Chemistry of Heterocyclic Compounds, Vol. 46, No. 7, 2010

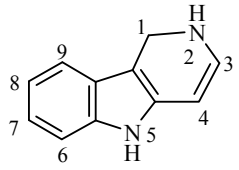
γ-CARBOLINES AND THEIR HYDROGENATED DERIVATIVES. 2.* HYDROGENATED DERIVATIVES OF γ-CARBOLINES: METHODS OF SYNTHESIS (REVIEW)

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

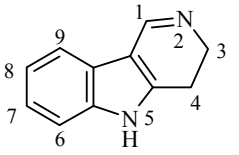
Published data on methods for the synthesis of dihydro-, tetrahydro-, and hexahydro-γ-carbolines are reviewed.

Keywords: 1,2- and 3,4-dihydro-, 1,2,3,4-tetrahydro-, and 1,2,3,4,4a,9b-hexahydro-γ-carbolines, Bischler–Napieralski reaction, Fischer synthesis, stereoselective reduction.

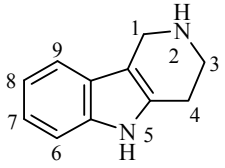
In the chemical literature there are several versions of nomenclature for carbolines and the numbering of the carbon atoms in these cyclic systems. In our review, for convenience and simplicity as in the case of aromatic γ-carbolines [1], we will use the numbering in [2], which has now become generally accepted.



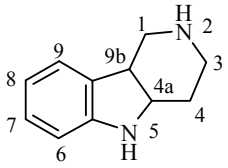
1,2-dihydro-γ-carboline



3,4-dihydro-γ-carboline



1,2,3,4-tetrahydro-γ-carboline



1,2,3,4,4a,9b-hexahydro-γ-carboline

The undiminishing interest in compounds of this type is due to the fact that hydrogenated γ-carbolines and their derivatives have a broad spectrum of biological activity [3]. (Among them, for example, there are antihistamine preparations, neuroleptics, antiarrhythmics, adrenolytics, antidepressants, etc.) This aspect will be discussed in the next part of our review devoted to the chemical and biological properties of hydrogenated γ-carbolines. The neuroprotective action of the original home-produced Dimebon, which was recently found to be highly effective in the treatment of Alzheimer's disease and in August 2007 was nominated "*Molecule of the month*" in *Prous Science* [4], merits special attention.

* For Communication 1, see [1].

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

[1]I M. V. Lomonosov Moscow State University, Moscow 199991, Russia.

Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 963-1018, July, 2010, Original article submitted March 17, 2010.

METHODS FOR THE SYNTHESIS OF HYDROGENATED DERIVATIVES OF γ-CARBOLINES

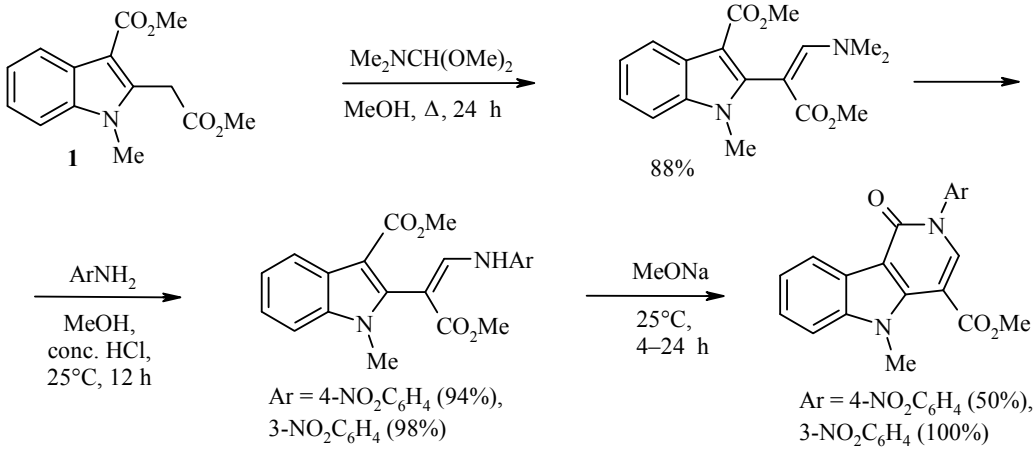
As the basis for classification of methods for synthesis of the hydrogenated derivatives of γ-carbolines we chose the type of bond formed, which is closely related to the retrosynthetic approach to the designed synthesis of heterocyclic structures.

METHODS FOR THE PRODUCTION OF DIHYDRO-γ-CARBOLINE STRUCTURES

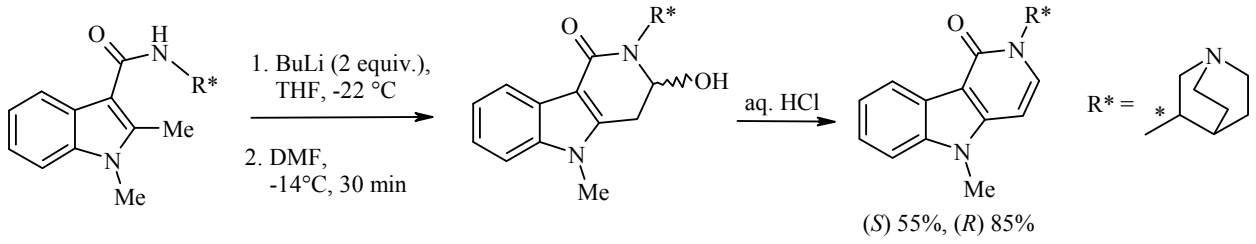
It is well known that the N(2)-unsubstituted oxo derivatives of hydrogenated γ-carbolines can exist in the tautomeric aromatic hydroxy form. Therefore, most of the material on oxocarbolines was presented in the first part of the review concerning aromatic γ-carbolines [1]. However, in view of the impossibility of tautomerism N(2)-substituted oxo-γ-carbolines must undoubtedly be included among the hydrogenated derivatives and will also be examined in the present review.

1,2-Dihydro-γ-carbolines

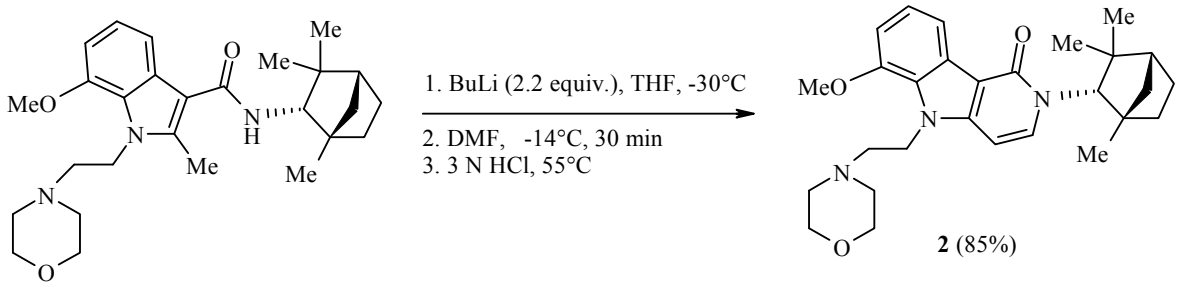
The general strategy for the synthesis of 1,2-dihydro-γ-carboline structures involves annelation of the dihydropyridine ring to the indole fragment. The overwhelming majority of examples of the production of 1,2-dihydro-γ-carbolines relate to the corresponding 1-oxo derivatives. For example, 2-aryl-1-oxo derivatives of 1,2-dihydro-γ-carboline were synthesized on the basis of the diester **1** with the formation of the C(1)–N(2) bond [5].



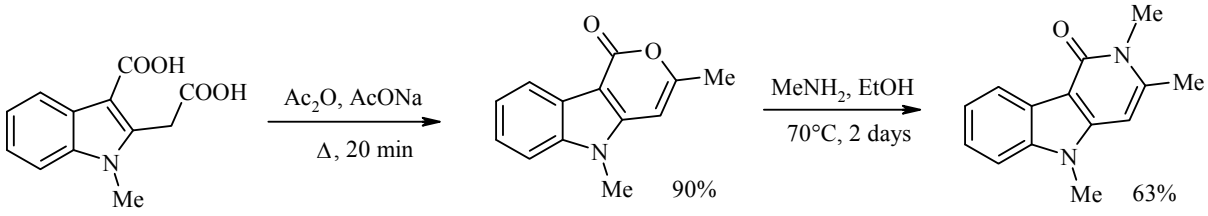
Similar 1,2-dihydro-1-oxo-γ-carboline structures can be obtained on the basis of the amides of 2-methylindole-3-carboxylic acid (with the creation of the C(3)–N(2) bond) [6, 7].



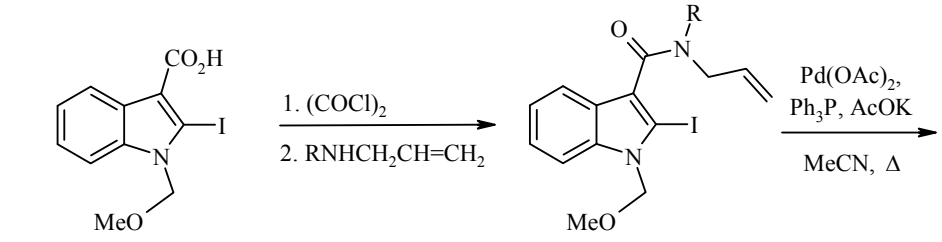
An analogous approach was used for the synthesis of the selective ligand for canabinoid CB_2-receptors **2** [8].

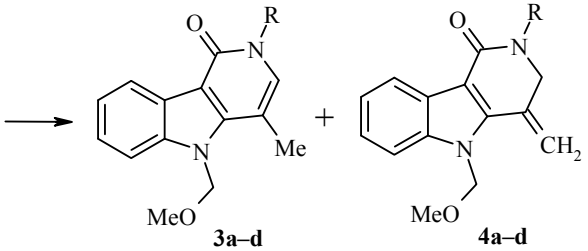


For the production of 1,2-dihydro-γ-carbolin-1-ones it is possible to use the reaction of pyrano[4,3-*b*]-indol-1(5H)-ones with primary amines [9], where the C(3)–N(2) and C(1)–N(2) bonds are formed in tandem.



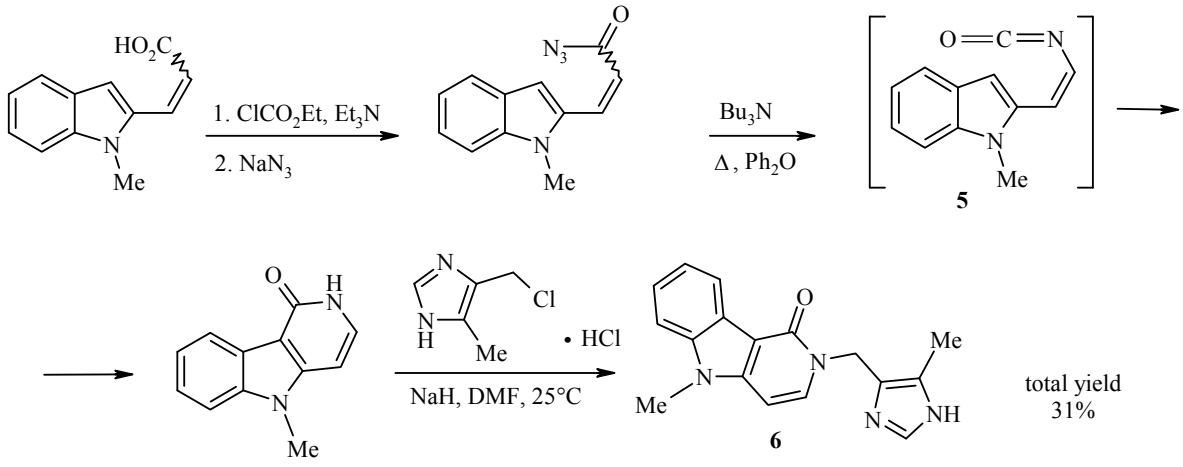
The N-substituted 1,2-dihydro-γ-carboline skeleton can also be constructed by an intramolecular Heck reaction with the creation of the C(4)–C(4a) bond [10]. Here, from the allylamides of 2-iodoindole-3-carboxylic acid the tetrahydro-γ-carbolines **4a-d** with an exocyclic double bond are also formed in addition to the desired compounds **3a-d**.



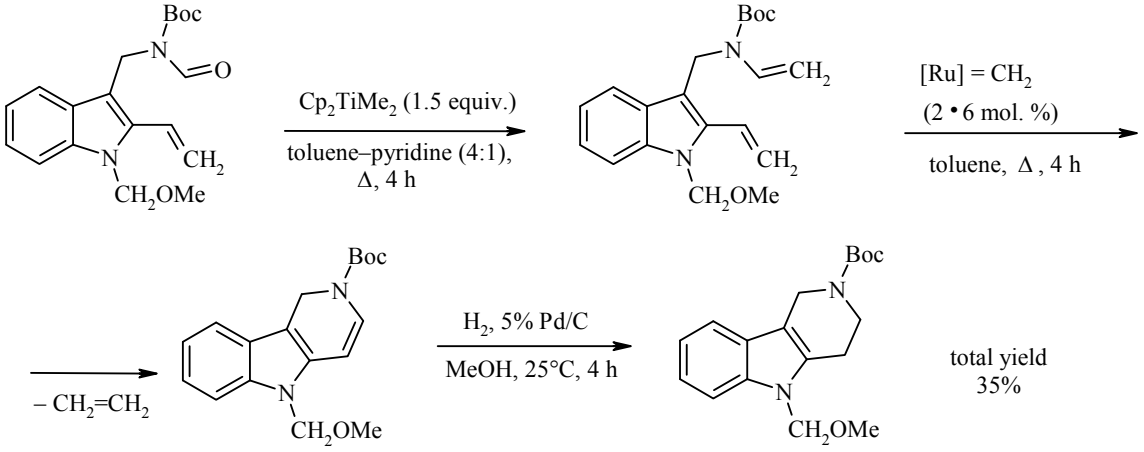


	R	3	4
a	H	26%	56%
b	Me	39%	26%
c	CH_2=$CHCH_2$	35%	38%
d	Ph	43%	55%

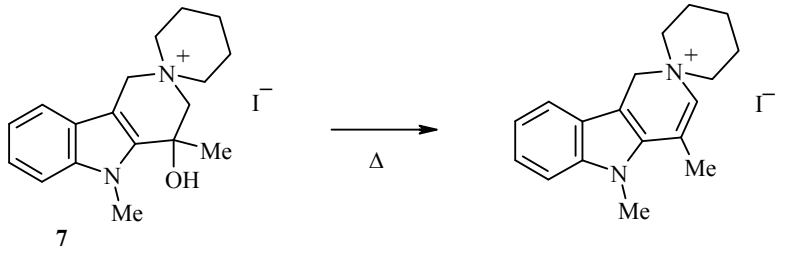
An interesting method for the synthesis of 1,2-dihydro-1-oxo-γ-carboline is based on closure of the pyridine ring with the formation of the C(1)–C(9b) bond in the corresponding isocyanate **5** formed *in situ* during Curtius rearrangement of 3-(1-methylindol-2-yl)acryl azide [11]. Alkylation of the obtained N(2)-unsubstituted γ-carboline at the nitrogen atom leads to compound **6** [11, 12].



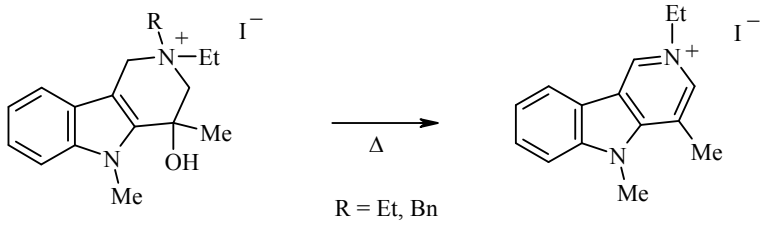
Relatively recently a convenient method was proposed for the production of 1,2-dihydro-γ-carbolines by ruthenium-catalyzed cyclization metathesis using second-generation Grubbs catalysts [13]. The obtained 1,2-dihydro-γ-carboline derivative is a very unstable cyclic enamide, which can be easily reduced to the corresponding 1,2,3,4-tetrahydro-γ-carboline. In the given example the carboline skeleton is formed by creation of the C(3)–C(4) bond.



A single example where the tetrahydro derivatives can serve as precursors of 1,2-dihydro-γ-carbolines is known. Thus, thermal dehydrogenation of the spirocyclic quaternary salts **7** leads to 1,2-dihydro-γ-carbolines [14], the production of which will be mentioned during discussion of methods for the synthesis of tetrahydro-γ-carbolines.

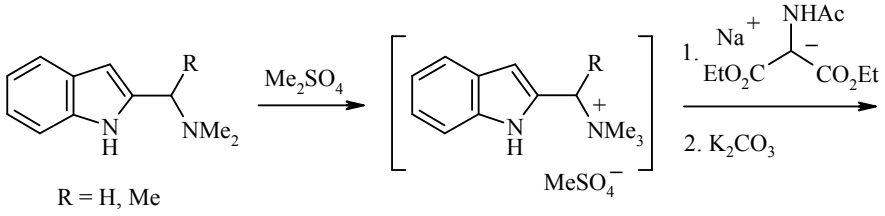


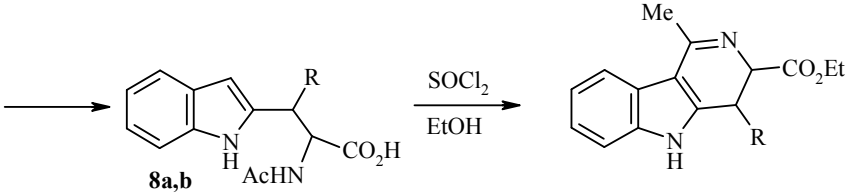
In the case of nonspirocyclic quaternary salts the reaction leads to the formation of quaternized aromatic γ-carbolines.



3,4-Dihydro-γ-carbolines

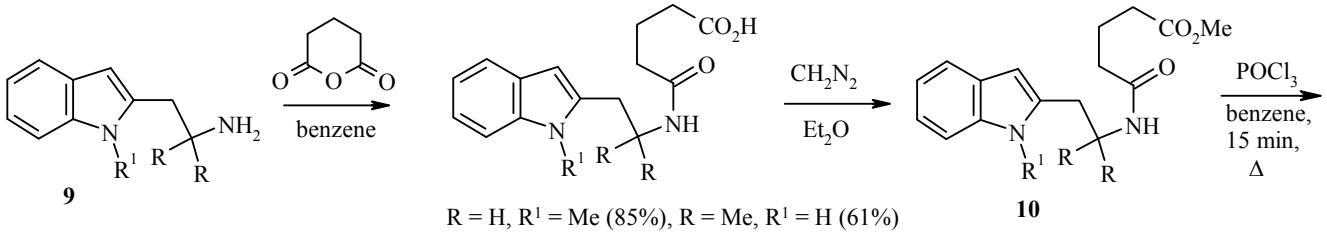
As in the case of the 1,2-dihydro derivatives, the 3,4-dihydro-γ-carboline skeleton is formed by annelation of the dihydropyridine ring to the indole fragment, and only examples with the formation of the C(1)–C(9b) bond are known. This is why the Bischler–Napieralski reaction is the main method for the production of 3,4-dihydro-γ-carboline structures based on isotryptamines and their derivatives, sources for the production of which are in most cases the corresponding isogramines. Thus, 3,4-dihydro-γ-carbolines were synthesized from 2-acetamido-3-(2-indolyl)propionic acids **8a**,**b** by the action of $SOCl_2$ [15, 16].



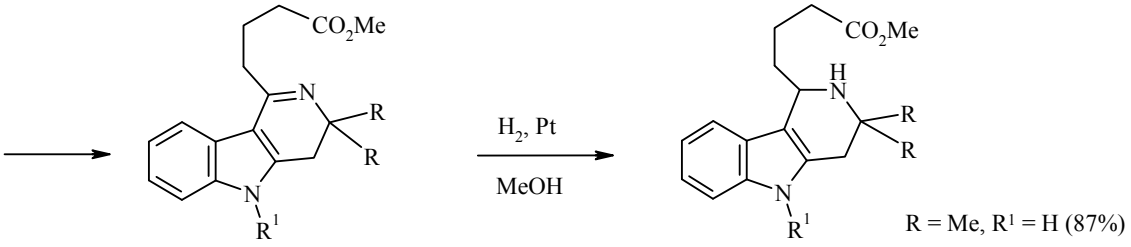


8 a R = H (78%), **b** R = Me (79%)

R = H (87%), R = Me (86%)



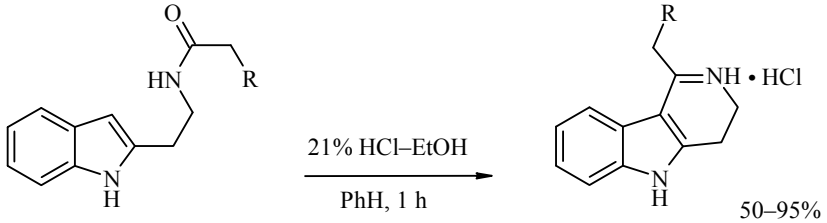
R = H, R¹ = Me (85%), R = Me, R¹ = H (61%)



R = H, R¹ = Me (64%), R = Me, R¹ = H (83%)
after two stages

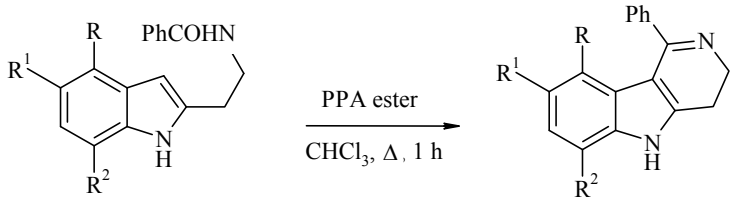
Glutaric anhydride can be used as acylating agent for the isotryptamines **9** [17-19]; the reaction leads to the formation of the monoamide, which is transformed into the methyl ester **10** by the action of diazomethane. In reaction with $POCl_3$ the ester **10** undergoes cyclization to the substituted 3,4-dihydro-γ-carboline, which can be converted into the corresponding tetrahydro derivative by hydrogenation.

