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γ-CARBOLINES AND THEIR HYDROGENATED DERIVATIVES

3.* HYDROGENATED DERIVATIVES OF γ-CARBOLINES: CHEMICAL AND BIOLOGICAL PROPERTIES (REVIEW)

R. S. Alekseyev[1], A. V. Kurkin[1], and M. A. Yurovskaya[1]**

Published data on the chemical transformations and biological properties of dihydro-, tetrahydro-, and hexahydro-γ-carbolines are reviewed.

Keywords: 1,2- and 3,4-dihydro-, 1,2,3,4-tetrahydro-, and 1,2,3,4,4*a*,9*b*-hexahydro-γ-carbolines, Dimebon, alkylation, nucleophilic substitution, transformation of tetrahydropyridine ring, biological activity.

The hydrogenated derivatives of γ-carboline are currently provoking undiminishing interest both in organic and medicinal chemistry and in pharmacology in connection with the broad spectrum of biological activity exhibited by them, as demonstrated by the increase in the number of publications on this subject. In particular, in 2010 a review [2] on the synthesis and physiological activity of 2,3,4,5-tetrahydro-1H-pyrido-[4,3-*b*]indoles (1,2,3,4-tetrahydro-γ-carbolines), partly overlapping the subject matter of our series of reviews on γ-carbolines as a class of compounds as a whole, appeared in the press.

At the present time a series of medicinal products containing a γ-carboline skeleton have been firmly incorporated into medical practise: Diazolin **1** [3], Dimebon **2** [4], Dorastine **3** [5] (antiallergic products) and Gevotroline **4** (an antipsychotic) [6] – derivatives of tetrahydro-γ-carboline; Carbidine **5** (a neuroleptic and antipsychotic) [7] and Stobadine **6** (an antiarrhythmic) [8] – derivatives of hexahydro-γ-carboline. Special attention is drawn to the neuroleptic action of the original domestically produced product Dimebon **2**, which was recently found to be highly effective for the treatment of Alzheimer's disease [9] and was named "Molecule of the month" in the August 2007 edition of Prous Science [10].

Our previous communication [1] was devoted to methods for the synthesis of hydrogenated derivatives of γ-carbolines and reflects a whole variety of synthetically accessible structures for this class of compound. However, hydrogenated γ-carbolines can be not only potential medicinal products but can also act as synthetic precursors for physiologically active compounds of the indole series [11]. This is why the main subject of discussion in this review is the varied and, at times, unusual chemistry of compounds of this type and their biological characteristics.

*For Communication 2, see [1].

** To whom correspondence should be addressed, e-mail: yumar@org.chem.msu.ru.

[1]M. V. Lomonosov Moscow State University, Moscow 199992, Russia.

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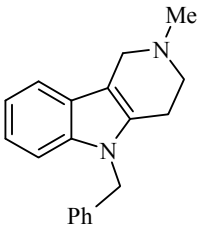
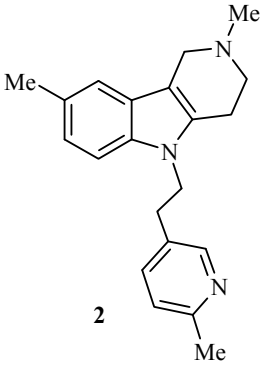


1

Diazoline



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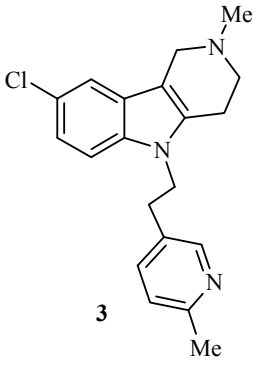
Dimebon



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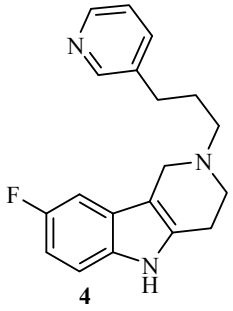
Dorastine



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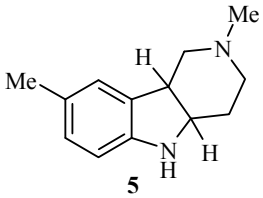
Gevotroline



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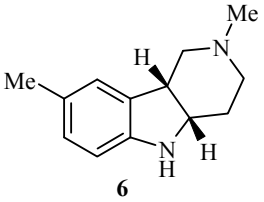
Carbidine



6

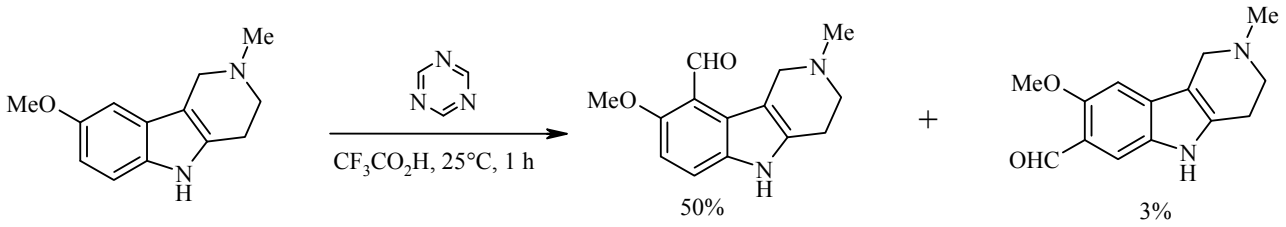
Stobadine

CHEMICAL PROPERTIES OF HYDROGENATED γ-CARBOLINES

The 1,2- and 3,4-dihydro-γ-carbolines have properties typical of 2,3-disubstituted indoles. As a rule, dihydro-γ-carbolines are used as the starting compounds for the production of aromatic γ-carbolines (examples in the review [12]) and tetrahydro-γ-carbolines (examples in the review [1]).

Similarly hexahydro-γ-carbolines do not exhibit specific chemical properties since they are structures containing condensed indoline and piperidine fragments, giving rise to their aniline character in chemical transformations; hexahydro-γ-carbolines are strong and stable bases (the piperidine fragment) and are capable of entering into electrophilic aromatic substitution in the benzene ring preferentially at the *para* position in relation to the aniline nitrogen atom [13]. Like normal anilines, 5-unsubstituted hexahydro-γ-carbolines undergo alkylation and acylation at the N(5) atom [13, 14] and also pyridylethylation under the conditions of acid catalysis [15]. Attempts at the oxidation of hexahydro-γ-carbolines containing substituents at positions 5 or 8 to the corresponding tetrahydro derivatives by means of chloranil or palladium black were unsuccessful [13].

Much greater interest is aroused by tetrahydro-γ-carbolines, which can be regarded as cyclic structural analogs of gramines, and it is this that determines their very diverse chemistry. In the case of tetrahydro-γ-carbolines we will not specially discuss the electrophilic substitution reactions in the benzene fragment, characteristic of all derivatives of indole, on account of the absence of a specific effect from the tetrahydropyridine ring on this process. However, it is worth mentioning, for example, that the corresponding 9- and 7-formyl derivatives are formed in a ratio of 17:1 during the Gattermann formylation of 8-methoxy-2-methyl-1,2,3,4-tetrahydro-γ-carboline under the modified conditions of Adams [16].



GENERAL CHARACTERISTICS OF TETRAHYDRO-γ-CARBOLINES

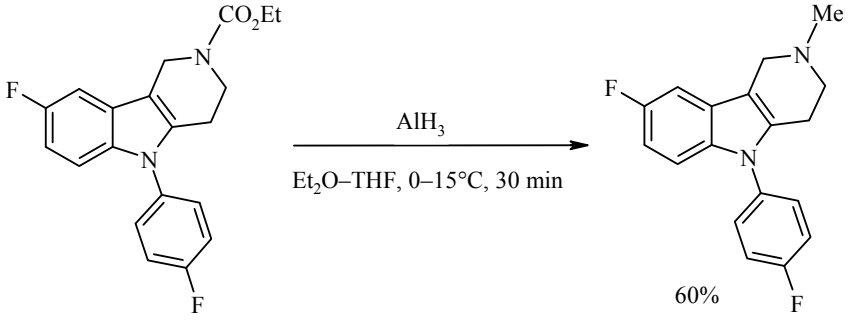
Tetrahydro-γ-carbolines are π-electron-donating aromatic systems, which allows them to form charge-transfer complexes with electron-deficient molecules such as 3,5-dinitrobenzonitrile [17]. In addition, derivatives of γ-carbolines containing electron-deficient substituents in the side chain can form intramolecular charge-transfer complexes on account of reaction of the electron-excessive indole and electron-deficient (particular in the protonated form) pyridine systems, as for example 5-[2-(6-methylpyridin-3-yl)ethyl]-substituted tetrahydro-γ-carbolines in trifluoroacetic acid [18].

1,2,3,4-Tetrahydro-γ-carbolines and their salts protonated at the N(2) atom have fluorescent properties in the near UV region (λ_{max} 348 nm at pH 5.0 and 357 nm at pH 10.5): the relaxation time for carboline (pH 10.5) is 4.6 nsec, for the salt (pH 5.0) 5.5 nsec; the quantum yields are 0.41 for the salt and 0.33 for the base [19]. The UV, IR, ^{1}H NMR, and mass spectra for some tetrahydro-γ-carbolines were examined in [20].

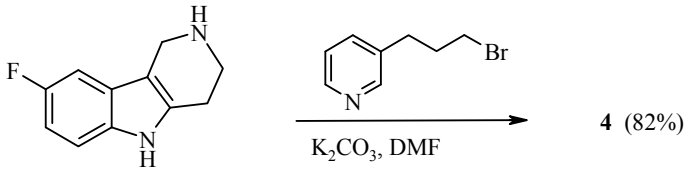
REACTIONS AT THE PIPERIDINE N(2) ATOM

Tetrahydro-γ-carbolines are strong bases and nucleophiles that form readily crystallizing protic salts with protic acids and methiodides [21].

For the basic piperidine nitrogen atom acylation and alkylation, characteristic of secondary amines, take place extremely readily in the presence of weak bases acting as hydrogen halide forming acceptors. Thus, acylation at the piperidine nitrogen atom is realized by the action of the acid chlorides of various carboxylic acids in dioxane in the presence of potassium carbonate [22], piperidine [23], or triethylamine [24]. Reduction of the corresponding 2-acyl derivatives leads to 2-alkyltetrahydro-γ-carboline derivatives.

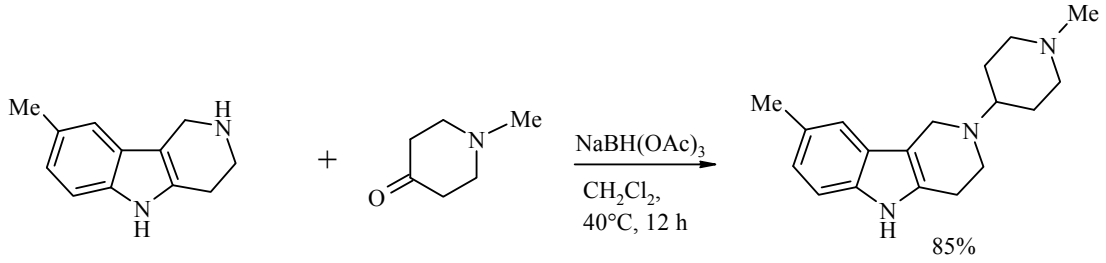


Alkylation at the N(2) atom can be realized by the action of the most varied alkyl halides in the presence of potassium carbonate and catalytic amounts of NaI in acetonitrile [25] and also of potassium carbonate [6, 26, 27] or triethylamine in DMF [6].



4 (82%)

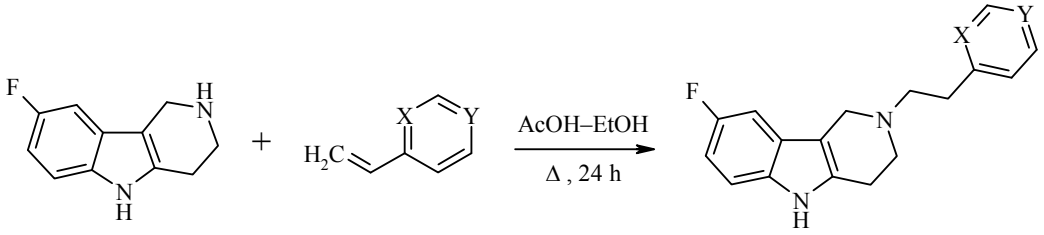
2-Alkyl-1,2,3,4-tetrahydro-γ-carboline derivatives can be obtained by reductive amination of the corresponding aldehydes and ketones. For example, 1,2,3,4-tetrahydro-γ-carbolines containing a piperidine substituent at the N(2) atom are formed during the reductive amination of 4-piperidone [28].



