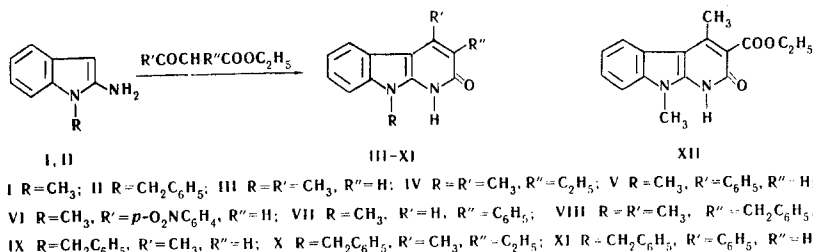


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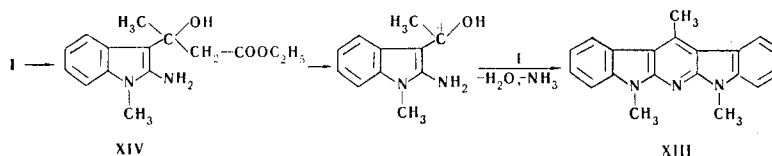
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The condensation of 1-substituted 2-aminoindoles with β -keto esters gives 2-oxo- α -carboline. Substitution of diketenes for the β -keto esters leads to a mixture of 2-oxo- and 4-oxo- compounds.

1-Substituted 2-aminoindoles condense comparatively readily with β -diketones [2] to form α -carboline, while the similar condensation with malonic ester, which leads to 2-oxo-4-hydroxy- α -carboline, proceeds only under severe conditions [3]. In the present study we have used the Conrad-Limpach synthesis to obtain monooxo- α -carboline by the reaction of 2-aminoindoles with various β -keto esters (Table 1).



The reaction proceeds to give good yields when a salt of the 2-aminoindole is refluxed with the β -keto ester in pyridine. In the case of malonic ester, we have noted [3] that the alkylation of the CH₂ group markedly hinders the condensation. In the case of acetoacetic ester, however, the introduction of a methyl or benzyl group leads only to a reduction in the yields. Under the same conditions (refluxing in pyridine, during which malonic ester does not enter into the reaction [3]), acetylmalonic ester apparently initially forms carboline XII with 1-methyl-2-aminoindole (I), and XII loses a carboxy group during the reaction to form carboline III. In some cases, another side process, which proceeds with cleavage of the carbon-carbon bond, was also observed. Thus, when aminoindole I is refluxed in isopropyl alcohol in the presence of a 1.5 equivalent amount of triethylamine, which is necessary for conversion of the aminoindole salt to the free base, indolocarboline XIII, which was previously obtained [4] by the reaction of aminoindole I with acetaldehyde, is formed instead of carboline III, which can be explained by the formation of a product of the condensation of I with the keto group of acetoacetic ester. After retrograde aldol cleavage, intermediate compound XIV reacts with a second molecule of I.



*See [1] for communication XXVII.

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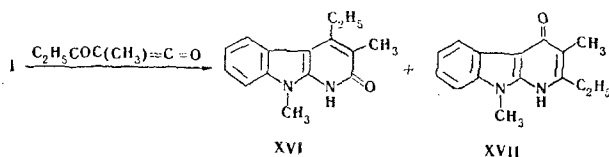
TABLE 1. 2-Oxo- α -carbolines

Compound	Mp, °C	Empirical formula	Found, %		Calc., %		Yield, %
			C	H	C	H	
III	310—312	C ₁₃ H ₁₂ N ₂ O	73.4	5.7	73.5	5.7	97
IV	271—273	C ₁₅ H ₁₅ N ₂ O	74.8	6.5	75.0	6.7	75
V	273—275	C ₁₈ H ₁₄ N ₂ O	79.3	5.2	78.8	5.2	58
VI	300—304	C ₁₈ H ₁₃ N ₃ O ₃	67.5	4.2	67.7	4.1	16
VII	270	C ₁₆ H ₁₄ N ₂ O	79.3	5.3	78.8	5.2	46
VIII	287—290	C ₂₀ H ₁₈ N ₂ O	79.9	6.2	79.4	6.0	46
IX	286—288	C ₁₉ H ₁₆ N ₂ O	78.8	5.6	79.1	5.6	85
X	263—266	C ₂₁ H ₂₀ N ₂ O	79.5	6.1	79.7	6.4	32
XI	226—228	C ₂₄ H ₁₈ N ₂ O	81.9	5.6	82.2	5.2	51

