TETRAHYDRO-γ-CARBOLINES

(REVIEW)

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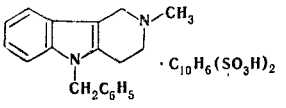
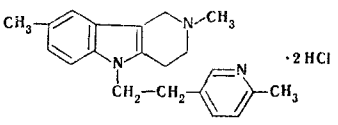
Methods for the preparation and analysis of tetrahydro-γ-carbolines and their chemical and physicochemical properties and pharmacological significance are reviewed.

Tetrahydro-γ-carbolines and their derivatives have antihistamine [1-14], anti-anaphylactic [15, 16], antiserotonin [17, 18], antiphlogistic [19], antidepressive [20], and antibradykinin [13, 21] action. Some of them display cholinolytic, local anesthetizing [1, 22-26], and antiemetic [27, 28] activity; they are also capable of reducing the permeability of skin capillaries [26].

The antihistamine preparation Omeril (I) (3-methyl-9-benzyl-1,2,3,4-tetrahydro-γ-carboline naphthalene-1,5-disulfonate salt), which is known in the Soviet Union as Diazolin, has found extensive practical application [1-3, 7, 29-32].



I

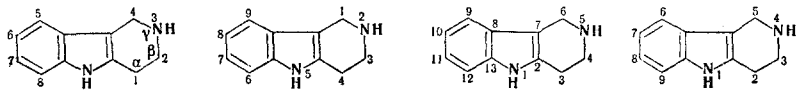


II

Dimebone (II) (or Dimeboline, 9-[2-(2-methyl-5-pyridyl)ethyl]-3,6-dimethyl-1,2,3,4-tetrahydro-γ-carboline), for which antiemetic and protective action has been noted during radiation-induced disease of the skin [13, 32, 33], has shown pronounced antihistamine action during clinical testing.

There are no reviews available on this problem, and methods for the preparation of such structures are described briefly only in a paper by Abramovich [34]. The present review encompasses the literature published through 1971.

A system in which the position of the nitrogen atom is designated by a Greek letter is most frequently used to name carbolines [35]. The most widespread system of numbering is similar to that used for carbazole:



A B C D

Precisely this numbering is recommended by the IUPAC rules (formula A) [36]. Of course, more strictly speaking one must give the nitrogen atoms lower numbers (formula B), but this procedure is less frequently adopted. In the Ring Index [37], γ-carbolines are considered to be pyrido[4,3-b]indoles, but these names are rarely used. According to the Perkin–Robinson system [38], the junction carbon atoms are also numbered (formula C). Some authors have taken the indole nitrogen atom as the starting point for numbering (formula D). The site of the piperidine nitrogen atom is sometimes designated by means of a number in-

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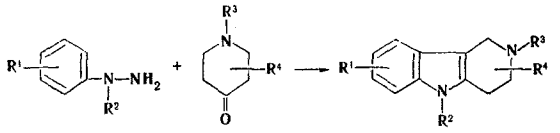
stead of letters. Finally, in the "oxa-aza" system, these structures can be called 3,9-diazafluorenes. We have presented this information in view of the considerable confusion in the literature. The IUPAC nomenclature is used in the present review.

Synthesis of Tetrahydro-γ-carbolines

Most methods for the preparation of tetrahydro-γ-carbolines are based on the Fischer indole synthesis or on condensations of the appropriate indole with building on of the piperidine ring.

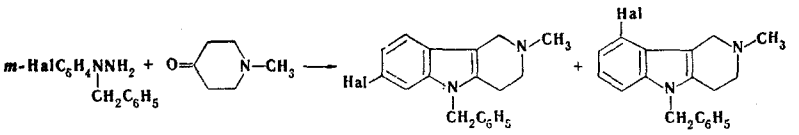
Synthesis on the Basis of the Fischer Reaction. Cyclization of arylhydrazones of γ-piperidone and its homologs under the conditions of the Fischer reaction leads to tetrahydro-γ-carbolines, but (as usual in this synthesis) the success of the reaction depends on the selection of the condensing agent.



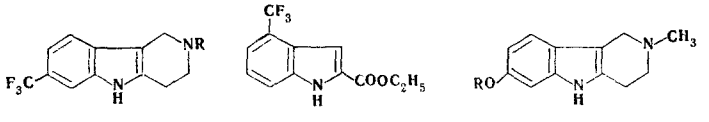
Thus glacial acetic acid and boron trifluoride etherate are unsuitable for the cyclization of 1,2,6-trimethyl-4-piperidone and tropinone phenylhydrazones [39]. The indolization of 1-methyl-4-piperidone phenyl- and p-tolylhydrazones proceeds successfully under the influence of dilute sulfuric acid [29, 40, 41], while arylhydrazones of 1,3-dimethyl- and 1,2,5-trimethyl-4-piperidones were only resinified under these conditions. The condensation of p-ethoxycarbonylphenylhydrazine and 1-(p-ethoxycarbonylphenyl)-1-n-butylhydrazine with 1-methyl-4-piperidone proceeds to give high yields in concentrated hydrochloric acid, but the carbethoxy group is saponified [42]. Triacetoneamine p-ethoxycarbonylphenylhydrazone undergoes 60-70% hydrolysis on treatment with hydrochloric acid, and only 5% indolization is observed [43]. The yield of the corresponding tetrahydro-γ-carboline was raised to 30% when a solution of HCl in absolute alcohol was used.

