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CARBOLINES

VIII.* α -CARBOLINE COMPOUNDS FROM β -(3-INDOLYL) KETONE OXIMES

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Anhydronium bases of 2-chloro- α -carbolines and 3,4-dihydro- β -carbolines are formed by Beckmann rearrangement of β -(3-indoly1) ketone oximes. In a number of cases the formation of anhydronium bases becomes the predominant process.

Using previously developed methods [2, 3] we have synthesized new substituted β -carbolines XIV-XVI, which are potential physiologically active compounds. Ethylidene- and isobutylideneacetones reacted with indole under the influence of perchloric acid to give indolyl ketones I and III, which were converted to oximes II and IV (for the synthesis of α -substituted oxime VI, tert-butyl α -propylacetoacetate was alkylated with gramine methylsulfate). Oximes II, IV, and VI were converted to 3,4-dihydro- β -carbolines by 1-min contact with phosphorous pentachloride in warm nitrobenzene. The resulting hydrochlorides of X-XIII were dehydrogenated by heating in glycol with palladium black prepared by the method in [4].

In the reaction of oxime II with PCl_5 , a considerable amount of a yellow substance that forms a hydrochloride that is difficult to dissolve in water was isolated along with carboline X. According to the mass-spectrometric data and the results of elementary analysis the base corresponding to this hydrochloride had the empirical formula $C_{13}H_{11}ClN_2$. Absorption characteristic for the NH bond in indole was not observed in its IR spectrum. The PMR spectrum contained a multiplet at 7.20-8.00 ppm, singlets of two methyl groups at 4.17 and 2.55 ppm, and a one-proton singlet at 6.52 ppm. From these data we proposed the 1H-1,4-dimethyl-2-chloro- α -carboline structure (XVII) for the isolated substance. The position of the chlorine atom was confirmed by the following data: The product of reductive dechlorination (XVIII) had a PMR spectrum in which the H_a proton appeared as a doublet at 6.67 ppm (J=6.5 Hz) and a new (as compared with XVII) one-proton doublet appeared at 8.16 ppm (J=6.5 Hz). The magnitude of the chemical shift and the spin-spin splitting constant indicate that the H_b proton that replaced the chlorine atom occupied an adjacent position with respect to the nitrogen atom and H_a.

The synthesis of the known 1H-1-methyl- α -carboline (XXIV) [5] by the action of phosphorus pentachloride on oxime VII [6] served as another confirmation of the correctness of formulas XVII and XVIII. α -Isocarboline XXIV and its ethiodide (XXVIII) had physical constants in agreement with the literature data [5].

*See [1] for communication VII.

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XII I п ш IV ν ٧I VII VIII Х XI IX i-C₃H7 H H i-C₃H7 H Н CH₃ CH₃ н CH3 C6H5 H H CH₃ i-C3H7 Н H H R¹ R² R³ X H H Η C₂H C₃H; H Н н Ĥ Ĥ CH₃ Н Н CH₆ CH₃ CO₀tBı CH₃ CH₃ CH CH CH₃ NOŬ 0 NOĚ NOH NOH NOH NOH XIII XIV H H CH₃ CH₃

As previously shown in [2], oximes VIII and IX, for which $R^3 = C_6H_5$, are not converted to β -carbolines by Beckmann rearrangement. We now have established that if the rearrangement is carried out by the action of PCl₅ in nitrobenzene, these compounds (VIII and IX) give high yields of anhydronium bases XIX and XXI, which can be readily converted to XX and XXII.

It is apparent that the first step in the process leading to formation of α -carboline compounds is Beckmann rearrangement of the oximes with migration of the R³ grouping. It can further be assumed that cation XXVIII, which arises as a result of Beckmann rearrangement [7], undergoes chlorination to intermediate XXIX, which undergoes cyclization of the Hofmann-Loffler type [8], splits out HCl, and is oxidized under the influence of nitrobenzene.



According to the theory of the Beckmann rearrangement [7], the trend of the reaction should be determined by the stereochemistry of the oximes. However, the situation is more complex in this case.