During the production of 3,4-dihydro-γ-carbolines PCl_5 in $POCl_3$ [20], P_2O_5 [21], or a 21% solution of HCl in alcohol [22] can also be used as condensing agents in the Bischler–Napieralski reaction.

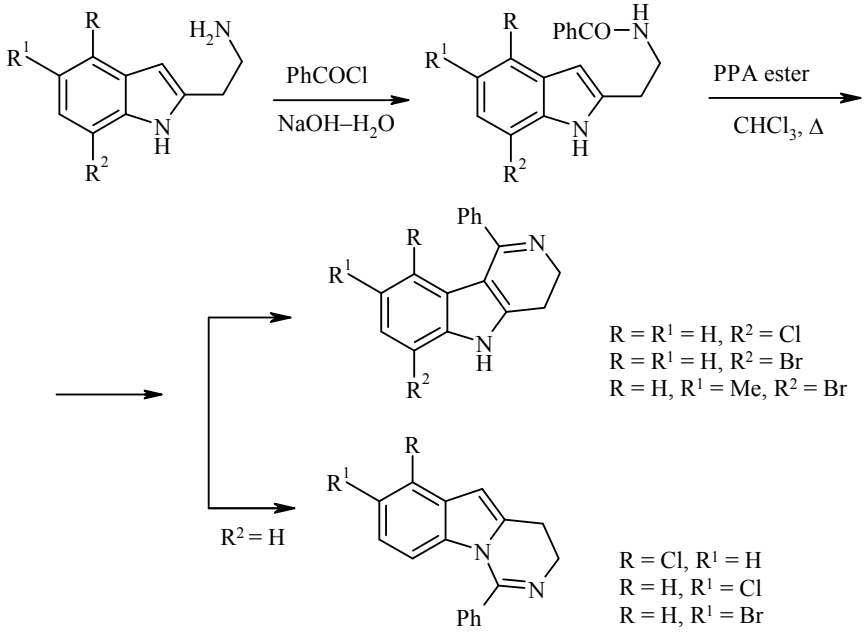


R = Cl, $(CH_2)_5N$, $O(CH_2CH_2)_2N$

The ester of PPA can also be used as cyclization agent; it is effective both for the unsubstituted amides of isotryptamines [23] and for those substituted in the benzene ring [24].



R = H, R^1 = Me, R^2 = H (67%); R = Me, R^1 = H, R^2 = Me (68%);
R = H, R^1 = R^2 = Me (58%)

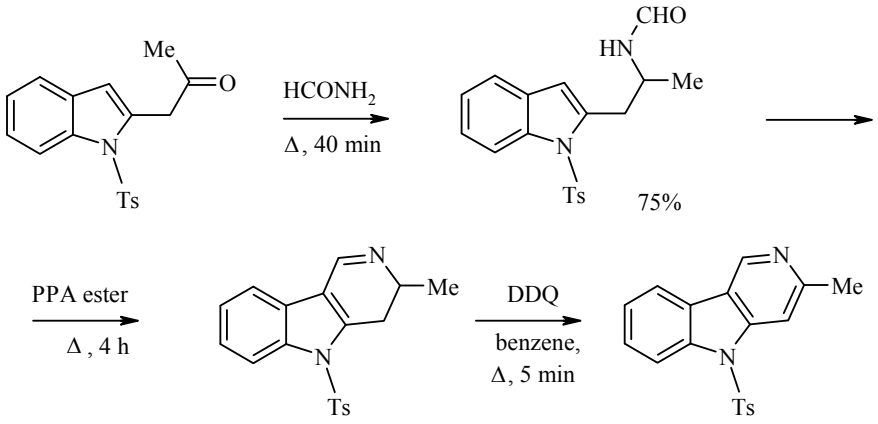


R = R^1 = H, R^2 = Cl
R = R^1 = H, R^2 = Br
R = H, R^1 = Me, R^2 = Br

R = Cl, R^1 = H
R = H, R^1 = Cl
R = H, R^1 = Br

It is important to note that in the case of the 7-halo-substituted isotryptamines under the conditions of the Bischler–Napieralski reaction 3,4-dihydropyrido[4,3-*b*]indoles are formed, whereas in the absence of the halogen atom at position 7 the formation of only 3,4-dihydropyrimido[1,6-*a*]indoles is observed [25].

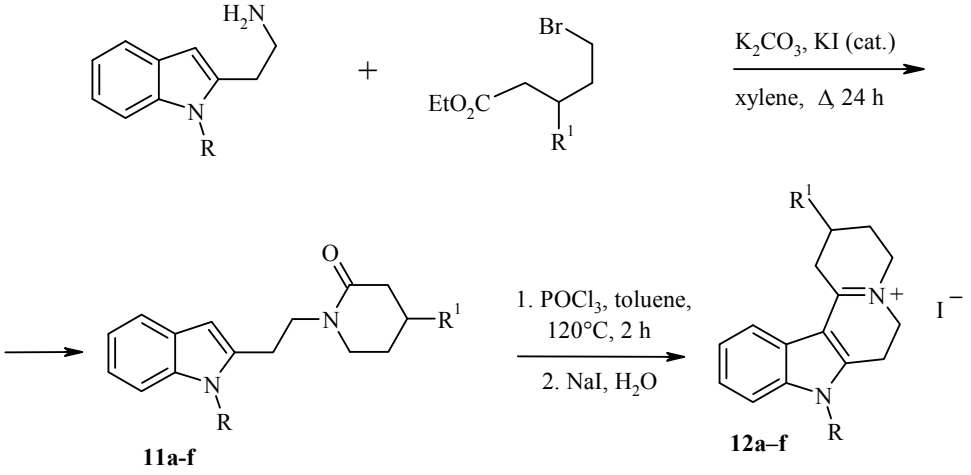
The ethyl ester of polyphosphoric acid can also be used for the cyclization of isotryptamine formamides into the corresponding 3,4-dihydro-γ-carbolines, but the authors of [26] were unable to isolate the 1-unsubstituted derivative in the pure form. The cyclization product was therefore converted into the aromatic γ-carboline.



The yield after two stages was 38%

DDQ = 2,3-dichloro-5,6-dicyano-1,4-benzoquinone

The lactams of isotryptamines **11a-f** also undergo Bischler–Napieralski cyclization with the formation of tetracyclic systems **12a-f** containing the 3,4-dihydro-γ-carboline fragment [18, 19].

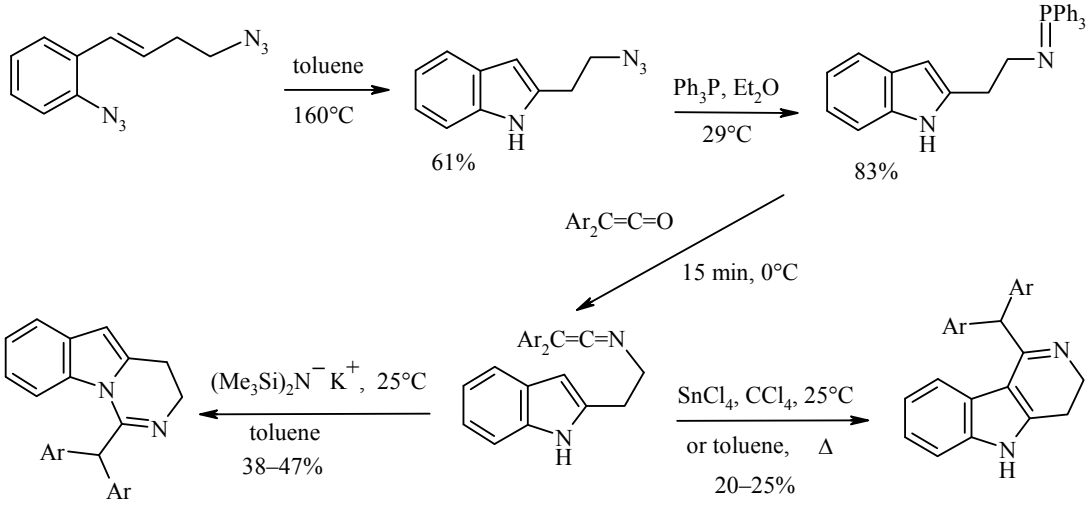


11a-f **12a–f**

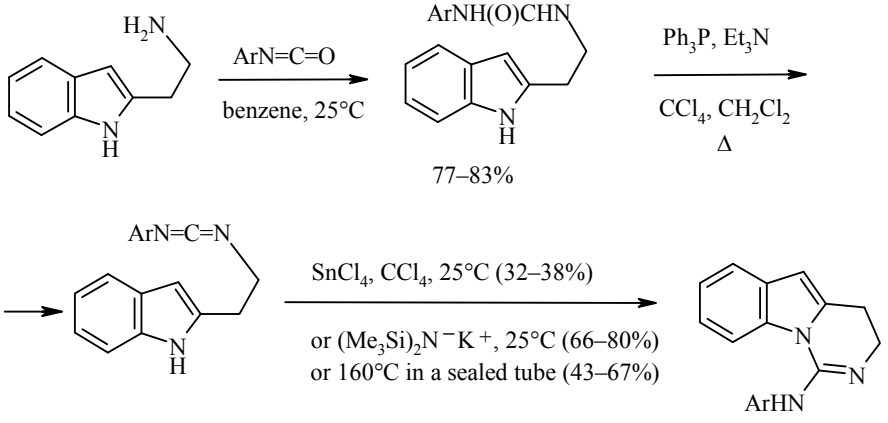
	R	R[1]	**11**	**12**
a	H	H	58%	91%
b	H	Me	48%	88%
c	H	4-ClC_6H_4	35%	94%
d	H	3,4-$(OCH_2O)C_6H_4$	48%	80%
e	Me	Me	44%	79%
f	Me	4-ClC_6H_4	34%	100%

An alternative method for the production of 3,4-dihydro-γ-carbolines is the regiospecific intramolecular cyclization of a heterocumulene-substituted indole in which the heterocumulene group and the indole ring are linked by a hydrocarbon chain containing two carbon atoms [27, 28]. For this type of compounds annelation will mostly take place in two ways: First, electrocyclic closure of the ring may occur at position 3 of the indole with the formation of the C(1)–C(9b) bond, leading to dihydro-γ-carbolines (path A); Second, nucleophilic attack by the indole nitrogen atom may occur at the central carbon atom of the heterocumulene fragment, accompanied by the formation of 3,4-dihydropyrimido[1,6-*a*]indoles (path B).

The reaction of diarylketenes with iminophosphoranes gives ketene imines. Cyclization of the latter in the presence of Lewis acids, which facilitate electrocyclic reaction at position 3 of the indole (path A), leads to dihydro-γ-carbolines, while the use of a strong base promotes nucleophilic addition of the indolyl anion at the C=C bond of the heterocumulene fragment with the formation of pyrimido[1,6-*a*]indoles.



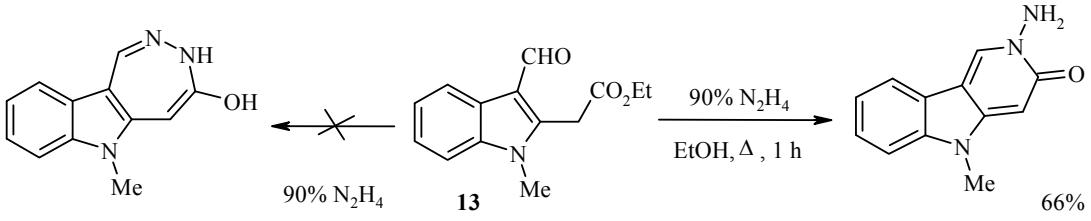
If alkylcarbodiimides are used only 3,4-dihydropyrimido[1,6-*a*]indoles are formed under any cyclization conditions.



2,3-Dihydro-γ-carbolines

It is necessary to say a few words about N-substituted 3-oxo-γ-carbolines, which can be regarded formally as 2,3-dihydro-γ-carboline derivatives on account of the absence of tautomerism. Thus, one example of the formation of N-substituted 3-oxo-γ-carbolines and the diester of 2-(3-formyl-2-indolyl)malonic acid by the action of primary amines [29] has already been considered in the previous review ([1], p. 1139); here the closure of the pyridine ring was accompanied by tandem formation of the C(1)–N(2) and C(3)–N(2) bonds.

The analogous transformation for the (3-formyl-2-indolyl)acetic ester **13** by the action of hydrazine leads to a 2-amino-γ-carboline derivative [30] and not to diazepino[5,6-*b*]indole as suggested by another team of authors [31].



METHODS OF SYNTHESIS OF TETRAHYDRO-γ-CARBOLINE STRUCTURES

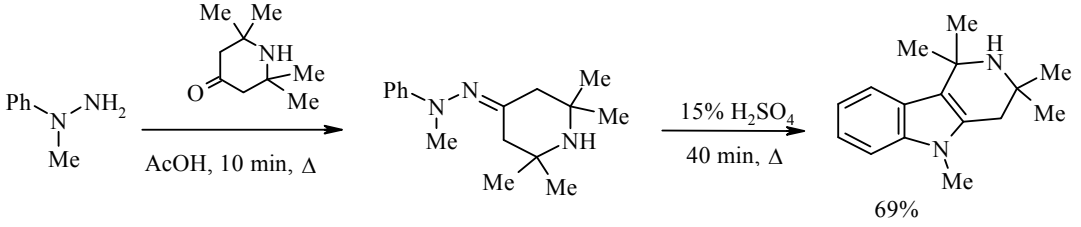
During the synthesis of tetrahydro-γ-carboline structures, in contrast to dihydro-γ-carbolines, there are two approaches to the construction of the heterocyclic system: Closure of the pyrrole ring and annelation of the piperidine fragment to the indole molecule. These two approaches will be examined separately.

FORMATION OF THE PYRROLE RING

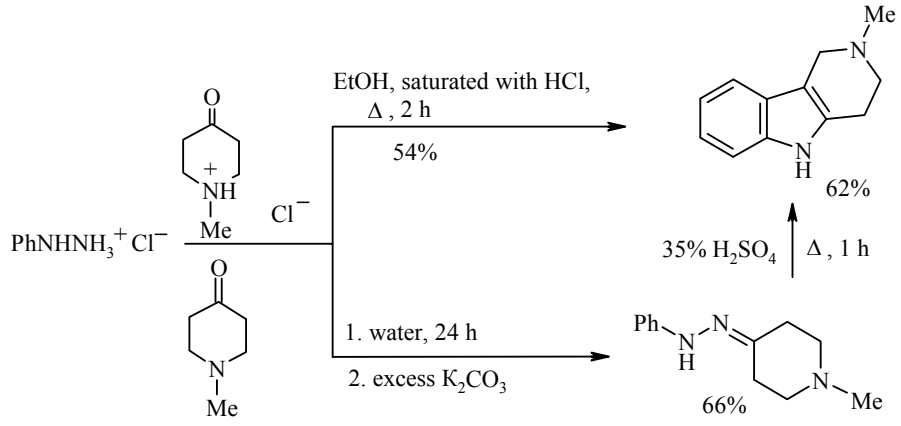
Syntheses with the Formation of the C(9a)–C(9b) Bond

The Fischer synthesis is a universal method for the production of tetrahydro-γ-carboline structures, and various 1,2,3,4-tetrahydro-γ-carbolines have been synthesized from the corresponding phenylhydrazones of piperid-4-ones.

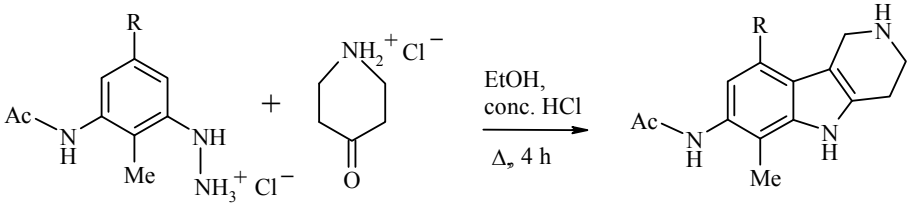
The use of the Fischer reaction for the production of indoles has been known since 1886, and in 1924 this method was first used by Robinson and Thornley for the production of 1,1,3,3,5-pentamethyl-1,2,3,4-tetrahydro-γ-carboline from the phenylmethylhydrazone of triacetoneamine [32].



As a rule the cyclization of piperid-4-one arylhydrazones by the Fischer method is conducted in an acidic medium, and this may be dilute sulfuric acid [32-34]. However, somewhat better yields are obtained with an alcohol solution of phenylhydrazone saturated with hydrogen chloride (this is the most universal condensing agent [3, 35-38]).



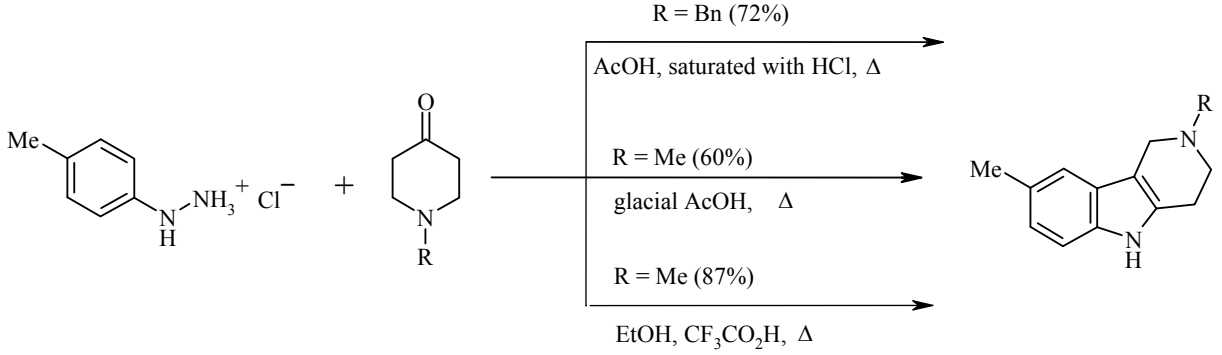
In this case there is no need to isolate the hydrazone that is formed *in situ* in the pure state, and this makes possible to achieve a one-pot synthesis of the carboline [39-41].



R = H (65%), R = Me (51%)

Thus, with ethanol saturated with hydrogen chloride it was possible to produce 1,1,3,3-tetramethyl-1,2,3,4-tetrahydro-γ-carboline from triacetoneamine phenylhydrazone [42], which could not be achieved in 15% sulfuric acid.

The application of this method requires special attention to the cyclization conditions: In addition to dilute H_2SO_4 [32-34] and alcohol solutions of HCl with various concentrations, it is also possible to use a solution of HCl in acetic acid [43], formic acid [44], glacial acetic acid [45, 46], or CF_3COOH [45, 47], H_2SO_4 in dioxane [48], mixtures of acetic acid and conc. H_2SO_4 in various ratios, or pure conc. HCl [50] as acidic catalyst. The use of conc. HCl often leads to very low yields of the targeted γ-carboline due to hydrolysis of the initial arylhydrazone [46].



There is also an example of the cyclization of phenylhydrazine hydrochloride with piperid-4-one in pyridine; the pyridinium chloride that is formed is present in the reaction mixture at the equilibrium concentration, and it is possible to obtain very goods yields of the tetrahydro-γ-carbolines **14** [51-53].

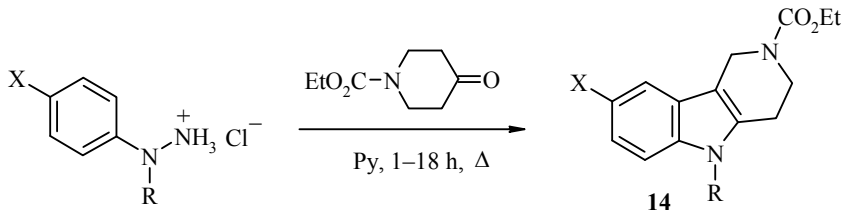
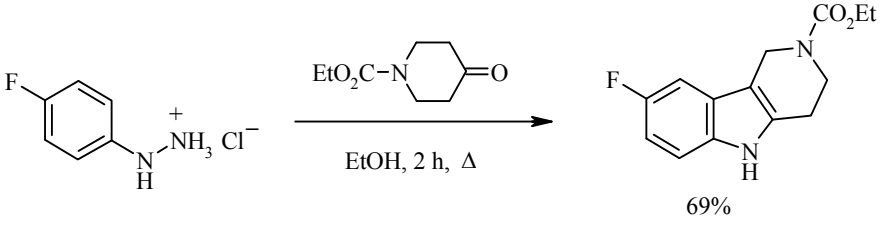


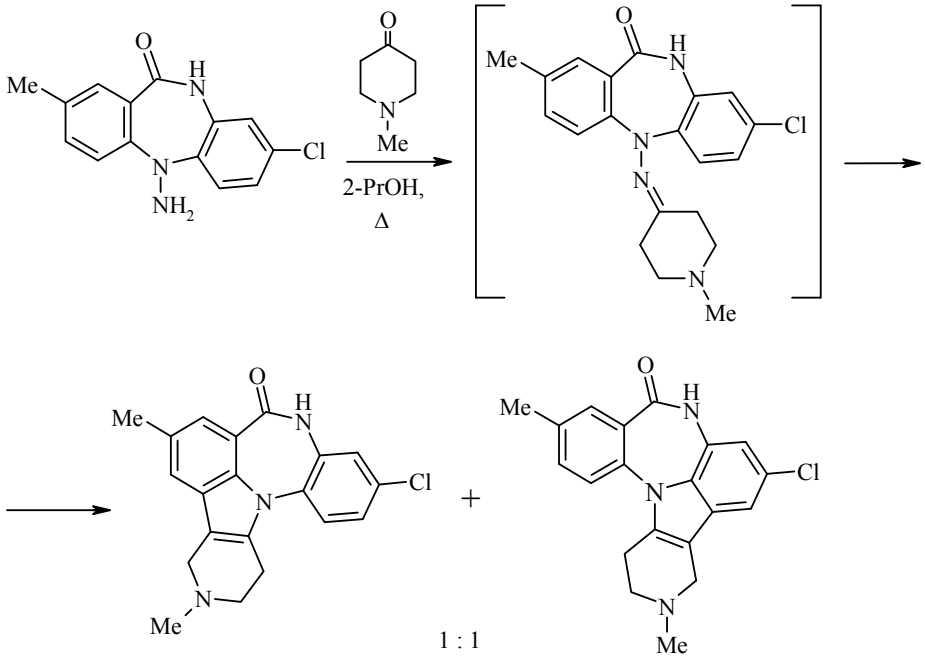
TABLE 1. Reaction Conditions and Yields of Compounds **14**

R	X	Reaction time, h	Yield of compounds **14**, %
H	H	1.4	98
H	OMe	1.5	82
H	F	5	47
Ph	H	12	86

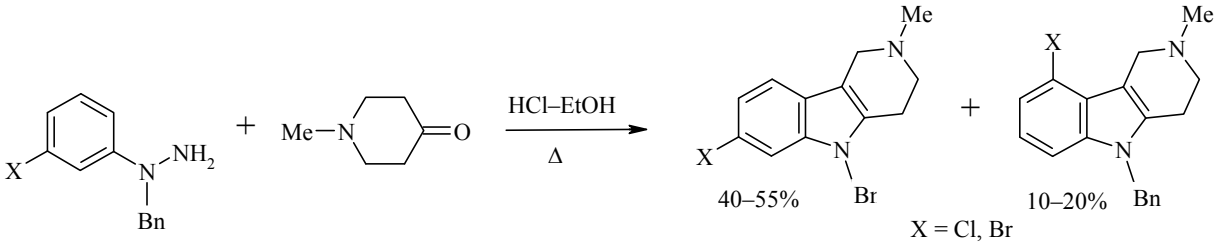
Hydrogen chloride directly combined with hydrazine can also act as acidic catalyst [54].