85%

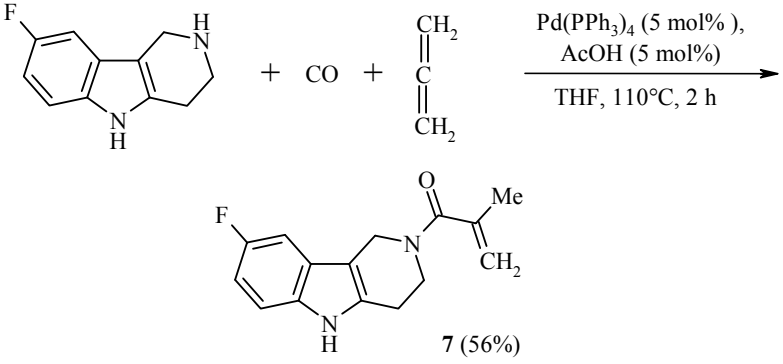
In the case of N(2)-substituted tetrahydro-γ-carbolines the reaction with alkyl halides in the absence of bases leads to the formation of quaternized tetraalkylammonium derivatives, among which the example of a carboline structure quaternized with alkyl bromide containing a D-glucose fragment is well known [29].

Having nucleophilic characteristics, N(2)-unsubstituted tetrahydro-γ-carbolines add at an multiple activated bond, e.g., to 2- and 4-vinylpyridines with the formation of the corresponding pyridylethyl derivatives [6].



X = N, Y = CH (38%);
X = CH, Y = N (54%)

N(2)-Unsubstituted 1,2,3,4-tetrahydro-γ-carbolines enter into an unusual Pd-catalyzed transformation with allenes and carbon(II) oxide and form a γ-carboline amide of methacrylic acid **7** [30].

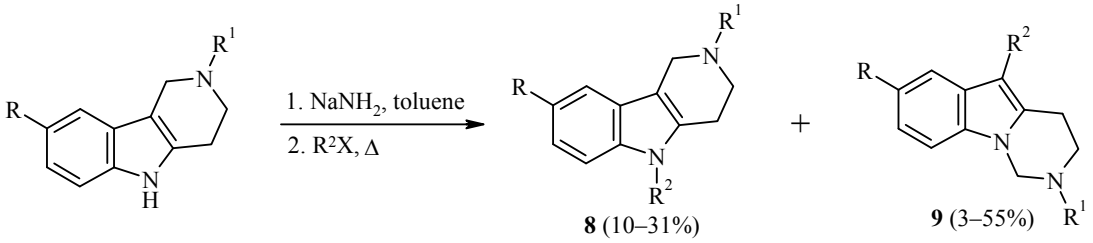


7 (56%)

REACTIONS AT THE INDOLE N(5) ATOM

The acylation and alkylation of the NH-acidic indole nitrogen atom in tetrahydro-γ-carbolines takes place through the formation of an anion, and this requires the presence of strong bases (EtONa, Na, NaH, $NaNH_2$) and polar aprotic solvents (DMF, DMSO) [20, 31-33].

Attempts at the alkylation of tetrahydro-γ-carbolines at the indole nitrogen atom with sodium amide in nonpolar solvents (toluene, xylene, etc.) led to the formation of N-alkyl derivatives **8** (10-31%) and tetrahydropyrimido[3,4-*a*]indoles **9** (3-55%) [34]. The reasons leading to such behavior in this transformation will be discussed in greater detail in the section on the recyclization of the piperidine fragment.



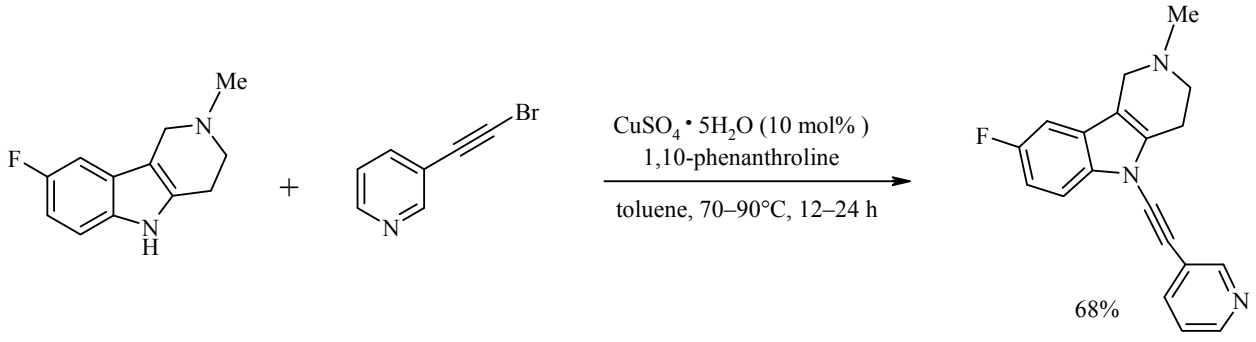
R = H, Cl, Me; R^1 = Me, Bn; R^2 = Bn, Pr, Bu, All; X = Cl, Br

It is interesting to note that the alkylation of 2-benzyltetrahydro-γ-carboline with 3-(dimethylamino)-propyl chloride in toluene in the presence of $NaNH_2$ takes place at the N(5) atom with a yield of 71% [35].

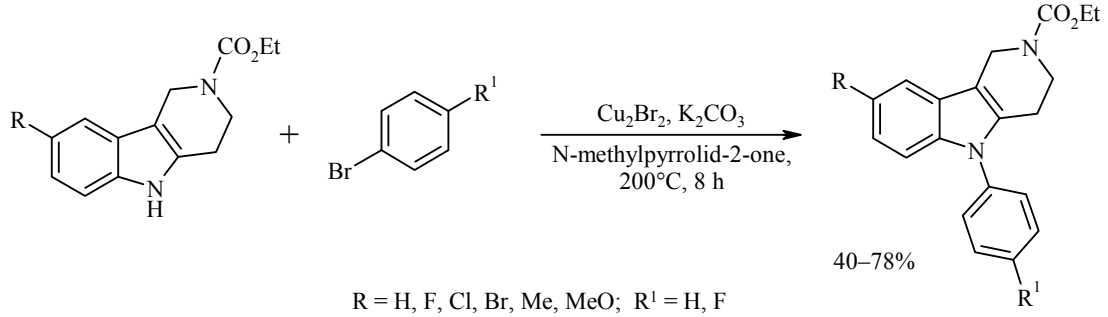
Oxiranes can also act as alkylating agents, and their reaction in the presence of K_3PO_4 in DMF leads to the corresponding 5-(2-hydroxy)ethyl derivatives of tetrahydro-γ-carbolines [2].

Alkylation at the indole nitrogen atom can also be realized under the conditions of phase-transfer catalysis [36].

An example of the ethynylation of a tetrahydro-γ-carboline derivative at the N(5) atom with 3-(bromoethynyl)pyridine in the presence of copper sulfate is known [37]. There are data on the occurrence of similar transformations for bromoethynylbenzene [2].



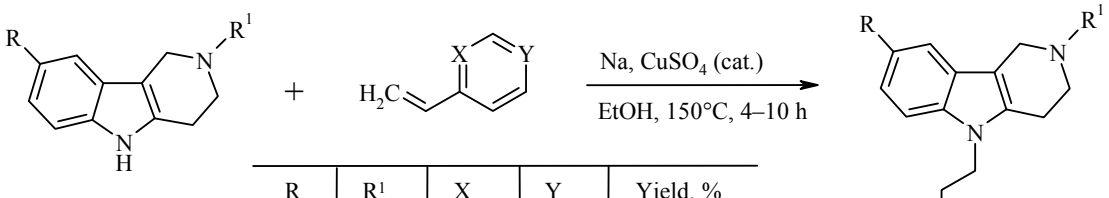
The arylation of 1,2,3,4-tetrahydro-γ-carbolines can be realized under the conditions of the Ullmann reaction [24, 38, 39].



R = H, F, Cl, Br, Me, MeO; R^1 = H, F

Under analogous conditions with bromoazines in the presence of N,N'-dimethylethylenediamine it was possible to obtain 25-56% yields of the corresponding derivatives containing an azine fragment at position 5 of the γ-carboline skeleton [37].

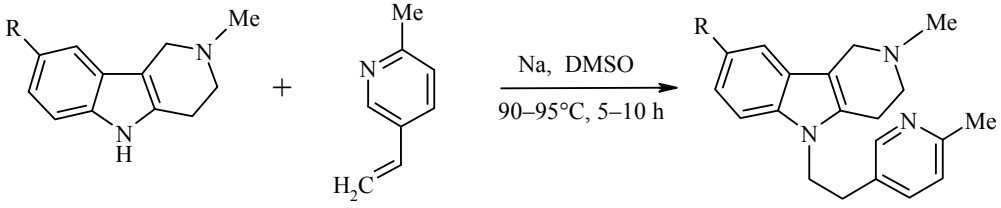
Apart from alkylation by alkyl halides, N(5)-alkyltetrahydro-γ-carbolines can also be obtained by the addition of the γ-carboline fragment at an activated multiple bond. 2-Alkyltetrahydro-γ-carbolines add readily to 2- and 4-vinylpyridine under the influence of metallic sodium in alcohol [15].



R	R^1	X	Y	Yield, %
H	Pr	CH	N	62
H	Pr	N	CH	48
H	Bu	CH	N	58
H	Bu	N	CH	50
Me	Bu	CH	N	14

For 2- and 4-vinylpyridines the process can be realized with higher yields of the desired compounds in the DMSO–60% aqueous KOH system with tetrabutylammonium sulfate as phase-transfer catalyst [28].

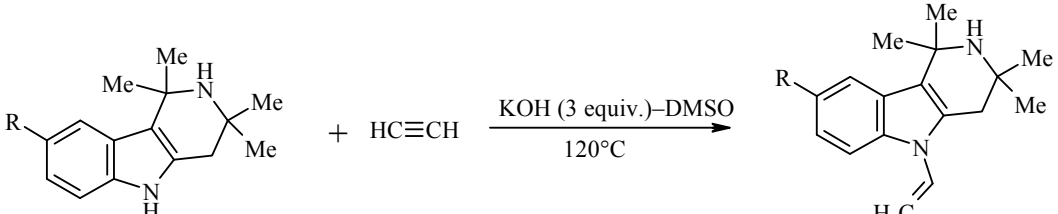
If however the vinyl group is attached at position 3 of the pyridine ring its polarization is significantly reduced, and direct pyridylethylation of the indole structures cannot occur. However, if bases (Na, EtONa, or NaH) in aprotic polar solvents are used (a superbasic medium) direct introduction of the pyridylethyl substituent at position 5 becomes possible [40].



R	Yield, %
H	54
Me	46
Br	19
MeO	10

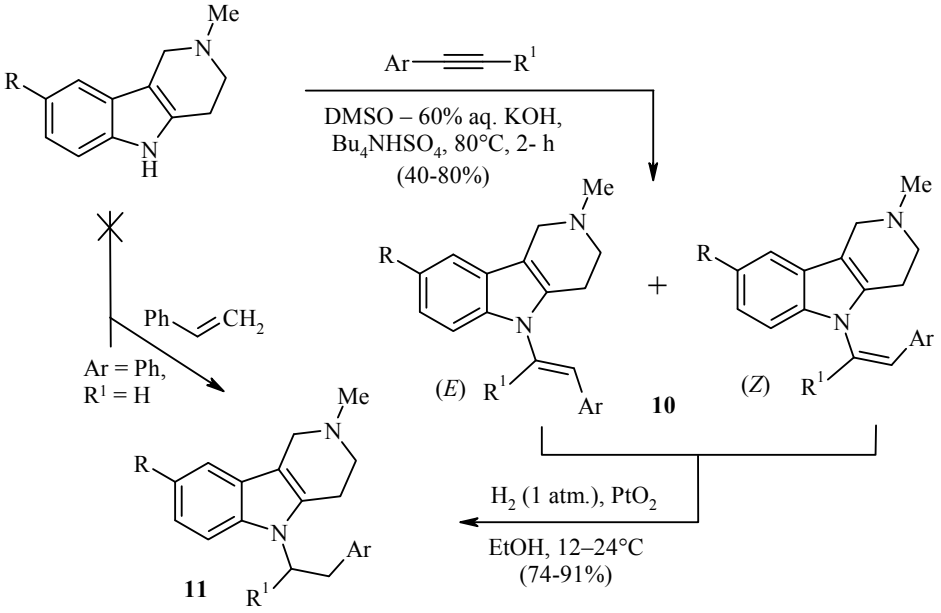
Tetrahydro-γ-carbolines also add through the N(5) atom to other compounds containing an activated double bond, e.g., to ethyl acrylate or acrylonitrile in the presence of triton B (Rodionov's catalyst) [41].

With the superbasic system KOH–DMSO it is possible to realize the N-vinylation of 1,2,3,4-tetrahydro-γ-carbolines by the action of acetylene at 100-120°C and atmospheric pressure [42].



R = H (93%), R = Me (99%)

Tetrahydro-γ-carbolines add to aryl- and pyridylalkynes with good yields under the conditions of phase-transfer catalysis with the formation of a mixture of the (*Z*)- and (*E*)-isomers of the 5-vinyl derivatives **10**; they can be reduced to the corresponding 5-(2-arylethyl)tetrahydro-γ-carbolines **11**, which cannot be obtained by addition to styrenes [37, 43].



