PYRIDO[2,3-b]INDOLES (α-CARBOLINES) (REVIEW)

A. A. Semenov and V. V. Tolstikhina

UDC 547.752

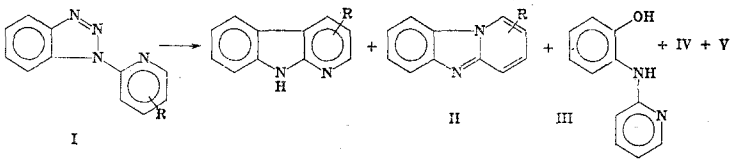
Data on the methods for the synthesis of α-carbolines and on their physicochemical and biological properties are correlated.

Pyrido[b]indoles are known as carbolines. Depending on the way in which the rings are fused, they are designated α-, β-, γ-, and δ-carbolines. The chemistry of β- and γ-carbolines has been illuminated extensively in the review literature [1-3]. Little attention has been paid to the other two types of pyrido[b]indoles, whereas new methods for the preparation of α-carbolines have been developed in recent years, diverse derivatives have become accessible, and their value for chemotherapy and toxicology has been demonstrated. The correlation of these data was the goal of the present review, in which we did not attempt to give an exhaustive list of literature sources. For brevity, we have presented only the data that most successfully, in our opinion, illustrate the main points of the appropriate sections.

1. METHODS OF SYNTHESIS

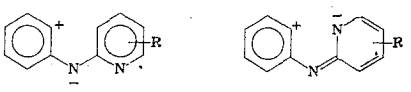
1.1. Graebe–Ullmann Reaction and Other Types of Interannular Cyclization

The synthesis of carbazoles from 1-phenylbenzotriazoles is called the Graebe–Ullmann reaction. Pyridylbenzotriazoles I undergo similar cyclization to α-carbolines upon pyrolysis or photolysis. Pyrolysis is catalyzed by acids. The best results are obtained when azoles I are heated in polyphosphoric acid (PPA) [4-6]. The preponderant decomposition products are α-carbolines in the case of alkyl derivatives (I, R = alkyl). The yields of α-carbolines decrease markedly when compounds with electron-acceptor substituents (I, R = NO_2, CO_2R) are used, and pyrido[1,2-a]benzimidazole derivatives II, 2-(2-hydroxyanilino)-pyridine derivatives III, 2-hydroxypyridine derivatives IV, and benzotriazole derivatives V predominate in the reaction mixtures [7-10].



I II III

It is assumed [8, 10] that a molecule of nitrogen is eliminated in aqueous media as a result of heterolytic cleavage of the triazole ring to give phenyl cation VI, which is attacked by the pyridine ring to give the α-carboline. The presence of an electron-acceptor group stabilizes mesomeric form VII and facilitates the formation of pyridobenzimidazole II. Nucleophilic attack on cation VI by a hydroxy or phosphate anion leads to hydroxyaniline derivatives III.



VI VII

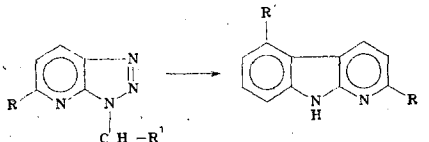
Thus the direction of the Graebe–Ullmann reaction depends on the nature of the substituents in the pyridine ring. In addition, the starting I are obtained from benzotriazole and halopyridines, which are not always readily accessible, and the reaction between them

Irkutsk Institute of Organic Chemistry, Siberian Branch, Academy of Sciences of the USSR, Irkutsk 664033. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 435-447, April, 1984. Original article submitted April 6, 1983.

0009-3122/84/2004- 0345$08.50

proceeds under severe conditions and gives the products in low yields. For example [11], the overall yield of 4-ethyl-α-carboline is only 8% in its synthesis from benzotriazole and 2-bromo-4-ethylpyridine. At the same time, this method can be extremely efficient for the preparation of individual representatives of α-carbolines that are substituted in the benzene and pyridine rings [12].

Pyrido[3,2-d]triazoles VIII have also been used as the starting compounds for the acid catalyzed Graebe–Ullmann reaction. As in the case of benzotriazoles, the pyrolysis of these substances proceeds smoothly upon heating to 180°C in polyphosphoric acid [13].

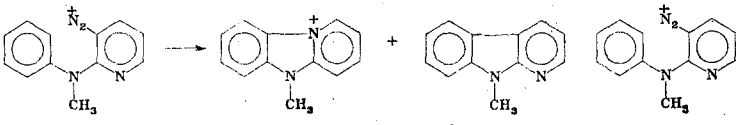


VIII

R = H, Cl; R' = H, C_6H_5, Py

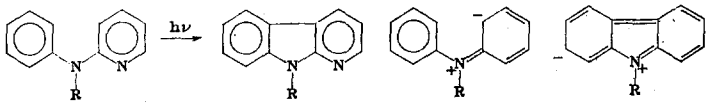
The photochemical decomposition of pyridylbenzotriazoles is not of preparative value for the synthesis of α-carbolines. Thus the principal product of the photolysis of I (R = H) is pyrido[1,2-a]benzimidazole (II, R = H), and the yield of α-carboline does not exceed 5-10% [5, 6].

Similar difficulties were noted [14] in an attempt to obtain α-carboline from diazonium salt IX via the Pschorr reaction. However, if the diazo group is located in the pyridine ring [14, 15], as in X, stirring with copper powder at room temperature initiates the formation of α-carbolines in yields that exceed 70%.



IX X

The photolysis of anilinopyridines and azides serves as an efficient method of interannular cyclization. Thus the conversion of substituted anilinopyridines XI to carbolines is realized [16] by irradiation of solutions of these compounds in cyclohexane or tetrahydrofuran with UV light at room temperature; the yields reach 80% in this case.