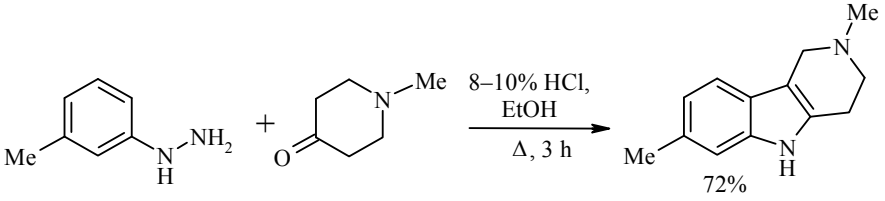
Cyclization of the arylhydrazones of 1-methylpiperid-4-one can also be realized without the acidic catalyst by boiling the reaction mixture in a suitable solvent, e.g., in 2-PrOH [47].



The structure of the hydrazine affects the ease of cyclization, the yield, and the position of the substituents in the final γ-carboline. Whereas *p*-substituted phenylhydrazines react unambiguously in these syntheses and without complications, in the case of *m*-halophenylhydrazones two isomeric tetrahydro-γ-carbolines are formed with a preference for the 7-halo-substituted isomer [3, 55].



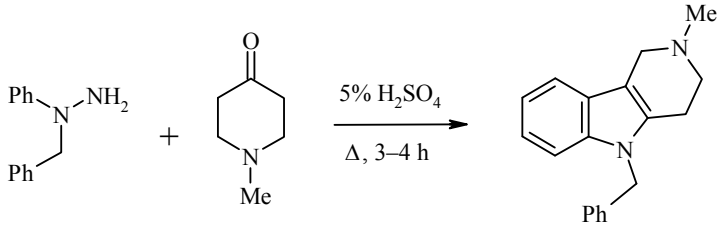
However, in the case of *m*-tolylhydrazine only one 2,7-dimethyl-1,2,3,4-tetrahydro-γ-carboline is formed although the authors do not give any explanation for this effect [56].



During the cyclization of *o*-substituted phenylhydrazones it is necessary to take account of the possibility of anomalous indolization, which can lead not only to the 6-derivative but also the 8-derivative [3].

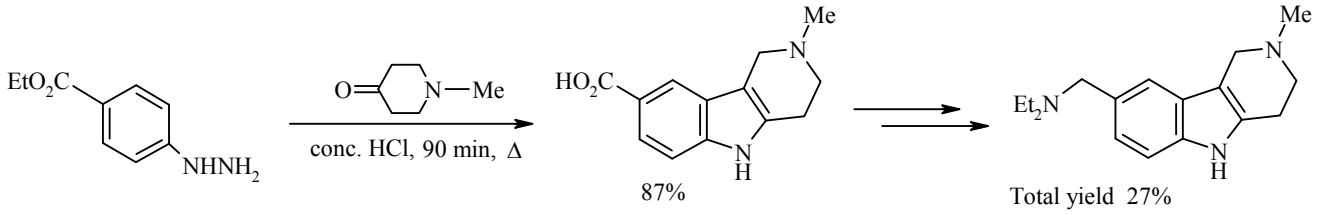
Condensation takes place quite readily if there is an electron-donating substituent at the *p*-position of the phenylhydrazine. Thus, during the Fischer cyclization of N,N-diphenylhydrazones substituted differently at the *p*-positions by Me and MeO groups a mixture of 5-aryl-γ-carboline derivatives is formed. The observed intramolecular competition indicates that the orienting ability of the substituents in the aromatic ring increases in the order H < Me < MeO (1:1.5:4.5) [57]. The presence of electron-accepting substituents requires more severe conditions for condensation. For example, trifluoromethyl-substituted tetrahydro-γ-carbolines are obtained with a yield of ~21% by boiling in a mixture of glacial acetic acid and conc. H_2SO_4 [49], while the 8-nitro derivatives of tetrahydro-γ-carboline are obtained with yields of 3-20% only when a solution of HCl in glacial acetic acid is used [35].

The Fischer reaction has been widely used for the production of a series of physiologically active derivatives of 1,2,3,4-tetrahydro-γ-carbolines. For example, this is how the synthesis of 5-benzyl-2-methyl-1,2,3,4-tetrahydro-γ-carboline – the active principle of the antihistamine product Mebhydrolin (Diazolin) **15** – was achieved [58]. The use of hydrazine and piperidine hydrochlorides with 10% H_2SO_4 as cyclization agent reduces the yield to 31% [34].

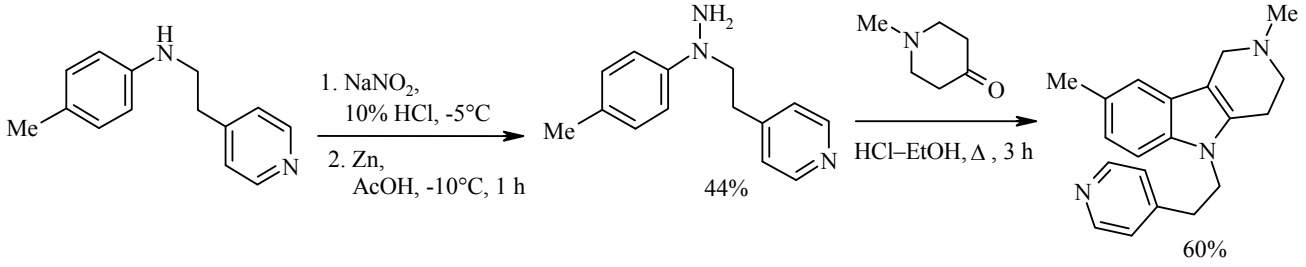


15 (69%)

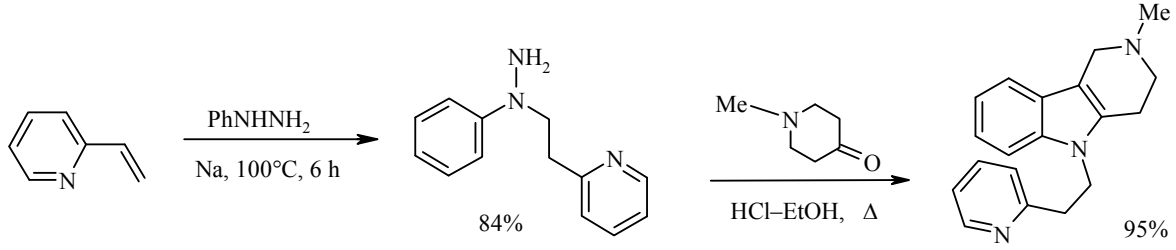
8-Carboxy-2-methyl-1,2,3,4-tetrahydro-γ-carboline was obtained similarly, and from this it was possible to synthesize 8-(diethylaminomethyl)-2-methyl-1,2,3,4-tetrahydro-γ-carboline (a potential antagonist of serotonin) according to the scheme presented below [59].



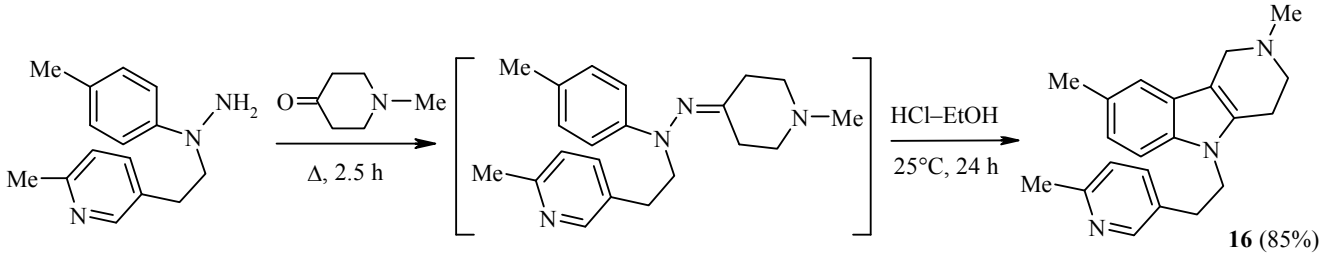
By using α-substituted arylhydrazines it is possible to obtain good yields of tetrahydro-γ-carbolines with a substituent at the indole nitrogen atom. The initial arylhydrazines can be produced from the respective anilines by successive nitrosation and reduction [39].



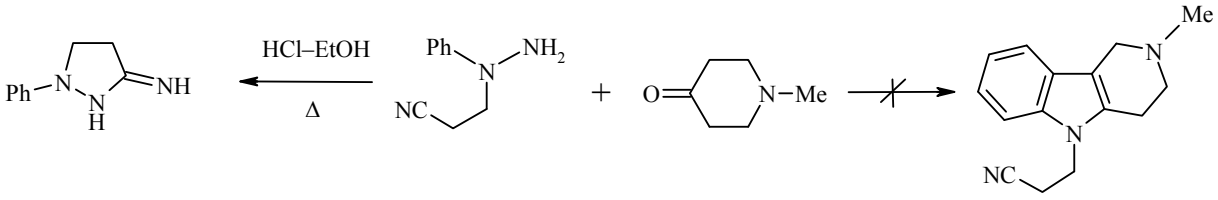
In the presence of metallic sodium arylhydrazines add to vinylpyridines through the NH group since the amino group of hydrazine is more capable of forming the N-anion under the conditions of alkaline catalysis (on account of conjugation with the aromatic ring) [60].



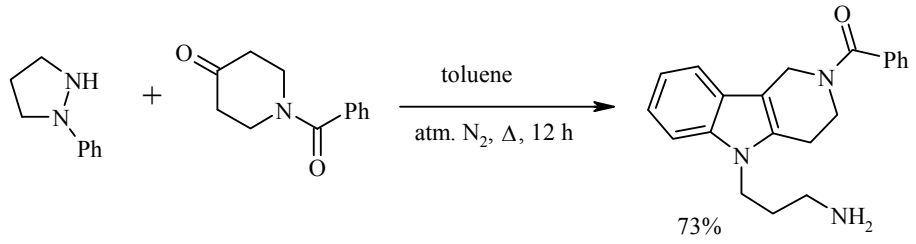
The original nationally produced antihistamine preparation Dimebon (**16**) was synthesized for the first time [36].



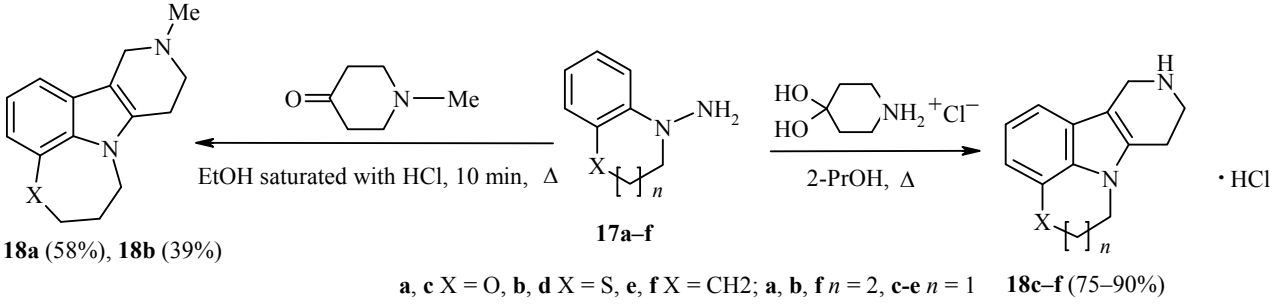
An attempt at the cyclization of 1-(2-cyanoethyl)-1-phenylhydrazine with 1-methylpiperid-4-one did not lead to the corresponding tetrahydro-γ-carboline, but instead 1-phenyl-3-pyrazolidone imine (the product from intramolecular cyclization of the initial hydrazine) was isolated [61].

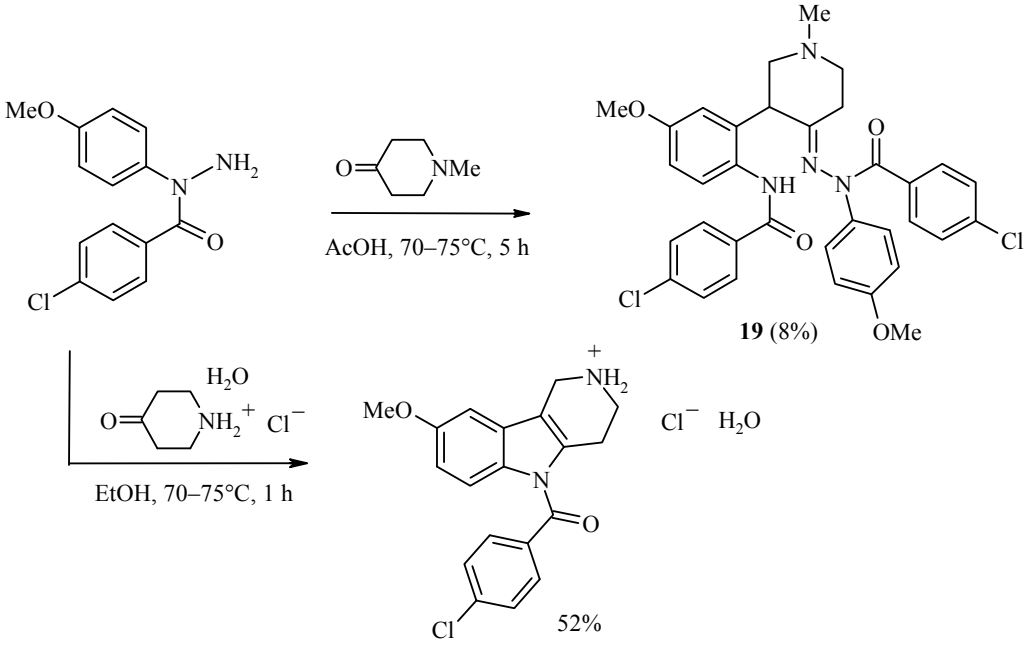


1-Phenylpyrazolidines – the cyclic analogs of phenylhydrazones – react with piperid-4-ones with the formation of good yields of 5-aminoalkylated 1,2,3,4-tetrahydro-γ-carbolines [62].



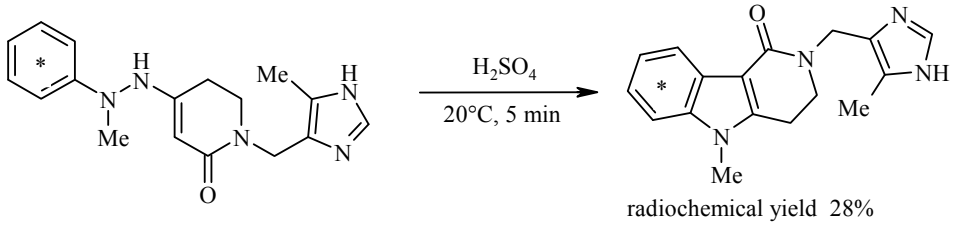
Tetracyclic γ-carboline structures **18a-f**, containing fragments of 2,3,4,5-tetrahydro-1,5-benzoxa-(thia)zepines [63] and also 1,4-benzothia(oxa)zines and tetrahydroquinoline [64], were synthesized on the basis of the Fischer reaction with the bicyclic N,N-disubstituted hydrazines **17a-f**.





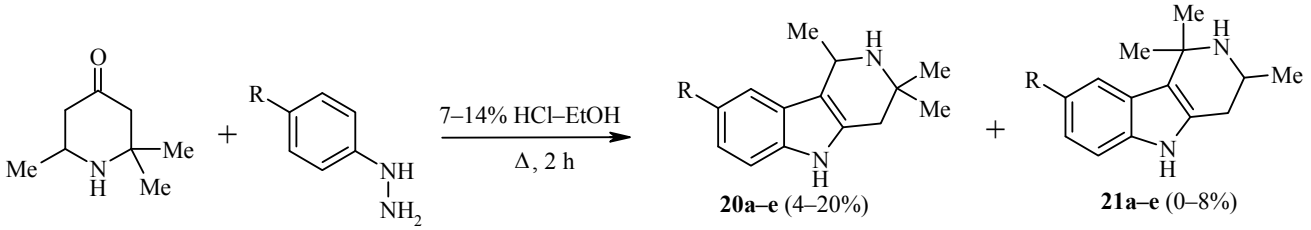
5-Acyl-1,2,3,4-tetrahydro-γ-carbolines can be obtained by the reaction of N(1)-acetylarylhydrazines with the hydrochloride of N-unsubstituted piperid-4-one in alcohol [65]. This approach was used successfully for the production of a library of structural analogs of indomethacin containing a γ-carboline skeleton [66]. With 1-methylpiperid-4-one in acetic acid, however, the reaction unexpectedly leads to the formation of the acyclic compound **19** [65].

In the general case the nature of substitution at the nitrogen atom of the carbonyl component does not have a significant effect on the cyclization process: Both piperid-4-one [41] itself and its N-alkyl [32-40, 42-50] and N-acyl [51, 54] derivatives can also take part in the transformation, as can be demonstrated by the synthesis of the C^{14}-labeled medical product Alosetron [67].



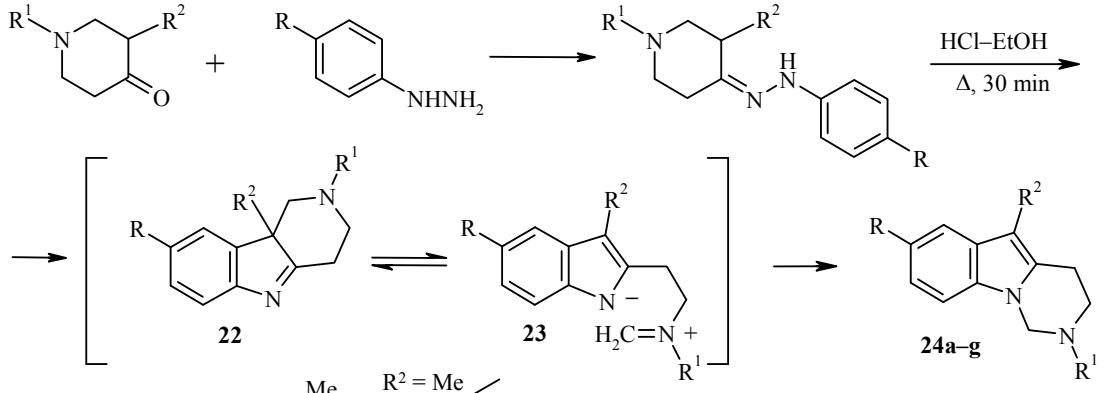
radiochemical yield 28%

Of substantial importance for the Fischer reaction is the spatial structure of the piperidine carbonyl component. For the arylhydrazones of 2,2,6-trimethylpiperid-4-one it is possible to expect two series of isomeric tetrahydro-γ-carbolines **20a-e** and **21a-e**, and here the predominant formation of the less sterically hindered isomer **20** is observed [68].



20a–e (4–20%) **21a–e** (0–8%)

a R = H, **b** R = Me, **c** R = Cl, **d** R = Br, **e** R = MeO



22 **23** **24a–g**

25a–d (8–23%)

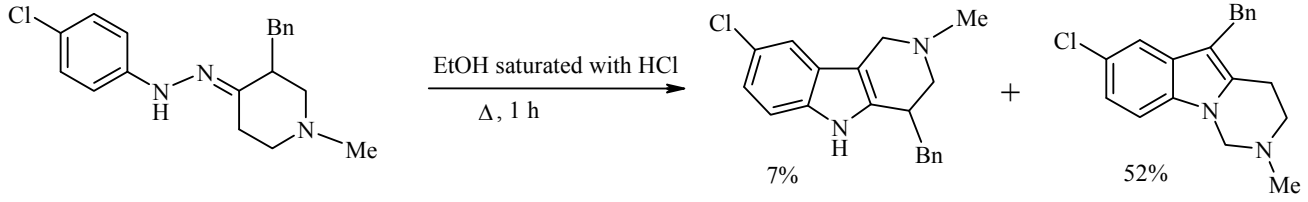
25a–c R = H, **a** R^1 = Me, **b** R^1 = Et, **c** R^1 = Bn; **d** R = Cl, R^1 = Me

	R	R^1	R^2	Yield, %
24a	H	Me	Me	78
24b	H	Me	Ph	71
24c	H	Bn	Me	80
24d	H	Bn	Ph	51
24e	Me	Me	Me	56
24f	Cl	Me	Me	77
24g	Br	Me	Ph	73

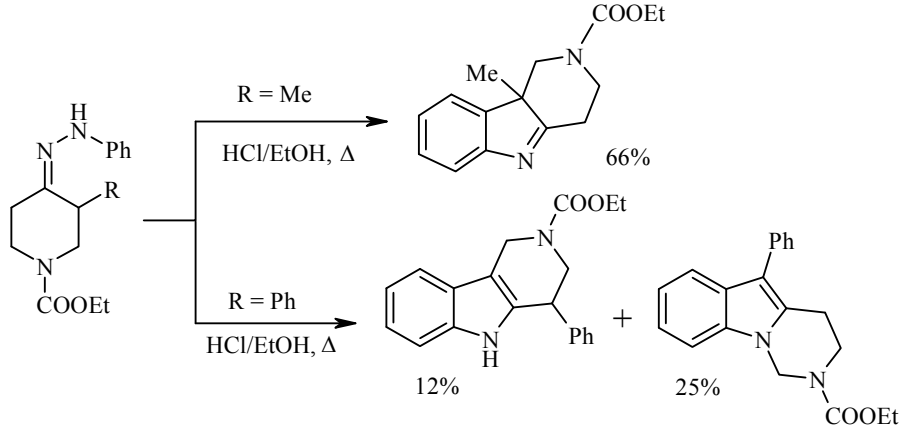
For 1,2,5-trimethylpiperid-4-ones it was only possible to realize the indole synthesis with arylhydrazines not having a second substituent at the nitrogen atom. This is explained by steric hindrances in the N,N-disubstituted hydrazones. For 1,3-disubstituted piperidines cyclization takes place with skeletal isomerization, leading predominantly to 1,2,3,4-tetrahydropyrimido[1,6-*a*]indoles [69].