A study of the PMR spectrum of II showed that the substance is a mixture of two isomers. The signal of the $C(H_b)_3$ group consists of two peaks at 1.63 and 1.78 ppm with a relative intensity of ~1:2.5. We assigned these signals to two isomers – the syn (XXX) and anti (XXXI) isomers. The syn oxime, in the spectrum of which the signal of the methyl H_b protons is shifted to the weak-field region because of coupling with the OH group, predominates in the mixture.

Oxime VIII gave two spots on Silufol corresponding to two stereoisomers, which we were able to separate. The configuration of the isomers was established by a study of the PMR signals of the H_c protons, which are nonequivalent as a result of retarded internal rotation. In the spectrum of the low-melting and more polar (R_f 0.43) anti isomer (XXXI, $R = C_6H_5$) the multiplet corresponding to the indicated protons is situated at 3.1-3.3 ppm, whereas the multiplet in the spectrum of the high-melting and less polar (R_f 0.63) syn isomer is at 2.8-3.1 ppm. However, any one of the stereoisomers of VIII on treatment with PCl₅ in nitrobenzene gave only an α -isocarboline, whereas 3-methyl-3-(3-indolyl)propionic acid anilide [2] was obtained from the reaction of toluenesulfonyl chloride in pyridine. It follows from this that the trend of the reaction is not determined by the stereoisomeric composition of the reacting oximes, and one should assume the possibility of facile interconversion of the stereoisomer during the reactions. The fact that the pure syn-VIII oxime is converted to a mixture of isomers with predominance of anti-VIII on refluxing in methanol containing traces of HCl for 5 min serves as an experimental confirmation of this assumption.

α -carbolines
1H-2-Chloro-
trbolines and
,4-Dihydro- <i>β</i> -c
TABLE 1. 3

Yield.		24 14	46	02	34	60	35	_
λ _{max} (ig ε), nm / 21		247 (4,19), 300 (4,55), 368 (3,82) 207 (4,19), 203 (4,55), 368 (3,82) 207 (4,19) 223 (4,08): 242 (3,75) 272 (4,29): 282	(4,35), 326 (4,03)	248 (2,83), 355 (3,45)	224 (4,11), 265 (4,19), 273 (4,21), 282 (4,23), 331	(4,01) 210 (4,16), 224 (4,17), 243 (4,06), 273 (4,36), 282	$\begin{pmatrix} 4, , , 3 \end{pmatrix}, \begin{array}{c} 529 \\ 204 \\ 4 \\ 05 \end{pmatrix}, \begin{array}{c} 228 \\ 228 \\ 4 \\ 05 \end{pmatrix}, \begin{array}{c} 271 \\ 4 \\ 05 \end{pmatrix}, \begin{array}{c} 284 \\ 4 \\ 05 \end{pmatrix}, \begin{array}{c} 346 \\ 4 \\ 05 \end{pmatrix}$	
	z	16,5 12,1	10,7	10,7	12,9	9,6	7,9	_
ited, %	ប	15.4	13,5	13,5	16,4	12,1	10,0	
Calcul	н	4,0 4,0	7,3	7,3	4,2	4,5	4,3	_
	c	53,4 67 7	68,6	68,6	66,5	73,8	6'12	-
	z	16,4 12.0	10,6	10,5	13,0	9,2	7,8	-
d. %	ū	15.7	13,7	13,5	15,7	13,0	10,1	-
Foun	н	4,0 5.1	7,6	7,6	4,1	4,8	4,4	-
	c	53,0 67.8	68,8	68,9	66,5	73,9	77,5	_
Empirical formula		C ₁₃ H ₁₄ N ₂ ·C ₆ H ₃ N ₃ O ₇ C ₁₃ H ₁₁ ClN ₅	C ₁₅ H ₁₈ N ₂ ·HCI	C ₁₅ H ₁₈ N ₂ ·HCl	Çı₂H₀CIN₂	C ₁₈ H ₁₆ CIN ₂	C ₂₃ H ₁₆ CIN ₂	
mp, °C		238—239 118—119	223-225	230-233	175 ^C 152—154	171172	202-203	-
Salt		Picrate	Hydro-	Hydro-	cnloride			- 1
Car- boline		XVII	XI ^a	XII ^b		хIX	XXI ^e	
Dxime		п	N	Ŋ	ΝI	NIII	IX	

^a The α -carboline was not isolated. ^b The α -isocarboline was not formed. ^c According to [9], this compound has mp 180-181°.