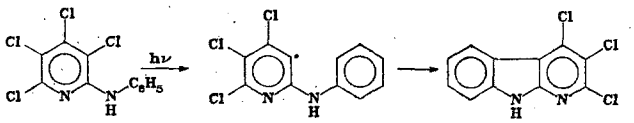


XI XII XIII

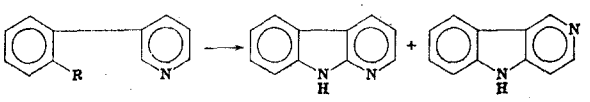
In a study of the photoconversion of diphenylamines Grellmann and co-workers [17] observed the formation of intermediate short-lived particles, viz., excited ion XII and cyclic intermediate XIII. The formation of ion XII is a consequence of charge transfer from the nitrogen atom to the ring in the excited state with subsequent intramolecular cyclization. The generation of analogous intermediate substances probably also occurs in the photocyclization of anilinopyridines.

The preparation of halogenated α-carboline XV by the photolysis of polyhalosubstituted pyridylamine XIV serves as an interesting example of the use of this method. The reaction is based on the photolability of the $C_{(3)}$–Cl bond in starting XIV and probably proceeds through an intermediate 3-pyridyl radical [18].

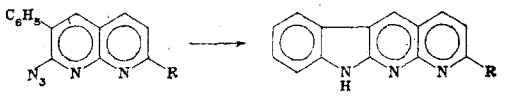
Another type of interannular cyclization is the thermolysis and photolysis of azides. If the azido group is attached to the phenyl ring, as in XVI, a mixture of α- and γ-carbolines is formed in the case of thermal decomposition. This negative feature can be avoided by using pyridyl azides. In any case, no difficulties are encountered in the photolysis of phenylnaphthyridinyl azides XVII [20].



XIV XV



XVI R =N_3, NO_2, NO

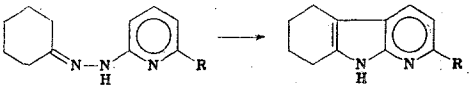


XVII R = Cl,OCH_3,NH_2,OH

These reactions proceed through intermediate nitrenes [21]. Since the latter can also be formed in the reduction of nitro and nitroso compounds, substances of the XVI type (R = NO_2 or NO) also form mixtures of α- and γ-carbolines under the influence of some reducing agents [22, 23].

1.2. Fischer Reaction

The synthesis of indoles from phenylhydrazones via the Fischer reaction has found rather extensive application for the preparation of partially hydrogenated α-carbolines. Two principal variants of the Fischer reaction are known: the action of excess amounts of strong acids on phenylhydrazones and catalytic or noncatalytic thermal indolization [24]. The presence of a pyridine ring and its quaternization in acidic media hinder the electrophilic attack necessary for one of the intermediate steps in the Fischer reaction. Despite this, cyclohexanone pyridylhydrazones XVIII can be used successfully, although under more severe conditions than in the case of the corresponding phenylhydrazones.



XVIII XIX

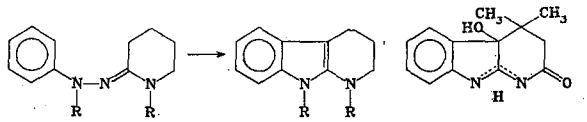
The conversion of hydrazone XVIII to 5,6,7,8-tetrahydro-α-carbolines XIX was accomplished for the first time by heating in polyphosphoric acid [25]. Yakhontov and co-workers [26-29] subsequently made a detailed study of the conditions and catalysts for this reaction. They established that the results depend to a great extent on the nature of the catalyst and the character and position of the substituents in the pyridine ring. The indicated factors not only determine the yields of normal reaction products but even change the direction of the process in a number of cases. Of the investigated catalysts, mineral and sulfonic acids were found to be the most effective substances. The highest yields of tetrahydro-α-carbolines are obtained when p-toluenesulfonic acid is used. In the case of hydrogen chloride and boron trifluoride the process is accompanied by side and anomalous reactions [26, 27].

The cyclization of cyclohexanone 2-pyridylhydrazones in the presence of Lewis acids depends on the amount of catalyst used [28]. In the arylhydrazone series the Fischer process is due to reaction of the nitrogen atom of the hydrazine part of the molecule and the catalyst. A competitive center, viz., the pyridine nitrogen atom, which ties up the Lewis acid, is present in pyridylhydrazones. As a consequence of this, the cyclization of hydrazones XVIII via the catalytic method gives the products in low yield or does not proceed at all. Only the use of a large excess of Lewis acid gives successful results. The bromine atom in the 6 position of pyridylhydrazone XVIII (R = Br) decreases the ability of the heterocyclic nitrogen atom to add the catalyst. Cyclohexanone 6-bromo-2-pyridylhydrazone is therefore converted to 2-bromo-5,6,7,8-tetrahydro-α-carboline under the influence of a catalytic amount of boron trifluoride.

Electron-donor substituents in the 5 and 6 positions of the pyridine rings significantly facilitate the cyclization of hydrazones XVIII; the yields of tetrahydro-α-carbolines increase, and the yields of anomalous products decrease in this case. Electron-acceptor substituents, which decrease the electron density on the carbon atoms of the pyridine ring, inhibit indolization even in the presence of a strong catalyst such as p-toluenesulfonic acid [28, 29].

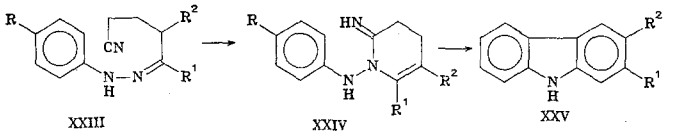
The conversion of pyridylhydrazone XVIII to a carboline is also realized by refluxing in diethylene glycol [30].

The Fischer reaction has also been used for the preparation of α-carbolines that are hydrogenated in the pyridine ring. 1,2,3,4-Tetrahydro-α-carbolines XXI were obtained from 2-piperidone phenylhydrazones XX, and oxocarboline XXII was obtained from 4,4-dimethylglutarimide monohydrazone [2, 31].



XX XXI XXII

Substituted pyrido[2,3-b]indoles are formed in the anomalous cyclization of δ-keto nitrile phenylhydrazones XXIII [32]. The mechanism of the reaction was studied by means of the labeled-atom method and mass spectrometry. It was shown that cyclic enehydrazines XXIV serve as intermediates, which undergo rearrangement to carbolines XXV.