In the opinion of the authors the indolenines **22** are formed initially and rearrange with cleavage of the C(1)–C(9*b*) bond by a Mannich-type retroreaction to the intermediates **23**, which in turn rearrange into the pyrimido[1,6-*a*]indoles **24a**-**g**. In certain cases 3-substituted isotryptamines **25** are formed in addition to the pyrimido[1,6-*a*]indoles **24** [70].

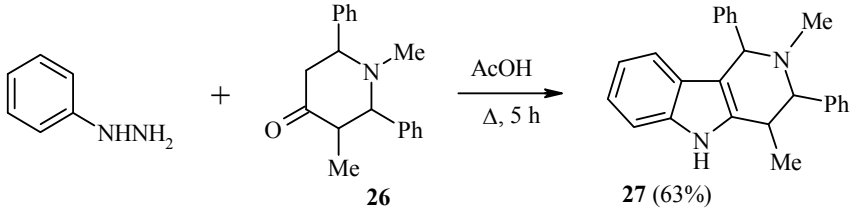
A 4-substituted tetrahydro-γ-carboline was obtained with a small yield during the cyclization of 3-benzyl-1-methylpiperid-4-one 4-chlorophenylhydrazone, while the main product was pyrimido[1,6-*a*]indole [70].



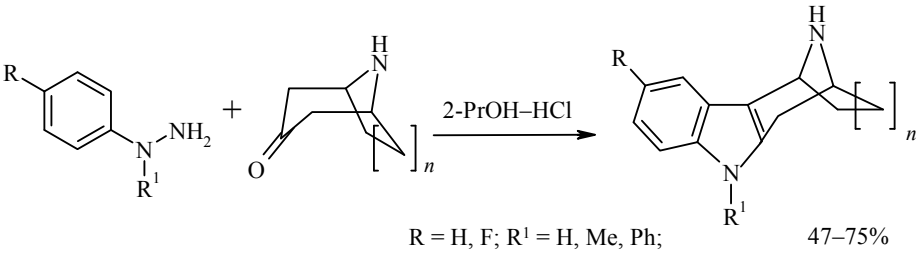
Tetrahydropyrimido[1,6-*a*]indole is only formed when there is a mobile unshared electron pair at the piperidine nitrogen atom and the formation of the iminium compound **23** is possible. Electron-deficient substituents at the piperidine nitrogen atom (R^1 = Ac, CO_2Et, etc.) must hinder the formation of pyrimido-[1,6-*a*]indole or make it impossible [69].



It is interesting to note that the transformations described above are not realized in the case of the cyclization of the tetrasubstituted piperid-4-one phenylhydrazone **26**, and a single product 1H-pyrido-[4,3-*b*]indole **27** is formed [71].

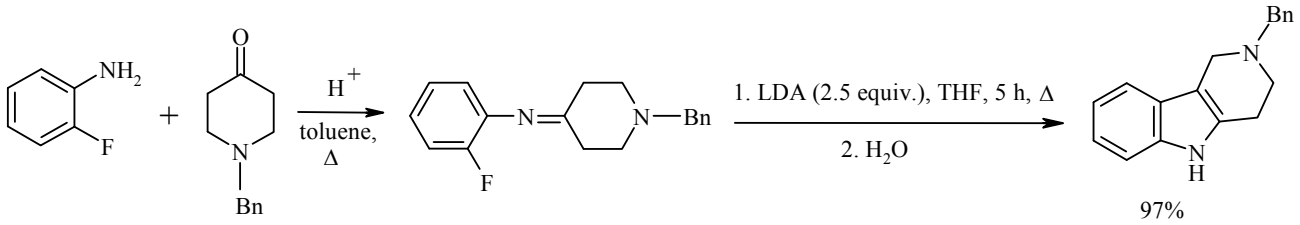


As carbonyl component for the production of the corresponding tetrahydro-γ-carboline derivatives it is also possible to use such "bridged" analogs of piperid-4-one as tropinone and nortropinone [72, 73].



R = H, F; R^1 = H, Me, Ph; 47–75%
n = 1, 2

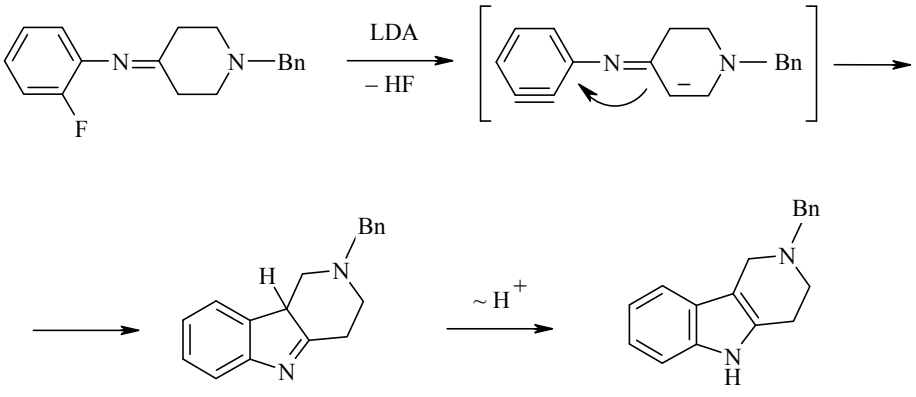
Methods for the synthesis of tetrahydro-γ-carboline structures with the formation of the C(9a)–C(9b) bond are not restricted solely to cyclization of the corresponding hydrazones of piperid-4-ones under the conditions of the Fischer reaction. 1,2,3,4-Tetrahydro-γ-carbolines are obtained readily and with almost quantitative yields from 2-fluorophenylimines [74] by the action of an excess of a base not having nucleophilic characteristics, e.g., lithium diisopropylamide.



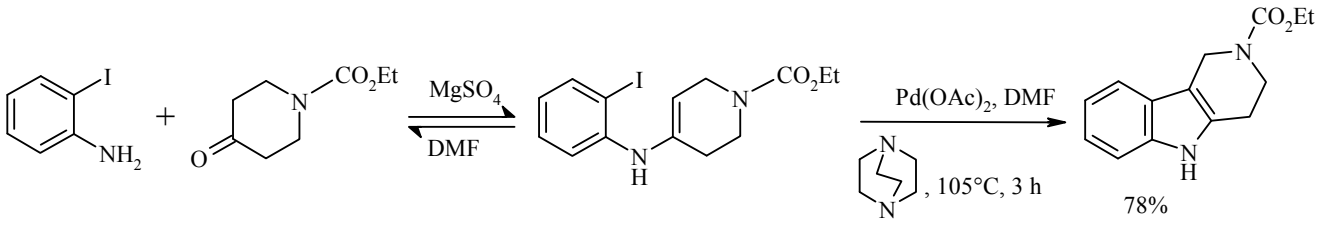
97%

LDA – lithium diisopropylamide

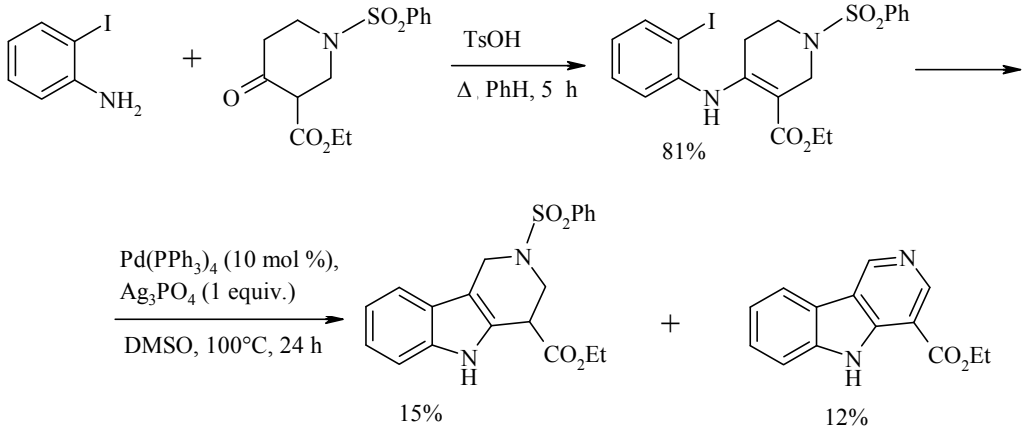
The process evidently takes place by an aryne mechanism with the initial elimination of hydrogen fluoride under the influence of the strong base and subsequent intramolecular nucleophilic addition of the iminolate anion at the triple bond.



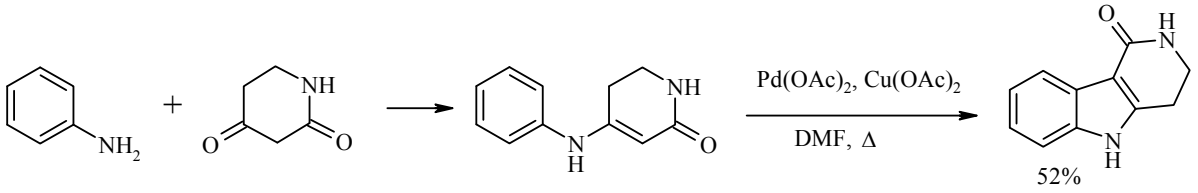
Closure of the pyrrole ring also accompanies the intramolecular Heck reaction, and this makes it possible to produce γ-carboline derivatives from *o*-iodoaniline enamine formed *in situ* and N-ethoxycarbonyl- or N-Boc-piperid-4-one [75, 76]. The Heck reaction in this version can be regarded as an alternative to the Fischer reaction.



If silver phosphate and ethyl 4-oxo-N-phenylsulfonylpiperidine-3-carboxylate as carbonyl component are used a good yield of a mixture of tetrahydro and aromatic γ-carboline derivatives is obtained [77].

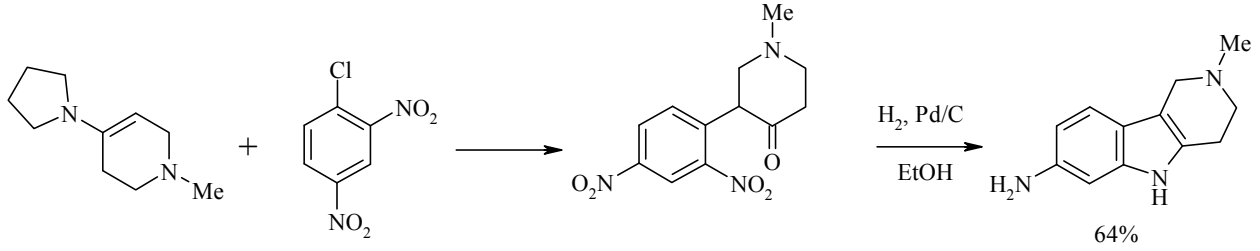


If the halogen atom in the aromatic ring of the enamine is absent the oxidative variant of the Heck reaction, in which copper salts that simultaneously regenerate the catalyst act as oxidizing agent, is realized successfully [67].

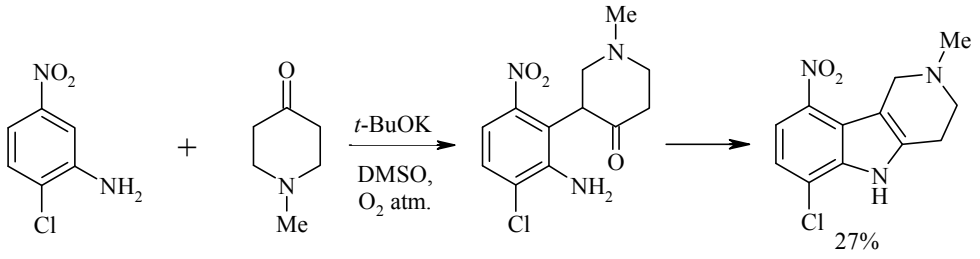


Syntheses with Successive Formation of the C(9a)–C(9b) and C(4a)–N(5) or C(5a)–N(5) Bonds

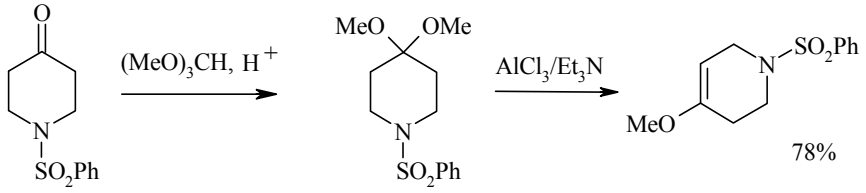
Tetrahydro-γ-carboline derivatives can be obtained from 2-(*o*-nitroaryl)piperid-4-ones [78]. For example, the reductive Pd-catalyzed cyclization of 3-(2,4-dinitrophenyl)-1-methylpiperid-4-one, which is the product from arylation of an enamine (1-methyl-4-pyrrolidin-1-yl-3-piperideine) with 2,4-dinitrochlorobenzene, leads to the formation of 7-amino-2-methyl-1,2,3,4-tetrahydro-γ-carboline with a good yield (the formation of the C(4a)–N(5) bond).



The oxidative nucleophilic substitution of hydrogen in 2-chloro-5-nitroaniline by the enolate ion of 1-methylpiperid-4-one at the *ortho* position to the amino group and subsequent intramolecular condensation in a Baeyer type reaction lead to a small yield of difficultly obtainable 9-nitro-1,2,3,4-tetrahydro-γ-carboline derivatives [79].



An extremely interesting method for the production of 1,2,3,4-tetrahydro-γ-carbolines is based on the cyclocondensation of the enolic ethers of 4-piperidone with 2-methoxy-4-(N-phenylsulfonyl)-1,4-benzoquinone imines catalyzed by Lewis acids, and this can be regarded as an alternative to the Nenitzescu reaction [80]. The initial enolic ethers of N-phenylsulfonylpiperid-4-one are obtained from its dimethyl acetal by the action of aluminum chloride and triethylamine [81].



The monoimines of benzoquinone react with the enolic ether of piperid-4-one with the formation of both γ-carboline derivatives **28** and 1,2,3,4-tetrahydro[1]benzofuro[3,2-*c*]pyridines **29** depending on the Lewis acid used.

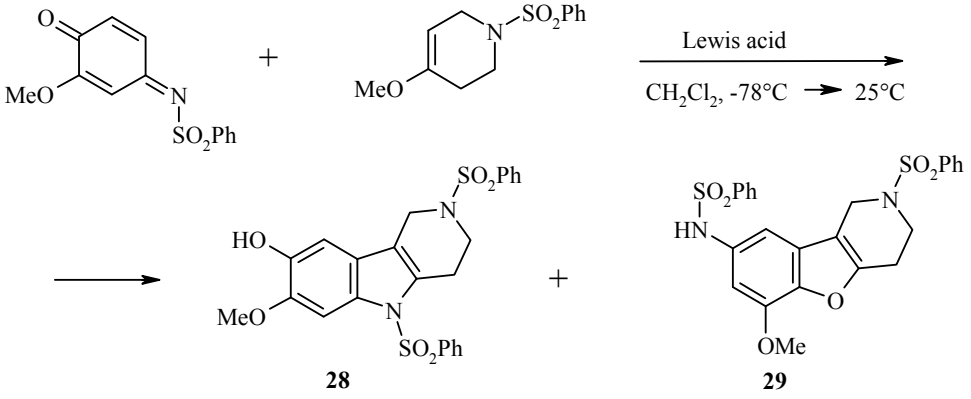
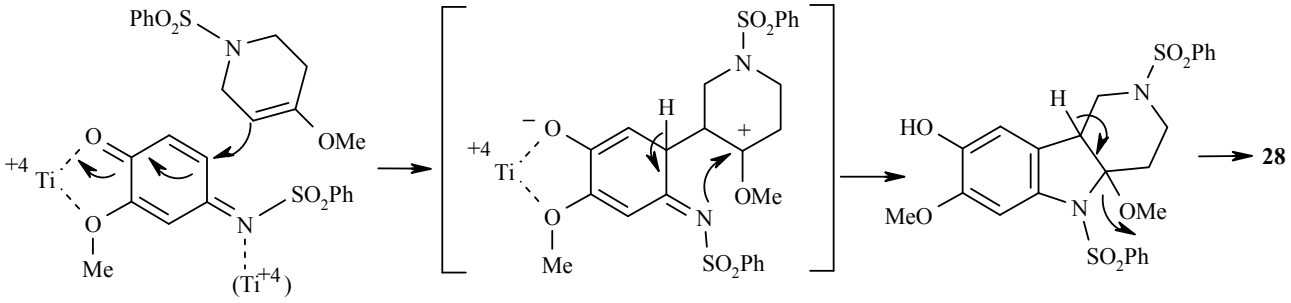


TABLE 2. The Ratio of the Yields of Compounds **28** and **29** in Relation to the Employed Lewis Acid

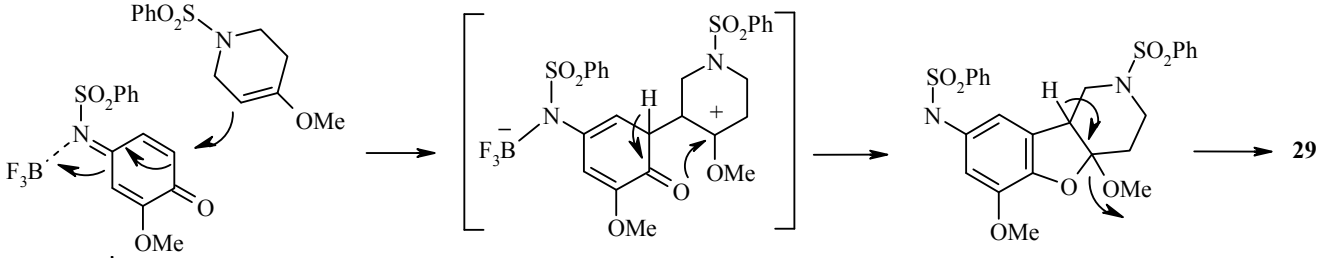
Lewis acid	Yield, %	
	28	**29**
1:1 $TiCl_4$: $Ti(OPr\text{-}i)_4$ (5 equiv.)	78	—
1:1 $TiCl_4$: $Ti(OPr\text{-}i)_4$ (1 equiv.)	49	20
$BF_3 \cdot Et_2O$ (1 equiv.)	—	65

It is seen from the presented data that only the tetrahydro-γ-carboline derivative **28** is formed in the presence of an excess of the complex catalyst $TiCl_4$–$Ti(OPr\text{-}i)_4$ (1:1), whereas the reaction with the addition of boron trifluoride etherate leads to the formation of only the benzofuran adduct **29**. The use of other Lewis acids such as $SnCl_4$ leads to a mixture of compounds **28** and **29**.

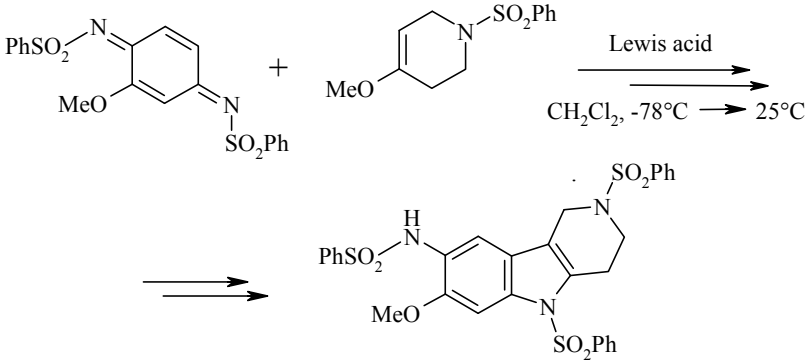
The following mechanisms were proposed to explain the observed regioselectivity of the process [82].



Bidentate Ti^{+4}, which combines with the oxygen atoms of the carbonyl and methoxy groups, activates the nucleophilic addition of the enol ether with subsequent cyclization to the tetrahydro-γ-carboline derivative **28**, accompanied by the elimination of a molecule of MeOH. The use of an excess of $TiCl_4$–$Ti(OPr\text{-}i)_4$ is due to the formation of a benzoquinone monoimide–$[Ti(IV)]_2$ complex. In the case of monodentate BF_3 bonding with the more basic nitrogen atom of the imide group occurs, and this activates addition of the enol ether at position 6 and leads to the formation of the benzofuran derivative **29**.