A 7-10% solution of hydrogen chloride in alcohol should be considered to be the most universal condensing agent [41, 43]. It was precisely in this manner that Robinson and Thornley in 1924 [44] obtained 2,2,4,4,9-pentamethyl-1,2,3,4-tetrahydro-γ-carboline from methylphenylhydrazine and N-acetyltriacetoneamine. When they used unsubstituted phenylhydrazine, they observed only qualitatively the formation of a tetrahydro-γ-carboline without a substituent attached to the indole nitrogen atom. Unsubstituted tetrahydro-γ-carboline was obtained by reduction of γ-carboline in alcohol [44].

While p-substituted phenylhydrazines react without complications in these syntheses [42, 45, 46], two isomeric tetrahydro-γ-carbolines are obtained in the case of m-halophenylhydrazones [14]:

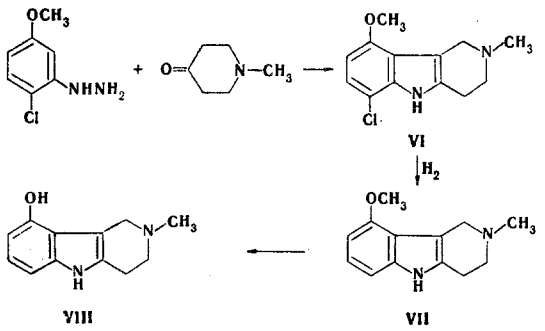


However, only one isomer was isolated in the condensation of 3-(trifluoromethyl)phenylhydrazine with 4-piperidone or 1-methyl-4-piperidone [46, 47], but the position of the CF_3 group was not accurately established. In analogy with the synthesis of a similar tetrahydrocarbazole [48], it can be assumed that this group is in the 7 position (III), although according to [49] the cyclization of pyruvic acid m-trifluoromethylphenylhydrazone gives mainly the 4-trifluoromethyl derivative (IV).



III IV V

Only the 7 isomer (V) was also isolated in the synthesis from m-alkoxyphenylhydrazones [46, 50]. The position of the substituent was established by means of the method used for tetrahydrocarbazoles [51-53] – dealkylation of different V gives the same 7-hydroxytetrahydro-γ-carboline. A roundabout path was used for the synthesis of the 5-alkoxy derivatives [46]:



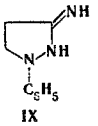
VI

VIII VII

In the cyclization of o-substituted phenylhydrazones, one should reckon with the possibility of anomalous indolization [54], which may lead not only to the 8-substituted derivative but also to the 6-substituted derivative.

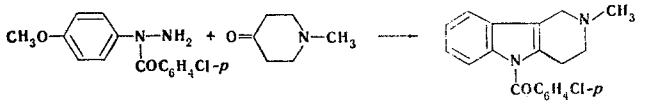
The use of α-substituted phenylhydrazines makes it possible to obtain 9-substituted tetrahydro-γ-carbolines. This route was used to synthesize 9-pyridylethyl derivatives of the II type [55-59] and several other compounds [60-65]. Labeled Dimebone (II) was synthesized in high yield via the usual scheme from labeled 1-(^{14}C-methyl)-4-piperidone [66].

An attempt to cyclize 1-(2-cyanoethyl)-1-phenylhydrazine with 1-methyl-4-piperidone did not give the corresponding tetrahydro-γ-carboline, but 1-phenyl-3-pyrazolidonimine (IX), i.e., the product of cyclization of the starting hydrazine, was isolated instead of it [67].



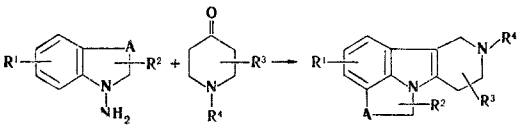
IX

Yamamoto [19, 68], in the case of the synthesis of 9-(p-chlorobenzoyl)-3-methyl-6-methoxy-1,2,3,4-tetrahydro-γ-carboline (X), showed the fundamental possibility of obtaining 9-acyltetrahydro-γ-carbolines from acylphenylhydrazines:



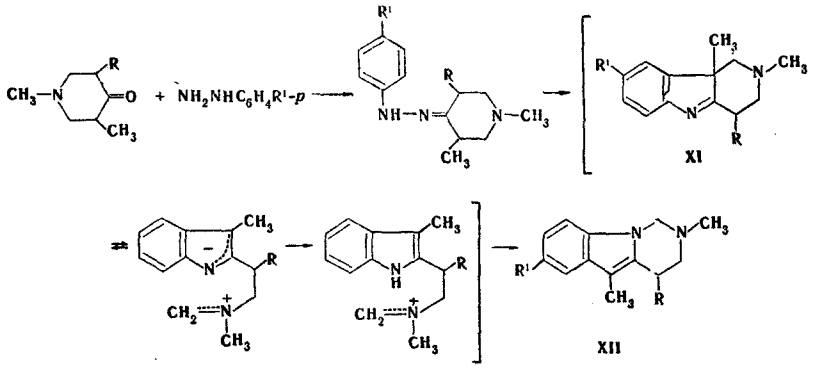
X

Phenylhydrazine analogs were also used in this reaction. For example, four-ring structures of the pyrrolo[1,2,3-f,g]- and pyrido[1,2,3,-f,g]-γ-carboline series were synthesized from 1-aminoindolines and 1-aminotetrahydroquinolines [69]:



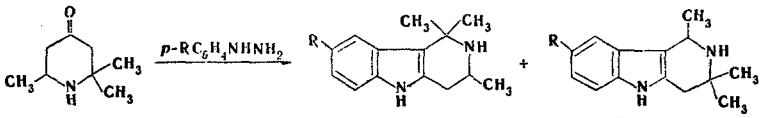
A = CH_2; CH_2CH_2

The structure of the piperidine component is of substantial importance in this synthesis. The indole synthesis for 1,2,5-trimethyl-4-piperidones could be carried out only with arylhydrazines without a second substituent attached to the nitrogen atom [29]. In addition, the synthesis was unsuccessful with nitrogen-substituted phenylhydrazines when triacetoneamine was used [43]. This is explained by the ready hydrolysis and steric hindrance of such hydrazones [43]. The structures of the substances that were obtained by this path require special verification, particularly if there was a substituent next to the carbonyl group of the piperidone. The process for such α-substituted piperidones occurs with skeletal isomerization to give 1,2,3,4-tetrahydropyrimido[3,4-a]indoles [70-73] (see scheme on top of next page). In the opinion of some investigators [72-74], indolenines XI are initially formed and then rearrange to tetrahydropyrimido[3,4-a]-indoles with cleavage of the C_4-C_{4a} bond in the manner of the reverse Mannich reaction. Indolenines XI themselves cannot be isolated or detected, but it was found that tetrahydro-γ-carbolines are rearranged to pyrimido indoles XII (R = Br) under the influence of N-bromosuccinimide [75]. The reverse transition from XII to tetrahydro-γ-carbolines was also accomplished by reduction with lithium aluminum hydride [75].



R = H, CH_3, $COOC_2H_5$; R' = H, CH_3, CH_3O, COOH, Cl, $COOC_2H_5$

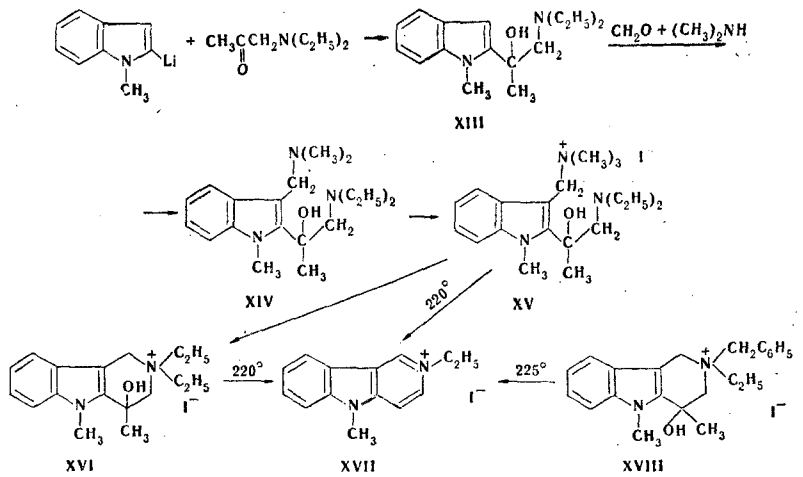
The reaction proceeds without anomalies in the case of unsymmetrical β,β'-disubstituted γ-piperidones, and the two possible isomers can be isolated [76]:



The use of 4-piperidone ketal (4,4-diethoxypiperidine) in place of 4-piperidone is also known [20].