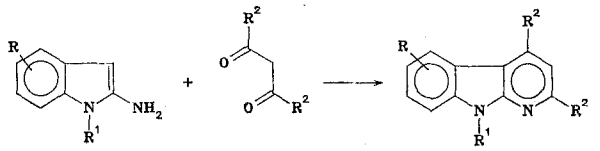
XXIII XXIV XXV

XXVI XXVII

In addition to α-carbolines, normal cyclization products, viz., indolenine-substituted nitriles XXVI, are also formed in this reaction. The maximum yields of carbolines XXV are obtained by refluxing the cyanohydrazones in glacial acetic acid. 2-Cyanoethylcyclohexanone phenylhydrazone [34] is converted to 2,3-tetramethylene-α-carboline (XXVII) under these conditions.

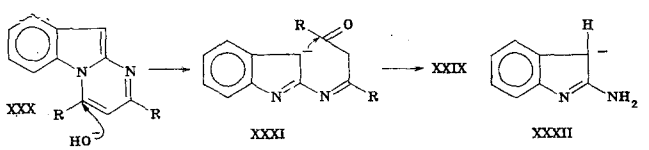
1.3. Syntheses Based on 2-Aminoindole

Convenient methods of synthesis based on 2-aminoindole have been developed. It has been established [35, 36] that 2-aminoindoles alkylated at the ring nitrogen atom (XXVIII) react with β-dicarbonyl compounds to give α-carbolines XXIX. The reaction proceeds when the components are refluxed in pyridine or anhydrous ethanol in the presence of zinc chloride.



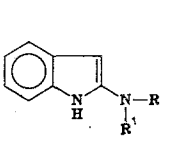
XXVIII XXIX

N-Unsubstituted analogs XXVIII (R^1 = H) undergo cyclization to pyrimido[1,2-a]indole derivatives XXX. Attempts [35] to obtain unsubstituted α-carbolines with the use of detachable protective groups were unsuccessful. This goal was achieved by other methods. First and foremost, it was established that the direction of the reaction depends on the basicity of the medium. If the reaction of 2-aminoindole with dicarbonyl compounds is carried out at high pH values (with triethylamine in isopropyl alcohol and with alcoholic alkali), only α-carbolines are formed [37]. It is assumed [38] that the change in the direction of cyclization is due to two factors. First, carbanion XXXII is generated in alkaline media, and the reaction commences with its attack on the carbonyl group of the diketone. Second, the simultaneously formed pyrimidoindole undergoes cyclization through intermediate azomethine XXXI, as shown in the scheme.



XXX XXXI XXXII

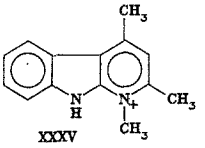
Another route to the preparation of N-unsubstituted derivatives was discovered when it was established [39, 40] that p-tolylsulfonyl- and benzyloxycarbonylaminoindoles XXXIII react with β-diketones upon heating in concentrated HBr or H_2SO_4 to give only α-carbolines with simultaneous splitting out of the protective groups; the products are obtained in excellent yields. The amide nitrogen atom is not protonated in this case, and amide XXXIII reacts as an indole in which the $C_{(3)}$ position serves as the site of highest electron density in acidic media. Initial attack by the $C_{(3)}$ atom on the carbonyl group ensures that the reaction proceeds unambiguously.



XXXIII R = H

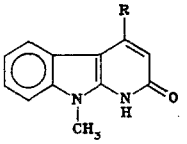
XXXIV R = CH_3

R^1 = $SO_2C_6H_4CH_3$; $C_6H_5CH_2OCO_2$



XXXV

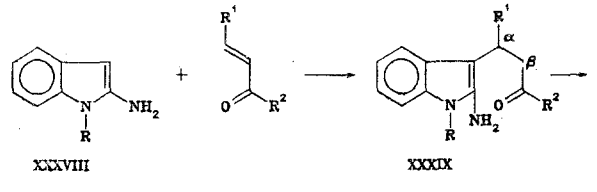
It has been shown [41] that by using substituted tolylsulfonylamidoindole XXXIV in the reaction under consideration one can obtain α-carboline salts XXXV that are methylated at the pyridine nitrogen atom. 2-Oxo-4-hydroxy-α-carboline XXXVI was obtained using malonic ester as the dicarbonyl component [42], and lactam XXXVII was obtained from acetoacetic ester or diketene [43].



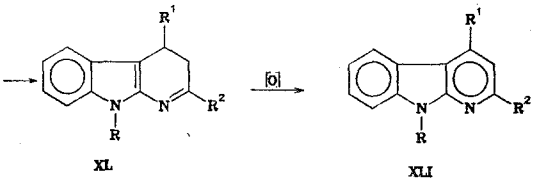
XXXVI R = OH

XXXVII R = CH_3

The synthesis of 1,3-disubstituted α-carbolines from aminoindole and diketones gives excellent results. However, it is not distinguished by its regioselectivity, and its preparative application is limited to symmetrical β-diketones. Another method based on the reaction of 2-aminoindole with α,β-unsaturated aldehydes and ketones does not have this disadvantage. The reaction between these substances proceeds in alkaline media and consists of the steps shown in the scheme [44, 45]. A noteworthy feature of this sequence is the facile aromatization of dihydrocarboline XL under the influence of atmospheric oxygen.



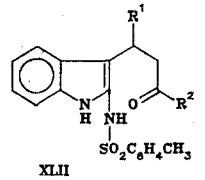
XXXVIII XXXIX



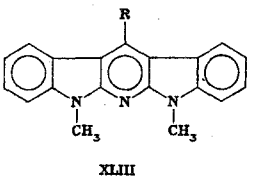
XL XLI

R^1 = Alk, Ar; R^2 = Alk, Ar

As in the preceding method, indole N-unsubstituted derivatives XLI (R = H) are obtained by using protected analogs of aminoindole XXXIII. In this case intermediate amino ketones XLII, which are converted to the final products by heating in dimethyl sulfoxide in the presence of zeolites, are isolated [46].