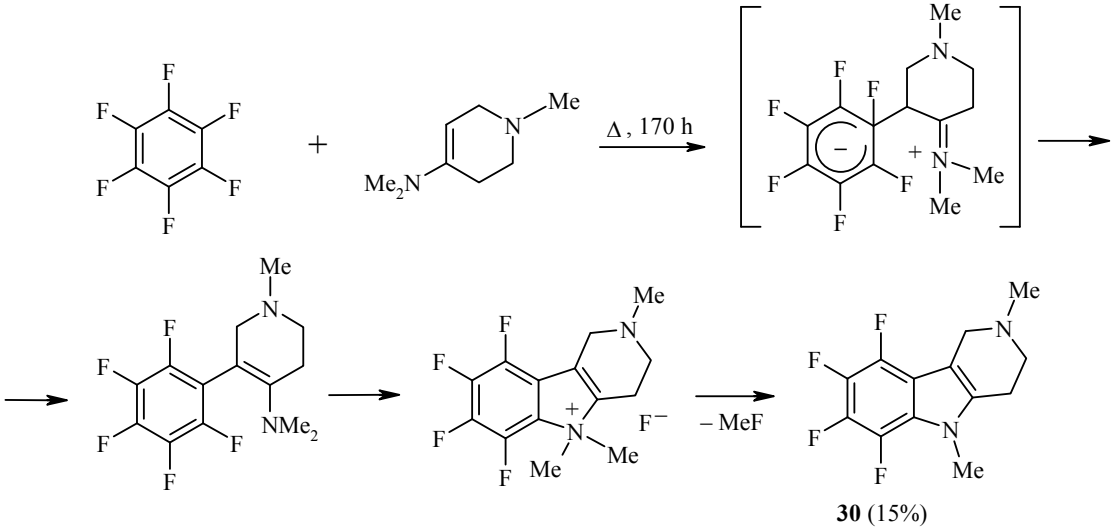
Similar transformations occur with benzoquinone bisimides. In this case only derivatives of 1,2,3,4-tetrahydro-γ-carboline are formed with good yields. The regioselectivity in the addition of the enol ether results from the activation of the bisamide, combines with the acids at the more basic nitrogen atom adjacent to the methoxy group.



$BF_3 \cdot Et_2O$ 74%

1:1 $TiCl_4$:$Ti(OPr\text{-}i)_4$ (5 equiv.) 81%

The method for the synthesis of 6,7,8,9-tetrafluoro-γ-carboline **30** from perfluorobenzene and the enamine of N-methylpiperid-4-one, accompanied by closure of the pyridine ring with the subsequent formation of the C(9a)–C(9b) and C(5a)–N(5) bonds, is of theoretical interest [83].

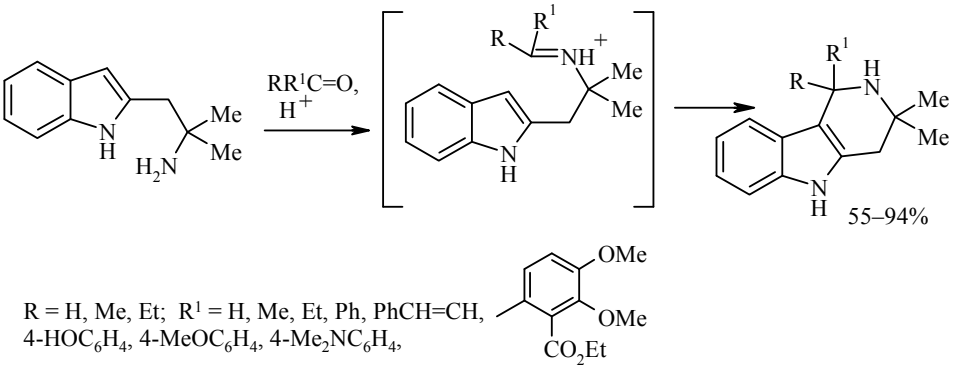


FORMATION OF THE PIPERIDEINE RING

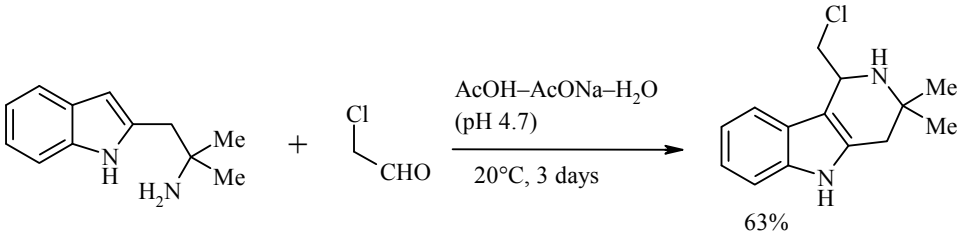
A completely different approach to the synthesis of tetrahydro-γ-carbolines is annelation of a piperideine ring at the C(2)–C(3) bond of the indole molecule; the formation of the tetrahydro-γ-carboline skeleton here is possible as a result of the formation both of the C(1)–C(9b), C(1)–N(2), C(3)–N(2), C(3)–C(4), and C(4)–C(4a) bonds and of the synchronously formed C(3)–N(2) and C(4)–C(4a) bonds.

Syntheses with the Formation of the C(1)–C(9b) Bonds

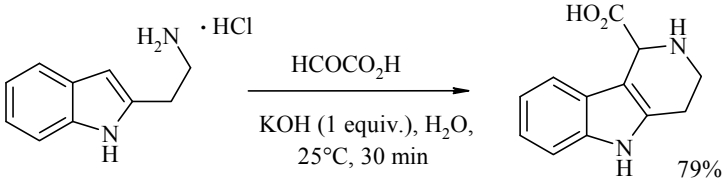
The general method for the production of 1,2,3,4-tetrahydro-γ-carbolines with the formation of the C(1)–C(9b) bond is the Pictet–Spengler condensation of 2-(β-aminoethyl)indoles with carbonyl compounds, conducted in an acidic medium. The transformations take place under fairly mild conditions and with good yields of the required tetrahydro-γ-carboline compounds not substituted at positions 2 and 5 [17, 22, 84-87].



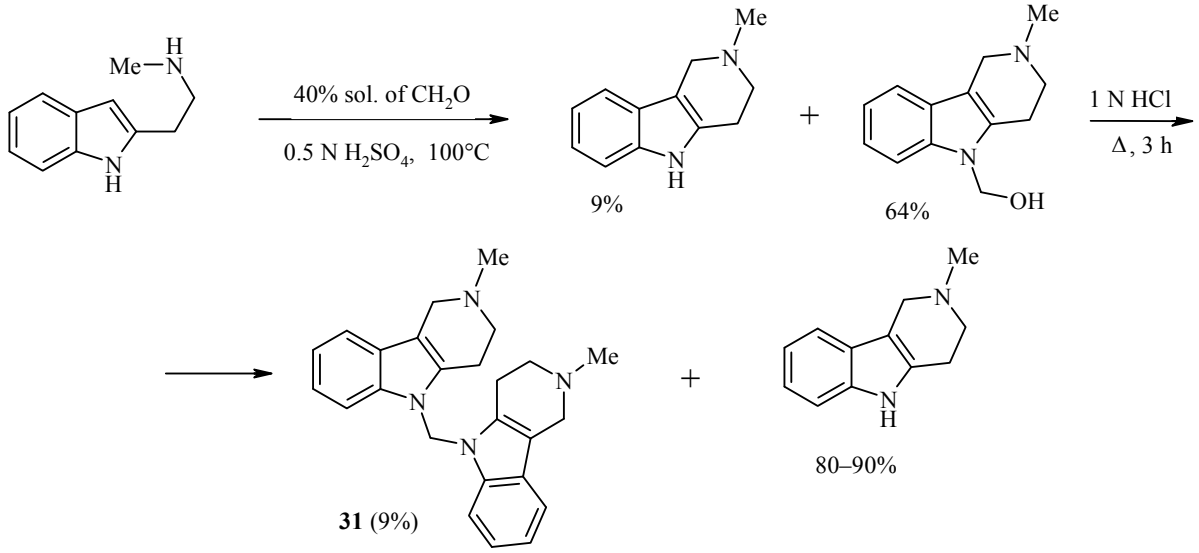
Intramolecular condensation takes place fairly smoothly both in an acetate buffer (pH 4.7) at room temperature [22] and when solutions of the isotryptamines hydrochlorides in the benzene–ethanol–water ternary system are boiled [84].



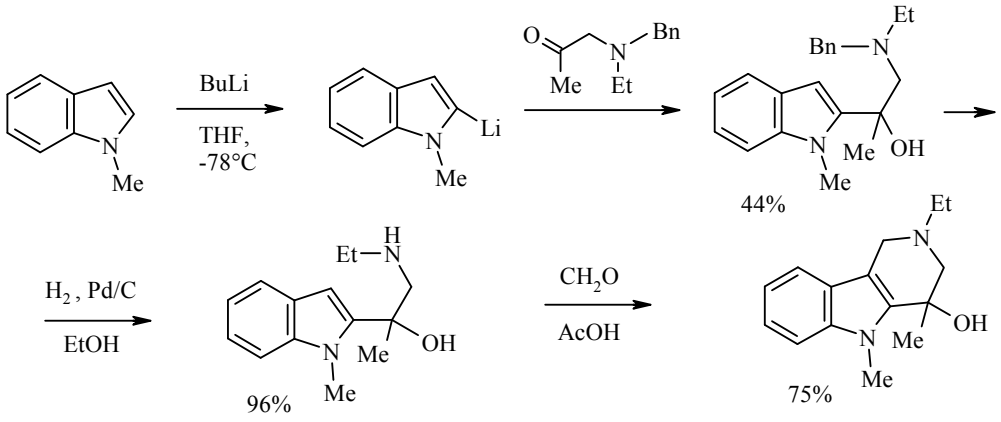
If glyoxalic acid is used it is possible to obtain tetrahydro-γ-carboline-1-carboxylic acid with a good yield from isotryptamines under very mild conditions [86].



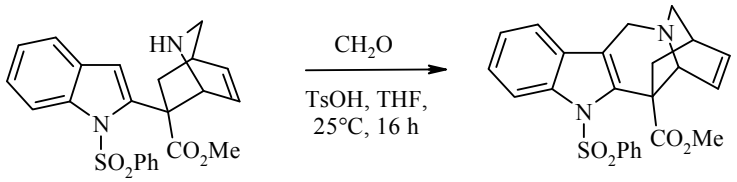
In the case of 1-unsubstituted isotryptamines Pictet–Spengler condensation with formaldehyde leads to the preferential formation of a 5-hydroxymethylated tetrahydro-γ-carboline derivative, which is hydrolyzed in an alkaline medium to 5-unsubstituted tetrahydro-γ-carboline with the formation of a small amount of the dimeric compound **31** [88].



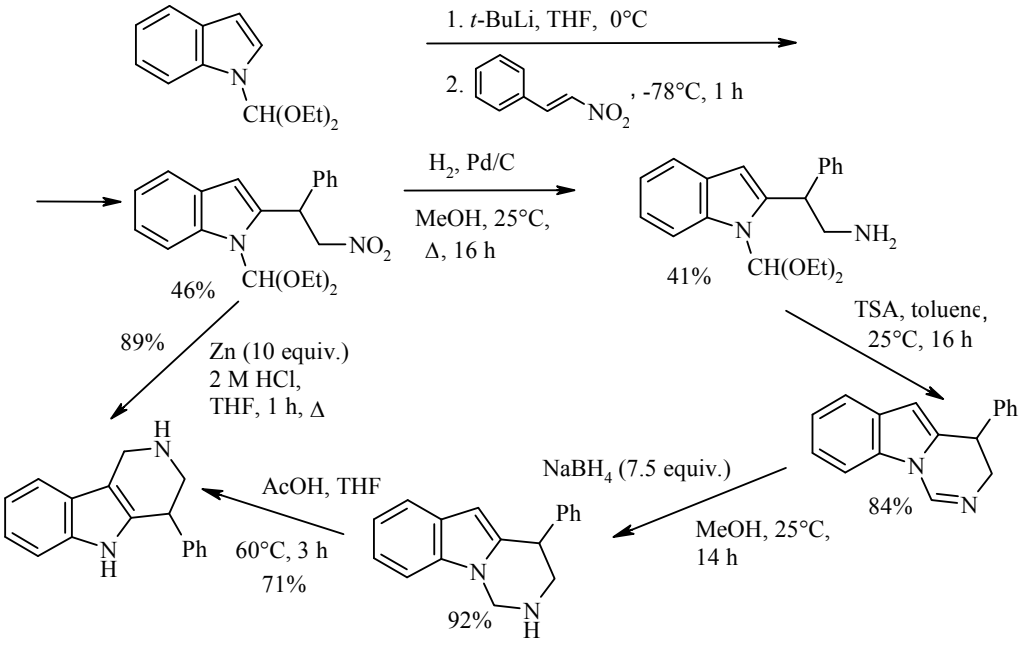
It is known that the reaction of 1-methylindole with butyllithium leads to the formation of a derivative metallated at position 2 [89], which reacts readily with carbonyl compounds. If monoalkylaminoacetones are used it is possible to obtain the 4-hydroxy-1,2,3,4-tetrahydro-γ-carboline derivatives at once (similar to the formation of tetrahydro-β-carbolines from tryptamines and formaldehyde) [90].



The Pictet–Spengler reaction was also used for the production of a structural analog of the alkaloid catharanthine containing a γ-carboline skeleton, which belongs to the ibogaine group [91].

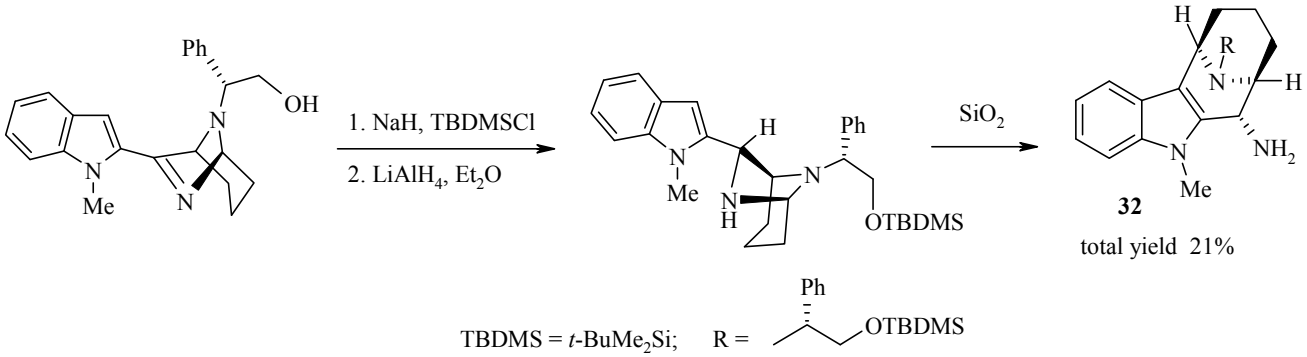


By using a diethoxymethyl group as protecting group for the indole nitrogen atom it is possible to realize regioselective metallation at position 2 with subsequent annelation of the piperideine ring with nitrostyrene. In this case the diethoxymethyl group also plays the role of a one-carbon building block, taking part in the formation both of tetrahydro-γ-carboline and of the isomeric tetrahydropyrimido[1,6-*a*]indole, which can also serve as precursor for the production of tetrahydro-γ-carboline according to the following scheme [92]:

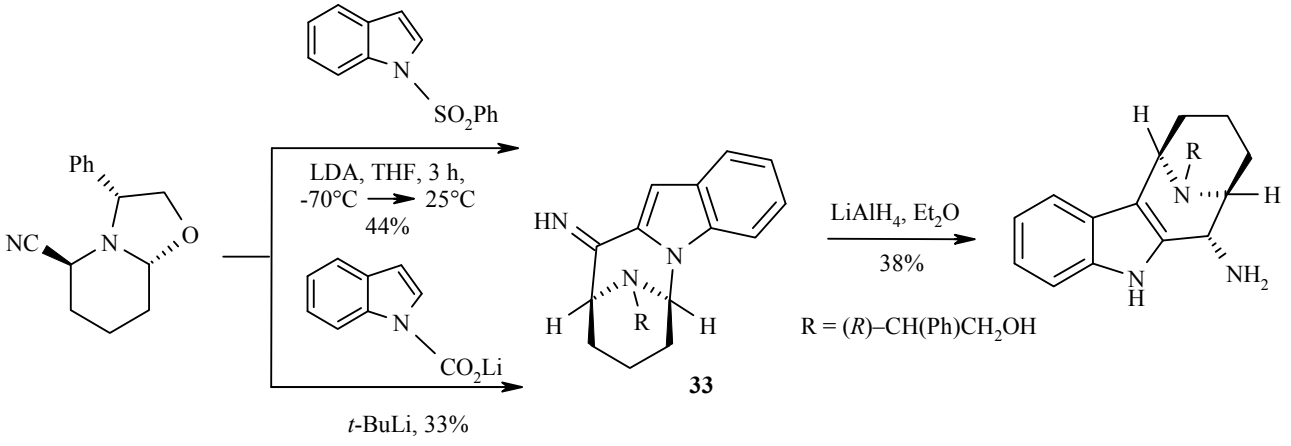


TSA – *p*-toluenesulfonic acid

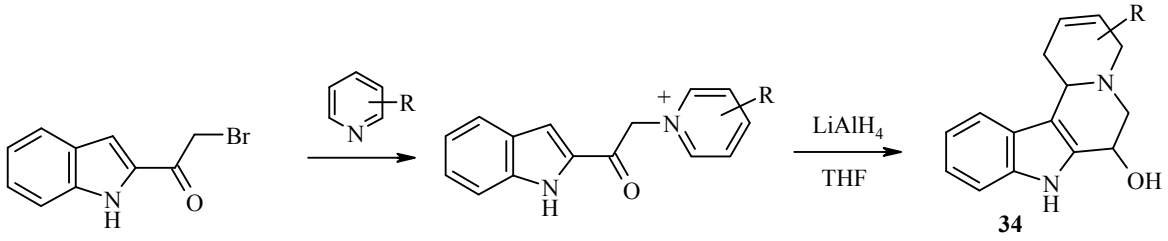
A synthetic equivalent of the carbonyl compound for the Pictet–Spengler condensation can be not only an acetal fragment at the nitrogen atom of indole (as in the previous example) but also an aminal fragment in the side chain. Here, however, the yield of the bridged γ-carboline derivative **32** is low on account of the chemoselective transformation of the respective bicyclic aminal [93].



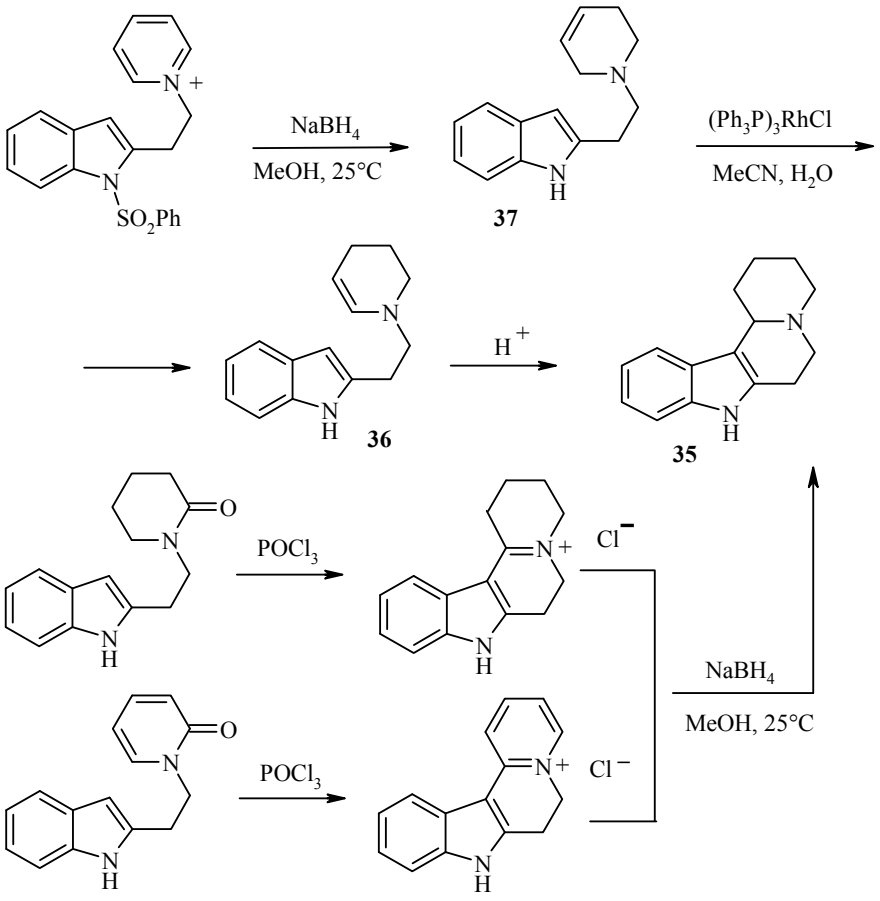
During the reduction of compound **33** by the action of $LiAlH_4$, accompanied by rearrangement, a 5-unsubstituted structure analogous with compound **32** is formed as a single diastereomer [93].