R = H, Me, MeO, F, CF_3; R^1 = H, Me;
Ar = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-FC_6H_4, 4-$CF_3C_6H_4$, 2-Py, 3-Py, 4-Py

Sulfonyl halides react readily with N(5)-unsubstituted γ-carbolines in the presence of NaH in DMF with the formation of the corresponding N-sulfonyl derivatives [2, 44].

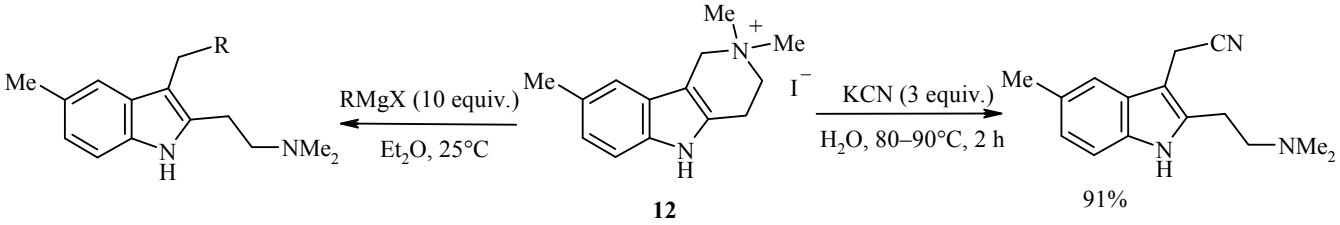
TRANSFORMATIONS WITH THE PARTICIPATION OF THE PIPERIDEINE RING

A special feature of 1,2,3,4-tetrahydro-γ-carbolines is the possibility of chemical transformations with the participation of the piperideine ring accompanied by its opening, recyclization, or enlargement. In this section we examine all these types of transformations of the γ-carboline skeleton in turn.

Transformations Accompanied by Opening of the Piperideine Ring

Tetrahydro-γ-carbolines are cyclic analogs of gramines, and the reaction of their quaternized derivatives with nucleophilic agents must therefore be accompanied by opening of the piperideine ring with cleavage of the C(1)–N(2) bond, leading to the formation of derivatives of isotryptamines difficult to obtain by other methods [45]. The reactivity of γ-carboline structures is much lower than that of gramines, and it is therefore essential to use their quaternized derivatives for nucleophilic opening of the compounds.

Only a small number of examples illustrating successful opening by the action of C- [45-48], S- [49-51], N-, and O- [45] nucleophiles are known from the published data. Thus, the reaction of the methiodide **12** with such C-nucleophiles as MeMgI, PhMgBr, and cyanide ion leads smoothly and with good yields to cleavage of the piperideine fragment with the formation of the corresponding derivatives.

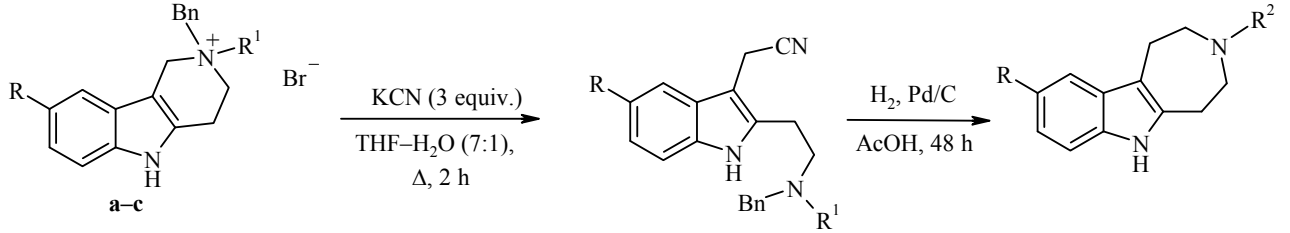


12

R = Me, X = I (74%); R = Ph, X = Br (78%)

Similar N,N-dialkylisotryptamine derivatives can be used for the production of the corresponding 2-vinylindoles by means of a Hofmann elimination [46].

The indole derivatives **13** and **14**, obtained during opening of quaternized tetrahydro-γ-carbolines by C-nucleophiles, can be used for the synthesis of the corresponding 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]- and 2,3,4,5,6,11-hexahydroazocino[4,5-*b*]indoles **15** and **16** [48].

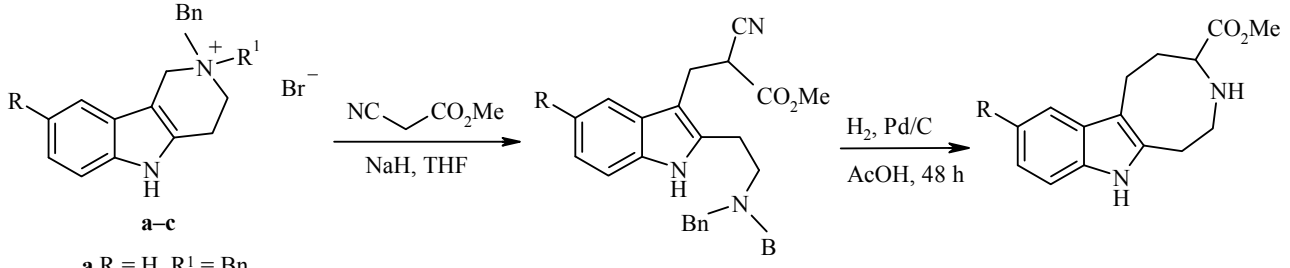


a–c

a R = H, R^1 = Bn,
b R = OMe, R^1 = Bn,
c R = H, R^1 = Me

13 a (92%), **b** (93%), **c** (90%)

15 a R^2 = H (85%), **b** R^2 = H (80%), **c** R^2 = Me (90%)



a–c

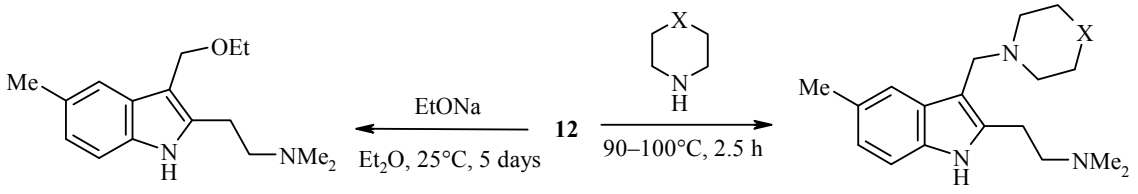
a R = H, R^1 = Bn,
b R = OMe, R^1 = Bn,
c R = H, R^1 = Me

14 a (70%), **b** (85%)

16 a (40%), **b** (30%)

The opening of the quaternized derivative **12** with EtONa as nucleophile takes place best of all in ether (46%). Here a series of side products of basic character are formed (mostly 2-vinylindoles – products of the Hofmann elimination) [45].

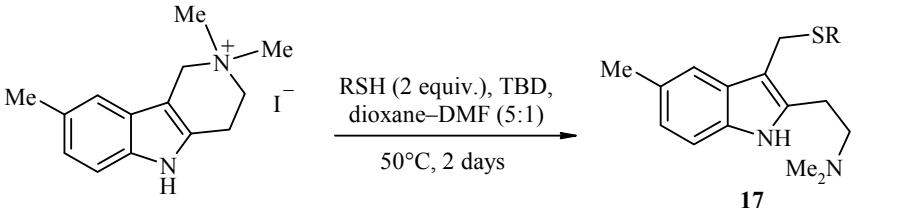
With less basic N-nucleophiles (piperidine, morpholine) the reaction of compound **12** takes place with significantly higher yields (70-86%) after boiling in piperidine or heating in morpholine [45].



46%

X = CH_2 (70%); O (86%)

With more nucleophilic and less basic S-nucleophiles the opening of the quaternized piperideine ring takes place extremely easily and leads to the final isotryptamines **17** with very high yields [51].

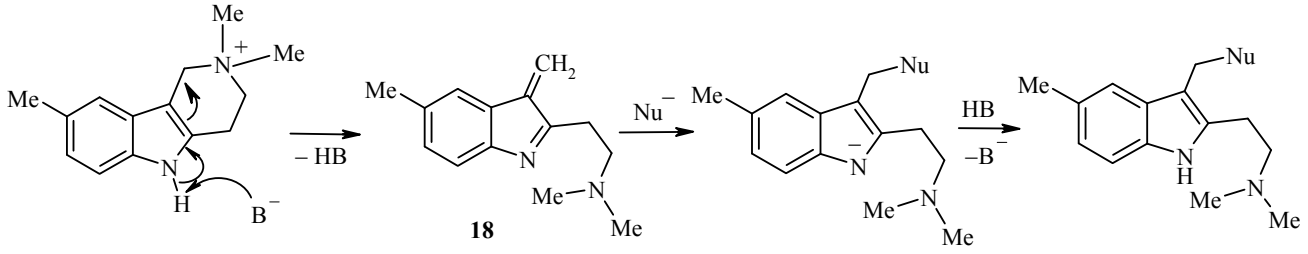


17

R = Alk (80–95%), Ar (42–94%)

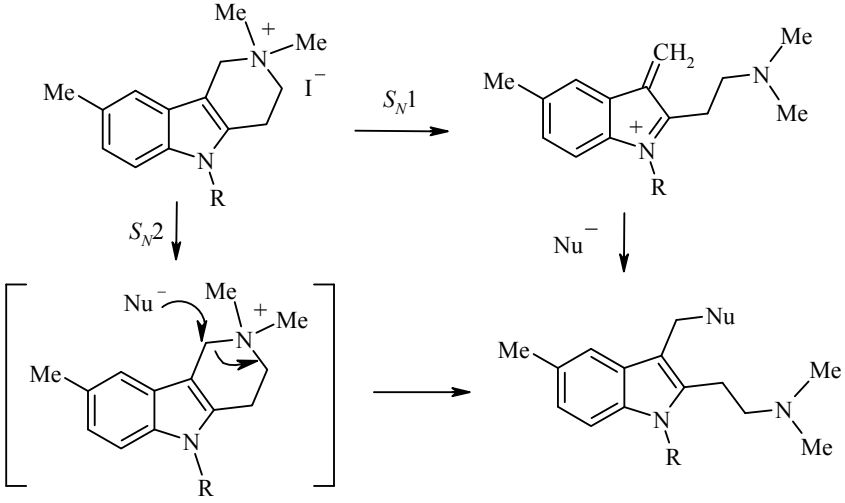
TBD = 1,5,7-triazabicyclo[4.4.0]dec-5-ene

It is known that the methiodides of tetrahydro-γ-carboline and its derivatives alkylated at the indole nitrogen atom exhibit varying activity toward nucleophilic agents due to the differences in the reaction mechanisms [45]. The behavior of the methiodides of N-unsubstituted γ-carbolines both in reactivity and in the nature of the interaction is similar to the behavior of gramine derivatives: opening takes place by an elimination–addition mechanism [52] with the formation of an intermediate of the 3-methylene[3H]indole type **18**.

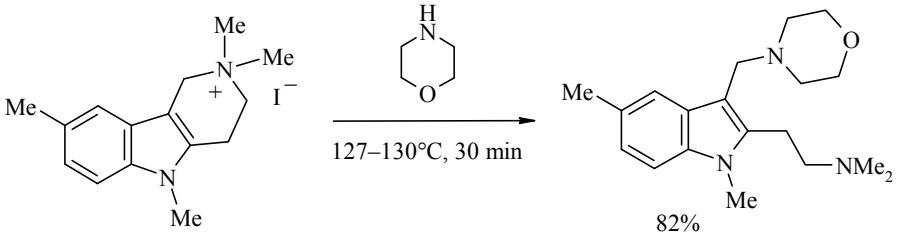


18

The methiodides of N(5)-alkyl-substituted tetrahydro-γ-carbolines, which have substantially lower activity than the unsubstituted derivatives in reaction with nucleophilic reagents, are apparently characterized by direct substitution by S_N1 or S_N2 mechanisms similar to 1-methylgramine [53].