XLII

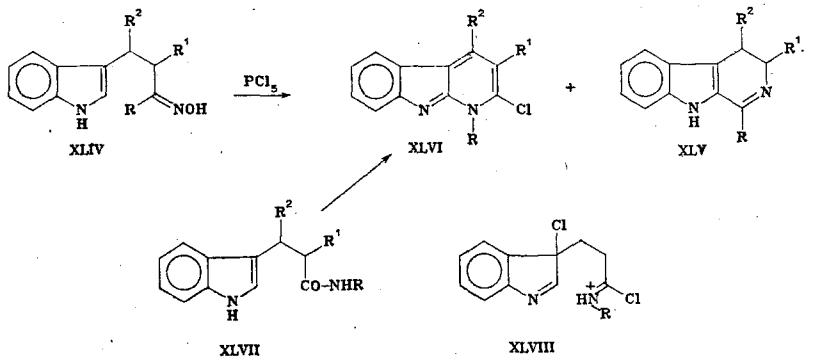


XLIII

Under severe conditions the α,β- bond in amino ketone XXXIX may be cleaved [47, 49]. The resulting carbonium ion of the benzyl type reacts with a second molecule of the aminoindole to give XLIII as a side product.

1.4. Synthesis of α-Isocarbolines from β-(3-Indolyl) Ketone Oximes and β-(3-Indolyl)propanamides

New methods for the preparation of anhydronium bases of the α-carboline series, viz., 1H-pyrido[2,3-b]indoles (α-isocarbolines), have been discovered in recent years. These methods are based on heterocyclization of β-(3-indolyl) ketone oximes and β-(3-indolyl)-propanamides. The Beckmann rearrangement-cyclization of oximes XLIV has been proposed [50] as a method for the preparation of 3,4-dihydro-β-carbolines XLV. However, in some cases oximes XLIV are capable of undergoing cyclization to α-isocarbolines XLVI under the influence of phosphorus pentachloride in warm nitrobenzene.



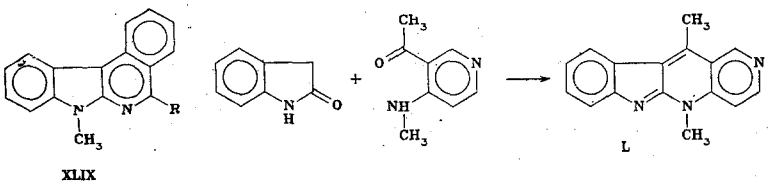
The ratios of the two reaction products (XLV and XLVI) depend to a considerable extent on the nature of the substituents in oxime XLIV. Only α-isocarbolines are formed when R^1 and R^2 are aromatic substituents [51]. In the case of alkyl substituents the α-isocarbolines are obtained in very low yields or are not formed at all. A method for the synthesis of anhydronium bases [52-54] in which the cyclization of indolylpropanamides XLVII, which proceeds under the same conditions as the rearrangement of oximes, is therefore more convenient in a preparative respect. Intermediate imido chloride XLVIII probably participates in the formation of the pyridine ring in both reactions. The reactions proceed extremely rapidly. One-minute contact of the amide or oxime with phosphorus pentachloride in nitrobenzene solution is sufficient for completion of the process at 60-70°C. Other solvents and cyclizing agents are ineffective.

The cyclization of amides XLVII serves as a convenient preparative method for the production of 1H-2-chloropyrido[2,3-b]indoles with alkyl and aryl groups (CH_3, C_2H_5, C_3H_7, C_4H_9, C_6H_{11}, and C_6H_5) in the 1, 3, and 4 positions. The halogen can be easily removed from these compounds by catalytic reduction [51].

1.5. Other Methods of Synthesis

α-Carbolines that contain additional aromatic rings can be obtained by cyclodehydration and related reactions. For example, benzo[c]carbolines XLIX are formed via the Bischler–Napieralski reaction [55, 56] from N-acyl derivatives of 3-aryl-2-aminoindole. The rearrangement of 3-phenylindole-2-carboxylic acid azide by the Curtius method serves as a modification of the method for the synthesis of four-ring system XLIX [57].

Benzo[b]-α-carbolines were obtained [58] by the reaction of aromatic o-amino ketones with oxindole. This reaction was used [59] for the synthesis of indolonaphthyridine L — the aza analog of the natural antineoplastic alkaloid ellipticine.



Several other condensed systems that contain the α-carboline three-ring system are known. However, their examination is not the task of our review. Studies in which individual representatives of α-carbolines were obtained by methods that have not found further application are also not mentioned.

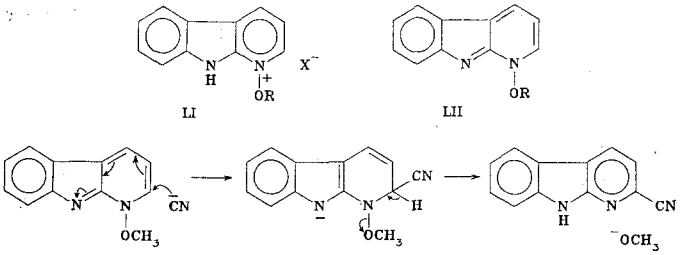
2. CHEMICAL PROPERTIES

2.1. Electrophilic Substitution Reactions

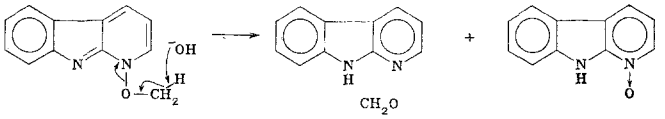
The pyridine ring of α-carboline is resistant to electrophilic attack. Substitution occurs in the benzene ring in the case of nitration and iodination. The indole nitrogen atom orients substitution to the 6 position. The formation of derivatives at the $C_{(8)}$ atom has not been noted [60-62].