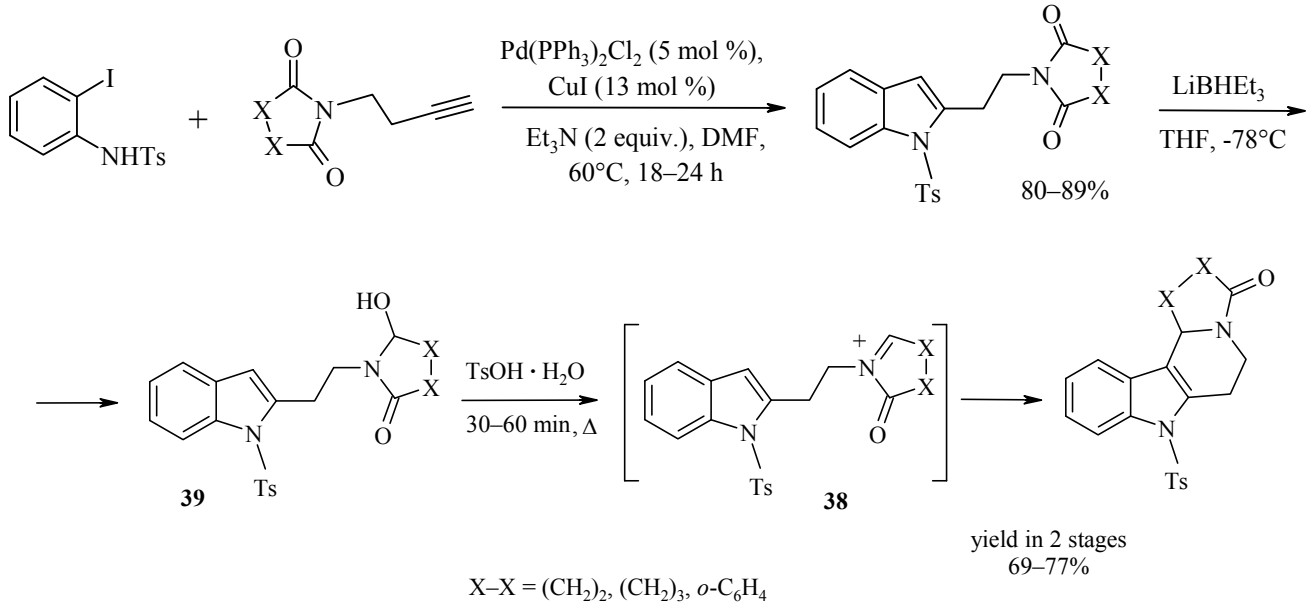
2-(Bromoacetyl)indole can be transformed into the tetrahydro-γ-carboline **34** through a stage involving the formation of a pyridinium salt followed by reductive cyclization with lithium aluminum hydride [94]. In this case, evidently, electrophilic attack by the α-carbon atom of the pyridinium cation occurs at position 3 of the indole ring.



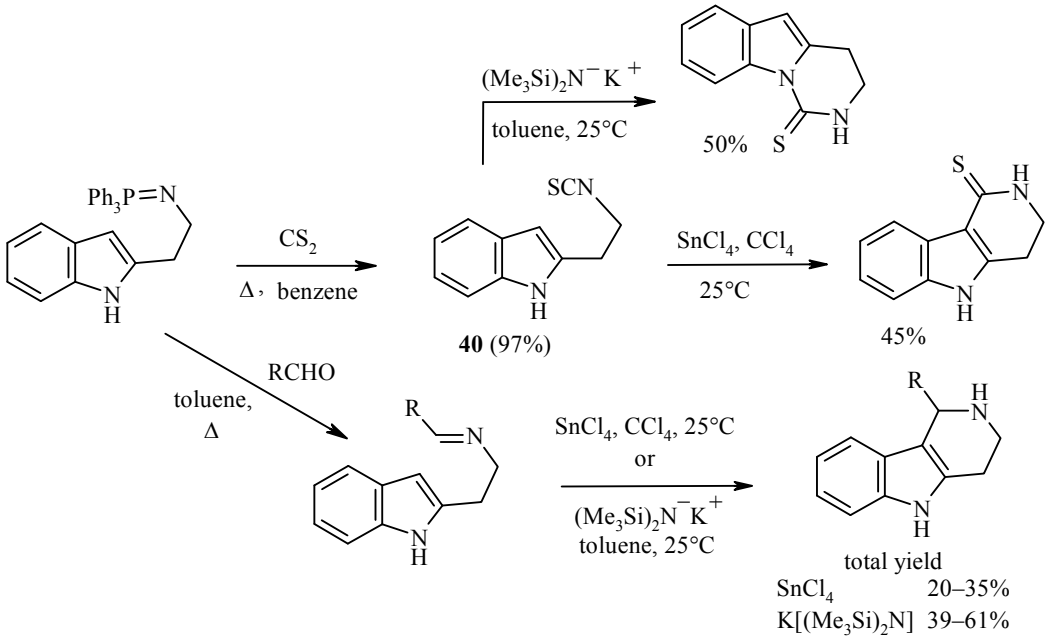
Cyclization of the cyclic enamine **36**, obtained by isomerization of the allylamine **37** at a rhodium catalyst, in an acidic medium leads to a similar γ-carboline structure – 1,2,3,4,6,7,8,12*c*-octahydroindolo-[3,2-*a*]quinolizine (**35**). Compound **35** can also be obtained by reduction of the corresponding 3,4-dihydro-γ-carbolinium salts, synthesized from the respective amides [95].



Recently it was shown that acyliminium cations **38**, obtained from the respective hydroxylactams **39**, can act as intermediates in the synthesis of tetracyclic tetrahydro-γ-carbolines. Compounds are synthesized by the Sonogashira reaction from *o*-iodo-N-tosylanilines with imides containing a 3-butyne substituent at the nitrogen atom, followed by partial reduction [96].

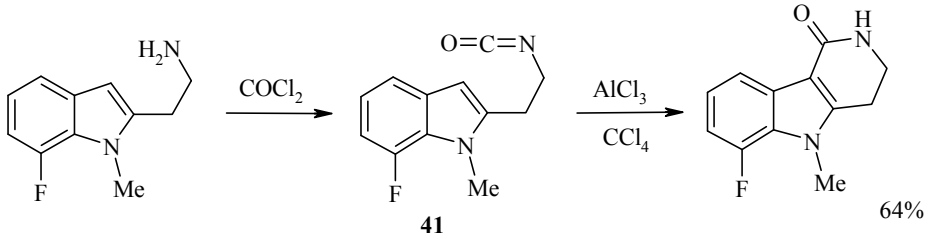


Intramolecular cyclization of the products from the reaction of isotryptamine iminophosphorane with carbon disulfide or aldehydes leads to the formation of the corresponding 1-thio- or 1-alkyl(aryl)-substituted γ-carbolines [28]. Here, in the case of the isothiocyanate **40** either 2,3,4,5-tetrahydro-1H-pyrido[4,3-*b*]indole-1-thione or 3,4-dihydropyrimido[1,6-*a*]indole-1(2H)-thione is formed depending on the reaction conditions, but in the case of aldimines only the γ-carbolines are formed irrespective of the conditions. (We discussed a similar transformation above in the section devoted to the synthesis of 3,4-dihydro-γ-carbolines.)



R = Ph, 4-MeC_6H_4, 4-$MeOC_6H_4$, 2-$N_3C_6H_4$, PhCH=CH, Et

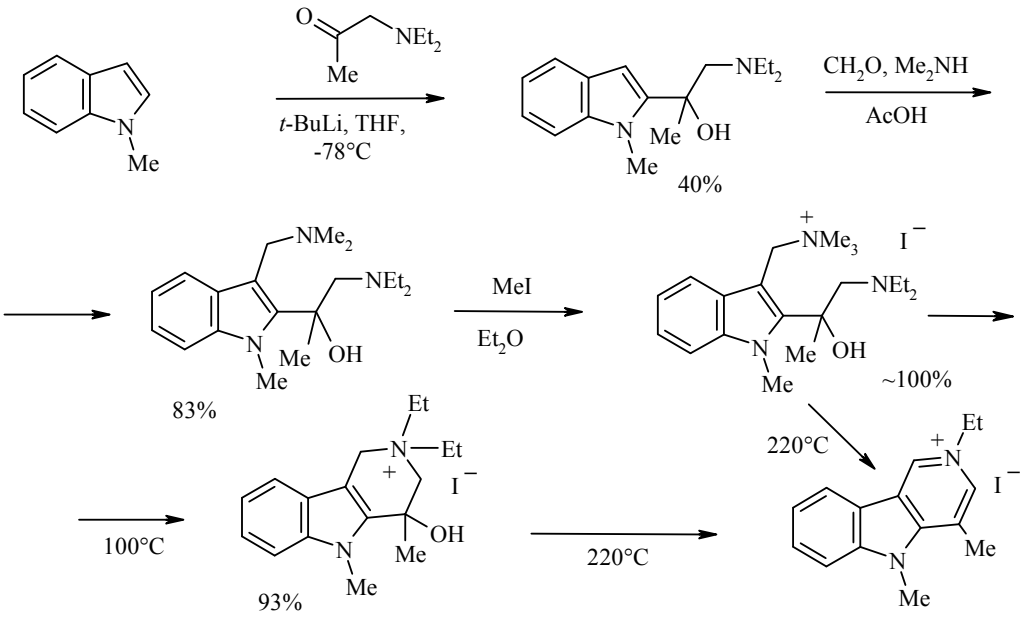
Closure of the piperidine ring with a moderate yield can also be realized by the action of $AlCl_3$ on the isocyanate **41**, obtained from the respective isotryptamine [67].



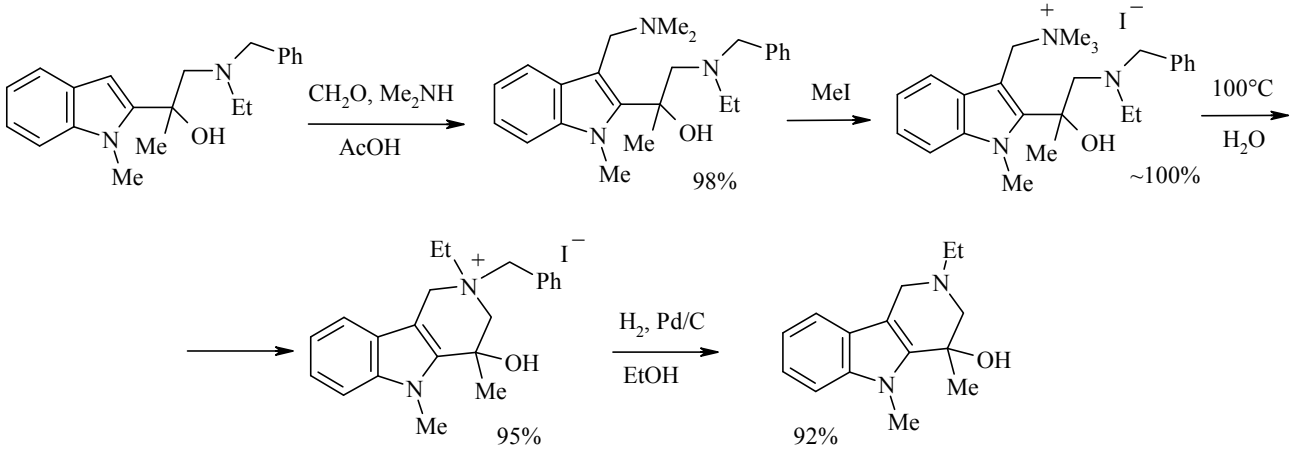
41

Syntheses with the Formation of the C(1)–N(2) Bond

Examples of transformations accompanied by closure of the tetrahydropyridine ring with the formation of the C(1)–N(2) bond are quite few in number and mainly depend on intramolecular nucleophilic substitution of the gramine amino group by an isotryptamine amino group. Here, as a rule tetrahydrocarbolinium salts, which are aromatized are 220°C, are formed [90].



In the case of benzyl-substituted isotryptamine derivatives containing a gramine fragment tetrahydro-γ-carbolinium salts are formed initially; from them 4-hydroxy-4-methyl-1,2,3,4-tetrahydro-γ-carbolines are formed by hydrogenolytic debenzylation.



The method for the synthesis of 1,2,3,4-tetrahydro-γ-carboline derivatives **42**, formed with high yields during the addition of $NaBH(OAc)_3$ to a mixture of 1-phenylsulfonyl-2-(prop-1-enyl)-1H-indole-3-carbaldehyde and a primary amine in acetic acid, is quite interesting [97]. The formation of the secondary amine **43** as side product is possible.

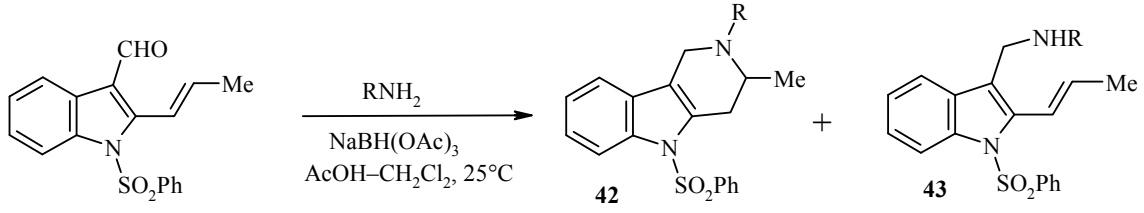
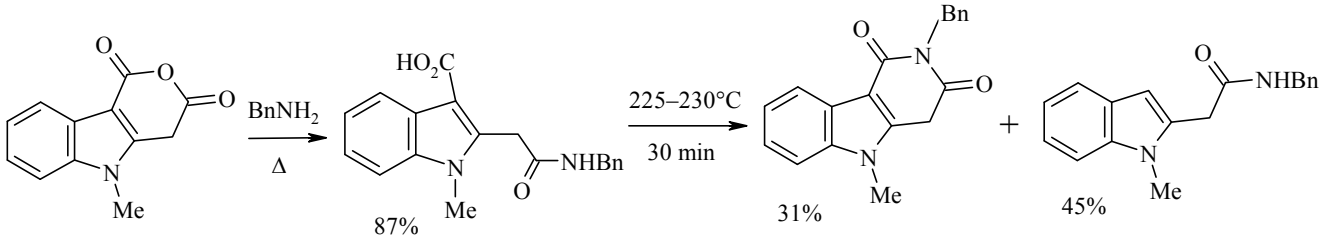


TABLE 3. The Yields of Compounds **42** and **43**

R	Yield, %	
	42	**43**
Allyl	90	—
$PhCH_2$	85	—
Ph	35	35
p-$NO_2C_6H_4$	7	83
p-$MeOC_6H_4$	63	7

Initially, the authors assumed that the reaction took place through the formation of an aldimine, which then entered into an electrocyclic reaction with the diene fragment of the indole. However, such transformations are usually realized at elevated temperatures (>100°C), and the mechanism does not explain the observed dependence of the yield of the desired product on the substituent at the amino group. They therefore proposed an alternative mechanism, making it possible to explain the observed results; according to this mechanism the process involves initial nucleophilic addition of the amino group (a reaction of the Michael type) at the activated double bond of the side chain and cyclization of the obtained adduct to an iminium salt followed by reduction to the tetrahydro-γ-carboline derivative. When such nucleophilic addition at the double bond is hindered the formation of a side product of the reaction is observed. This occurs for amines in which the basicity and nucleophilicity are reduced on account of delocalization of the free electron pair (aromatic amines with electron-accepting substituents). In this case an imine, which is reduced to a secondary amine, is formed.

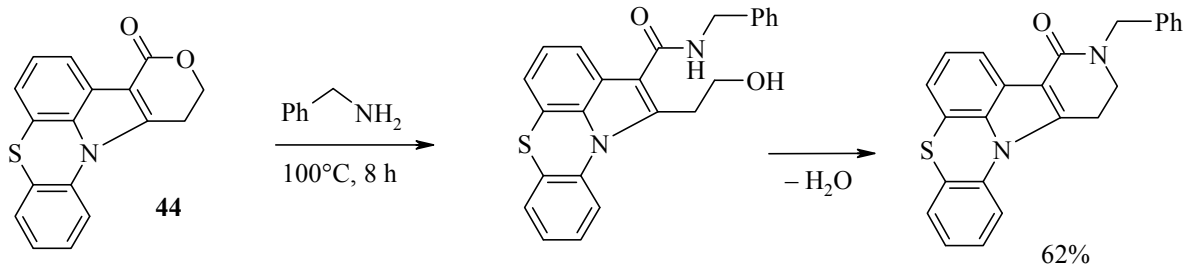
The reaction of (3-carboxy-1-methylindol-2-yl)acetic anhydride with primary amines leads to the formation of (3-carboxyindol-2-yl)acetamides, which undergo cyclization to 1,3-dioxotetrahydro-γ-carbolines when heated above the melting point [98]; here (indol-2-yl)acetamides are formed as a result of decarboxylation.



A 2-amino-1,3-dioxotetrahydro-γ-carboline derivative is formed similarly with a 22% yield when (3-methoxycarbonylindol-2-yl)acetic ester is boiled with a 40% solution of hydrazine [30].

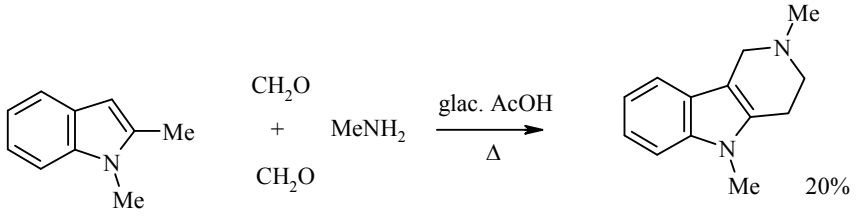
Syntheses with the Formation of the C(3)–N(2) Bond

A possible variant of the strategy is opening of the lactone **44** by primary amines with the formation of lactams containing the structural fragment of tetrahydro-γ-carboline [99]. Aminolysis of the lactone evidently occurs initially with the formation of an acyclic amide, heating of which leads to condensation with the formation of the C(3)–N(2) bond of the γ-carboline skeleton.

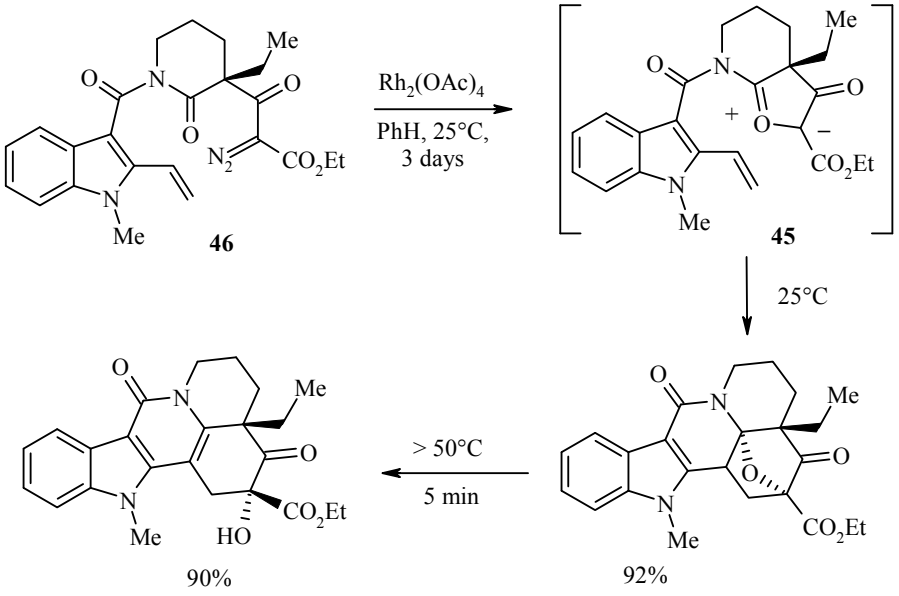


Syntheses with the Formation of the C(3)–C(4) Bond

The formation of the C(3)–C(4) bond during closure of the piperideine ring can be regarded as the concluding stage of the reaction of 1,2-dimethylindole with 2 equiv. of formaldehyde and 1 equiv. of methylamine, leading to the formation of 2,5-dimethyl-1,2,3,4-tetrahydro-γ-carboline [100]. However, the α-methyl group is not active enough, and the reaction gives a low yield.

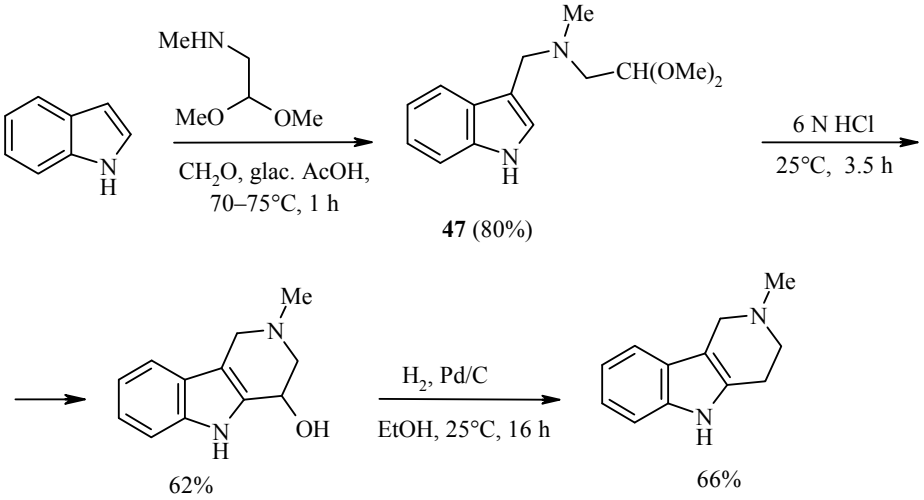


An example is known where the tetrahydro-γ-carboline skeleton is constructed with the formation of the C(3)–C(4) bond through intramolecular [3+2]-dipolar cycloaddition of the zwitterion **45**, formed from the corresponding diazo compound **46** with $Rh_2(OAc)_4$ [101]. If the tetrahydro-γ-carboline derivative is heated above 50°C opening of the five-membered oxygen-containing ring occurs.

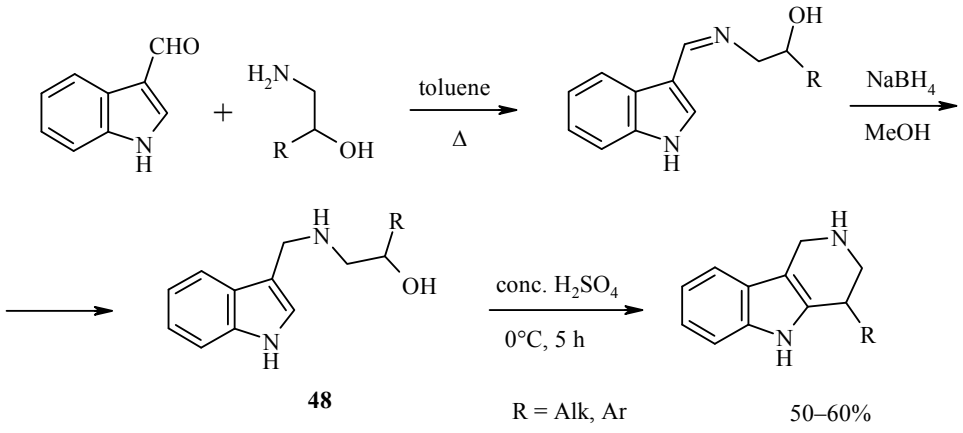


Syntheses with the Formation of the C(4)–C(4a) Bond

Methods for the synthesis of 1,2,3,4-tetrahydro-γ-carbolines entailing closure of the piperideine ring with the formation of the C(4)–C(4a) ring take second place after the methods based on the formation of the C(1)–C(9b) bond in the number of transformations. The overwhelming majority of the methods for the creation of the C(4)–C(4a) bond involve intramolecular alkylation of an indole derivative at position 2. For example, the Mannich base **47**, obtained from methylaminoacetaldehyde acetal, readily undergoes cyclization in HCl solution to the corresponding 4-hydroxy derivative, which can then be easily reduced to 4-unsubstituted tetrahydro-γ-carboline [102].