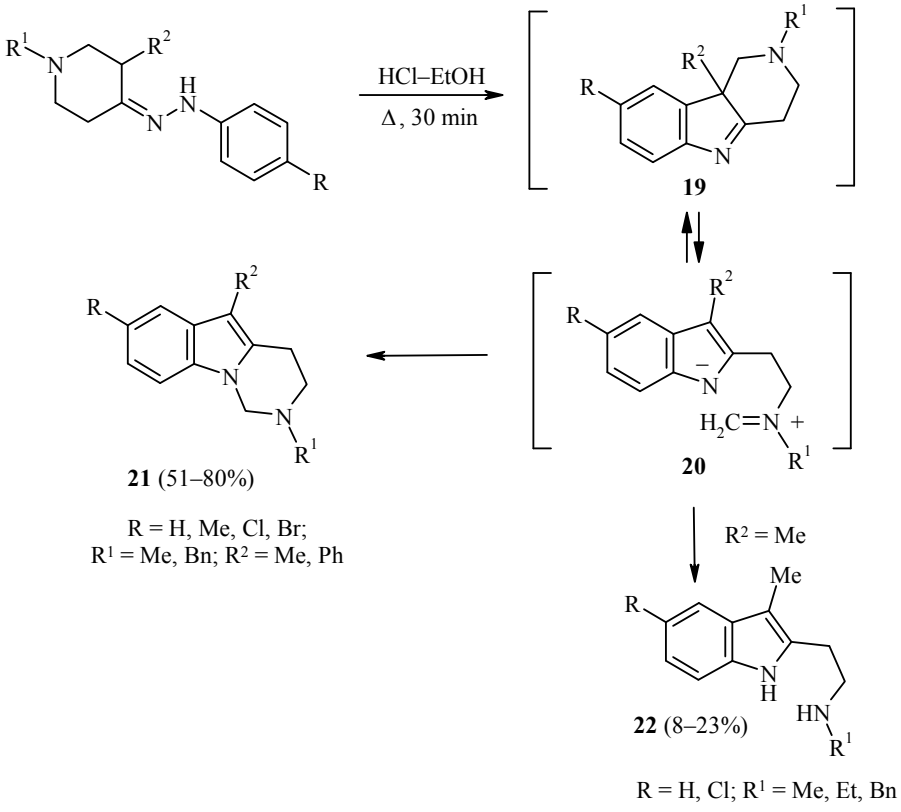
Thus, 2,2,5,8-tetramethyl-1,2,3,4-tetrahydro-γ-carbolinium iodide enters into reaction with morpholine only on boiling (~127°C), whereas the formation of the substitution product is not observed at all at 90-100°C, irrespective of the heating time [45].



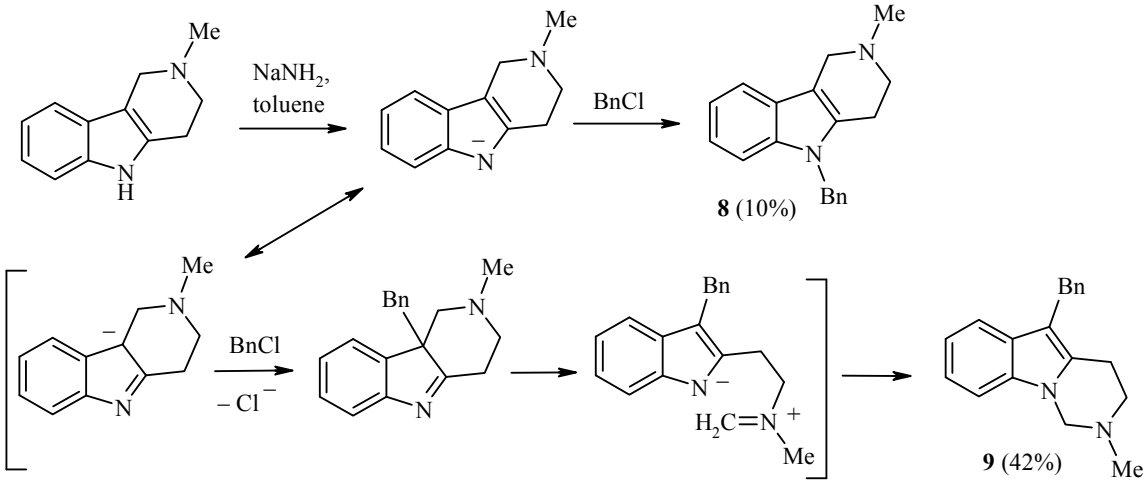
Recyclizations with the Participation of the Piperideine Ring

In this section a few examples of transformations of the piperideine ring accompanied by its subsequent opening at the C(1)–C(9b) bond and cyclization at another position of the indole ring will be discussed.

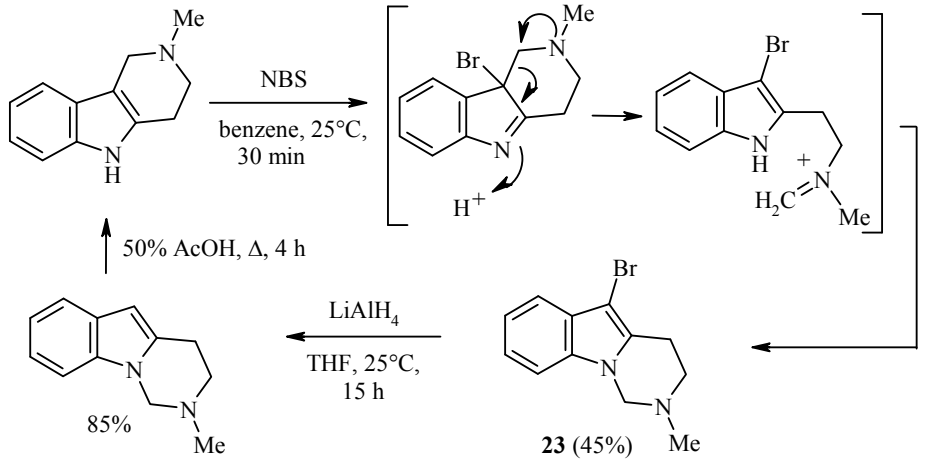
Such transformations have already been examined partly in the section on the production of tetrahydro-γ-carbolines by the Fischer method from 1,3-disubstituted piperid-4-ones (in the review [1]). In this case the cyclization takes place with the formation of the indolenines **19**, which are transformed into the intermediates **20** with cleavage of the C(1)–C(9b) bond in a retroreaction of the Mannich type, and they subsequently rearrange to the pyrimido[1,6-*a*]indoles **21** [54]. In a number of cases 3-substituted isotryptamines **22** are formed in addition to the pyrimido[1,6-*a*]indoles **21** [55].

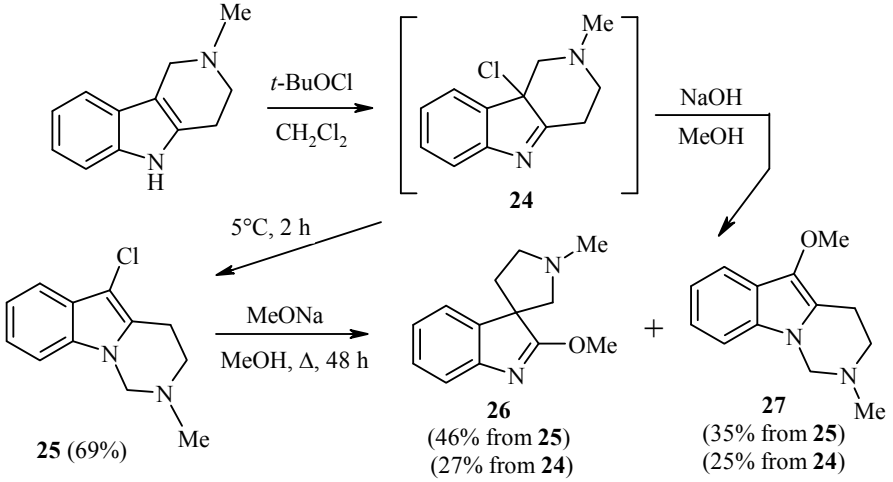


A similar scheme can be proposed to explain the formation of pyrimido[1,6-*a*]indoles **9** along with the γ-carbolines **8** during the alkylation of N(5)-unsubstituted 1,2,3,4-tetrahydro-γ-carbolines in nonpolar solvents with $NaNH_2$ as base [34].



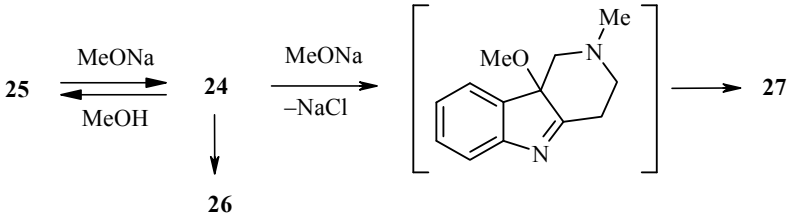
The intermediates of type **19** were neither isolated nor detected in the free form, but it was found that tetrahydro-γ-carbolines rearrange under the action of N-bromosuccinimide to pyrimidoindoles **23** through an analogous sequence of stages [56]. It was also possible to realize the reverse transition from the pyrimidoindoles **23** to tetrahydro-γ-carbolines by reductive debromination followed by recyclization in an acidic medium.



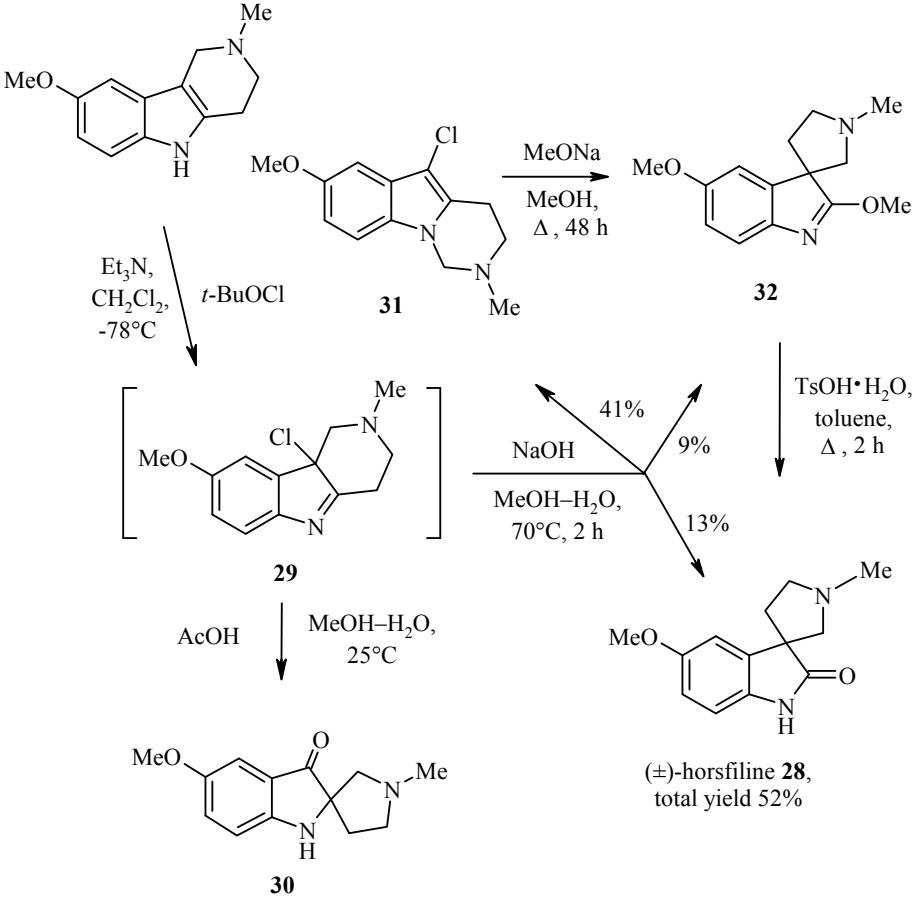


In the reaction of tetrahydro-γ-carbolines with *t*-BuOCl the (9*b*-chloroindolenine derivatives **24**, which cannot be isolated, are formed initially. They are transformed according to an analogous scheme (by a retroreaction of the Mannich type) into 5-chlorotetrahydropyrimido[1,6-*a*]indoles **25**, which can be converted by the action of MeONa in boiling methanol into the imidic ester **26** and the 5-methoxy derivative **27** [57]. It is interesting that the same compounds are formed when the indolenine **24** is treated with a solution of alkali in methanol.

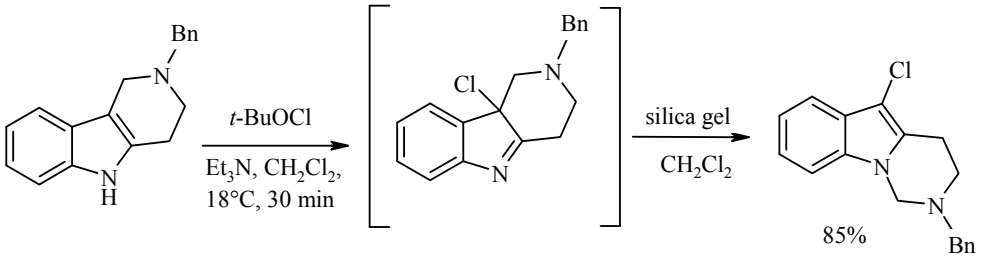
The following reaction scheme was proposed in order to explain the occurrence of the observed transformations, accompanied by skeletal rearrangements and nucleophilic substitution of the chlorine atom in the pyrimidoindole **25** [57]:



The scheme of transformations described above was used for the production of the racemic form of the oxindole alkaloid horsfiline **28**, isolated from the plant *Horsfieldia superba* and possessing analgesic activity [58]. Special attention is drawn to the fact that in an acidic medium the derivative **29** rearranges to the indoxyl derivative **30**; in an alkaline medium processes leading to the formation of chloropyrimido[1,6-*a*]indole **31**, the imidic ether **32**, and oxindole **28** occur; the latter is also formed by treatment of the indole **31** with sodium methoxide (the formation of the imidic ether **32**) followed by acid hydrolysis.