2.2. Nucleophilic Substitution Reactions

Reactions involving nucleophilic substitution in the pyridine ring are most characteristic for α-carbolines. Thus pyrido[2,3-b]indole N-oxide forms a 4-chloro derivative under the influence of phosphorus oxychloride. Salts LI, which are obtained by the reaction of α-carboline N-oxide with dimethyl sulfate or triethyloxonium tetrafluoroborate, have high activities in reactions with nucleophiles [61, 64, 65]. A large number of 2-substituted derivatives have been obtained as a result of the reaction of these salts, as well as an hydronium bases LII, with nucleophiles, i.e., nucleophilic attack is directed selectively to the α-carbon atom of the pyridine ring. The alkoxy group is split out in this case in the form of an anion via the scheme presented below.



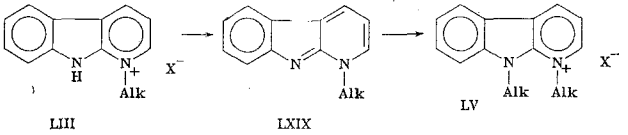
Side products in such nucleophilic reactions are formed as a result of dealkylation and dealkoxylation:



The role played by side processes is usually small [66], and the method has preparative value.

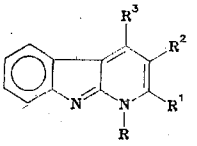
2.3. Substitution Reactions at the Nitrogen Atoms

The basic nitrogen atom of the pyridine ring in α-carboline is readily quaternized by alkyl halides or alkyl sulfates [4, 67-69] to give N-alkylcarbolinium salts LIII. Further alkylation of the anhydro bases obtained from these salts under the influence of alkalis occurs at the indole nitrogen atom. The positive charge in the resulting cations LV is localized on the nitrogen atom of the pyridine ring.



Derivatives that are monoalkylated at the indole nitrogen atom are obtained by deprotonation of α-carbolines by strong bases such as sodium hydride [70] with the subsequent action of alkylating agents.

TABLE 1. Basicity Constants and Partition Coefficients (P) of α-Isocarbolines



R	R¹	R²	R³	pK	Lit.	P [77]	
						base	salt
CH_3	H			7,55	72	104	0,05
				7,75	74		
				7,93	75		
CH_3	Cl			7,10	75	163	0,12
C_3H_7	Cl			7,30	75		0,44
C_4H_9	Cl			7,36	75		1,42
$CH_2C_6H_5$	Cl			6,53	75	2488	3627
CH_3	Cl	CH_3		7,69	75	771	0,32
CH_3	Cl	C_2H_5		7,73	75		0,76
CH_3	Cl	C_3H_7		7,77	75		
CH_3	Cl		CH_3	7,45	76		0,21
CH_3	Cl		C_2H_5	7,46	76		0,44
CH_3	Cl		C_3H_7	7,48	76		1,39
CH_3	Cl		C_6H_{13}	7,00	76		64
CH_3	Cl		C_6H_5	6,55	76		6,46
CH_3	Cl		$C_6H_3(OMe)_2$	6,84	76		
C_6H_5	H		C_6H_5	7,51	76		

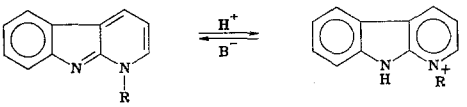
2.4. Properties of Alkyl Groups

It follows from [71] that the reactivities of alkyl groups in the pyridine ring of α-carboline are very low. Reactions such as condensation with benzaldehyde, metallation with phenyllithium, etc. do not occur in the case of 2- and 4-methyl-α-carbolines, although they are characteristic for alkylpyridines and many heterocycles that contain a pyridine fragment.

3. PHYSICAL PROPERTIES OF α-CARBOLINES AND THEIR ANHYDRONIUM BASES

3.1. Characteristics of the UV Spectra

Simple α-carbolines are colorless. The corresponding anhydronium bases are brightly colored substances, in agreement with their covalent quinoid structure LVI. The color becomes weaker in ionizing solvents; this is explained by coordination of a proton from the solvent with the indole nitrogen atom, thereby promoting an increase in the percentage of the colorless carbolinium ion LVII [72, 73]. Thus the long-wave maximum in the UV spectrum of 1-methyl-α-isocarboline experiences a hypsochromic shift from 412 to 398 nm on passing from chloroform to ethanol.



LVI LVII

The UV spectra of α-carbolines display a dependence on the pH of the medium. Thus spectra that are identical to the spectrum of carbolinium ion LVII are observed in the case of solutions in aqueous 0.1 N HCl and neutral alcohol. The UV spectra of alkaline solutions at certain pH values correspond to the absorption of anhydro base LVI.

α-Isocarbolines are monoacidic bases. All of the published data on their acid-base and lipophilic properties are presented in Table 1. It is apparent from Table 1 that the basicities and partition coefficients of the 3-substituted isomers are higher than those of the 4-substituted analogs. This can be explained by the stronger effect of the substituents in the para-(3) position on the nucleophilic $N_{(9)}$ center. The nature of the substituent in the pyridine ring also affects the pK value. Electron-acceptor substituents decrease the basicity, whereas electron-donor substituents increase it.

3.2. NMR Spectroscopy

The signals in the PMR spectrum and the spin–spin coupling constants (SSCC) in the α-carboline molecule have been completely identified [78]. The heteroatom of the indole ring affects the ortho constants of the aromatic ring protons: J_{56} (8.2 Hz) is greater than J_{67} (7.5). This small but constant effect, which is also observed for indole, benzofuran, and quinoline, may be of diagnostic value in the interpretation of the PMR spectra. The SSCC of the ortho protons of the pyridine ring also conform to the principle: $J_{34} > J_{23}$ (7.6 and 4.9 Hz, respectively). A peculiarity of N-methyl-substituted α-isocarbolines [51] is the unusually strong shift of the signal of the methyl group to the weak-field region.

Data from ^{13}C NMR spectroscopy are presented in [79].