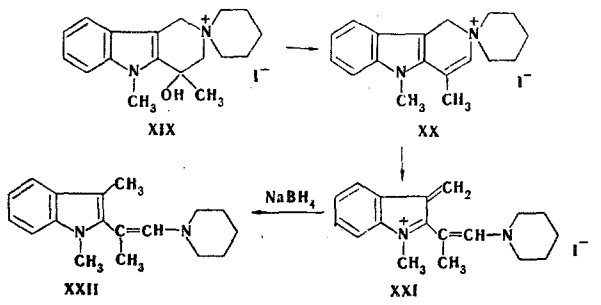
The preparation of tetrahydro-γ-carbolines with an unsubstituted piperidine nitrogen atom is fraught with difficulties due to the instability of the starting 4-piperidone. This was successfully overcome by using 1-benzyl-4-piperidone, which is readily condensed with various arylhydrazines to give 3-benzyl-tetrahydro-γ-carbolines. Debenzylation of the latter gives unsubstituted tetrahydro-γ-carbolines. Simultaneous dehydrogenation occurs when the 3-benzyl derivatives are heated with Pd/C, and this gives completely aromatized structures [77].

Synthesis on the Basis of Indole Structures. Amino alcohol XIII, which readily gives gramine derivative XIV, is formed on condensation of 2-lithio-1-methylindole with diethylaminoacetone. Selective methylation gives quaternary salt XV, which quantitatively liberates trimethylamine on rapid heating in aqueous solutions and cyclizes to tetrahydro-γ-carboline XVI [78, 79]. The latter is aromatized on heating to give 1,9-dimethyl-γ-carboline ethiodide (XVII):

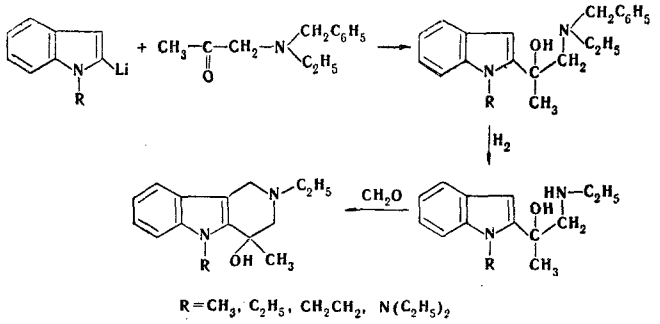


At 225°, model compound XVIII splits out a benzyl group to give the same γ-carboline (XVII).

At 220°, spirocyclic salt XIX is converted to dihydro-γ-carboline XX. When attempts are made to aromatize it, the C_4-N_3 bond is cleaved to give intensely colored salt XXI, the reduction of which with sodium borohydride gives enamine XXII.



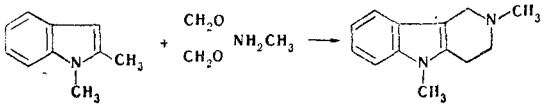
For the synthesis of nonquaternized 1-hydroxytetrahydro-γ-carbolines [78, 80], the reaction of 1-substituted 2-lithioindoles with ethylbenzylaminoacetone is carried out, the benzyl group is removed by hydrogenation, and the resulting base is cyclized by the action of formaldehyde:



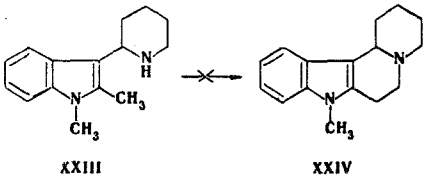
R = CH_3, C_2H_5, CH_2CH_2, $N(C_2H_5)_2$

Several condensed structures that include yet another cyclohexane [78, 80] or pyridine ring [78-82] were similarly obtained.

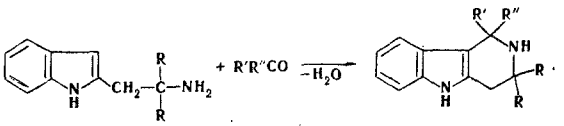
An interesting variant of this method is the reaction of 1,2-dimethylindole with 2 moles of formaldehyde and 1 mole of methylamine to form 3,9-dimethyl-1,2,3,4-tetrahydro-γ-carboline [83]:



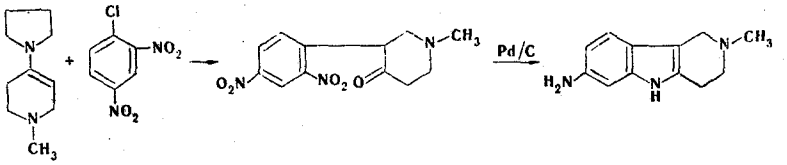
However, the α-methyl group is not sufficiently active, and the reaction gives a low yield (20%) of product. An attempt to carry out the analogous cyclization of amine XXIII with formaldehyde did not give XXIV:



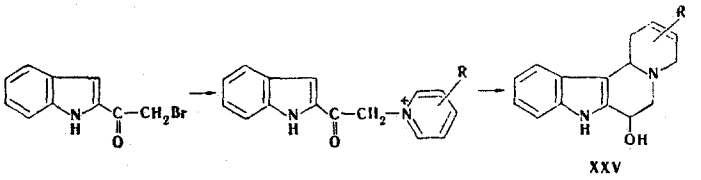
The condensation of 2-(2-aminoalkyl)indoles with aldehydes and ketones [84] proceeds more successfully. This method is limited by the low degree of accessibility of the starting amines. It was recently used for the synthesis of 4,4-dimethyl-1,2,3,4-tetrahydro-γ-carboline [85].