TABLE 2. IR and UV Spectroscopic Data

Compound	IR spectra, ν_{\max} , cm ⁻¹		UV spectra	
	NH	C=O	λ_{\max} , nm	lg ϵ
III	3300—2100	1645	269	3.98
			302	3.96
			318	3.77
			331	3.76
IV	3300—2100	1640	272	4.28
			303	4.25
			323	4.06
			337	4.08
V	3200—2100	1640	267	4.40
			320	4.19
VI	3150—2100	1635	—	—
VII	3100—2150	1645	—	—
VIII	3150—2100	1640	275	4.40
			305	4.32
			326	4.18
			339	4.24
IX	3450, 3150—2200	1640	266	4.35
			302	4.33
			316	4.21
			330	4.19
X	3450, 3150—2200	1645	—	—
XI	3450, 3150—2200	1645	264	4.08
			317	3.84
			329	3.83
			—	—
XV	3150—2100	1590	262	4.20
			290	4.12
			315	3.52
			328	3.43
			365	1.95
XVI	3150—2150	1640	272	4.21
			305	4.20
			325	4.03
			339	4.13
XVII	3150—2100	1590	—	—
XVIII	3150—2200	1640	265	4.21
			294	4.12
			303	4.17
			322	4.01
			337	4.09

The condensation with diketenes proceeds more readily than with acetoacetic ester but leads to a mixture of isomeric compounds. Thus carboline III and the isomeric 2,9-dimethyl-4-oxo- α -carboline (XV) are obtained when I is refluxed with diketene in isopropyl alcohol or triethylamine. Similarly, the reaction of I with methylpropionylketene gives a mixture of oxocarbolines XVI and XVII with predominance of α -oxo compound XVI; however, in the case of the reaction of aminoindoles II with methylpropionylketene, only 3-methyl-4-ethyl-9-benzyl-2-oxo- α -carboline (XVII) could be isolated in 60% yield.



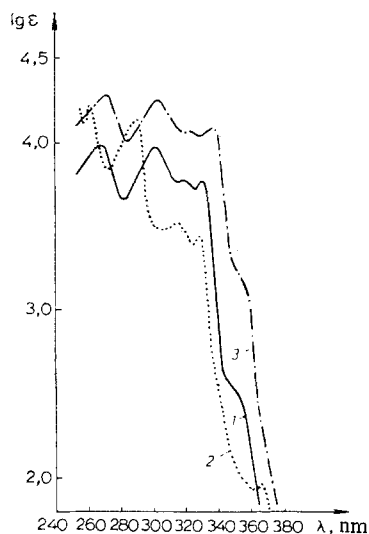


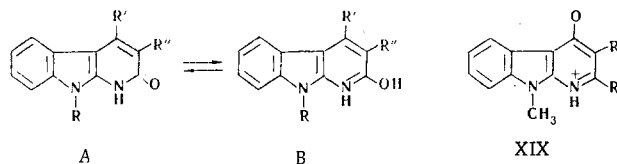
Fig. 1. UV spectra of dimethylformamide solutions: 1) 4,9-dimethyl-2-oxo- α -carboline (III); 2) 2,9-dimethyl-4-oxo- α -carboline (XV); 3) 4,9-dimethyl-3-ethyl-2-oxo- α -carboline (IV).

Thus the presence of several reaction centers in both the 2-aminoindole molecule and the carbonyl component leads to ambivalent processes.

In establishing the structures of the substances obtained, it was necessary to take into account the possibility of tautomerism of the compounds, which have a hydroxypyridine ring [5]. In this connection, to evaluate the structures of the isomeric substances of the XVI or XVII types, we used the set of spectroscopic methods that was thoroughly developed in the quinolone series in the establishment of the structures of the products of the Conrad-Limpach reaction (for example, see [6, 7]). The a priori solution of this sort of problem can lead to erroneous assertions, as was the case, for example, in the study of the condensation of acetoacetic ester with 5-aminopyrazole [8], especially since conversions of some intermediate compounds to others [9, 10] and isomerization of the final product [11] are possible in individual steps under the reaction conditions.

When acetoacetic ester was refluxed with 2-aminoindoles in pyridine, 2-oxo- α -carbolines were obtained. The IR spectra of the products (in mineral oil) contain strong absorption bands at 1645 (III) or 1640 cm^{-1} (IX) that are related to the stretching vibrations of an amide carbonyl group. The introduction of other alkyl substituents, as well as aralkyl or aryl substituents, into the 3 or 4 positions of the pyridine ring has practically no effect on the position and intensity of this band (Table 2).