3.3. Mass Spectrometry

The mass spectrum of α-carboline is simple and is due to splitting out of H, HCN, and C_2H_2 particles from both the molecular ion and the intense [M − 1] ion [33]. The fragmentation of alkyl-substituted derivatives differs from the fragmentation of α-carboline [80] but is similar to the fragmentation of alkylpyridines. The formation of a rearranged ion with an azatropylium ion structure due to the loss of a hydrogen atom of the alkyl group becomes the dominant process. The elimination of a molecule of acetonitrile and hydrogen from the [M − 15] fragment is characteristic for compounds that have a 2-methyl group.

The presence of an electron-acceptor substituent in 3-nitro-α-carboline results in initial fragmentation of the molecular ion with the detachment of NO_2 and NO particles. The mass spectrum does not contain an $[M - 1]^+$ ion peak, since the nitro group is not capable of stabilizing the positive charge.

Fragmentation with splitting out of the substituent in the 4 position, which is accompanied by dehydrogenation of the molecular ion, is characteristic for 3,4-dihydro-α-carbolines [46]. The principal peak in the mass spectrum of 4-methyl-5,6,7,8-tetrahydro-α-carboline corresponds to retrodiene fragmentation at the two β bonds with respect to indole with the detachment of a molecule of ethylene [81].

4. BIOLOGICAL PROPERTIES

Little study was devoted to the pharmacology of α-carbolines prior to the 1970's. It was established [82-84] only that the hypotensive properties and the ability to inhibit monoamine oxidase that are characteristic for β-carbolines are weakly expressed in the case of α-carbolines.

The first reports of the significant antivirus activity of α-carbolines were published in patents [63-65]. Interest in the study of the biological properties of α-carbolines is currently increasing. Ishizumi and Katsube [85] have synthesized a 4,5-benzo-α-carboline derivative that has antineoplastic properties. Cytotoxic activity has been observed for α-carboline and its 6-chloro, 2-phenyl, and 2-pyridyl derivatives [86].

2-Chloro-α-isocarbolines have strong cytotoxic and moderate antineoplastic properties [52, 53]. Their biological activity depends regularly on their physicochemical properties (primarily their pK values) and the nature of the substituents [77]. Compounds with small alkyl substituents and with pK values ranging from 7.0 to 7.8 units have the maximum level of biological activity. The biochemical mechanism of the action of α-isocarbolines consists in the formation of intercalation complexes with DNA [87]. Data on the anti-inflammatory [88], anxiolytic [89], and CNS-stimulating [70] activity of α-carbolines are available.

2-Aminopyrido[2,3-b]indoles display mutagenic properties [90]. They have been detected in the products of pyrolysis of protein-containing food products and in cigarette smoke [91-94] and consequently constitute part of the mutagenic background of the environment.

LITERATURE CITED

1. W. O. Kermack and J. E. McKail, in: Heterocyclic Compounds, Vol. 7, R. C. Elderfield, editor, Wiley, New York (1961), p. 344.
2. R. A. Abramovitch and I. D. Spenser, in: Advances in Heterocyclic Chemistry, Vol. 3, New York (1964), p. 79.

3. G. T. Tatevosyan, Anhydronium Bases of the Carboline Series [in Russian], Izd. Akad. Nauk Armyansk. SSR, Yerevan (1966).
4. B. Witkop, J. Am. Chem. Soc., 75, 3361 (1953).
5. A. J. Hubert, J. Chem. Soc. (D), Chem. Commun., No. 7, 328 (1969).
6. A. J. Hubert, J. Chem. Soc. (C), No. 10, 1334 (1969).
7. P. Natka-Namirskii and J. Kalinowski, Acta Pol. Pharm., 30, 1 (1973).
8. P. Natka-Namirski and J. Kalinowski, Acta Pol. Pharm., 27, 533 (1970).
9. P. Natka-Namirski and J. Kalinowski, Acta Pol. Pharm., 28, 219 (1971).
10. P. Natka-Namirski and J. Kalinowski, Acta Pol. Pharm., 31, 137 (1974).
11. P. Natka-Namirski and J. Kalinowski, Polish Patent No. 80610; Chem. Abstr., 86, 89787 (1977).
12. P. Natka-Namirski and J. Kalinowski, Polish Patent No. 72751; Chem. Abstr., 84, 17314 (1976).
13. P. Natka-Namirski, Pol. J. Pharmacol. Pharm., 30, 569 (1978).
14. R. A. Abramovitch, D. H. Hey, and R. D. Mulley, J. Chem. Soc., No. 12, 4263 (1954).
15. P. I. Abramenko, Zh. Vses. Khim. Ova., 18, 715 (1973).
16. V. M. Clark, A. Cox, and E. J. Herbert, J. Chem. Soc. (C), No. 7, 831 (1968).
17. K. H. Grellmann, J. M. Cherman, and H. Linschitz, J. Am. Chem. Soc., 85, 1881 (1963).
18. J. Bratt and H. Suschitzky, J. Chem. Soc. (D), Chem. Commun., No. 16, 949 (1972).
19. R. A. S. Smith and J. H. Boyer, J. Am. Chem. Soc., 73, 2626 (1951).
20. A. Da Settimo, G. Primofiore, V. Santerini, G. Biaggi, and L. D'Amico, Chim. Ind., 58, 878 (1976).
21. G. Smolinsky, J. Am. Chem. Soc., 82, 4717 (1960).
22. R. A. Abramovitch, I. Ahmad, and D. Newman, Tetrahedron Lett., No. 21, 752 (1961).
23. P. J. Bunyan and J. I. G. Cadogan, J. Chem. Soc., No. 1, 42 (1963).
24. N. N. Suvorov and V. P. Manaev, in: Reactions and Methods for the Investigation of Organic Compounds [in Russian], Vol. 9, Khimiya, Moscow (1959), p. 7.
25. S. Okuda and M. M. Robinson, J. Am. Chem. Soc., 81, 740 (1959).
26. L. N. Yakhontov, E. V. Pronina, and M. V. Rubtsov, Khim. Geterotsikl. Soedin., No. 4, 687 (1967).
27. L. N. Yakhontov, E. V. Pronina, and M. V. Rubtsov, Dokl. Akad. Nauk SSSR, 169, 361 (1966).
28. L. N. Yakhontov and E. V. Pronina, Khim. Geterotsikl. Soedin., No. 6, 1121 (1969).
29. L. N. Yakhontov, E. V. Pronina, and M. V. Rubtsov, Khim. Geterotsikl. Soedin., No. 2, 186 (1970).
30. A. H. Kelly and J. Parrick, Can. J. Chem., 44, 2455 (1966).
31. T. Yamazaki, K. Matoba, S. Imoto, and M. Terashima, Chem. Pharm. Bull., 24, 3011 (1976).
32. L. G. Yudin, A. N. Kost, and N. B. Chernyshova, Khim. Geterotsikl. Soedin., No. 4, 484 (1970).
33. P. A. Sharbatyan, A. N. Kost, V. V. Men'shikov, L. G. Yudin, and N. B. Chernyshova, Khim. Geterotsikl. Soedin., No. 9, 1227 (1980).
34. A. N. Kost, L. G. Yudin, and N. B. Chernyshova, Dokl. Akad. Nauk SSSR, 183, 112 (1968).
35. A. N. Kost, R. S. Sagitullin, and V. I. Gorbunov, Dokl. Akad. Nauk SSSR, 182, 838 (1968).
36. A. N. Kost, R. S. Sagitullin, V. I. Gorbunov, and N. N. Modyanov, Khim. Geterotsikl. Soedin., No. 3, 359 (1970).
37. R. S. Sagitullin, T. V. Mel'nikova, A. N. Kost, V. F. Snegirev, and E. N. Frenkel', Khim. Geterotsikl. Soedin., No. 8, 1043 (1973).
38. R. S. Sagitullin, T. V. Mel'nikova, and A. N. Kost, Khim. Geterotsikl. Soedin., No. 10, 1436 (1974).
39. A. N. Kost, V. V. Men'shikov, and R. S. Sagitullin, Zh. Org. Khim., 12, 2234 (1976).
40. A. N. Kost, R. S. Sagitullin, T. Yagodzinski, and V. V. Men'shikov, Vestn. Mosk. Gos. Univ., Khim., 17, 618 (1976).
41. V. V. Men'shikov and R. S. Sagitullin, Zh. Vses. Khim. Ova., 27, 589 (1982).
42. R. S. Sagitullin, A. N. Kost, and N. N. Borisov, Khim. Geterotsikl. Soedin., No. 9, 1207 (1970).
43. N. N. Borisov, R. S. Sagitullin, and A. N. Kost, Khim. Geterotsikl. Soedin., No. 1, 48 (1972).
44. R. S. Sagitullin, N. N. Borisov, A. N. Kost, and N. A. Simonova, Khim. Geterotsikl. Soedin., No. 1, 61 (1971).
45. R. S. Sagitullin, A. N. Kost, T. V. Mel'nikova, and P. A. Sharbatyan, Khim. Geterotsikl. Soedin., No. 7, 945 (1977).