The synthesis of tetrahydro-γ-carbolines [86], which is based on the reductive condensation of α-(o-nitroaryl) ketones, has been described. Thus the enamine obtained from 1-methyl-4-piperidone is arylated with 2,4-dinitrochlorobenzene and then hydrogenated over Pd/C. This method was used to synthesize 6-amino-3-methyl-1,2,3,4-tetrahydro-γ-carboline in 64% yield:



2-(Bromoacetyl)indole can be converted to tetrahydro-γ-carboline XXV through the pyridinium salt after reduction with lithium aluminum hydride [87]:



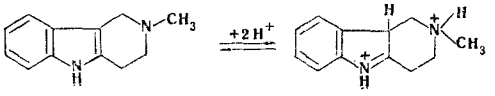
XXV

In this case, the pyridinium cation apparently attacks the 3 position of the indole ring.

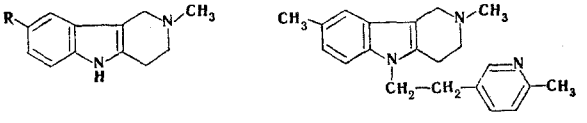
Properties of Tetrahydro-γ-carbolines

There is practically no information regarding the spectral characteristics of tetrahydro-γ-carbolines in the literature. According to our data, regardless of the character of the substituent in the 6 position, the stretching vibrations of the NH group in the IR spectra of 9H-tetrahydro-γ-carbolines appear at 3480 cm^{-1}; this is also characteristic for other compounds of the indole series.

The UV spectra of tetrahydro-γ-carbolines [88] differ considerably from the spectra of indoles [89]. The first short-wave and most intense band lies at 225-228 nm and practically does not experience any effect of the substituents in the 6 position. The second less intense band with a resolved fine structure undergoes a bathochromic shift in the series 6-CH_3, 6-Br, 6-OCH_3 (from 285 to 306 nm). Similar regularities are observed in 5-substituted indoles [89-91]. The only difference is the presence of a low-intensity maximum in the 350-360-nm region in the case of tetrahydro-γ-carbolines. Protonation at the piperidine nitrogen atom does not change the UV spectrum, but the use of a stronger protonating agent such as concentrated sulfuric acid leads to protonation not only at N_3 but also at C_{4a}, and the spectrum becomes characteristic for the indolenine system [92].

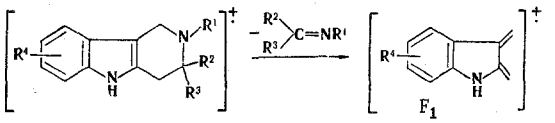


The position of the signals of the 4-H protons at 3.6 ppm, which is due to the deshielding effect of the piperidine nitrogen atom and of the 3-indolyl group, is extremely characteristic for the PMR spectra of tetrahydro-γ-carbolines [93]. These same factors cause a drawing together of the signals of the 1-H and 2-H protons, which appear at 2.5 ppm. An investigation of the PMR spectra of pyridylethylated (at the indole nitrogen atom) tetrahydro-γ-carbolines in trifluoroacetic acid [88] demonstrated the presence in them of charge-transfer complexes (CTC) formed due to the interaction of the electron-donor indole and electron-acceptor (particularly in the protonated form) pyridine systems. The appearance of the α-H signal of pyridine at anomalously strong field (δ 7.76 ppm instead of 9.3 ppm for the model compound 2-methyl-5-vinylpyridine), which is caused by shielding of it by the π-electron system of the indole ring, served as a basis for this assumption.



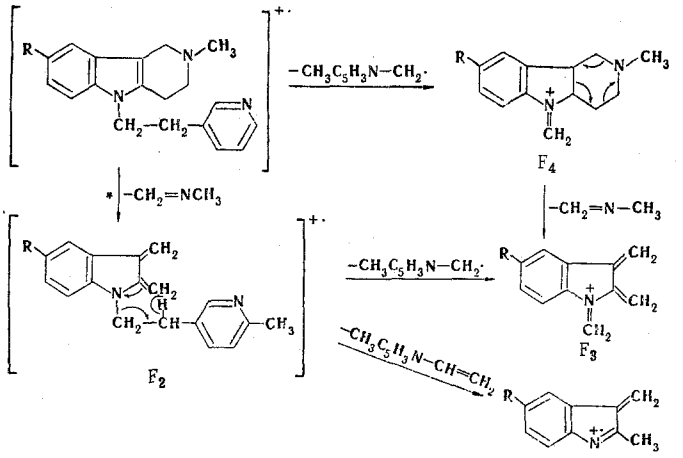
The presence of a CTC was confirmed by an investigation of the resistance of these compounds to electron impact [88], which increases in the order R=H, Br, OCH_3, CH_3. The intensification of the donor character of the substituents in this series leads to enrichment by the electrons of the indole system and consequently to strengthening of the complex. The stability of the molecular ion decreases in the same order for 9H-tetrahydro-γ-carbolines [94].