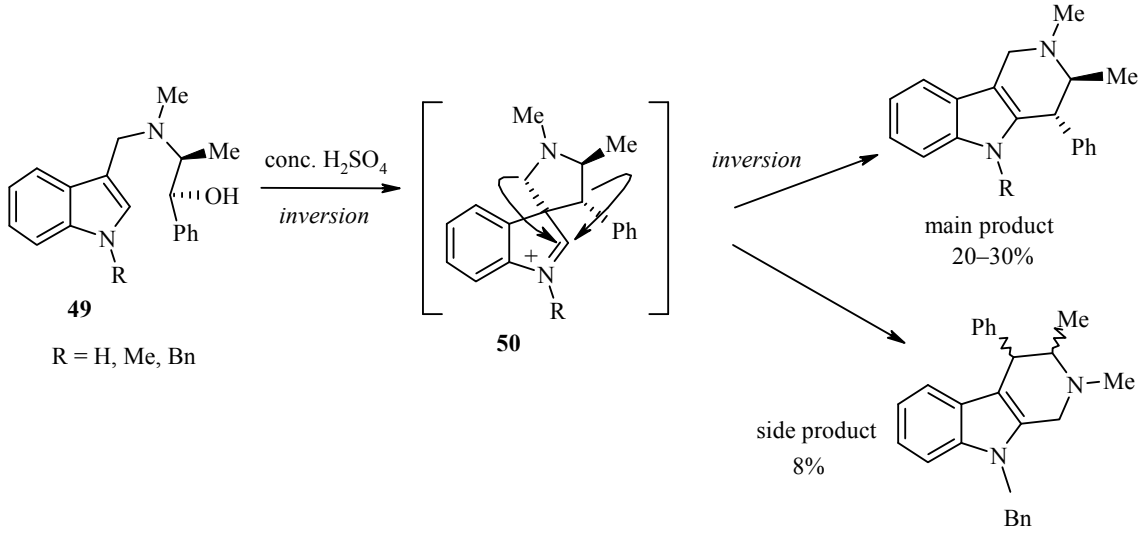


N-β-Hydroxyethyl derivatives of 3-aminomethylindole **48** [103], synthesized from 3-formylindole and the respective amino alcohol by reductive amination [104], also undergo acid-catalyzed intramolecular cyclization with the formation of 1,2,3,4-tetrahydro-γ-carbolines.

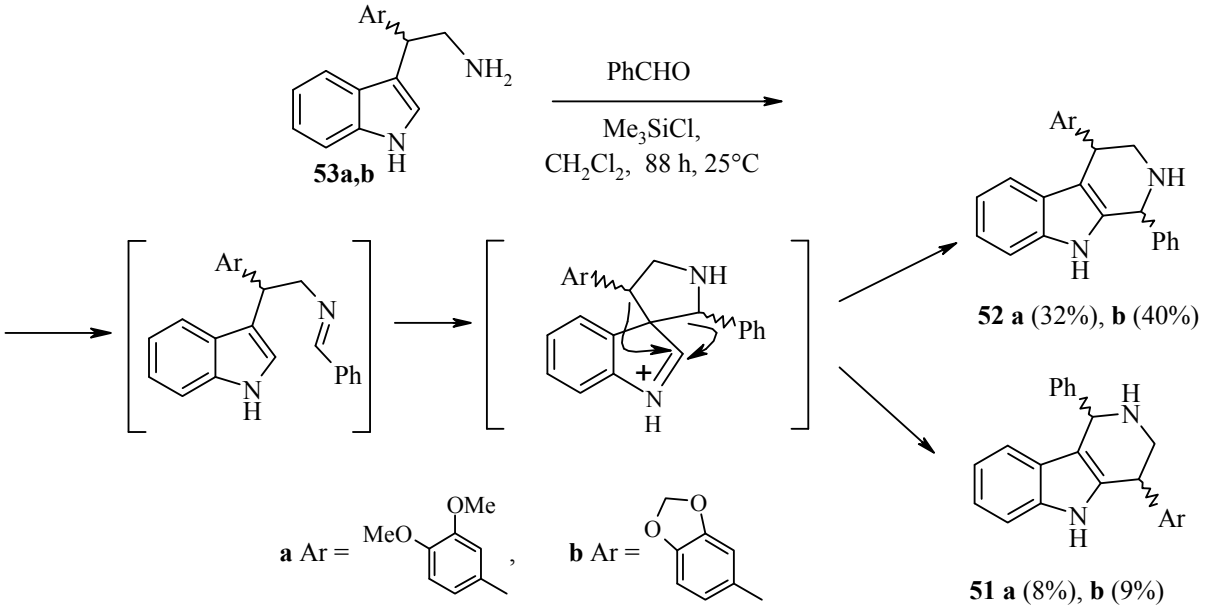


In the case of cyclization of the ephedrine derivative **49** the configuration of the phenyl substituent is retained in the obtained compound; this can be explained by the occurrence of the process through the formation of the spirocyclic intermediate **50** with two consecutive inversions [105]. The spiro compound **50** is formed as a result of attack by the carbocation at the more nucleophilic position 3 of the indole derivative **49** accompanied by

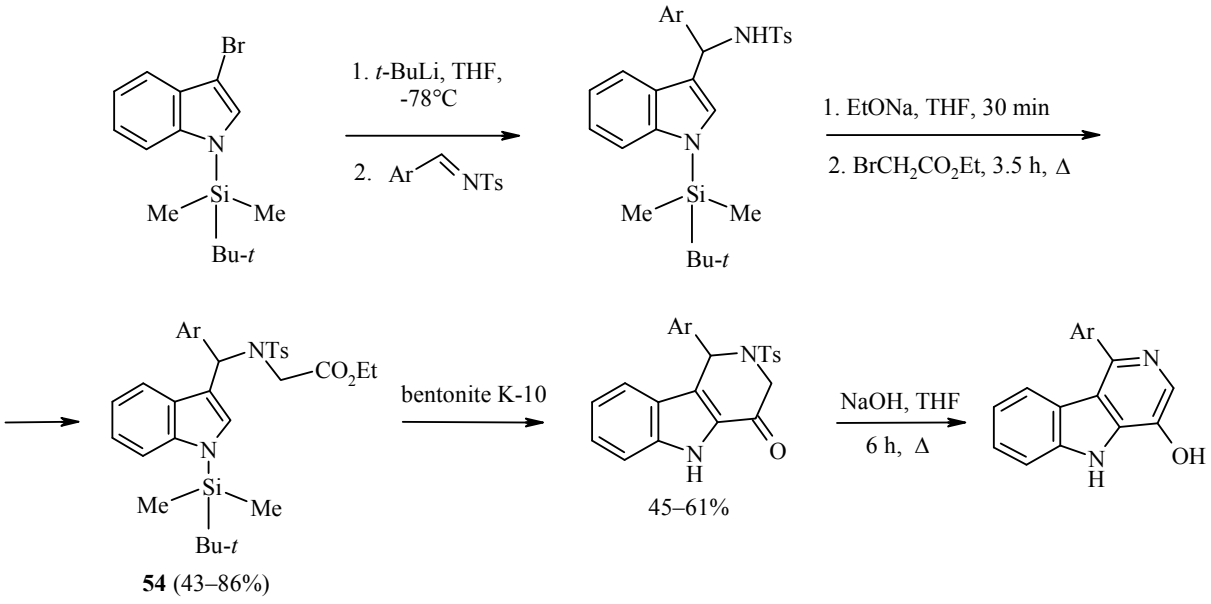
inversion, after which a stereoselective reaction then occurs at position 2. It is important to note that the opening of the spirocyclic intermediate can take place both in the C–Ph fragment (the main product) and in the C–N fragment (the side product).



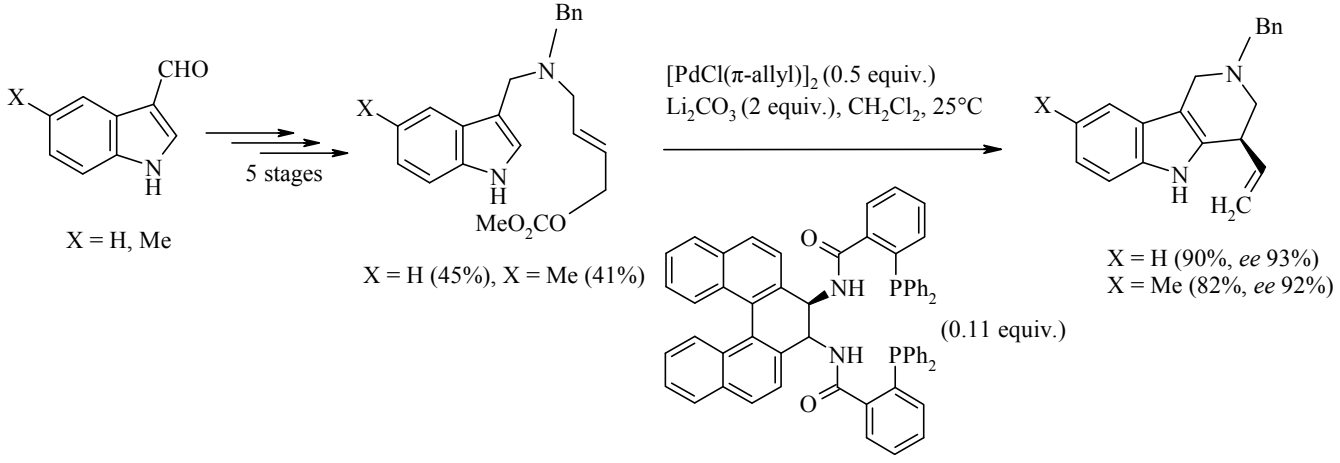
Evidence in favour of the proposed mechanism with the formation of the intermediate **50** can be obtained from the formation of the tetrahydro-γ-carbolines **51a**,**b** as side products during an attempt to synthesize 1,4-diaryl-substituted tetrahydro-β-carbolines **52a**,**b** from the corresponding aryltryptamines **53a**,**b** by the Pictet–Spengler reaction [106].



A completely different approach to the production of 1,4-disubstituted tetrahydro-γ-carbolines involves preliminary lithiation of N-protected 3-bromoindole followed by condensation with N-tosylarylaldimines. The alkylation of 3-[(arylamino)methyl]indoles with bromoacetic ester makes it possible to obtain compound **54**, which readily undergoes cyclization to 1-aryl-4-oxo-1,2,3,4-tetrahydro-γ-carbolines by the action of Lewis acids [107]. Variation of the aryl fragment in the N-tosyl-substituted aldimines leads to various 1-aryl-substituted γ-carbolines. If the 1-aryl-4-oxo-1,2,3,4-tetrahydro-γ-carboline is boiled with alkali aromatization occurs, and the 1-aryl-4-hydroxy-γ-carboline is formed.

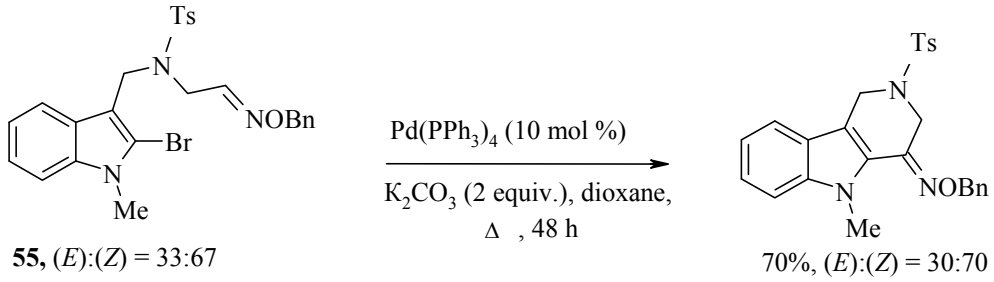


Of special significance for the synthesis of tetrahydro-γ-carbolines with the formation of the C(4)–C(4a) bond are the methods employing metal-complex catalysis, since they are distinguished by fairly high enantioselectivity, which is very important for the synthesis of the analogs of natural compounds. For example, Pd-catalyzed intramolecular alkylation of indoles with the use of a chiral ligand takes place regiospecifically and with high enantioselectivity [108].



In the section on methods for the synthesis of 1,2-dihydro-γ-carbolines it was mentioned that tetrahydro-γ-carbolines **4a**-**d** can be obtained from the allylamides of 2-iodo-1H-indole-3-carboxylic acid by an intramolecular Heck reaction [10], but in this case the isomeric compounds **3a**-**d** with an endocyclic double bond are formed.

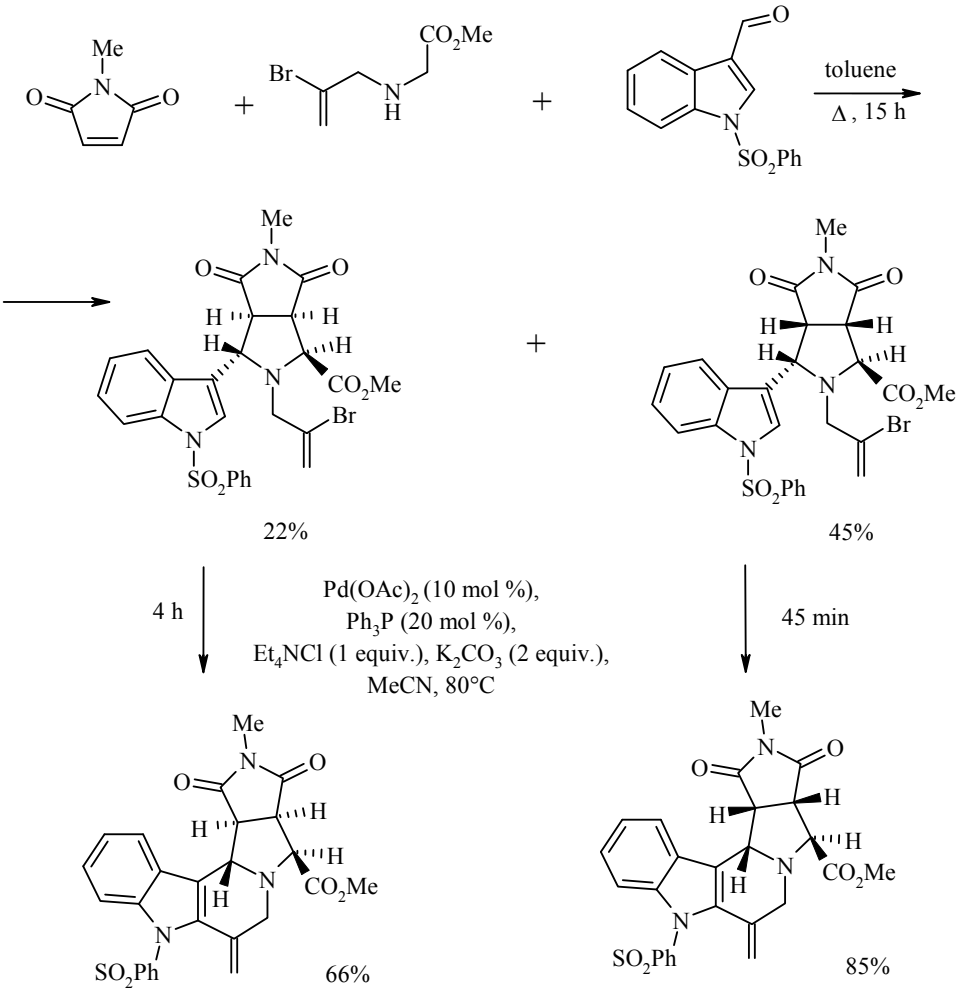
If the allylamides are replaced by the O-benzylated oxime **55** during the intramolecular Heck reaction it is possible to obtain a γ-carboline derivative containing only an exocyclic double bond with the (*E*) and (*Z*) isomers in a ratio of 30:70 [109].



55, (*E*):(*Z*) = 33:67

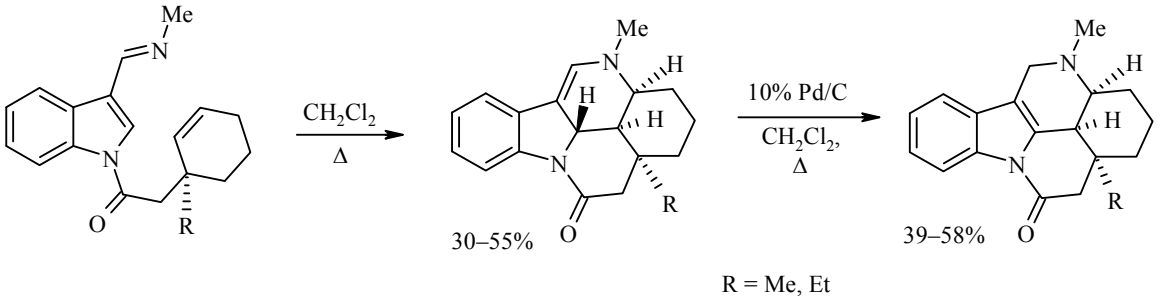
70%, (*E*):(*Z*) = 30:70

A one-pot synthesis of structures containing γ-carboline fragment can be realized by 1,3-dipolar cycloaddition and closure of the piperideine ring during intramolecular cyclization catalyzed by palladium [110].



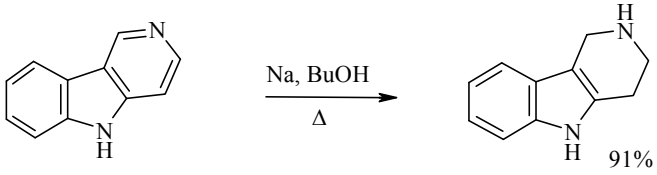
Syntheses with the Synchronous Formation of the C(4)–C(4a) and C(3)–N(2) Bonds

Of undoubted interest are the synthetic methods that make it possible to produce γ-carboline structures by the synchronous formation of several bonds by means of [4+2] cycloaddition reactions. An example is the formation of a pentacyclic structure containing a γ-carboline fragment during successive intramolecular Diels–Alder reaction and catalytic isomerization [111].

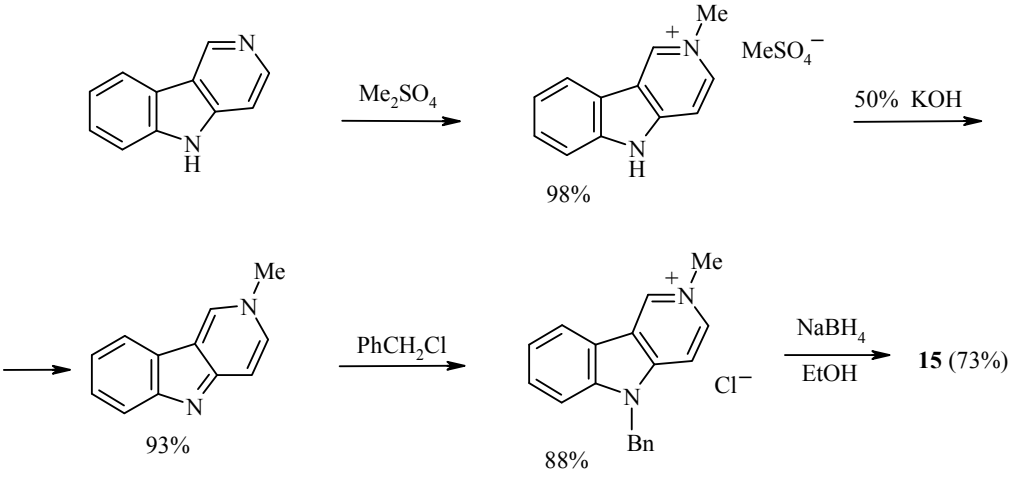


REDUCTION OF A PYRIDINE RING IN UNSATURATED γ-CARBOLINES

An alternative and fairly convenient method in synthetic respects for the production of tetrahydro-γ-carbolines is reduction of the corresponding aromatic precursors. Thus, the first example of the reduction of γ-carbolines is the production of 1,2,3,4-tetrahydro-γ-carboline with metallic sodium in boiling butyl alcohol [32].



Tetrahydro-γ-carbolines are also obtained with high yields by the reduction of γ-carbolinium salts quaternized at the nitrogen atom with sodium borohydride in ethanol [112-114]. This approach was proposed as an alternative for the synthesis of the medicinal product Mebhydrolin (Diazolin) **15** with a total yield of 60% [115], whereas the yield in the Fischer method was only 31% [34].



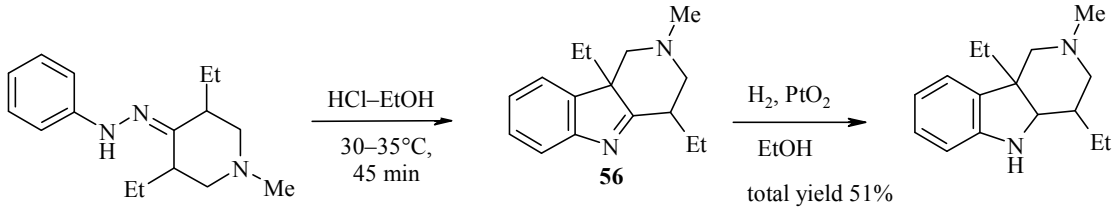
The respective 1,2- and 3,4-dihydro derivatives can also act as precursors of tetrahydro-γ-carbolines. Here the reduction of 1,2-dihydro-γ-carbolines is as a rule accomplished with hydrogen over Pd/C [6, 13], whereas 3,4-dihydro-γ-carbolines can be reduced with hydrogen over platinum [17] or even with $NaBH_4$ in methanol [20].