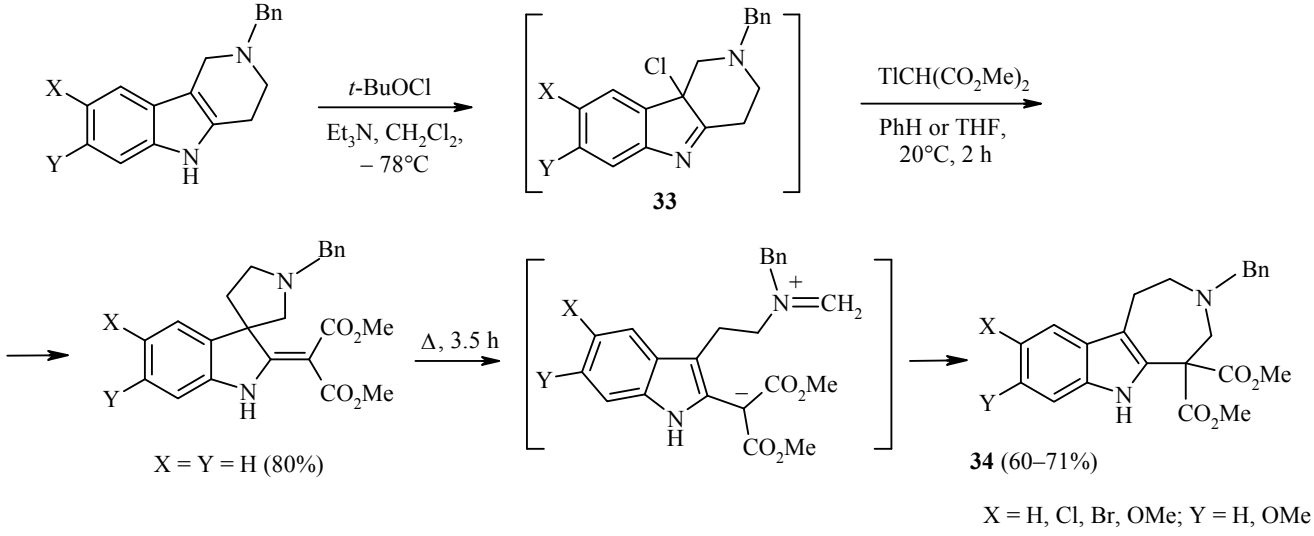


It is worth mentioning that during an attempt at chromatographic purification of the N(2)-benzyl-9b-chloroindolenine of type **24** on silica gel it underwent recyclization to the corresponding 2-benzyl-5-chloro-1,2,3,4-tetrahydropyrimido[1,6-*a*]indole [59].



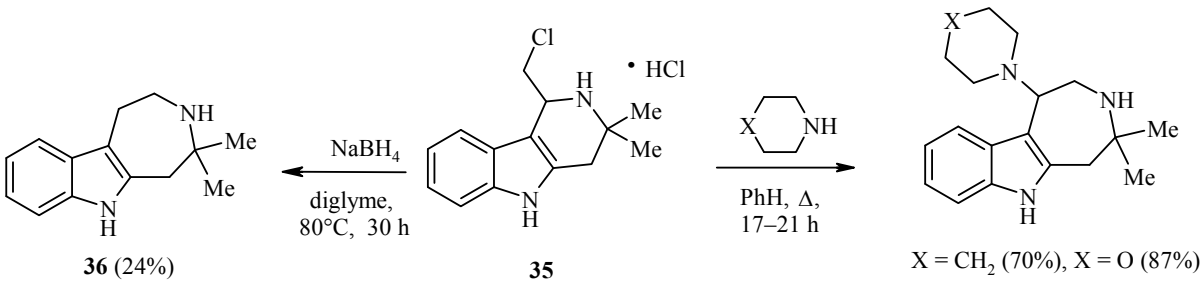
Transformations Accompanied by Enlargement of the Piperideine Ring

In the previous section it was shown that 9*b*-haloindolenine systems of types **24** and **29** are unstable and readily undergo various rearrangements under the action of various nucleophilic particles. Examples of transformations involving O-nucleophiles, accompanied by recyclizations, were examined above. However, in the case of C-nucleophiles there is the possibility of their incorporation into the carbon skeleton of the initial γ-carboline, leading to enlargement of the piperideine ring. For example, during treatment of the chlorindolenines **33** with thallium(I) dimethylmalonate there is a rearrangement leading to the formation of 3-benzyl-5,5-bis(methoxycarbonyl)-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indoles **34** [60].

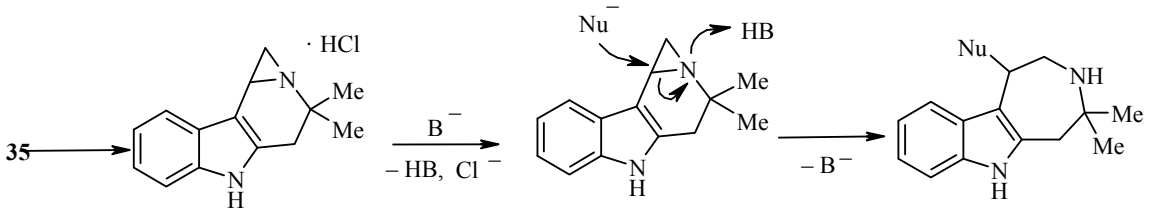


The analogous transformation in tetrahydro-γ-carbolines containing a chiral substituent at the N(2) atom leads to good yields (~ 80%) of the respective azepino[4,5-*b*]indoles with a chiral group at position 3 [61].

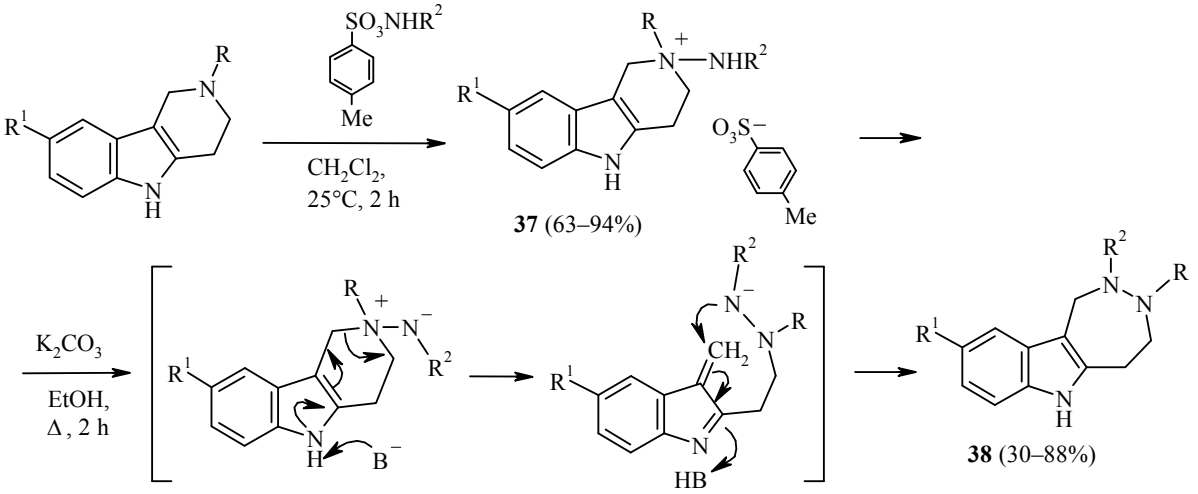
Derivatives of 1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indole can be obtained from N(2)-unsubstituted 1-chloromethyl-3,3-dimethyl-1,2,3,4-tetrahydro-γ-carboline (**35)** by the action of various nucleophilic agents. If $NaBH_4$ is used the 1-unsubstituted azepinoindole **36** is formed, whereas in the case of amines 1-amino-4,4-dimethyl-1,2,3,4,5,6-hexahydroazepino[4,5-*b*]indoles are formed [62]. It is worth noting that the azepinoindole **36** is also formed with a yield of 39% during the reduction of 1-chloromethyl-3,3-dimethyl-3,4-dihydro-γ-carboline under analogous conditions.



The following scheme was proposed to explain the occurrence of the observed transformations in the piperideine fragment of γ-carboline under the influence of nucleophilic agents:



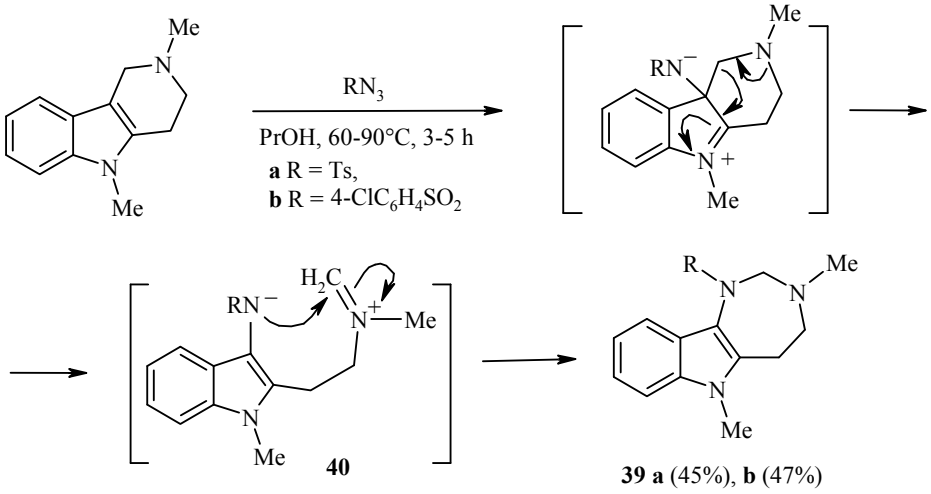
Tetrahydro-γ-carbolines enter into reactions accompanied by enlargement of the piperideine ring to a diazepine ring. Thus, 1,2,3,4-tetrahydro-γ-carbolines react with *p*-$MeC_6H_4SO_3NHR^2$ with the formation of salt-like intermediates **37**, which during treatment with bases rearrange with ring enlargement to hexahydro-2,3-diazepino[5,4-*b*]indoles **38** with yields of 30-88% [63, 64].

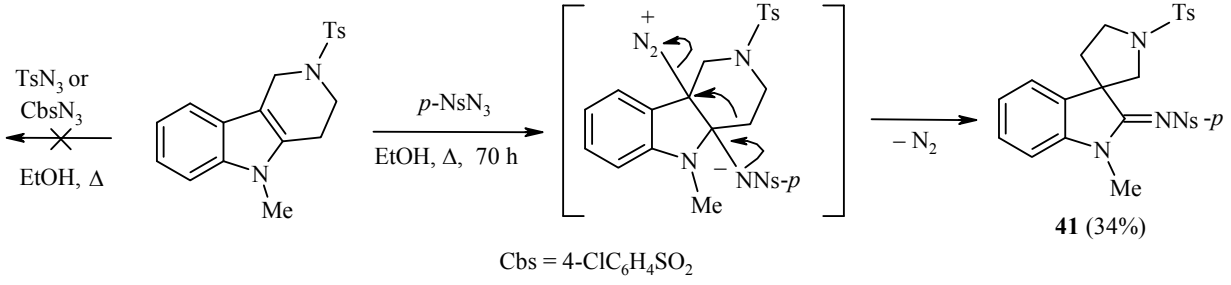


R = Me, Bn; R^1 = H, Me, Cl, Br; R^2 = Me, Et

N(5)-Substituted 2-alkyltetrahydro-γ-carbolines react with arenesulfonyl azides with the formation of 1,2,3,4,5,6-hexahydro-1,3-diazepino[5,4-*b*]indole derivatives **39** [65]; here attack by the azide takes place at the C(9*b*) atom with subsequent cleavage of the C(1)–C(9*b*) bond and the formation of the intermediate **40**, which undergoes recyclization with the formation of a seven-membered ring.