In an investigation of the mass spectra of tetrahydro-γ-carbolines, we have shown that the major process in the dissociative ionization of them under the influence of electron impact is retrodiene disintegration of the carboline system with loss of a nitrogen atom (together with the substituent) and the C_2 atom (with the substituent):



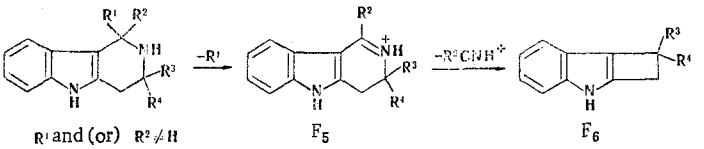
In most cases, this process gives the maximum ion (F_1) in the spectrum, regardless of the substituent in the benzene ring. The remaining fragment ions, which are formed both by disintegration of the maximum ion and by disintegration of the molecular ion via other paths, do not exceed 2-5% of the maximum.

This type of fragmentation is also retained when the hydrogen atom attached to the indole nitrogen atom is replaced by a pyridylethyl grouping, but the F_2 ion formed in this case has reduced stability and dissociates further at the β-C−C bond of the pyridylethyl group with the loss of 106 units and the formation of a stable F_3 fragment. In addition to this, one observes the formation of ion F_4 from the molecular ion by cleavage of the β-C−C bond of the pyridylethyl group and subsequent formation of an F_3 ion:



This sequence for the formation of the F_3 ion is confirmed by the corresponding metastable transitions.

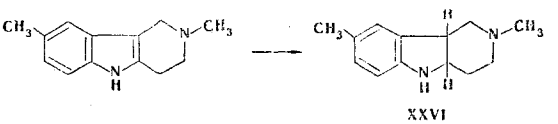
When one or two substituents are present in the 4 position of the carboline system, the fragmentation changes sharply, and disintegration proceeds primarily with the loss of a radical (or one of the radicals) to give the maximum F_5 ion, which then loses a nitrile or protonated nitrile molecule to give ion F_6.



Thus the fragmentation of 4-substituted tetrahydro-γ-carbolines differs markedly from the dissociative ionization of 2- and 3-substituted derivatives; this provides a possibility to distinguish isomeric carbolines from one another by mass spectrometry.

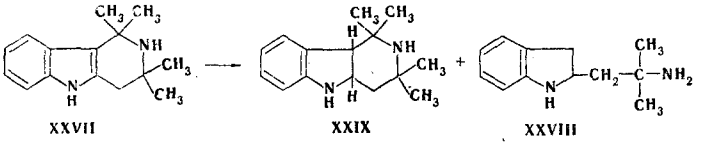
Tetrahydro-γ-carbolines are strong stable bases that form readily crystallizable salts and methiodides [41, 44].

Reduction of tetrahydro-γ-carbolines with zinc dust in hydrochloric acid−alcohol in the presence of mercuric chloride gives 1,2,3,4,4a,9a-hexahydro-γ-carbolines in 65-70% yields [95]. An interesting neuroleptic and antidepressant – carbidine (XXVI) [96] – has been discovered among them:



XXVI

Polyalkylated structures, like hexahydro-γ-carbolines, give products of reductive destruction [97-99]; for example, primarily 2-(2-methyl-2-aminopropyl)-2,3-dihydroindole (XXVIII) is formed from 2,2,4,4-tetramethyl-1,2,3,4-tetrahydro-γ-carboline (XXVII), while the corresponding hexahydrocarboline (XXIX) is obtained in only 3% yield [97].