^aThe β -carboline was not formed. ^ePMR spectrum (in CDCl₃), δ , ppm: 2.68, s (3H); 4.23 s (3H); 6.62, s (1H); 7.3, m (4H).

Carbolines	
1H-α-	
5	
ABLE	
겉	

	Yield,	∿	8	52	}	8		65			
	, пш		(4.32) (4.38)	(4,09), (4,61).	(4,32)	(4.36)	(4,17)	(4,33)	(4,38)	: (3,38)	
	12.0	3911	219	, 316 . 221	, 265	, 253	, 288	220	, 278	, 402	
	l, max		(4,38) (4,04)	(4,44) (4,06) (4,61)	(4,19)	(3,56) (4,38)	(4, 35) (4, 14)	(4, 14) (3, 90)	(4, 33)	(4,08)	
			207 240	278 324 205	241 281	409 225	273 329	204 240	274	[321	
	%	z	14,3	10.9		8,7		15,4			
1	alc.,	Ш	6,2	5.5		5.0		5,5			
	,Ŭ	υ	79,6	83.7	-	86.2		1,67			
	d/0	z	14.2	11.1		8,4		15,5			
	•punc	Ξ	6,1	5.5		5,3		5,6		_	43°.
	F(c	6'62	83.4		86,7		79,0			10 2
	Empirical	formula	C ₁₃ H ₁₂ N ₂	C ₁₈ H ₁₄ N ₂		C ₂₃ H ₁₆ N ₂		C ₁₂ H ₁₀ N ₂			V had n
	mp , ° C		130-131	139-141		162-164		124			dide XX
	Com -	punod	XVIII ^{a,b}	XX		XXII ^c	e p			;	^a Methio

^aMethiodide XXV had mp 243°. ^bMethiodide XXV had mp 243°. ^cPMR spectrum (C₃DCOCD₃), δ , ppm: 2.80, s (3H); 4.19, s (3H); 6.64, d (H_a), J = 6.5 Hz; 7.11-7.89, m (4H, aromatic protons); 8.10, d (1H), J = 6.5 Hz.

Methiodide XXVI had mp 320°.

d Methiodide XXVII had mp 195-196°. ⁶ According to [5, 10], this compound has mp 132-133°.

EXPERIMENTAL

All of the melting points were determined with a Kofler block and were not corrected. The spectral data were obtained with UR-10, Specord UV-vis, MKh-1303, PC-60, and JNM-MH-100 spectrometers. The assignment of the PMR signals in the necessary cases was accomplished by the double-magnetic resonance method.

<u>4-(3-Indolyl)-2-pentanone (I).</u> A 1.9-g sample of 70% perchloric acid was added slowly with vigorous stirring at a temperature no higher than -5° to a cooled (to -10°) solution of 38 g (325 mmole) of indole in 38 g (425 mmole) of ethylideneacetone, after which the mixture was stirred for another 40 min. It was then diluted with ether and washed with sodium bicarbonate solution to completely remove the acid. The ether solution was dried with sodium sulfate, and the ether and excess ethylideneacetone were removed by vacuum distillation. The residue was chromatographed on activity III aluminum oxide in a benzene-petroleum ether system (4:1) to give 50.3 g (77%) of ketone I as a viscous liquid. The thiosemicarbazone had mp 169-171° (from methanol). Found: C 61.2; H 6.6; N 20.5; S 11.6%. C₁₄H₁₈N₄S. Calculated: C 61.3; H 6.6; N 20.4; S 11.7%.