Consequently, all of the α -carbolines synthesized from β -keto esters exist in the crystalline state in the lactam form with a hydrogen atom attached to the ring nitrogen and an oxo group in the α -position of the pyridine ring; i.e., tautomeric form A is characteristic for them.



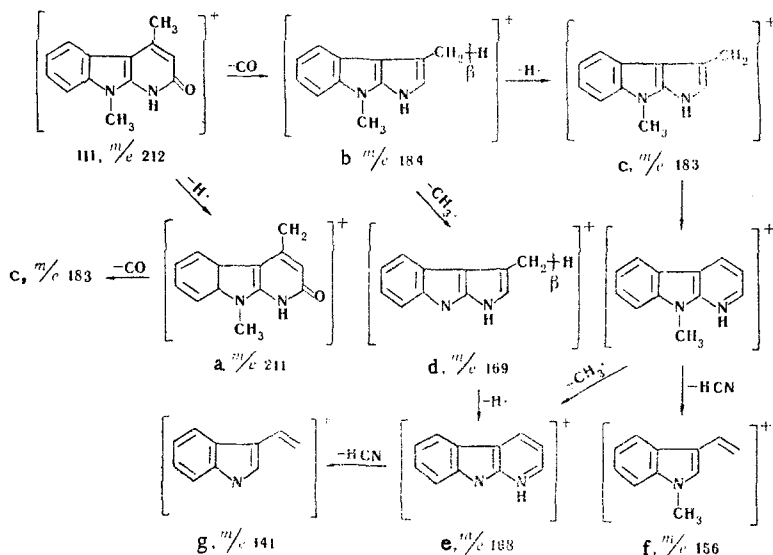
In contrast to other heteroaromatic oxo compounds [12], it is very difficult to use the NH vibrational frequencies in this case to distinguish the isomers and to establish the major tautomeric form in connection with the pronounced shift in these frequencies because of the intense intermolecular interaction (formation of hydrogen bonds). The NH band in the spectra of these α -carbolines is very broad and strong at 2100-3300 cm^{-1} , and the center of the band is at $\sim 2800 \text{ cm}^{-1}$. The low solubility of 2-oxo- α -carbolines makes it impossible to record the spectra of solutions.

A strong intermolecular interaction is also observed in the spectra of 4-oxo- α -carbolines XV and XVII: the NH bands are very broad and strong at 2100-3150 cm^{-1} . The intense absorptions vanish above 1600 cm^{-1} , but a strong band, which is probably related to the C=O vibrations, appears at 1590 cm^{-1} . Similar behavior of the carbonyl group was noted in γ -pyridone structures by a number of investigators [13-15], who identified the C=O frequency in this region by different methods. This sort of shift in the absorption of the carbonyl group is apparently explained by the large contribution of the mesomeric structure of dipolar ion XIX. In this case also, the low solubility made it impossible to make a more detailed examination of the absorption bands responsible for the stretching vibrations of the NH and C=O groups.

It is known that 2-pyridones and 4-pyridones differ with respect to their absorptions in the UV region [16]. This difference is also substantial in the case of 2-oxo- and 4-oxo- α -carbolines and can be used to determine the isomeric forms. In the case of the isomeric α -carbolines III and XV, it was shown (Fig. 1) that a hypsochromic shift of the absorption maxima, as compared with the absorption of the 2-oxo form, is characteristic for the 4-oxo form.

The signals of the methyl groups in the 4 and 9 positions and the signal of one proton in the 3 position for the 2-oxo form of III are observed in the PMR spectra at 2.69, 3.74, and 6.50 ppm, respectively; the signals of these protons for the 4-oxo form of XV are shifted to stronger field (2.49, 3.56, and 6.36 ppm). The signals of the protons of the benzene ring were obtained as an unresolved multiplet for both forms.

A mass spectrometric investigation of carboline III showed that it is extremely stable and highly aromatic. The molecular ion peak (M^+) with m/e 212 is the major peak, and its value is in agreement with the molecular weight calculated for $C_{13}H_{12}N_2O$. The next most intense peak (43.2%) is the $(M-1)^+$ peak (a, m/e 211). Further fragmentation is accompanied by the CO elimination that is characteristic for oxo structures [7, 17], which leads to the formation of ions b with m/e 184 (24.7%) and c with m/e 183 (21.6%).



