1-Methyl-4-benzyl-3,4-dihydro-β-carboline (Va). Amine IIIa was acetylated by treatment with excess acetic anhydride in **pyridine at** room temperature for 24 h, amorphous acetyl derivative IVa was obtained in quantitative yield. A solution of 2.65 g (9 mmole) of IVa in 27 ml of nitrobenzene was added in the course of 1 min at 60-65° to a stirred suspension of 5.7 g (27 mmole) of phosphorus pentachloride in 27 ml of nitrobenzene. The mixture was cooled rapidly and **shaken** with dilute hydrochloric acid and ether, and the precipitated crystals were separated. The ether layer was extracted repeatedly with hydrochloric acid, and the combined acid extracts were washed with ether and made alkaline with sodium hydroxide. The liberated base was converted to the ester, and the hydrochloride was precipitated by the addition of an ether solution of hydrogen chloride. The solvent was decanted from the resulting oily precipitate, and the latter was dried in a desiccator and crystallized from alcohol. The product was combined with the first portion of crystals.

The other 3,4-dihydro-β-carbolines (V), the physical constants of which are presented in Table 4, were similarly obtained.

1-Methyl-4-benzyl-β-carboline (VIa). A 1.32-g sample of hydrochloride Va and 0.65 g of palladium black were heated in 14 ml of ethylene glycol in a CO_2 atmosphere at 150° for 50 min. The hot reaction mixture was filtered, the catalyst was washed on the filter with hot water, and the wash waters were added to the filtrate. The latter was allowed to stand in the cold, after which the resulting crystals were separated and dried. An additional amount of hydrochloride VIa, which was combined with the first portion, was obtained by alkalization of the mother liquor, extraction with ether, and precipitation with an ether solution of hydrogen chloride. The overall yield of product with mp 350-352° (from methanol; in a sealed capillary) was 0.69 g (53%). Found: C 74.2; H 5.9; N 9.2; Cl 11.4%. $C_{19}H_{16}N_2 \cdot HCl$. Calculated: C 73.9; H 5.6; N 9.2; Cl 11.5%. UV spectrum, λ_{max} (log ε), nm: 208 (3.99), 253 (4.30), 303 (3.94), and 373 (3.57). The base had mp 241-242° and M^+ (mass spectrally) 272. $C_{19}H_{16}N_2$. Calculated: 272.

1-Methyl-4-(1-methyl-4-pyrazolylmethyl)-β-carboline (VIe). A solution of 0.25 g of dihydrochloride Ve in 250 ml of 10% HCl in a quartz vessel was irradiated with vigorous stirring with a low pressure PRK-7 mercury lamp for 2 h, after which it was made alkaline with solid sodium hydroxide and extracted with ether. The extract was dried with sodium sulfate, the solvent was removed by distillation to dryness, and the residue was crystallized from acetone to give 0.09 g (48%) of VIe with mp 218-219°. Found: C 73.6; H 6.1;

N 20.0%. $C_{17}H_{16}N_4$. Calculated: C 73.9; H 5.9; N 20.3%. UV spectrum, λ_{max} (log ε), nm: 217 (4.03), 236 (4.48), 244 (4.49), 252 (4.31) (inflection), 267 (3.51), 279 (3.68), 288 (4.02), 339 (3.61), and 353 (3.68).

A similar method was used to obtain 1-methyl-4-(2-pyridylmethyl)-βcarboline (VId) with mp 196-198° (from acetone) in 34% yield [Found: C 79.2; H 5.8; N 15.7%. $C_{18}H_{15}N_3$. Calculated: C 79.1; H 5.5; N 15.4%. UV spectrum, λ_{max} (log ε), nm: 212 (4.27), 237 (4.61), 243 (4.61), 252 (4.46) (inflection), 268 (3.98), 279 (3.90), 288 (4.14), 339 (3.15), and 353 (3.81)]; 1-methyl-4-(3-pyridylmethyl)-β-carboline (VIc) with mp 230° (from acetone) in 41% yield [Found: C 78.8; H 5.6; N 15.1%. $C_{18}H_{15}N_3$. Calculated: C 79.1; H 5.5; N 15.4%] 1-methyl-4-(4-pyridylmethyl)-β-carboline (VId) [The dipicrate had mp 132-134° and 212-216° (from methanol). Found: C 48.7; H 2.9; N 17.0%. $C_{18}H_{15}N_3 \cdot 2C_6H_3N_3O_7 \cdot 0.5H_2O$. Calculated: C 48.7; H 3.0; N 17.0%. The chromatographically pure base obtained from the dipicrate was an oily product. UV spectrum, λ_{max} (log ε), nm: 213 (4.21), 239 (4.33), 244 (4.36), 252 (4.18) (inflection), 280 (3.82), 290 (4.04), 339 (3.68), and 353 (3.73)] and 1-methyl-4-(4-methyl-2-thiazolylmethyl)-β-carboline (VIi) [The picrate had mp 228-230° (from methanol). Found: C 52.7; H 3.7; N 16.2; S 6.0%. $C_{17}H_{15}N_3S \cdot C_6H_3N_3O_7$. Calculated C 52.9; H 3.5; N 16.1; S 6.1%. The oily base was obtained from the picrate; UV spectrum, λ_{max} (log ε), nm: 212 (4.17), 238 (4.60), 243 (4.60), 250 (4.40) (inflection), 266 (3.90) (inflection), 281 (3.87), 288 (4.16), 340 (3.80) and 354 (3.91).

2-Acetyl-1-methyl-4-(2-furylmethyl-1,2,3,4-tetrahydro-β-carboline (VIII). A solution of 0.98 g (22.3 mmole) of acetaldehyde in 7 ml of 50% formic acid was added slowly to a solution of 2.68 g (11.2 mmole) of amine IIIg in 20 ml of the same solvent. After 2.5 h, the solution was extracted with ether, it was then cooled with ice and made alkaline with ammonia. The resinous precipitate was separated by decantation, dissolved in methanol, and again made alkaline with a methanol solution of ammonia. The mixture was then diluted with water and extracted with ether. Evaporation of the dry extract at 20° gave 2.06 g (7.8 mmole) of unstable tetrahydro-β-carboline VII, which was dissolved in 21 ml of pyridine and treated with 2.37 g (23.2 mmole) of acetic anhydride. After 20 h,the mixture was poured into water and extracted with ether. The residue that remained after the removal of the solvent was crystallized from trichloroethylene. The resulting crystals were subjected to fractional crystallization from methyl ethyl ketone to give two epimers of VIII with mp 186° (0.1 g) and 204-206° (0.33 g), which had identical elementary compositions and mass spectra and were not separated by chromatography on aluminum oxide. An additional 0.01 and 0.43 g of epimers VIII were obtained from the mother liquors after purification on aluminum oxide and fractional crystallization. Found: C 73.6; H 6.7; N 9.4%; M^+ 308. $C_{19}H_{20}N_2O_2$. Calculated: C 74.0; H 6.5; N 9.1%; M 308.

1,4-Dimethyl-β-carboline. A 200-mg sample of 1,4-dimethyl-3,4-dihydro-β-carboline perchlorate in 4 ml of acetone was stirred with 2 g of active manganese dioxide at room temperature for 40 min. The excess oxidizing agent was removed by filtration, the acetone was removed by distillation, and the residue was crystallized from ethanol to give 142 mg (71%) of 1,4-dimethyl-β-carboline perchlorate. When the reaction was carried out in dimethylformamide and water, respectively, the yields were 55% and 5%.

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