Amorphous oxime II was obtained from ketone I in quantitative yield by the usual method. PMR spectrum, δ , ppm: 1.23, d, J=6.5 Hz (3H_a); 1.63 and 1.78 (3H_b); 2.42, m (2H_c); 3.16, m (H_d); 6.45 and 6.58, two d, J=2.5 Hz (indole 2-H); 6.70-7.10, m (aromatic protons); 7.28, m (indole 1-H); and 7.52, s (OH).

<u>5-Methyl-4-(3-indolyl)-2-hexanone (III)</u>. This compound was similarly obtained in 42% yield from indole and isobutylideneacetone at 50-55° (the reaction time was 45-50 min). Oxime IV had mp 147-148° (from benzene). IR spectrum: 3400 (NH), 3180-3250 (OH), and 1665 (C = N) cm⁻¹. Found: C 73.6; H 8.1; N 11.4%. $C_{15}H_{20}N_2O$. Calculated: C 73.7; H 8.3; N 11.5%.

<u>3-Skatyl-3-tert-butoxycarbonyl-2-hexanone (V).</u> A total of 8.82 g (0.07 mole) of dimethyl sulfoxide (DMSO) was added at 0° to 12.2 g (0.07 mole) of gramine in 80 ml of anhydrous alcohol, and the mixture was allowed to stand overnight. The resulting solution was treated with 14 g (0.07 mole) of tert-butyl α -propylacetoacetate, the mixture was cooled with ice, and a solution of 1.61 g (0.07 g-atom) of sodium in 30 ml of anhydrous alcohol was added slowly dropwise with stirring. The mixture was then stirred and refluxed in an inert atmosphere for ~8 h. The alcohol was removed in vacuo, and the residue was treated with water and extracted with ether. The oil remaining after removal of the ether by distillation was chromatographed on 800 g of aluminum oxide in a benzene—ether system (95:5) to give 9.35 g (41%) of a slowly crystallizing oil with mp 73-75° (from alcohol). IR spectrum: 3330 (NH), 1710 (COOBu), 1700 (CO) cm⁻¹: Found: C 72.8; H 8.1; N 4.2%. C₂₀H₂₇NO₃. Calculated: C 73.0; H 8.4; N 4.3%.

<u>3-Skatyl-2-hexanone Oxime (VI)</u>. A 5-g (0.013 mole) sample of keto ester V was heated in an inert atmosphere at 225-230° for 15 min, after which the pyrolyzate was cooled and dissolved in 15 ml of anhydrous pyridine. Hydroxylamine hydrochloride [3.6 g (0.05 mole)] and 18 ml of anhydrous methanol were added to the pyridine solution, and the resulting solution was refluxed for 1 h. It was then cooled and poured into water, and the aqueous mixture was extracted with ether. The extract was freed of pyridine in the usual way and dried with sodium sulfate. The solvent was removed by vacuum distillation, and the residue was crystallized from carbon tetrachloride to give 2.7 g (73%) of colorless crystals with mp 116-118°. IR spectrum: 3420 (NH), 3190 (OH), and 1675 (C=N) cm⁻¹. Found: C 73.0; H 8.2; N 11.4%. $C_{15}H_{20}N_2O$. Calculated: C 73.8; H 8.2; N 11.5%.

<u>3-Methyl-3- (3-indolyl)-1-phenylpropanone Oxime (VIII).</u> This compound was obtained by the method in [2]. A 400-mg sample of the mixture of stereoisomers was separated by preparative chromatography in a thin layer of L 5/40 nm silica gel in an acetone-chloroform system (1:9) to give 300 mg of the syn isomer with mp 134-136°. PMR spectrum, δ , ppm (CDCl₃): 1.34, d, J=6.5 Hz (3H_a); 2.80-3.30, m (2H_cH_d); 6.81, d, J=2.5 Hz (indole 2-H); 7.00-7.54 (aromatic H); and 7.81, s (OH). Also obtained was 96 mg of the anti isomer with mp 124-130°. PMR spectrum, δ , ppm (CDCl₃): 1.29, d, J=6.5 Hz; 3.07-3.50 (2H_c, H_d); 6.64, d, J=2 Hz (indole 1-H); 6.78-7.46 (aromatic H); and 9.25 (OH).

