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XV. The Conversion of δ-Oxonitrile Arylhydrazones into α-Carbolines*

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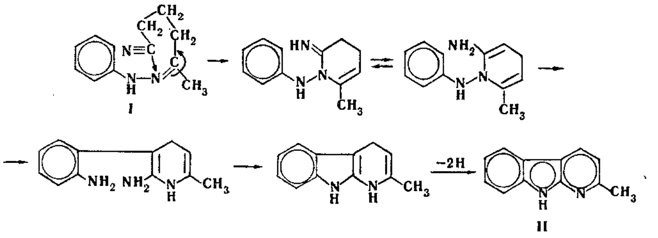
It has been established that when δ-oxonitrile arylhydrazones are boiled in glacial acetic acid substituted α-carbolines are formed.

We have shown that when 2-(2'-cyanoethyl)cyclohexanone phenylhydrazone is heated with glacial acetic acid, in addition to the normal products of Fischer cyclization, 2,3-tetramethyl-α-carboline is formed. The formation of an α-carboline was explained by an electrophilic attack by the carbon atom of the nitrile group of the nitrogen of the C =N in the hydrazone with a subsequent rearrangement of the amidine type similar to the Fischer reaction. If this mechanism is correct, under similar conditions 5-oxacarponitrile hydrazone (I) should form 2-methyl-α-carboline (II).



In actual fact, when the hydrazone I was boiled with glacial acetic acid, the carboline II, identical with an authentic, sample, was obtained. The authors thank E. V. Pronina who provided a sample of 2-methyl-α-carboline synthesized from 2-hydrazino-6-methylpyridine and cyclohexanone with subsequent aromatization [3]. Similarly, 2,3-dimethyl-α-carboline (III) is formed from 4-methyl-5-oxocapronitrile phenylhydrazone. As can be seen from Table 1, when the acid is diluted the yields fall, and under the action of sulfuric acid resinification or the normal formation of 3-cyanoethyl-2,3-dimethyl-3H-indole is the main process.

Table 1. Influence of the Reaction Conditions of the Yield of 2,3-Dimethyl-α-carboline

Cyclizing agent	Temperature, °C	Reaction time	Yield, %
Glacial CH_3COOH	Boiling	10 hr	33—35
95% CH_3COOH	Boiling	10 hr	4—5
Glacial CH_3COOH	20	2 months	0
Polyphosphoric acid	85	2 hr	8
Conc. H_2SO_4	20	6 hr	0
20% H_2SO_4	100	15 min.	4*
Conc. HCl	170—180	1 hr	3—4*

*The main product of the reaction (yield about 50%) was 3-(2'-cyanoethyl)-2,3-dimethyl-3H-indole.

It might be assumed that the α-carbolines are formed by some rearrangement or other of the corresponding indoles and 3H-indoles, but when 3-cyanoethyl-2,3-dimethyl-3H-indole (IV), 3-cyanoethyl-2-methylindole, or 1-(2'-cyanoethyl)-2,3-dimethyl-3H-indole was subjected to prolonged (10-12 hr) heating with glacial acetic acid, no formation of the corresponding α-carboline (II or III) could be detected even chromatographically. If the decomposition of the arylhydrazone under the action of the glacial acetic acid gives rise to derivatives of 2-pyridone or dihydro-2-pyridone which again react with phenylhydrazone forming amidrazones, the latter may cyclize in the manner of a Fischer reaction.

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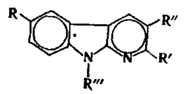
*For part XIV, see [1].

Table 2. α-Carbolines



R	R′	R″	R‴	Mp, °C	Empirical formula	Found, %			Calculated, %			UV spectrum (methanol)		Yield, %
						C	H	N	C	H	N	λ_{max}, nm	log ε	
H	CH_3	H	H	257—255*	$C_{12}H_{10}N_2$	79,29 79,26	5.74 5.59	15.02 15.30	79.09	5,54	15,37	258 297 328	4.03 4.22 3.54	8
CH_3	CH_3	H	H	260—262	$C_{13}H_{12}N_2$	80.00 80.03	6.41 6.42	14,27 14.16	79.52	6,48	14,31	265 303	4.05 4,26	7
H	CH_3	CH_3	H	262—263	$C_{13}H_{12}N_2$	79.62 79,64	6 37 6.26	14.24 14,13	79.52	6.48	14,31	260 302 332	4,12 4,32 3,81	32,5
CH_3	CH_3	CH_3	H	268—269	$C_{14}H_{14}N_2$	80.25 80,21	6,87 6.93	13,37 13,14	79,96	6,71	13,33	—	—	22,5
H	CH_3	H	$COCH_3$	110—111	$C_{14}H_{12}N_2O$	75.12 75,19	5.39 5.48	—	75.29	5,55	—	230 262 294	4.45 4 11 4,15	93
CH_3	CH_3	H	$COCH_3$	121—122	$C_{15}H_{14}N_2O$	75.45 75.46	6,01 5,85	—	75,50	5.83	—	235 267 298	4.59 4.22 4,31	85
H	CH_3	CH_3	$COCH_3$	132—133	$C_{15}H_{14}N_2O$	75,81 75.84	6.08 6,06	—	75.61	6.06	—	232 262 292	4.34 3.91 4.15	82
CH_3	CH_3	CH_3	$COCH_3$	152—153	$C_{16}H_{16}N_2O$	76,40 76,41	6.73 6,54	—	76.19	6.37	—	235 267 300	4.51 4,13 4.29	84