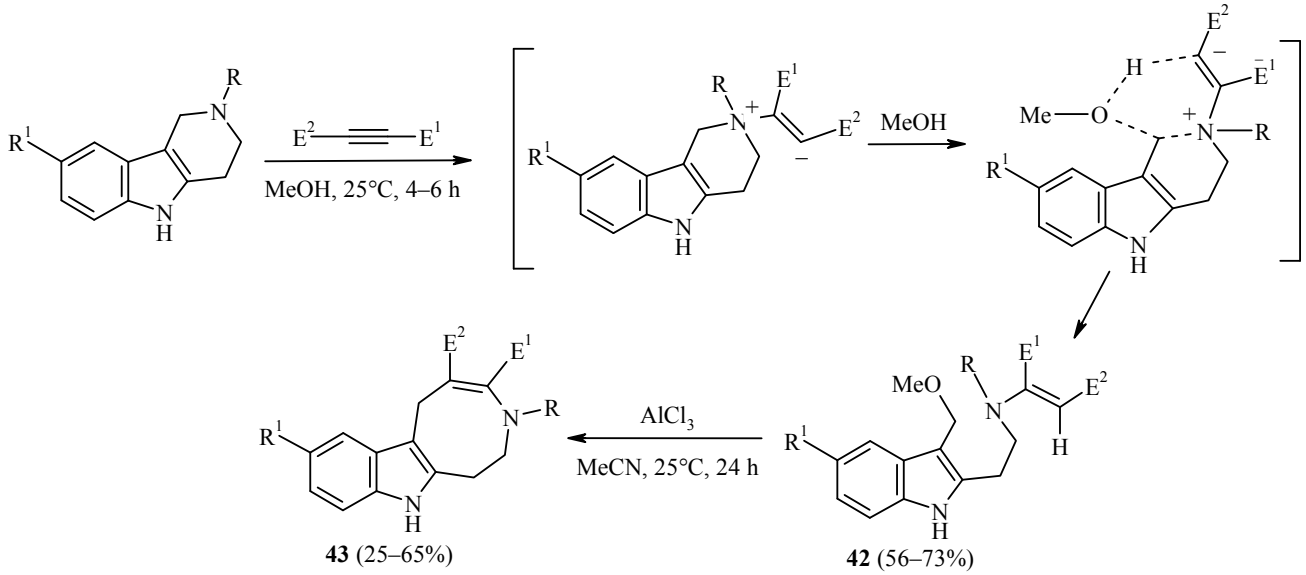
In the case of the less reactive 2-sulfonyl-substituted tetrahydro-γ-carbolines the reaction only takes place with *p*-nitrophenylsulfonyl azide (*p*-NsN_3), and instead of enlargement of the piperideine ring to a 1,3-diazepine ring recyclization with the formation of the spirocyclic indole derivative **41** occurs [66].





Cbs = 4-$ClC_6H_4SO_2$

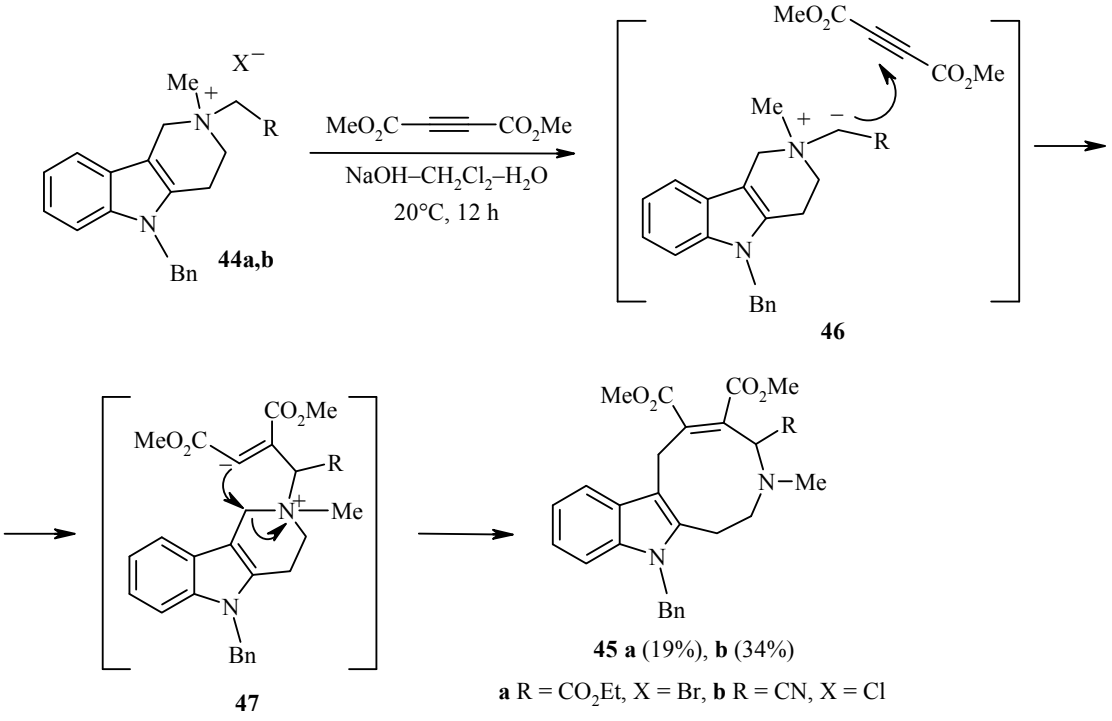
The reaction of 1,2,3,4-tetrahydro-γ-carbolines with activated acetylenes (acetylenedicarboxylic ester, ethyl propiolate) in protic solvents leads to cleavage of the tetrahydropyridine ring with the formation of high yields of the indoles **42** [67, 68], which are converted by the action of $AlCl_3$ in MeCN into the corresponding azocino[4,5-*b*]indoles **43** according to the following scheme:



R = Et, *i*-Pr; $E^1 = E^2 = CO_2Me$, R^1 =F, H, OMe, E^1 = H, $E^2 = CO_2Et$, R^1 = F, H

During comparison of the effectiveness of the various Lewis acids it was shown that the yields of the azocinoindoles **43** can be increased substantially if trimethylsilyl triflate ($Me_3SiOSO_2CF_3$) in THF is used for the cyclization of the indoles **42** [69].

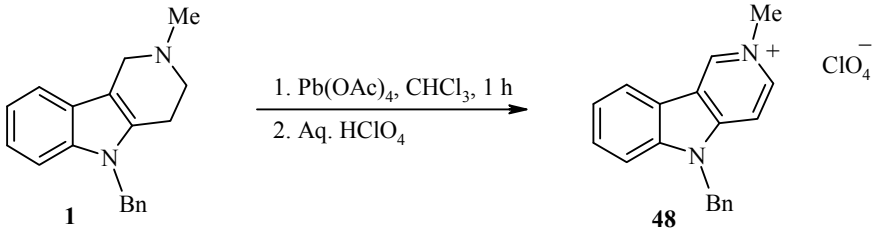
The quaternized tetrahydro-γ-carboline derivatives **44**, containing an active methylene group at the N(2) atom, react with acetylenedicarboxylic ester in the presence of alkali under the conditions of phase-transfer catalysis to form hexahydroazocino[4,5-*b*]indoles **45** with moderate yields [70]. The reaction apparently takes place through the formation of the N-ylides **46**, the carbanionic center of which attacks the activated bond with the formation of the 1,4-zwitterion **47**, and this undergoes a [1,4]-sigmatropic shift with the formation of the skeleton of azocino[4,5-*b*]indoles **45** [71].



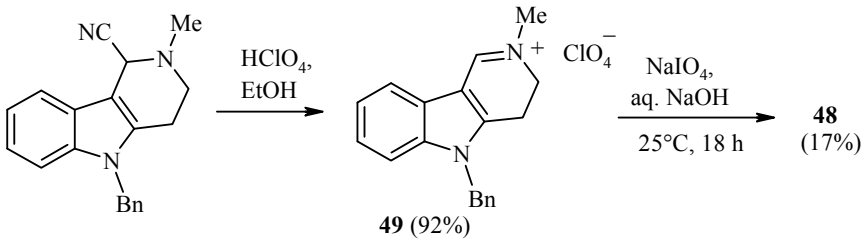
OXIDATION–REDUCTION REACTIONS

1,2,3,4-Tetrahydro-γ-carbolines are reduced to the corresponding 1,2,3,4,4a,9b-hexahydro-γ-carbolines by the action of various reagents. Here, in addition to the hexahydro derivatives the polyalkylated structures give the products from reductive degradation during reduction with metals in hydrochloric acid. All these matters are discussed in a fair amount of detail in the section on methods for the production of hexahydro-γ-carbolines, in the review [1], and in the references cited therein.

As a rule the oxidation of tetrahydro-γ-carbolines (like the oxidation of their 3,4-dihydro derivatives [72]) leads to aromatic γ-carbolines. For example, with lead tetraacetate Diazoline (**1**) is oxidized to the quaternized γ-carboline **48** [73].



The use of sodium periodate in an alkaline medium for the oxidation of the 3,4-dihydro-γ-carboline derivative **49** formed in the intermediate stage also leads to compound **48**, but the yield of the oxidation product is small [73].



During the oxidation of tetrahydro-γ-carbolines with sodium periodate a complex mixture of products is formed, and its composition varies depending on the reaction time and on the nature of the substituent at the N(5) atom. Among the compounds formed during the oxidation of tetrahydro-γ-carbolines the dilactams **50**, amine oxides **51**, iminium derivatives **52** and **53**, spiroindoxyls **54**, and their N-oxides **55** were isolated. In the case of the N(5)-unsubstituted tetrahydro-γ-carboline only the amino acid **56** is formed [74].

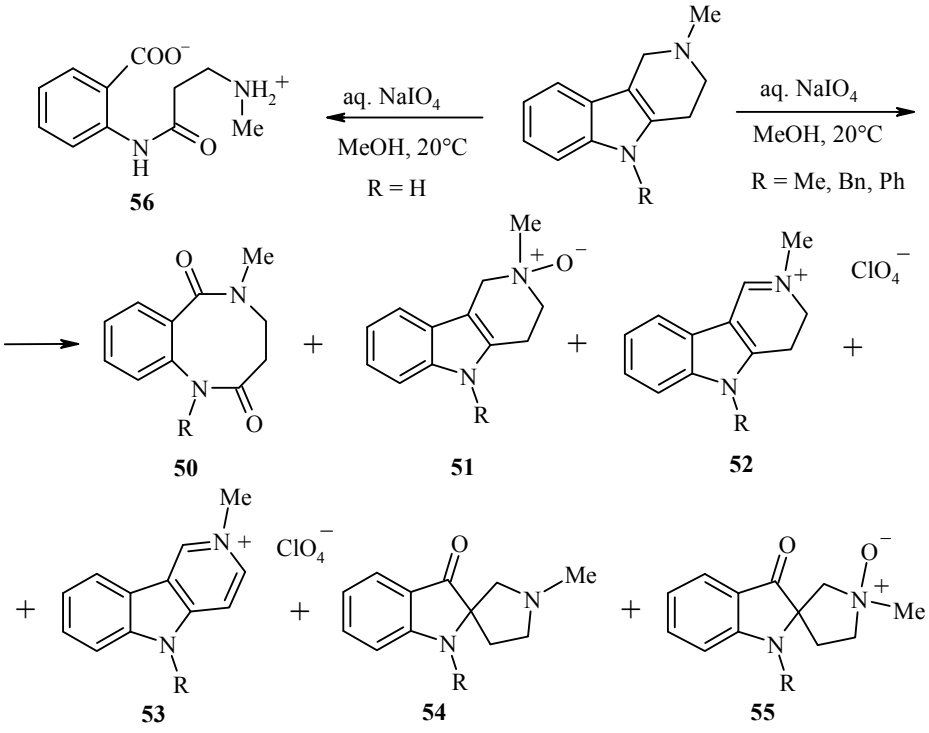
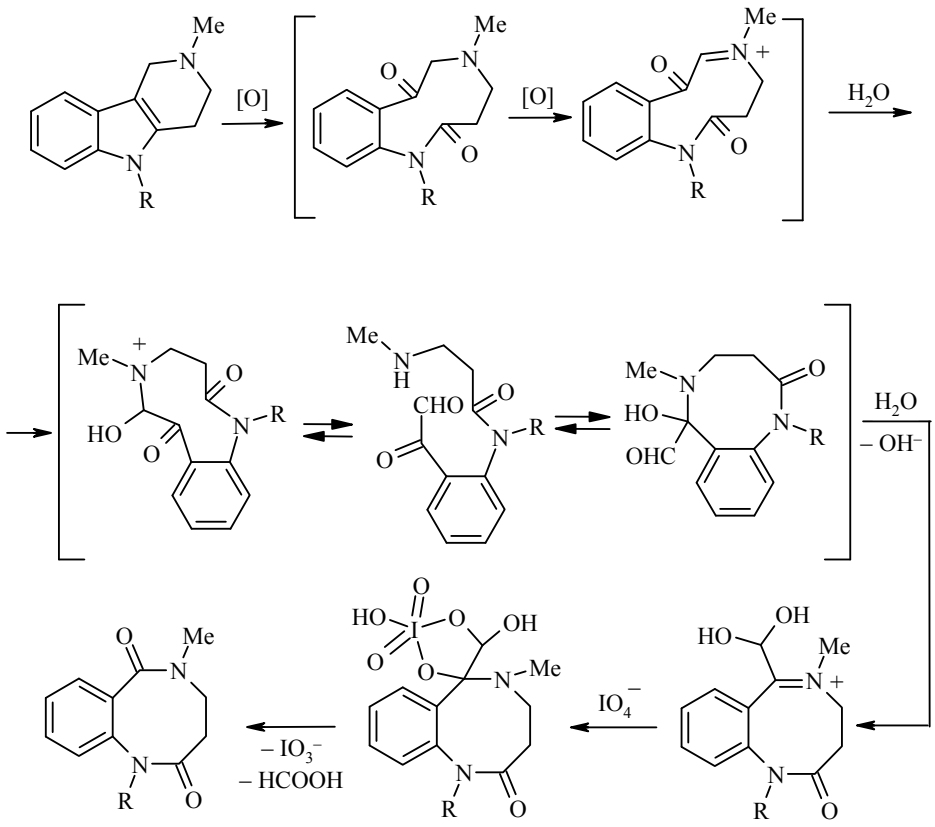