The loss of a CH_3 group by ions b and c leads to fragments d (m/e 169) and e (m/e 168) with intensities of 20 and 21.6%, respectively. The carbolinium cation structure assigned to fragment c explains the subsequent disintegration with the loss of an HCN molecule and the formation of ion f with m/e 156 (11.7%). The similar disintegration of fragment e gives ion g with m/e 141 (6.2%). Subsequent fragmentation apparently proceeds by the usual path characteristic for indole derivatives.

Under the influence of electron impact, isomeric carboline XV gives a maximum ion peak $(M-1)^+$, and the next most intense peak is the molecular ion peak (M^+) with m/e 212 (78.6%). The small peak with m/e 171 (2.7%) is possibly due to the loss of an acetonitrile molecule by the molecular ion. The fragments noted above for carboline III are also present in the spectrum.

EXPERIMENTAL

The IR spectra of hexachlorobutadiene and mineral oil suspensions were recorded with IKS-22 or UR-20 spectrometers. The UV spectra of dimethylformamide solutions were recorded with a Cary-15 spectrometer. The PMR spectra of trifluoroacetic acid solutions were recorded with an RS-60 spectrometer with hexamethyldisiloxane as the external standard. The mass spectra were obtained with a Varian CH-8 spectrometer.

4,9-Dimethyl-2-oxo- α -carboline (III). A) A mixture of 0.55 g (2 mmole) of the hydriodide of 1-methyl-2-aminoindole (I) and 0.52 g (4 mmole) of acetoacetic ester in 6 ml of dry pyridine was refluxed for 2.5 h. The mixture was then cooled to room temperature and poured with stirring into 80 ml of cold water. The resulting white precipitate was removed by filtration, washed with water until the odor of pyridine vanished, and air dried to give 0.41 g (97%) of carboline III with mp 310-312° (dec., from tetrahydrofuran).

B) A total of 0.24 g (57%) of carboline III with mp 306-308° (dec.) was similarly obtained from 0.55 g (2 mmole) of the hydriodide of I and 1.08 g (5.35 mmole) of acetylmalonic ester by refluxing in 8 ml of dry pyridine for 3 h. This product did not depress the melting point of a sample of the product described above.

4,9-Dimethyl-3-ethyl-2-oxo- α -carboline (IV). A total of 0.72 g (75%) of IV with mp 271-273° (dec., from benzene) was similarly obtained from 1.1 g (4 mmole) of the hydriodide of I and 1.26 g (8 mmole) of acetoethylacetic ester in 12 ml of dry pyridine by refluxing for 5 h.

9-Methyl-4-phenyl-2-oxo- α -carboline (V). A mixture of 0.27 g (1 mmole) of the hydriodide of I and 0.38 g (2 mmole) of benzoylacetate in 3 ml of pyridine was refluxed for 4 h. The reaction mixture was cooled to room temperature and poured into cold water. The resulting dark precipitate was separated, washed with water, dried, and dissolved in the minimum amount of benzene. Hexane was added to the benzene solution to give 0.16 g (58%) of carboline V with mp 273-275° (from chloroform).

9-Methyl-4-(p-nitrophenyl)-2-oxo- α -carboline (VI). A similar reaction was carried out with 0.27 g (1 mmole) of the hydriodide of I and 0.48 g (2 mmole) of ethyl p-nitrobenzoylacetate. The resulting resinous brown precipitate was treated with diethyl ether, and the mixture was filtered to give 0.05 g (16%) of carboline VI as a crumbly yellow powder with mp 300-304° (dec., from ethanol).

9-Methyl-3-phenyl-2-oxo- α -carboline (VII). A total of 0.25 g (46%) of carboline VII with mp 270° (from toluene) was similarly obtained from 0.55 g (2 mmole) of the hydriodide of I and 0.8 g (4 mmole) of ethyl α -formylphenylacetate by refluxing in 8 ml of pyridine for 1.5 h.

4,9-Dimethyl-3-benzyl-2-oxo- α -carboline (VIII). A mixture of 0.55 g (2 mmole) of the hydriodide of I and 0.88 g (4 mmole) of benzylacetoacetic ester in 5 ml of dry pyridine was refluxed for 1.5 h. The reaction mixture was poured into cold water, and the resulting oily precipitate was separated, washed with water, and dried. The precipitate was then dissolved in benzene, and the solution was stirred with activated charcoal and filtered. Dilution of the benzene solution with hexane precipitated 0.28 g (46%) of VIII with mp 287-290° (dec., from benzene).