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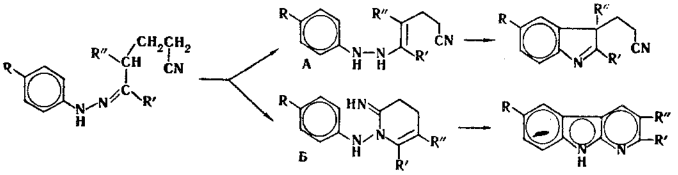
*Mp 255°C [6].

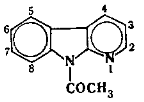
However, even boiling 5,6-tetramethylene-2-pyridone [4, 5] with phenylhydrazine in glacial acetic acid for several hours did not lead to the formation of a carboline, and the starting materials were recovered unchanged. In addition, if the water is not eliminated beforehand and an attempt is made to cyclize not the phenylhydrazones but a mixture of phenylhydrazine and 4-methyl-5-oxocapronitrile in glacial acetic acid, the yield of carboline III falls from 33 to 5-6%.

Thus, in our case two competing reactions apparently take place: under the action of a strong acid the protonation of the hydrazone nitrogen atom takes place, an enehydrazine (A) arises, and an ordinary Fischer reaction takes place; in the second case, the nitrile group attacks the hydrazones nitrogen atom with the formation of a cyclic amidrazone system (B) which then, under the action of the acid, rearranges with the closure of the second ring.



The PMR spectra (taken in CCl_4 on an RS-60 instrument for the acetyl derivatives of 2-methyl-, 2,3,8-trimethyl-, and 2,3-tetramethylene-α-carbolines and on a JNM-100 instrument for the others) agree well with the structure of the substances obtained. All the spectra have a doublet with J = 7-10 Hz in the weak-field region which could be ascribed to the α-pyridine proton (8.6 ppm). But since in all the α-carbolines that we obtained there is a substituent in the α-position of the pyridine part of the molecule and since the components of the doublet are weakly split additionally (1.5 Hz, meta splitting), it cannot be ascribed to one of the pyridine protons. There is an acetyl group in all the compounds, and therefore it might be assumed that the doublet relates to H_8, which is subject to the descreening influence of the carbonyl group. Apparently, free rotation of the acetyl group is hindered because of the closeness of the electron pair of the nitrogen of the pyridine nucleus, and the carbonyl group is also close to H_8. In actual fact, in 2,3,8-trimethyl-α-carboline there is no doublet in the weak-field region. The chemical shifts of the methyl group and the H_8 proton are given in Table 3. The complete assignment of all the signals in the PMR spectra of the α-carbolines is complicated by the overlapping of the resonance frequencies of the protons of the pyridine and benzene moieties of the molecule, but it can be done without special calculations for certain compounds. Figure 1 shows the spectrum of 9-acetyl-4-methyl-α-carboline (a sample with the authentic structure was kindly given to us by P. Nantka-Namirsky (Warsaw)): doublet with δ 8.55 ppm somewhat broadened (H_8, J = 7.5 Hz), two doublets with δ 8.2 ppm (H_2, J = 4 Hz), and δ 7.03 ppm (H_3, J = 4 Hz), and a doublet with δ 7.88 ppm (H_5, J = 7.5 Hz), each of one proton unit, and a multiplet (H_6 and H_7) of two proton units. The spectrum of 9-acetyl-2-methyl-α-carboline (Fig. 2) shows a doublet with δ 8.33 ppm (H_8, $J_{8,7}$ = 10 Hz, $J_{8,6}$ = 2 Hz) and a AB system of interacting protons with δ 6.7 ppm (H_3, $J_{3,4}$ = 12.7 Hz) and δ 7.49 ppm (H_4, $J_{4,3}$ = 12.7 Hz) superposed on the lines of the resonance frequencies of H_5, H_6, and H_7. The spectrum of 9-acetyl-2,3,6-trimethyl-α-carboline (Fig. 3) has a doublet with δ 8.3 ppm (H_8, $J_{8,7}$ = 8.75 Hz) interacting with H_7 (δ 7.01 ppm, $J_{7,8}$ = 8.75 Hz, $J_{7,5}$ = 1.5 Hz), and a sharp singlet with δ 7.4 ppm (H_4) and a somewhat broadened singlet of the signals of the H_5 proton (δ 7.25 ppm).