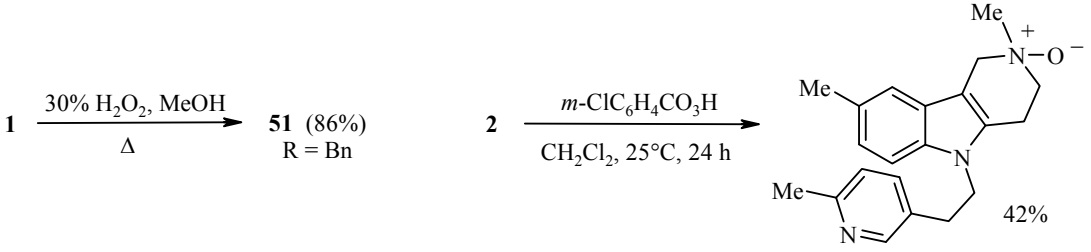
TABLE 1. The Products of the Oxidation of N(5)-Substituted Tetrahydro-γ-carbolines with $NaIO_4$

R	Reaction time, h	Yield, %				
		50	**51**	**53**	**54**	**55**
Me	24	—	—	—	42	—
	120	15	—	<1	—	60
Bn	24	18	10	10	12	23
Ph	168	18	—	—	—	24

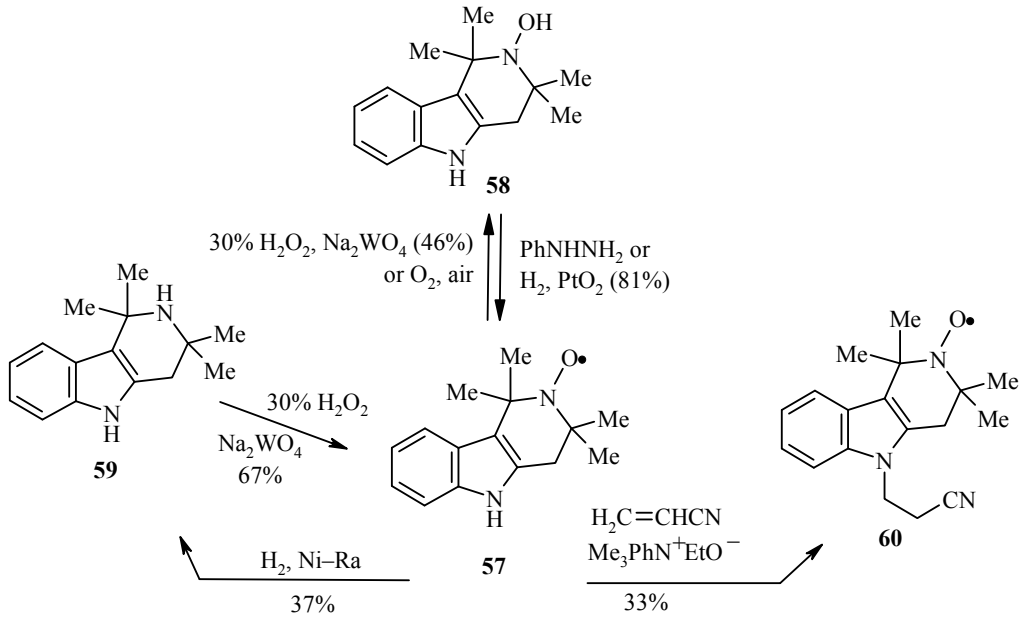
In order to explain the formation of the dilactam **50** the following mechanism was put forward and was partly confirmed:



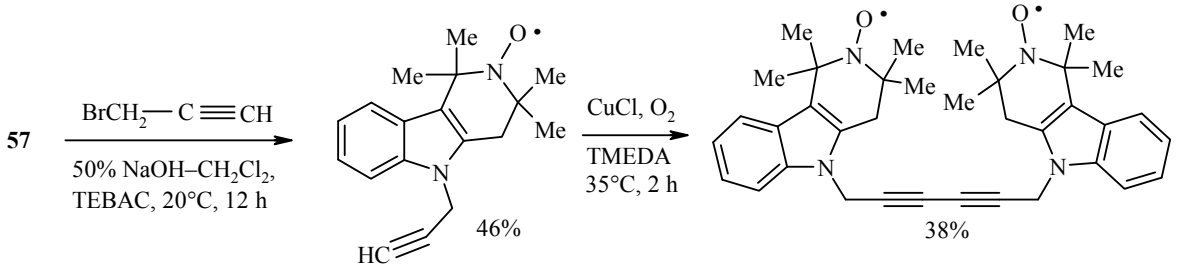
The N-oxides of tetrahydro-γ-carbolines **51** can be obtained with high yields by the action of 30% H_2O_2 with heat [73, 75]. It is also possible to obtain the N-oxides of γ-carboline derivatives with *m*-chloroperbenzoic acid. Here oxidation can be realized selectively at the N(2) atom if there are pyridine fragments in the side chain as, for example, in the case of Dimebon **2** [76].



During the catalytic oxidation of 1,1,3,3-tetramethyl-1,2,3,4-tetrahydro-γ-carboline with hydrogen peroxide in the presence of sodium tungstate the long-lived 1,1,3,3-tetramethyl-1,2,3,4-tetrahydro-γ-carboline-2-oxyl radical (**57**), characterized by the presence of a strong molecular ion peak in the mass spectrum, is formed [77]. Analysis of the ESR spectra showed that this substance is an individual free radical. The ESR spectrum of the crystalline radical **57** represents a curve of the singlet type, which changes to a triplet with splitting of 15.8 Oe between the components when the sample is dissolved in benzene [78].



The reduction of this radical by phenylhydrazine or hydrogen over Adams' catalyst leads to 2-hydroxy-1,1,3,3-tetramethyl-1,2,3,4-tetrahydro-γ-carboline (**58**). This is oxidized by hydrogen peroxide in the presence of Na_2WO_4 or by atmospheric oxygen to the radical **57**, the hydrogenation of which over Raney nickel leads to the initial tetrahydro-γ-carboline **59**. Cyanoethylation of compound **57** takes place without affecting the radical center and leads to the formation of compound **60** [79]. In addition, the radical **57** can be alkylated at the N(5) atom by epibromohydrin (yield 59%) [80] or propargyl bromide [81] under conditions of phase-transfer catalysis. The obtained derivative of a terminal alkyne enters into a Glaser–Eglinton reaction with the formation of a 1,3-diyne, and the radical center is not affected.



TEBAC = $(C_2H_5)_3(C_6H_5CH_2)NCl$, TMEDA = $Me_2NCH_2CH_2NMe_2$

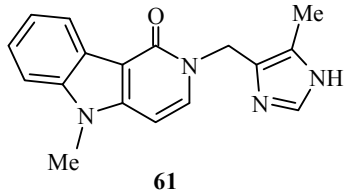
Tetrahydro-γ-carboline nitroxyl radicals, like any stable radicals, are capable of acting both as one-electron reducing agents (reaction with tetranitromethane) and as oxidizing agents (hydrazobenzene) [82].

BIOLOGICAL PROPERTIES OF HYDROGENATED γ-CARBOLINES

As already stated above, the increased interest in hydrogenated derivatives of γ-carbolines is due largely to the wide variety of biological properties exhibited by them, which require more detailed examination.

Dihydro-γ-carbolines

The series of 1-oxo-1,2-dihydro-γ-carboline derivatives exhibit the properties of antagonists of subtype 5-HT_3 serotonin receptors [83-86], which makes it possible to use the compounds as antiemetic agents (e.g., compound **61**), for the prevention of nausea and vomiting, particularly in anticancer chemo- and radiotherapy. In addition the γ-carboline derivative **61** and related compounds have been proposed for the treatment of gastric obstruction and such symptoms of gastroenteric dysfunction as dyspepsia, gastric ulcer, and duodenal ulcer, gastroesophageal reflux, meteorism, and irritable bowel syndrome [86, 87].



61

Antagonists of serotonin receptors of subtype 5-HT_3 can also be used for the treatment of a series of disorders of the central nervous system such as maniacal syndrome within the framework of bipolar affective disorder [86], schizophrenia, and anxiety states [88].

Among the derivatives of 1,2-dihydro-γ-carbolines there are also compounds that are selective ligands of cannabinoid CB_2-receptors [89], detected on the surface of the cells of the peripheral nervous system [90] and the immune cells (including the lymphatic cells) [91]. This makes it possible to use this type of substances as anti-inflammatory agents for the treatment of respiratory and nonrespiratory diseases associated with the activation of leukocytes [90].

Tetrahydro-γ-carbolines

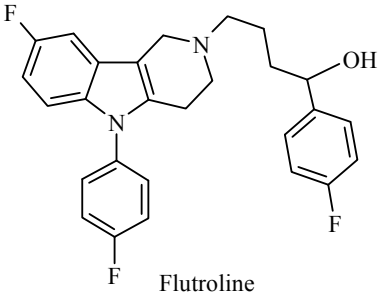
1,2,3,4-Tetrahydro-γ-carbolines and their derivatives have a broad spectrum of physiological action. The qualitative and quantitative aspects of the structure–activity relationship for tetrahydropyrido-[4,3-*b*]indoles were examined quite thoroughly in the review [2]. We will not therefore dwell on this aspect in detail, restricting ourselves solely to listing the biological targets on which the tetrahydro-γ-carboline derivatives have an effect, and we will list the diseases and functional abnormalities for the treatment and compensation of which it is possible to use preparations based on γ-carbolines.

For example, 5-(pyridylalkyl)tetrahydro-γ-carbolines (including Dimebon **2** and Dorastine **3**, drugs used in medical practise) and certain other γ-carboline derivatives (e.g., Diazoline **1**) have antihistamine [92-97] and antianaphylactic [20] properties. Apart from everything else, among the 5-(pyridylethyl)tetrahydro-γ-carbolines there are examples of analgesics, e.g., 4-pyridylethyl-1,2,3,4-tetrahydro-γ-carbolines [98]. A series of 5-pyridyl-ethyl-substituted γ-carbolines are capable of potentiating the action of nicotine and reducing the tone of smooth muscle [99]. Tetrahydro-γ-carbolines can act as agonists of κ-opiate receptors, having an anesthetic effect; here they are devoid of such side effects as respiratory impairment, physical dependence, and reduced gastroentero motility so characteristic of the agonists of opiate receptors of the μ-type (Morphine, Fentanyl) [100, 101].

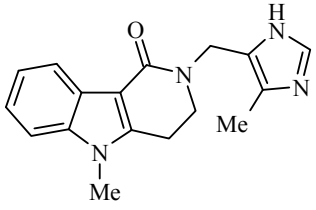
There are examples of tetrahydro-γ-carboline compounds having sedative (neuroleptics, anxiolytics, and tranquilizers) and antidepressant (thymoleptic) activity [23, 102, 103]. Thus, for example, it was found that derivatives of 8-fluoro-2-(3-hydroxypropyl)-2,3,4,5-tetrahydro-5H-pyrido[4,2-*b*]indoles are powerful anti-depressants [104, 105], whereas 8-fluoro-2-[3-(4-fluorophenylanilinopropyl)]-1,2,3,4-tetrahydro-γ-carbolines

are prospective tranquilizers [106]. 4-Phenyl-1,2,3,4-tetrahydro-γ-carbolines, which are selective agonists of dopamine receptors of the D_1 subtype and also have anxiolytic properties [107]. Tetrahydro-γ-carboline derivatives containing 3-(3-pyridinyl)propyl substituents at the N(2) atom and their N-oxides have high affinity to D_2-dopamine receptors, exhibiting antipsychotic activity without the appearance of extrapyramidal side effects [6, 108].

Antipsychotic and neuroleptic activity are also exhibited by 5-aryl-substituted 1,2,3,4-tetrahydro-γ-carbolines [24, 39, 109], among which Flutroline **62**, which exhibited high efficacy in the treatment of schizophrenia, stands out especially [110, 111]. Being tranquilizers, they also exhibit hypotensive and analgesic activity [112, 113].



Flutroline
62



Alosetron
63

Selective inhibitors of α_{2C}-adrenergic receptors, which are involved in the development of depression, were also found among the tetrahydro-γ-carbolines. Such compounds may be useful in the prevention and treatment of depression [114]. In addition, 2-(4-cyano-4-phenylbutyl)-1,2,3,4-tetrahydro-γ-carbolines exhibit the properties of inhibitors of adrenaline and apomorphine, having neuroleptic, sedative, and tranquilizing activity [115].