<u>3,4-Dihydro- β -carbolines and 1H-2-Chloro- α -carbolines.</u> A solution of 1.64 mmole of the oxime in 2 ml of nitrobenzene was added dropwise with vigorous stirring in the course of 30 sec to a heated (to 60-70°) solution of 4.9 mmole of phosphorus pentachloride in 2 ml of nitrobenzene, 30 sec after which the solution was cooled rapidly, and the excess PCl₅ was decomposed with lumps of ice. The organic layer was diluted with ether and extracted with dilute hydrochloric acid. In the case of oxime II, hydrochloride XVII, which was separated by filtration, was liberated when the acidic solution was allowed to stand. In other cases, the acid extract was made alkaline with sodium hydroxide, and the liberated bases were purified

by crystallization or chromatography with a column filled with aluminum oxide. The yields and physical constants of the β - and α -carbolines are presented in Table 1.

<u>1H- α -Carbolines</u>. A 500-mg sample of 1H-2-chloro- α -carboline was hydrogenated over 50 mg of 10% palladium on carbon in 20 ml of alcohol at atmospheric pressure until hydrogen absorption ceased (2-16 h). The catalyst was removed by filtration, and the solvent was evaporated to give the hydrochloride, which was converted to the base and crystallized from a suitable solvent. The physical constants and yields of the α -carbolines are presented in Table 2.

<u>1,4-Dimethyl-β-carboline (XIV)</u>. A solution of 1.36 g (36.3 mmole) of sodium borohydride in 71 ml of water was added with vigorous stirring at 25° in a nitrogen atmosphere to a solution of 2.58 g (12.1 mmole) of $PdCl_2 \cdot 2H_2O$ in 225 ml of water. After 1-2 min, the mixture was acidified with hydrochloric acid, and a large portion of the water was decanted without allowing the catalyst to come into contact with the air. A solution of 2.7 g (11.5 mmole) of hydrochloride X in 22.8 ml of glycol was then added to the residual suspension, and the mixture was heated to 40-50° and stirred in an inert atmosphere for 15-20 min. It was then cooled and diluted with water, and the catalyst was removed by filtration. The filtrate was made alkaline and extracted with ether, the solvent was removed, and the residue was crystallized from trichloroethylene to give colorless crystals of carboline XIV, with mp 239-240°, in 37% yield. Found: C 79.3; H 6.1; N 14.1%. $C_{13}H_{12}N_2$. Calculated: C 79.6; H 6.2; N 14.3%. The hydrochloride had mp 273° (from alcohol, in a sealed capillary).

<u>1-Methyl-4-isopropyl- β -carboline (XV)</u>. A mixture of 1.35 g of hydrochloride XI, 13.5 ml of glycol, and 0.68 g of palladium black, prepared by the method in [4], was stirred in a stream of nitrogen at 148° for 15 min, after which the suspension was cooled, another 0.68 g of the catalyst was added, and the mixture was heated for another 15 min. It was then worked up as described for carboline XIV to give XV with mp 162-163° (from trichloroethylene) in 89% yield. Found: C 80.7; H 7.1; N 12.3%. C₁₅H₁₆N₂. Calculated: C 80.3; H 7.2; N 12.5%. The hydrochloride had mp 283-284° (from alcohol, in a sealed capillary).

<u>1-Methyl-3-propyl- β -carboline (XVI)</u>. This compound was obtained from XII by the method used to prepare XV. The product was isolated in 64% yield in the form of the acid fumarate with mp 206-207° (from water). The picrate had mp 252-255° (from alcohol). Found: C 55.6; H 4.2; N 15.3%. C₁₅H₁₆N₂· C₆H₃N₃O₇. Calculated: C 55.6; H 4.2; N 15.4%.

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