46. R. S. Sagitullin, T. Yagodzinski, A. N. Kost, and V. V. Men'shikov, Khim. Geterotsikl. Soedin., No. 7, 925 (1978).
47. T. V. Mel'nikova, A. N. Kost, R. S. Sagitullin, and N. N. Borisov, Khim. Geterotsikl. Soedin., No. 9, 1273 (1973).
48. R. S. Sagitullin, A. N. Kost, E. D. Matveeva, and N. I. Nemudrova, Khim. Geterotsikl. Soedin., No. 7, 920 (1970).
49. A. N. Kost, R. S. Sagitullin, T. V. Mel'nikova, and G. V. Kaplun, Khim. Geterotsikl. Soedin., No. 10, 1368 (1972).
50. K. I. Kuchkova, A. A. Semenov, and I. V. Terent'eva, Khim. Geterotsikl. Soedin., No. 2, 197 (1970).
51. K. I. Kuchkova, E. P. Styngach, F. Sh. Rivilis, N. M. Frolova, and A. A. Semenov, Khim. Geterotsikl. Soedin., No. 3, 386 (1976).
52. V. V. Kononova, A. L. Vereschagin, V. M. Polyachenko, and A. A. Semenov, Khim.-farm. Zh., No. 12, 30 (1978).
53. V. V. Kononova, A. A. Semenov, E. G. Kirdei, A. P. Fedoseev, A. G. Bulavintsev, and V. I. Nechaev, Khim.-farm. Zh., No. 1, 60 (1981).
54. V. V. Kononova and A. A. Semenov, Izv. Sibirsk. Otd. Akad. Nauk SSSR, Ser. Khim. Nauk, No. 3, 147 (1979).
55. A. N. Kost, G. A. Golubeva, M. K. Ostrovskii, and V. G. Zabrodnyaya, Khim. Geterotsikl. Soedin., No. 1, 69 (1977).
56. G. Winters and N. Di Mola, Tetrahedron Lett., No. 44, 3877 (1975).
57. M. Ebisawa and K. Nishi, Japanese Patent No. 8049377; Chem. Abstr., 93, 186322 (1980).
58. W. Borsche, M. Wagner-Roemmich, and J. Barthenheier, Ann. Chem., 550, 160 (1942).
59. V. V. Kononova and A. A. Semenov, Khim. Geterotsikl. Soedin., No. 9, 1211 (1982).
60. R. R. Burtner, US Patent No. 2690441; Chem. Abstr., 49, 13297 (1955).
61. L. Stephenson and W. K. Warburton, J. Chem. Soc. (C), No. 10, 1355 (1970).
63. J. Elks, G. B. Webb, G. J. Gregory, and J. D. Cocker, West German Patent No. 1913124; Chem. Abstr., 72, 43636 (1970).
64. L. Stephenson, W. K. Warburton, G. I. Gregory, J. D. Cocker, and V. M. Clark, British Patent No. 1268771; Chem. Abstr., 77, 48432 (1972).
65. L. Stephenson, W. K. Warburton, D. Gregory, and J. D. Cocker, West German Patent No. 1913120; Chem. Abstr., 74, 13126 (1971).
66. R. Eisenthal and A. R. Katritzky, Tetrahedron, 21, 2205 (1965).
67. J. W. Armit and R. Robinson, J. Chem. Soc., 127, 1604 (1925).
68. R. H. Freak and R. Robinson, J. Chem. Soc., II, 2013 (1938).
69. A. P. Gray, E. E. Spinner, and C. J. Cavallito, J. Am. Chem. Soc., 76, 2792 (1954).
70. L. Paoloni, Sci. Rep. Inst. Super. Sanit., 1, 86 (1961).
71. W. Lauson, W. H. Perkin, and T. Robinson, J. Chem. Soc., 125, 626 (1924).
72. R. A. Abramovitch, K. A. H. Adams, and A. D. Notation, Can. J. Chem., 38, 2152 (1960).
73. J. P. Saxena, J. Indian Chem. Soc., 45, 628 (1968).
74. A. P. Gray, J. Am. Chem. Soc., 77, 5970 (1955).
75. N. N. Pogodaeva, V. V. Kononova, and A. A. Semenov, Khim. Geterotsikl. Soedin., No. 8, 1074 (1979).
76. N. N. Pogodaeva, V. V. Kononova, E. I. Terskikh, and A. A. Semenov, Khim.-farm. Zh., No. 10, 32 (1981).
77. N. N. Pogodaeva, E. I. Terskikh, N. D. Ivanova, and A. A. Semenov, Khim.-farm. Zh., No. 12, 49 (1982).
78. P. J. Black and M. Z. Heffernan, Aust. Chem., 18, 353 (1965).
79. B. M. Mustedza and J. Parrick, J. Chem. Res. (S), No. 1, 43 (1980).
80. A. A. Polyakova and R. A. Khmel'nitskii, Mass Spectrometry in Organic Chemistry [in Russian], Khimiya, Leningrad (1972).
81. R. Herbert and D. G. Wibberby, J. Chem. Soc. (B), No. 3, 459 (1970).
82. T. B. O'Dell, C. Luna, and M. D. Napoli, J. Pharmacol. Exp. Ter., 114, 306 (1955).
83. V. Z. Gorkin, L. V. Tatyanenko, D. M. Krasnokut-skaya, E. V. Pronina, and L. N. Yakhontov, Biokhimiya, 32, 510 (1967).
84. P. Natka-Namirski, S. Kurzepa, J. Kazimierczyk, H. Kierylowicz, and M. Kobylinska, Acta Physiol. Pol., 17, 145 (1966).
85. K. Ishizumi and J. Katsube, Japanese Patent No. 7879899; Chem. Abstr., 89, 197519 (1978).
86. P. Natka-Namirski and L. Kaczmarek, Pol. J. Pharmacol. Pharm., 30, 569 (1978).
87. N. N. Pogodaeva and A. A. Semenov, Khim.-Farm. Zh. (in press).