8-Phenoxy-1,2,3,4-tetrahydro-γ-carbolines are agonists of serotonin receptors of subtypes 5-HT_{1D}, 5-HT_{1B}, and 5-HT_{1F} and inhibit the release of neuropeptides, which stimulate the development of inflammatory processes of neurogenic etiology. This can be used for the treatment of certain acute inflammatory diseases (e.g., rheumatoid polyarthritis) or vascular diseases (e.g., venous insufficiency) and also skin lesions (e.g., psoriasis) [116-118]. A series of tetrahydro-γ-carboline derivatives are antagonists of receptors of the above-mentioned subtypes, which gives rise to their weak antidepressant effect [119].

Significant advances in the treatment of schizophrenia are linked to the inhibition of 5-HT_2 receptors, and quite a few blockers of serotonin receptors of this subtype have been found among derivatives of tetrahydro-γ-carboline [120]; in addition, paired antagonists of 5-HT_{2A}/D_2-receptors can be regarded as potential atypical antipsychotics [121]. The antagonists of 5-HT_{2B} and $5HT_7$ receptors, found in the series of γ-carbolines, can be used for the treatment of enhanced irritable bowel syndrome and migraine [122]. As a whole certain advances in the treatment of a whole series of disorders of the CNS, including addiction to narcotics and sleep disturbance and behavioral disorder, are linked to the ligands (agonists and antagonists) of serotonin 5-HT_2 receptors [123-125].

The treatment of neurodegenerative disorders, including Alzheimer's disease and abnormal eating behavior, has involved the $5HT_{5A}$-subtype of serotonin receptors, for which there is series of specifically bonding ligands based on 5-methyl-1,2,3,4-tetrahydro-γ-carboline [25, 126]. Fragments of 1,2,3,4-tetrahydro-γ-carbolines enter into the composition of selective agonists and antagonists of serotonin 5-HT_{1A} and 5-HT_{2A} receptors [127].

Antagonists of serotonin 5-HT_6-receptors, responsible for cognitive function since they are concentrated in the CNS and participate in the perception of information, learning, and memory [128], were also found among tetrahydro-γ-carboline derivatives. In addition, the $5HT_6$-receptors are involved in the regulation of such neurotransmitter systems as the cholinergic, glutamatergic, dopaminergic, and noradrenergic systems [129].

This makes it possible to regard the compounds as potential products for the treatment of neurodegenerative illnesses. Such compounds include, for example, 5-(2-hetarylethyl) [28], 5-(2-pyridylvinyl) [37], and 8-sulfonyl [44] derivatives of tetrahydro-γ-carbolines. The drug Dimebon **2** [28, 130], which will be discussed in greater detail below, is regarded as an antagonist of serotonin 5-HT_6-receptors.

The tetrahydro-γ-carboline derivatives include such products as Alosetron **63**, which is an effective of serotonin 5-HT_3-receptors, concentrated in the gastrointestinal tract, and has an antiemetic effect [131]. The drug is used for the irritable bowel syndrome, where it helps to eliminate the painful sensations and normalize the defecation. The 6-fluoro derivative of Alosetron has similar activity [132].

Serotonin 5-HT_3-receptors are also encountered in the CNS, where they play an important role in the regulation of mood, appetite, the psychomotor system, and memory. This type of agonist of serotonin receptors can therefore be used in the treatment of psychic disturbances (schizophrenia, bipolar affective disorder), anxiety and restless states [133], cognitive disorders, attention and memory defiency [134, 135], autism and other disorders due to mental retardation [136], and also for the removal of physical dependence and addiction brought about by opiates, benzodiazepines, alcohol, or nicotine [137].

The treatment of neurological and neuropsychic disorders, including schizophrenia, also involves the activation of glutamate receptors of the NMDA-subtype by selective inhibition of the type I glycine carrier by means of the corresponding tetrahydropyrido[4,3-*b*]indoles [138]. The use of this type of compounds makes it possible to modulate the operation of H_3-histamine receptors, which can also be useful in the therapy of various disorders of the CNS [139].

Derivatives of tetrahydro-γ-carbolines are also ligands of cannabinoid CB_1-receptors, localized in the CNS, and can therefore be used as pain-relieving agents [140-142]. There are examples of tetrahydro-γ-carbolines that are agonists of cannabinoid receptors of the CB_2-subtype and exhibit anti-inflammatory properties [89]. Modulators of cannabinoid CB_2-receptors are used for the treatment of respiratory and non-respiratory disorders due to leukocytic activity [90].

Some 1,2,3,4-tetrahydro-γ-carbolines exhibit the properties of antagonists of CRTH2-receptors and can therefore be used for the treatment of a series of chronic and acute diseases caused by the physiological activity of prostaglandin, such as asthma, rhinitis, allergic syndrome of the airways, allergic rhinobronchitis, inflammatory intestinal disorders, rheumatoid arthritis, various skin diseases (dermatitis, urticaria, eczema), systematic breakdown of mast cells, and also various disorders due to increased content of eosinophiles and basophiles in the blood plasma [143, 144]. Compounds of the 2,3,4,5-tetrahydropyrido[4,3-*b*]indole series, which are reversible inhibitors of cysteine protease cathepsin K, may be potential agents for the treatment of rheumatoid arthritis and neuropathic pain [145].

Compounds that reduce the secretion and inhibiting action of the parathormone (controls the level of Ca^{2+} ions in blood plasma) and are therefore potential agents for the treatment of osteoporosis or hyperparathyreosis were found among the tetrahydro-γ-carbolines [146].

A series of tetrahydro-γ-carbolines exhibit the properties of inhibitors of phosphodiesterase PDE4, which facilitates their use for the treatment of inflammatory and allergic diseases caused by the action of this enzyme and, in particular, asthma and chronic obstructive pulmonary disease [147]. In addition, there are tetrahydropyrido[4,3-*b*]indoles that are selective inhibitors of p38α-kinase – an enzyme active in the patho-genesis of many chronic inflammatory diseases [148]. Patented potential antagonists of bradykinin receptors may find similar application in medical practise [149].

It should be noted that certain tetrahydro-γ-carbolines are able to inhibit histone deacetylase (HDAC), which plays an important role in the proliferation and differentiation of cells, and can be used effectively in the therapy of oncological diseases [150, 151] and also for the treatment of heart failure and cardiac muscular hypertrophy [152].

Inhibitors of vascular endothelial growth factor (VEGF), found among the pyrido[4,3-*b*]indoles, suppress aberrant angiogenesis, and this has also been used successfully in the treatment of malignant neoplasms [153].

There are examples of inhibitors of fatty acid binding proteins of type 4 (FABP-4), which can be extremely effective in the therapy and prophylaxis of type II sugar diabetes, distinguished by insulin resistance, obesity, and a whole complex of accompanying metabolic disorders [154]. Another approach to the treatment of obesity and its associated diseases involves the use of selective antagonists of human melanin-concentrating hormone (MCH_1) receptors, examples of which are found among the investigated class of compounds [155]. In addition metabolic disorders can be treated with tetrahydropyrido[4,3-*b*]indoles exhibiting the properties of 5'-AMP-activated protein kinase (AMPK) activators [156].

A series of 2,3,4,5-tetrahydropyrido[4,3-*b*]indoles can be used in the therapy of such neurodegenerative diseases as Huntington's chorea [157] and Alzheimer's disease [9, 76, 158], and among them there are inhibitors of γ-secretase, which is involved in the development of the disease [159].

Some compounds of the tetrahydro-γ-carboline series possess antiprotozoal activity, particularly in relation to *Trypanosoma cruzi*, which makes them potential agents for the treatment of Chagas' disease (American trypanosomiasis) [160, 161].

Found quite recently among derivatives of 1,2,3,4-tetrahydro-γ-carbolines were compounds that prevent the penetration of HIV-1 into cells as a result of binding with the gp120 protein on the surface of the virion and, possibly, on account of interaction with the CD4-receptor on the surface of the cell, which makes it possible to use them for the treatment of HIV infections and AIDS [162, 163].

Examples of the manifestation of antibradykinin, cholinergic, and local anesthetic activity are also known for 1,2,3,4-tetrahydro-γ-carbolines; they are able to reduce the penetration of skin capillaries [20] and act as anticoagulants [164].

It is worth mentioning in particular that many compounds of the tetrahydro-γ-carboline series have a broad pharmacological profile, i.e., exert a simultaneous action on several biological targets (for examples, see [43]). The original domestic product Dimebon **2**, which is currently use in medical practise as a blocker of H_1-histamine receptors, is no exception [165, 166]. However, it has been established that Dimebon also exhibits cardioprotective properties (has a moderate effect on coronary blood circulation and has little effect on myocardial contractility) [167] and antiarrhythmic properties [168]. The product **2** has an effect on nerve impulse transmission since it inhibits the enzyme monoamine oxidase B (MAO-B), which is involved in the deamination of dopamine, and reduces its metabolism in the subcortical ganglia of the brain, increases the noradrenaline level, and suppresses the deamination of dopamine in the hypothalamus, thereby participating in the metabolism of catecholamines in the structures of the brain [169]. This drug is also marked by antiemetic activity and protective action during experimental radiation damage of the skin [20]. Dimebon protects neurons from the neurotoxic effect of β-amyloid (EC_{50} = 25 μM) and exhibits the properties of a calcium channel blocker (IC_{50} = 57 μM) and inhibiting action toward cholinesterases (IC_{50} = 7.9 and 42 μM respectively for butyryl- and acetylcholine esterases) [170] while demonstrating improvement of memory and cognitive capacity. It is also a blocker of glutamate receptors of the NMDA-subtype (ED_{50} = 42 mg/kg) while activating the AMPA-subtype at low concentrations [171] and has an effect on certain other biological targets (for more detail, see above and the review [2]).

At the present time Dimebon has been patented as a drug intended for the treatment of neurodegenerative disorders and for Alzheimer's disease [9, 158] and Huntington's chorea [157] in particular and has undergone double blind trials with a placebo lasting 52 weeks, revealing its neuroprotective properties; improvement of memory, dimensional orientation practical activity, and speech capabilities were observed in the patients [172]. Recently, however, the pharmaceutical giant Pfizer published information according to which the effectiveness of Dimebon as a product for the treatment of Alzheimer's disease in comparison with a placebo in phase III clinical trials was placed under doubt [173, 174].

Hexahydro-γ-carbolines

It is known that hexahydro-γ-carboline derivatives on the whole have a depressing effect on the CNS, expressed in the suppression of aggressive reactions, depression of motor activity, and decrease of the pain sensitivity threshold [175, 176]. All this finds application in the therapy of autism, abulia (lack of will), and also schizophrenia [177]. In addition, these compounds possess a characteristic property of neuroleptic preparations – hypothermic action – and increase the duration of the action of narcosis caused by Thiopental sodium [178] and intensify the action of Methamphetamine [177].

The *cis* derivatives largely exhibit psychotropic, neuroleptic, and antidepressive activity [179, 180], whereas apart from neuroleptic activity (antagonists of dopamine receptors) [181, 182] the *trans*-hexahydro-γ-carbolines exert analgesic and sedative effects, have anxiolytic, antipsychotic, myorelaxant, and hypotensive properties [183, 184], and can also act as tranquilizers [185]. Here the physiological action afforded by the derivatives with the *trans* structure is more clearly defined than for the *cis* isomers [182].

A series of drugs that have found application in medical practise have been created on the basis of hexahydro-γ-carbolines. For example, *cis*-2,8-dimethyl-1,2,3,4,4*a*,9*b*-hexahydro-γ-carboline (Carbidine) is effective in the treatment of schizophrenia, alcohol psychoses, and withdrawal syndromes [186]. *cis*-2-[3-(*p*-Fluorobenzoyl)propyl]-8-methyl-1,2,3,4,4*a*,9*b*-hexahydro-γ-carboline has similar activity [187].

The drug Stobadine – *cis*-(-)-2,8-dimethyl-1,2,3,4,4*a*,9*b*-hexahydro-γ-carboline – exhibits antiarrhythmic and cardioprotective properties, having an antihypoxic effect on the myocardium [188], and also possesses antioxidant activity [189]. (A detailed study of the metabolism of Stobadine is described in [190, 191].) Certain other derivatives of hexahydro-γ-carboline also possess antioxidant properties [192]. It is worth mentioning that certain derivatives of Stobadine are capable of inhibiting the enzyme aldose reductase, and this may be useful in the treatment of sugar diabetes [193].

A series of 1,2,3,4,4*a*,9*b*-hexahydro-γ-carbolines are ligands of 5-HT-receptors [194], including an agonist of serotonin receptors of the 5-HT_{2C} subtype responsible for the sense of satiety, which can be used effectively for the treatment of obesity [195].

Thus, the unusually broad spectrum of biological activity in the hydrogenated derivatives of γ-carbolines has led to the great interest in compounds of this class shown by synthetic organic chemists, pharmacologists, and biochemists and has stimulated study of their chemical characteristics with the aim of extending the range of new drugs.

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