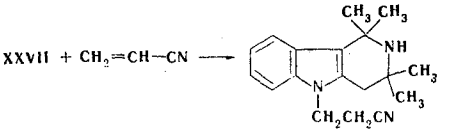


XXVII XXIX XXVIII

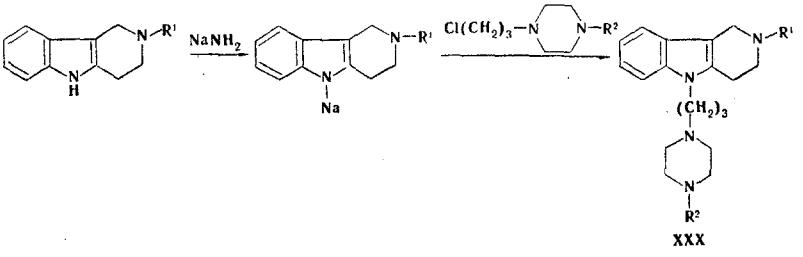
The only product in the reduction of 2,2,3,4,4-pentamethyl-1,2,3,4-tetrahydro-γ-carboline under the same conditions is 2-(β-methylaminoisobutyl)indoline [99]. The ratio of reaction products depends on the arrangement of the alkyl substituents. A decrease in the branching in the 4 position increases the yield of normal reaction product. Replacement of the methyl group in the 4 position by a phenyl group does not substantially affect the course of the reduction, which also leads to two reaction products [84]. If there is no substituent in the 2 or 4 position, the only product is the corresponding hexahydro-γ-carboline.

Alkylation and acylation at the indole nitrogen atom is hindered in tetrahydro-γ-carbolines. Thus they could not be acylated at N_9 by heating with acetic anhydride [43, 67]. To introduce a carbamide group, it was necessary to treat the sodium derivative of 3-methyl-1,2,3,4-tetrahydro-γ-carboline with carbamoyl chloride [29].

In 1966, Hahn and co-workers [67] were unable to cyanoethylate this carboline. They were apparently unfamiliar with the studies of Kamzolova, Kucherova, and Zagorevskii, who in 1964 had already shown that cyanoethylation of such structures proceeds with a Rodionov catalyst [43, 100].



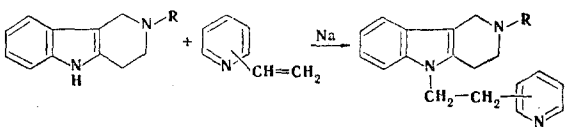
The alkylation of tetrahydro-γ-carbolines was studied in order to obtain 9-alkylaminoalkyl derivatives of pharmacological interest [29, 47]. For this, the sodium derivative was alkylated in xylene, toluene, or dimethylformamide with alkylaminoalkyl halides [20, 29]. Compounds XXX with a piperazine residue were similarly obtained [101]:



XXX

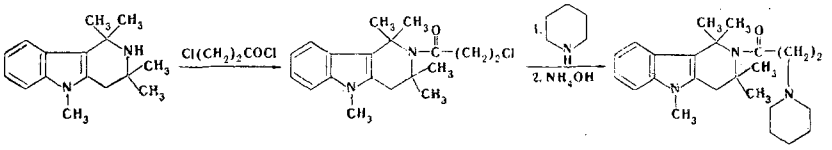
Quaternary salts at the piperidine nitrogen atom are formed with benzyl chloride [29]. However, benzylation at the indole nitrogen atom is successful when a suspension of sodium in dimethylformamide is used [102]. Alkylation with 2-(chloromethyl)pyridine also proceeds successfully to give the corresponding 9-(pyridylmethyl)tetrahydro-γ-carboline [60].

The addition of 2- and 4-vinylpyridines under the influence of sodium metal proceeds readily for tetrahydro-γ-carbolines with different alkyl groups in the 3 position [103].

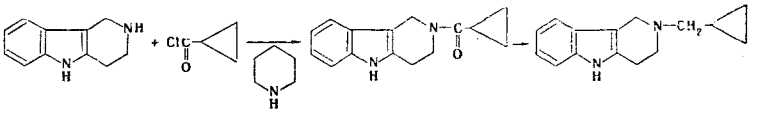


If the alkyl substituent is in the 6 position, the formation of an anion due to dissociation of the N–H bond is hindered. 3-Vinylpyridines do not add under such conditions [104]. However, if a polar aprotic solvent (dimethyl sulfoxide, for example) is used, the reaction proceeds even for alkyltetrahydro-γ-carbolines under the influence of sodium metal or sodium ethoxide [105].

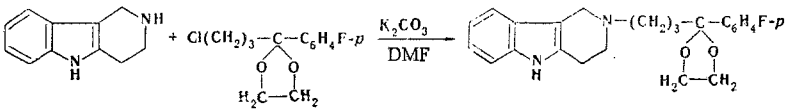
While the acylation and alkylation of the acidic indole nitrogen proceed through the formation of an anion and require the presence of strong bases ($NaOC_2H_5$, Na, NaH, $NaNH_2$) and polar aprotic solvents (of the DMF and DMSO type), these reactions for the basic piperidine nitrogen atom proceed readily in the presence of weak bases, which act as a hydrogen halide acceptor. Thus the action of β-chloropropionyl chloride in dioxane on 2,2,4,4,9-pentamethyltetrahydro-γ-carboline in the presence of potassium carbonate smoothly gives the corresponding acyl derivative (although the nitrogen atom is shielded by methyl groups), which was subsequently converted to the β-piperidinopropionyl derivative by successive treatment with piperidine and ammonium hydroxide [106].