4-Methyl-9-benzyl-2-oxo- α -carboline (IX). A mixture of 0.35 g (1.35 mmole) of the hydrochloride of 1-benzyl-2-aminoindole (II), 0.26 g (2 mmole) of acetoacetic ester, and 3 ml of dry pyridine was refluxed for 2.5 h, cooled to room temperature, and poured with stirring into cold water. The resulting precipitate was removed by filtration, washed with water, and air dried to give 0.33 g (85%) of IX with mp 286-288° (dec., from ethyl acetate, toluene).

4-Methyl-9-benzyl-3-ethyl-2-oxo- α -carboline (X). A mixture of 0.26 g (1 mmole) of the hydrochloride of II and 0.32 g (2 mmole) of acetoethylacetic ester was refluxed in 5 ml of dry pyridine for 2.5 h and poured into cold water. The resulting resinous brown precipitate was separated, washed initially with water and then with 5 ml of methanol, and air dried to give 0.1 g (32%) of X as a gray, free-flowing powder with mp 263-266° (dec., from toluene).

9-Benzyl-4-phenyl-2-oxo- α -carboline (XI). As in the previous experiment, 0.18 g (51%) of carboline XI with mp 226-228° (dec., from carbon tetrachloride) was obtained from 0.26 g (1 mmole) of the hydrochloride of II and 0.38 g (2 mmole) of benzoylacetate after reprecipitation from benzene solution by the addition of hexane.

5,7,12-Trimethylindolo[2,3-b]- α -carboline (XIII). A mixture of 0.27 g (1 mmole) of the hydriodide of I, 0.26 g (2 mmole) of acetoacetic ester, and 0.21 ml (1.5 mmole) of triethylamine was refluxed in 5 ml of isopropyl alcohol for 2 h. The precipitate that formed after cooling was separated and dissolved in the minimum amount of benzene. The benzene solution was passed through a column packed with aluminum oxide with elution by benzene. The eluate was evaporated to give 0.13 g (87%) of indolocarboline XIII with mp 262-264° (from acetone). This product did not depress the melting point of a sample of known structure [4].

2,9-Dimethyl-4-oxo- α -carboline (XV). Diketene [0.34 g (4 mmole)] was added dropwise with stirring to 0.27 g (1 mmole) of the hydriodide of I and 0.21 ml (1.5 mmole) of dry triethylamine in 5 ml of isopropyl alcohol, and the mixture was refluxed for 1 h. The mixture was then cooled with cold water, and the resulting crystalline precipitate was removed by filtration, washed with methanol, and air dried to give 0.14 g (66%) of III with mp 311-313° (dec., from tetrahydrofuran). This product did not depress the melting point of a sample of III described above. The slightly colored alcohol filtrate was combined with the wash methanol and diluted with water. The resulting precipitate was removed by filtration to give 0.035 g (16%) of carboline XV with mp 284-286° (dec., from acetone). Found: C 73.9; H 5.9%. $C_{13}H_{12}N_2O$. Calculated: C 73.6; H 5.7%.

3,9-Dimethyl-4-ethyl-2-oxo- α -carboline (XVI) and 3,9-Dimethyl-2-ethyl-4-oxo- α -carboline (XVII). As in the previous experiment, 0.18 g (75%) of XVI with mp 264-266° (from acetone) was obtained from 0.27 g (1 mmole) of the hydriodide of I, 0.21 ml (1.5 mmole) of triethylamine, and 0.45 g (4 mmole) of methylpropionylketene [18] by refluxing in isopropyl alcohol. Found: C 75.4; H 7.1%. $C_{15}H_{16}N_2O$. Calculated:

C 75.0; H 6.7%. The alcohol solution yielded 0.04 g (17%) of carboline XVII with mp 261-263° (from benzene). Found: C 74.7; H 6.4%. $C_{15}H_{16}N_2O$. Calculated: C 75.0; H 6.7%.

3-Methyl-4-ethyl-9-benzyl-2-oxo- α -carboline (XVIII). A total of 0.19 g (60%) of XVIII with mp 241-243° (from benzene) was similarly obtained from 0.26 g (1 mmole) of the hydrochloride of II, 0.21 ml (1.5 mmole) of triethylamine, and 0.45 g (4 mmole) of methylpropionylketene. Found: C 80.1; H 6.6%. $C_{21}H_{20}N_2O$. Calculated: C 79.7; H 6.4%.

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