88. T. Okamoto, T. Akase, T. Izumi, S. Inaba, and H. Yamamoto, Japanese Patent No. 7220196; Chem. Abstr., 77, 152142 (1972).
89. J. Winters and N. Di Mola, West German Patent No. 2442513; Chem. Abstr., 82, 156255 (1975).
90. T. Matsumoto, Agric. Biol. Chem., 43, 675 (1979).
91. D. Ioshida, Biochem. Biophys. Res. Commun., 83, 915 (1978).
92. D. Ioshida and T. Matsumoto, Japanese Patent No. 8036401; Chem. Abstr., 93, 132377 (1980).
93. D. Ioshida and T. Matsumoto, Cancer Lett., 10, 141 (1980).
94. T. Kawachi, Hepato-gastroenterol., Supplement, 187 (1980).

INVESTIGATION OF THE MASS-SPECTROMETRIC BEHAVIOR OF AMINOMETHYL AND AMINOMETHYLENE DERIVATIVES OF TETRAHYDROFURAN

R. A. Karakhanov, M. M. Vartanyan, R. B. Apandiev, P. A. Sharbatyan, and L. Yu. Brezhnev

UDC 453.51:547.722.3'822.3'861.3'867.4.07

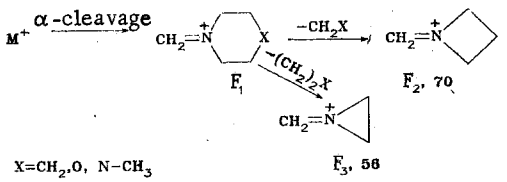
The principal pathway in the mass-spectrometric fragmentation of aminomethyltetrahydrofurans is cleavage of the α-C—C bond, in which a tetrahydrofuranyl radical is eliminated in the form of a neutral fragment, and the charge is retained on the amino fragment. This process is completely absent in methylene derivatives, for which one of the characteristic fragmentation pathways is cleavage of the β bond with retention of the charge on the hydrofuran fragment. The established mass-spectrometric principles makes it possible to reliably distinguish aminomethyl- and aminomethylenetetrahydrofurans.

New amino derivatives of the tetrahydrofuran series have been obtained by the reaction of 2-formyltetrahydrofuran with secondary amines, and some of their transformations have been studied [1, 2]. In the present research we studied the mass-spectrometric behavior of the following compounds under the influence of electron impact:

Ia-c IIa-c

a R=piperidyl, b R=morpholyl, c R=N N—CH_3

Compounds Ia-c give low-intensity molecular-ion peaks, and this constituted evidence for low stabilities of the molecules with respect to electron impact. In the case of Ic the the molecular-ion peak has a somewhat higher intensity (2.8%) as compared with the molecular-ion peaks of Ia, b (1.4%); this is due to the greater basicity of the substituent. The principal pathway in the fragmentation of Ia-c involves cleavage of the α bond of the substituent and the formation of F_1 ions, which have the same structure:



X=CH_2,O, N-CH_3

This sort of fragmentation pathway is extremely characteristic for alkylamines [3]. The peaks of these ions have considerable intensities (100, 100, and 70%, respectively).

N. D. Zelinskii Institute of Organic Chemistry, Academy of Sciences of the USSR, Moscow 117913. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 448-450, April, 1984. Original article submitted June 14, 1983.

 0009-3122/84/2004-0356$08.50