Acylation with cyclopropanecarboxylic acid chloride was accomplished in the presence of piperidine [20]. The reduction of this acyl derivative demonstrates one of the paths for the preparation of 3-alkyltetrahydro-γ-carbolines.

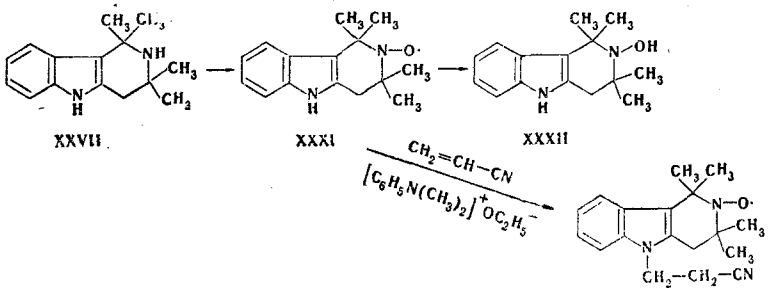


The direct alkylation of tetrahydro-γ-carbolines in DMF in the presence of potassium carbonate is also known. Thus, under these conditions, it was possible to alkylate the piperidine nitrogen atom of 4-(p-fluorophenyl)-4,4-ethylenedioxy-1-chlorobutane [20, 107]:



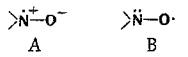
There are not examples of alkylation or acylation of 3H,9H-tetrahydro-γ-carbolines (for which these reactions at both nitrogen atoms might have been followed) in the literature.

Rozantsev and Shapiro [108] isolated a long-lived free radical – 2,2,4,4-tetramethyl-1,2,3,4-tetrahydro-γ-carboline 3-oxyl (XXXI) – in the catalytic oxidation of 2,2,4,4-tetramethyl-1,2,3,4-tetrahydro-γ-carboline (XXVII) with hydrogen peroxide in the presence of sodium tungstate.



Reduction of this radical gives 3-hydroxy-2,2,4,4-tetramethyl-1,2,3,4-tetrahydro-γ-carboline (XXXII), which is again oxidized to XXXI by air oxygen. Hydrogenation of XXXI over Raney nickel gives the starting XXVII. Cyanoethylation of XXXI proceeds without involving the free valence [109].

Calculation of the N–O fragment in such radicals by the Hückel MO method and investigation of the ESR spectra and dipole moments have shown that of the two possible resonance structures, structure A with an unpaired electron on the nitrogen atom makes the major contribution [110].



The λ_{max} band at 240 nm (ε 1500) in the UV spectrum of radical XXXI corresponds to a $\pi \rightarrow \pi^*$ transition, but Rozantsev and Shapiro assign the λ_{max} band at 460 nm (ε 10) to an $n \rightarrow \pi^*$ transition caused by excitation of the unshared pair of p_y^2 electrons on the oxygen atom with transition to a π^* molecular orbital.

The most intense ion peaks in the mass spectra of similar N-oxides are $(M-NO)^+$, $(M-NO-CH_3)^+$, $[M-NO-CH(CH_3)]^+$, and $(M-NO-CH_3-C_2H_4)^+$; this is evidence for preferred disintegration via an iminoxyl fragment [111].

Other radicals were similarly obtained from polyalkylated tetrahydro-γ-carbolines [109], and their antioxidant properties were investigated [112].

Analytical Methods for the Investigation of Tetrahydro-γ-carbolines

In connection with the use of antihistamine preparation in medicine, tetrahydro-γ-carbolines [primarily Diazolin (I)] have also been subjected to analytical study. Microcrystalline tests and color reactions that make it possible to distinguish it from other antihistamine preparations have been described for it [113-116]. Thus I reacts with mercuric chloride to give characteristic crystals in the form of rosettes and sometimes dense needles, but it reacts with ammonium thiocyanate to give rosettes; the sensitivities of the methods are 0.25 and 0.5γ, respectively [113, 114].

Of interest is a combination of a thermomicroscopic method with a spectrophotometric method that makes it possible to not only accurately determine the melting point but also to investigate the absorption spectrum near the melting point [117].

A yellow coloration with bromine water, which is appreciable even for a 0.05% solution, is characteristic for Diazolin [115]. The reaction with fuming nitric acid, during which a gelatinous precipitate that loses its yellow-green color on heating and reacquires it on cooling is formed, is of certain analytical value [115].

A combination of paper and thin-layer chromatography with development with formalin and sulfuric acid or with a modified Dragendorff reagent [116] is used in the analysis of mixtures of antihistamine preparations. According to our data, convenient solvent systems for aluminum oxide and paper, respectively, are chloroform : absolute alcohol (8 : 1) and butanol : acetic acid : water (10 : 1 : 10); these systems make it possible to distinguish diverse tetrahydro-γ-carbolines.

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