Table 3. Chemical Shifts of the Methyl Groups and H_8 Protons in the N-Acetyl-α-carbolines (δ Scale)



α - Carboline	2-CH_3	3-CH_2	4-CH_3	6-CH_3	8-CH_3	$COCH_3$	H_8	J, Hz
2-Methyl-	2.37	—	—	—	—	2.82	8.33	12.7
4-Methyl-	—	—	2.82	—	—	3.1	8.55	7.5
2,3-Dimethyl-	2,36	2.15	—	—	—	2.85	8.42	8.0
2,3,6-Trimethyl-	2.41	2.20	—	2.41	—	2.85	8.3	8.75
2,3,8-Trimethyl-	2.50	2.25	—	—	2.41	3.15	—	—
2,3-Tetramethylene-	—	—	—	—	—	2 85	8.5	7.5

EXPERIMENTAL

2,3-Dimethyl-α-carboline (III). Some 2.7 g (0.025 mole) of phenylhydrazine was added to 3.1 g (0.025 mole) of 4-methyl-5-oxocapronitrile, and the mixture was heated in the water bath for 3 hr; then the water liberated and the un-

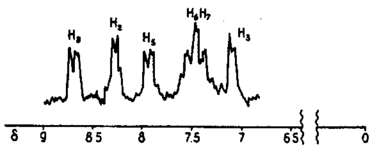


Fig. 1

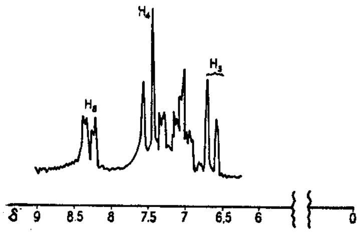


Fig. 2

Fig. 1. PMR spectrum of 9-acetyl-4-methyl-α-carboline.

Fig. 2. PMR spectrum of 9-acetyl-2-methyl-α-carboline.

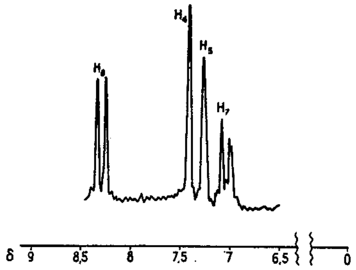


Fig. 3. PMR spectrum of 9-acetyl-2,3,6-trimethyl-α-carboline.

changed oxonitrile and phenylhydrazine were distilled off with benzene in a current of gas under reduced pressure. The resulting 4-methyl-5-oxocapronitrile phenylhydrazone was treated with 120 ml of glacial acetic acid and the mixture was boiled for 10 hr, cooled, diluted, with water, and brought to neutrality by the addition of 2 N NaOH, after which the precipitate that had formed was filtered off, washed with water on the filter, and recrystallized from benzene to give 1.32 g (32.5%) of the carboline III, with mp 262-263°C; R_f 0.45 [Al_2O_3, benzene-ethyl acetate (2 : 1)]; UV spectrum: λ_{max} 260, 302, 332 nm; log ε 4.12, 4.32, 3.81 (in methanol). Found %: C 79.62, 79.64; H 6.37, 6.26; N 14.24, 14.13. $C_{13}H_{12}N_2$. Calculated %: C 79.52; H 6.98; N 14.31.

9-Acetyl-2,3-dimethyl-α-carboline. A mixture of 0.2 g of the carboline III and 10 ml of acetic anhydride was boiled for 1 hr, cooled, diluted with water, and neutralized with sodium bicarbonate, and the precipitate that deposited was filtered off to give 0.2 g (82%) of 9-acetyl-2,3-dimethyl-α-carboline with mp 132-133°C (from ethanol). UV spectrum: λ_{max} 232, 262, 292 nm; log ε 4.34, 3.91, 4.15 (in methanol). Found %: C 75.81, 75.84; H 6.08, 6.06. $C_{15}H_{14}N_2O$. Calculated %: C 75.61; H 6.06.

The α-carbolines II, IV, and V and their acetyl derivatives were obtained similarly. Their constants and yields are given in Table 2.

REFERENCES

1. A. N. Kost, L. A. Sviridova, G. A. Golubeva, and Yu. N. Portnov, KhGS [Chemistry of Heterocyclic Compounds], 6, 371, 1970.
2. A. N. Kost, L. G. Yudin, and N. B. Chernyshova, DAN 183, 112, 1968.
3. L. N. Yakhontov, E. V. Pronina, and M. V. Rubtsov, KhGS [Chemistry of Heterocyclic Compounds], 3, 687, 1967.
4. N. P. Shusherina, R. Ya. Levina, and Huang Hua-min, ZhOKh, 32, 3599, 1962.
5. A. J. Meyers and G. Garcia-Munoz, J. Org. Chem., 29, 1435, 1964.
6. R. B. Burthner, US patent no. 2688022, 1954; C. A., 50, 1925, 1956.

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