METHODS FOR THE PRODUCTION OF HEXAHYDRO-γ-CARBOLINES

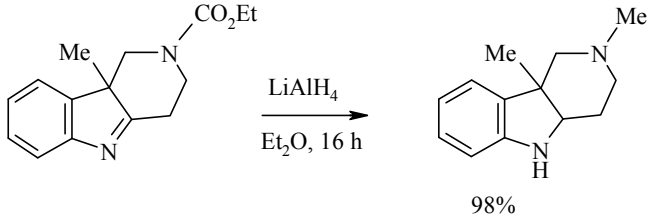
The production of hexahydro-γ-carboline structures in most cases amounts to reduction of the corresponding precursors, representing tetrahydro-γ-carboline or the isomeric indolenine derivatives. A feature of hexahydro-γ-carbolines is the possibility of both *cis* and *trans* coupling of the indoline and piperidine fragments; this must be taken into account during the selection of specific reduction systems characterized by different stereoselectivity.

NONSTEREOSELECTIVE METHODS

In the Fischer reaction with 1-methyl-3,5-diethylpiperid-4-one compound **56**, the catalytic hydrogenation of which leads to 4,9b-diethyl-2-methyl-1,2,3,4,4a,9b-hexahydro-γ-carboline, is formed [116].

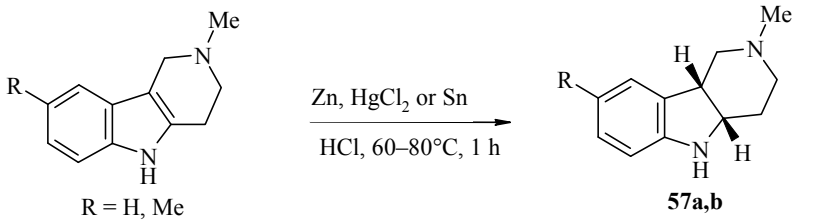


Indolenine derivatives analogous with compound **56** can also be reduced with almost quantitative yields by $LiAlH_4$ in ether [69].

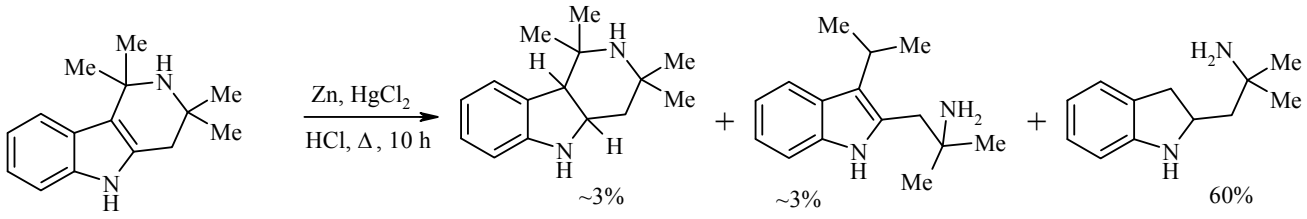


A fairly large number of papers have been devoted to methods for the reduction of indole derivatives to indolines by the action of most varied types of reagents, and most of them can be applied effectively to the reduction of tetrahydro-γ-carbolines to the corresponding hexahydro derivatives [117].

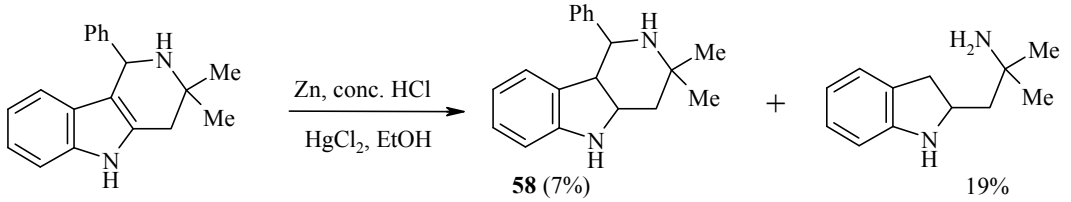
The reduction of 2,3-disubstituted indoles and carbazoles by metals such as Zn or Sn in strongly acidic media leads to the formation of a mixture of the *cis* and *trans* isomers of the respective reduction products in various ratios [118], and the method is therefore used infrequently. However, the reduction of 2-methyl-1,2,3,4-tetrahydro-γ-carboline with Zn in the presence of $HgCl_2$ or Sn in hydrochloric acid leads to 2-methyl-1,2,3,4,4a,9b-hexahydro-γ-carboline (**57a**) presumably with *cis* coupling of the fragments [119]. The medicinal drug Dicarbine **57b**, which is the racemate of the *cis* isomer, was obtained similarly [120].



Tetrahydro-γ-carbolines polyalkylated in the piperideine ring are reduced by the action of zinc amalgam in hydrochloric acid to the hexahydro derivatives to an insignificant degree and mainly undergo reductive degradation with the formation of the corresponding indoline and isotryptamine derivatives [21, 84, 121].



The instability of the polyalkylated piperideine ring under the conditions of the Clemmensen reaction is apparently due to the presence of *meta*-diaxial interaction. Thus, during the reduction of 1-phenyl-3,3-dimethyl-1,2,3,4-tetrahydro-γ-carboline with zinc dust both the corresponding hexahydro-γ-carboline **58** and 2-(2-amino-sobutyl)indoline are formed [84].



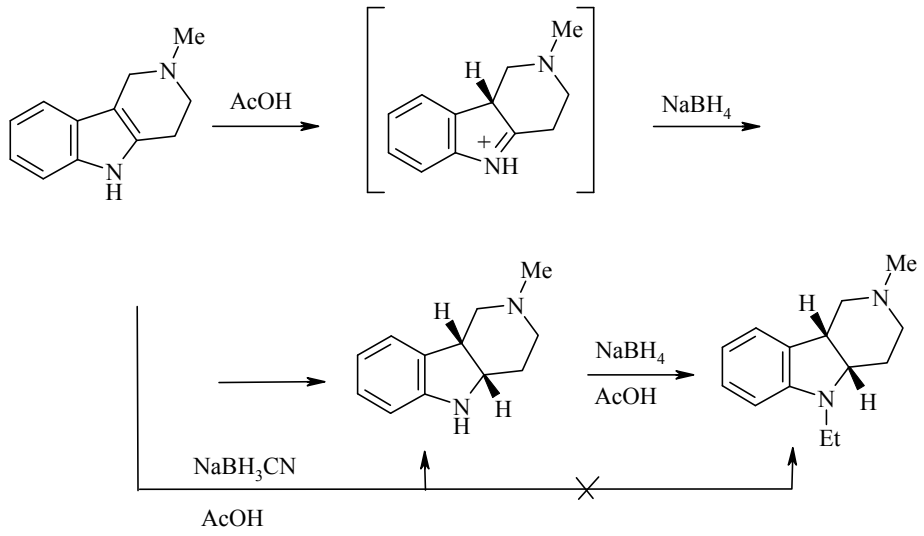
The ratio of the reaction products depends on the arrangement of the alkyl substituents. A decrease of branching at position 1 increases the yield of the hexahydro-γ-carboline. Replacement of the methyl radical at this position by phenyl does not have a substantial effect on the course of the reduction, which also leads to two reaction products, whereas 1,1- and 3,3-dimethyltetrahydro-γ-carbolines are only reduced to the corresponding hexahydro derivatives under these conditions [84]. Even in the case of 1,1,3-trimethyl-1,2,3,4-tetrahydro-γ-carboline only the hexahydro derivative is produced during reduction with a yield of 60% [68]. If the substituents at positions 1 and 3 are absent the only reaction product is the corresponding hexahydro-γ-carboline.

STEREOSELECTIVE METHODS

Researchers have paid special attention to the development of methods for the stereoselective reduction of tetrahydro-γ-carbolines to the *cis*- and *trans*-hexahydro derivatives, and considerable success has been achieved.

Synthesis of *cis*-Derivatives

cis-1,2,3,4,4a,9b-Hexahydro-γ-carbolines can be obtained by catalytic hydrogenation of the corresponding tetrahydro-γ-carbolines over PtO_2 in dilute hydrochloric acid [122]. The method is not used often on account of the need for special equipment; moreover, the complexity of catalytic hydrogenation again involves the possibility of more extensive reduction, and it is not always possible to stop at the formation of the hexahydro-γ-carboline.



Here and subsequently the relative configuration of only one of the formed enantiomers is given in the schemes.

If the $NaBH_4$–carboxylic acid reduction system is used it must be remembered that in the case of γ-carbolines unsubstituted at the indole nitrogen atom N-alkylation both of the initial indole compound and of its reduction product occurs in parallel in addition to reduction occurring through the formation of the 3H-indolinium ion, and in a number of cases the formation of intermediate N-acyl derivatives is observed [123, 24].

It was shown that if $Na(K)BH_4$ is added gradually to solutions of 1,2,3,4-tetrahydro-γ-carbolines in trifluoroacetic acid both reduction to the hexahydro derivative **59** and 2,2,2-trifluoroethylation at the indole nitrogen atom with the formation of 5-(2,2,2-trifluoroethyl)-1,2,3,4,4a,9b-hexahydro-γ-carbolines **60** with 70-90% yields occur, depending on the molar ratio of the components [125]. Here the obtained compounds are configurationally uniform and represent a racemic mixture of the two possible *cis* isomers.

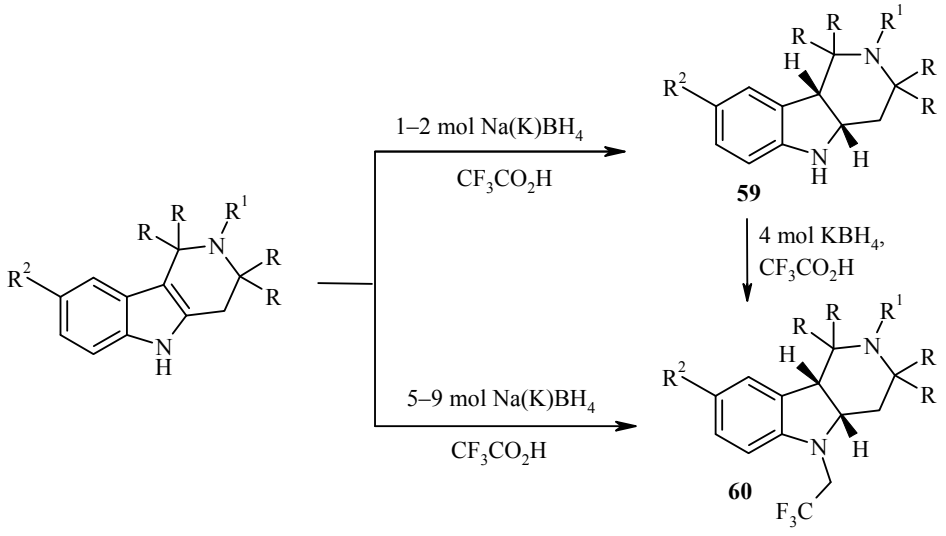
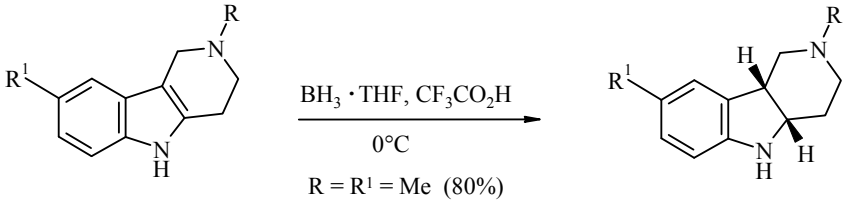


TABLE 4. The Yields of Compounds **59** and **60**

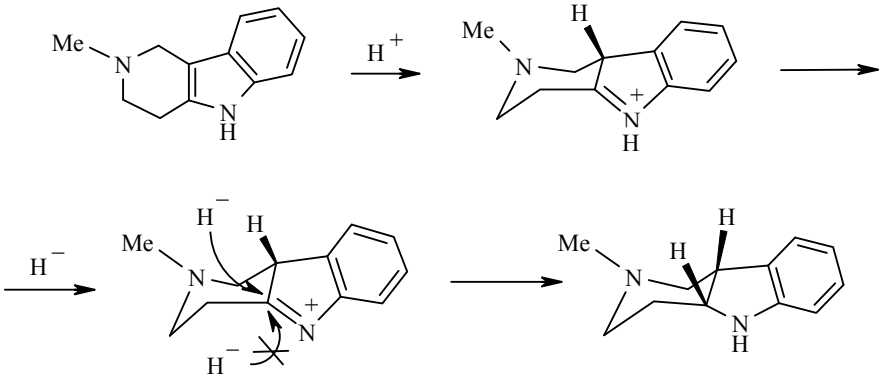
	R	R^1	R^2	Yield, %	
				59	**60**
a	H	Me	Me	80	89
b	H	Me	Cl	60	90
c	H	Me	Br	69	89
d	H	Me	F	—	89
e	H	Me	CO_2Et	—	98
f	Me	H	H	—	73
g	Me	H	Me	66	39

By using $NaBH_3CN$ instead of $NaBH_4$ it is possible to avoid the formation of the N-alkyl-substituted compounds completely [126-128], while the stereoselectivity here remains the same as before.

The reduction of tetrahydro-γ-carboline derivatives with borane and its complexes (e.g., borane–THF) in a strongly acidic medium (as a rule, in trifluoroacetic acid) is one of the most general methods for the production of the *cis* isomers of hexahydro-γ-carbolines. In the reaction of BH_3·THF with CF_3CO_2H bis(trifluoroacetoxy)borane $BH[OC(O)CF_3]_2$·THF, stable in the acidic medium, is formed [129]; this reduces the 1,2,3,4-tetrahydro-γ-carbolines stereospecifically to the *cis* isomer with high yields of 70-89% and does not lead to the formation of N-alkyl-γ-carboline derivatives.



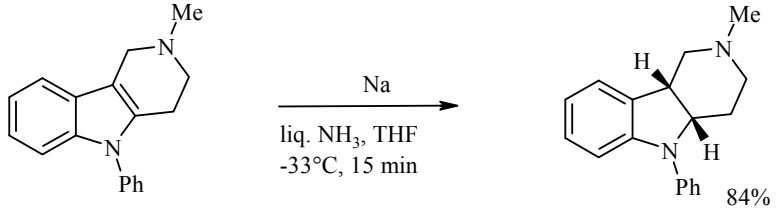
The stereospecificity of the reduction of the carbolines can be explained on the basis of the stereochemistry of the 3H-indolinium ion formed at the initial stage, which subsequently undergoes attack by the bis(trifluoroacetoxy)borane; this takes place from the most sterically accessible side and leads to the formation of the thermodynamically more favorable *cis* isomer [130].



It is necessary to stress in particular that bis(trifluoroacetoxy)borane is a powerful reagent capable of reducing various functional groups and certain heterocycles. This method of stereoselective reduction must therefore be used with extreme caution.

The stereospecific reduction of tetrahydro-γ-carboline with the trimethylamine–borane complex in conc. hydrochloric acid also leads to the *cis*-indoline derivative with yields of 70-90% [131].

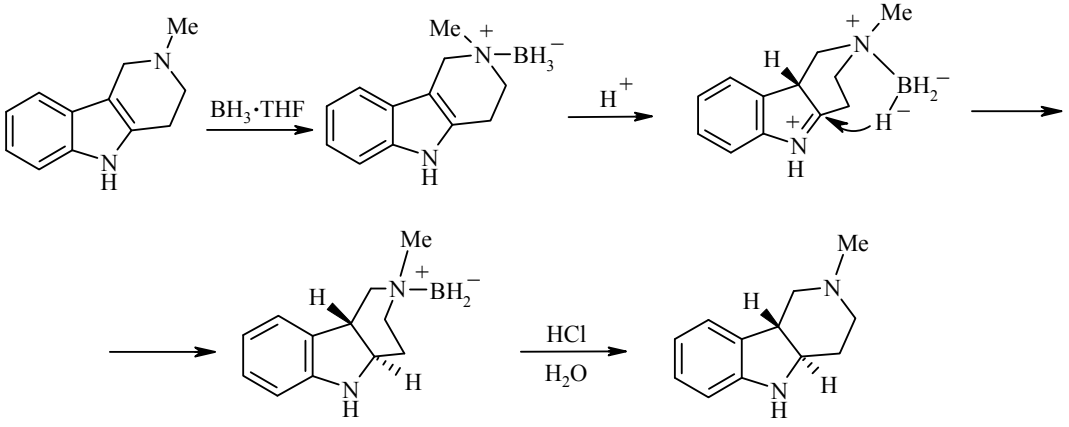
Another effective method for the stereospecific reduction of 1,2,3,4-tetrahydro-γ-carbolines to the *cis*-hexahydro-γ-carboline derivative uses metallic sodium in liquid ammonia [132-134].



Yet another promising method that makes it possible to realize the stereospecific reduction of tetrahydro-γ-carboline derivatives uses triethylsilane in trifluoroacetic acid [64, 135].

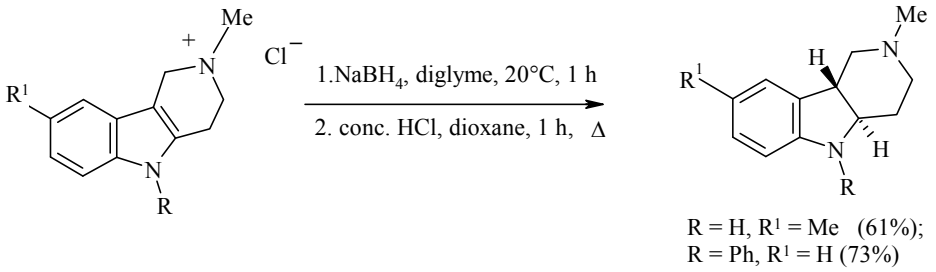
The Synthesis of *trans* Derivatives

1,2,3,4-Tetrahydro-γ-carbolines can also be reduced easily to the *trans*-hexahydro derivatives by the action of borane (or its unstable complexes) followed by treatment with a strong acid such as conc. HCl [133]. This demonstrates how much the reaction conditions (in this case the order of addition of the reagents) can affect the stereochemistry of the reduction process. Above it was mentioned that the use of the borane–THF complex in trifluoroacetic acid, for example, leads to stereoselective *cis* reduction [129, 130], whereas the initial formation of the complex of the substrate with borane followed by the addition of the acid lead to the product from *trans* reduction according to the following scheme:



At the first stage a stable aminoborane complex with a more basic nitrogen atom at position 2 is formed. The addition of acid leads to the 3H-indolinium cation, which undergoes intramolecular nucleophilic attack by the boron hydride complex. It is through intramolecular transfer of the hydride ion to the C(4a) atom of the indolenine fragment, taking place through a six-membered transition state, that the *trans* configuration of the hexahydro-γ-carboline derivative is formed.

A modification of the method provides for the production of borane–tetrahydro-γ-carboline complexes by the action of BH_3, generated *in situ* from sodium borohydride and the hydrochloride of the tetrahydro-γ-carboline derivative [136].



R = H, R^1 = Me (61%);
R = Ph, R^1 = H (73%)

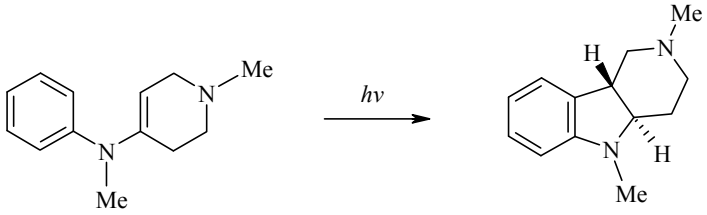
Tetrahydro-γ-carbolines containing a secondary N(2) atom do not undergo *trans* reduction under the influence of borane in hydrochloric acid. This is evidently due to the fact that the formed complex of borane with the secondary amine is hydrolyzed significantly more quickly than with the tertiary amine; in this case the hydrolysis can take place earlier than protonation of the indole ring and subsequent hydride transfer [137]. This is why reduction of the N-benzyl-substituted derivatives followed by catalytic debenzylation was used for the production of secondary *trans* isomers of hexahydro-γ-carbolines [122]. However, the use of CF_3COOH (strong enough for the formation of the 3H-indolinium ion and the non-nucleophilic acid) makes it possible to obtain *trans*-hexahydro-γ-carbolines containing a secondary amino group at position 2 with yields greater than 80% by direct reduction [138].

The methods presented above for the stereoselective reduction of tetrahydro-γ-carbolines to the hexahydro derivatives are universal and can be used for the reduction of other compounds containing an indole ring. However, it should be noted that the presence of nitrogen-containing substituents in the molecule of the γ-carboline or other compound of the indole series during reduction with borane and its complexes can change the stereochemistry of the reduction process. Here, as a rule, the formation of a mixture of *cis* and *trans* isomers in various proportions will be observed. An example of such reduction during the action of boron derivatives is given in [139]. In the presence of aminoalkyl substituents $(CH_2)_nNR_2$ at the indole nitrogen atom the BH_3 can bond with each of the two basic nitrogen atoms, and as a result there may be competition between the two versions of intramolecular reduction; this leads to the formation of a mixture of the *cis* and *trans* isomers, while the selectivity of reduction increases with increase of the length of the alkyl chain (when n = 2 *cis*/*trans* = 5:2, and when n = 3 *cis*/*trans* = 1:10) [140].

It is worth mentioning that the racemic mixtures obtained in the course of stereoselective reduction can be resolved successfully into the individual isomers by means of optically active mandelic [141], di-*p*-toluoyl-tartaric [142], or dibenzoyltartaric [143] acids or N-carbamoylphenylalanine [144].

On account of all the features mentioned above each specific case requires an individual approach to the selection of one or the other method of reduction.

The formation of the *trans*-hexahydro-γ-carboline system can arise not only as a result of stereoselective reduction but also on account of stereoselective cyclization. For example, it was shown that as a result of nonoxidative photocyclization N-arylenamines can be converted into the corresponding *trans*-hexa-hydro-γ-carbolines with the formation of the C(9a)–C(9b) bond and with observance of the orbital symmetry rules [133] by analogy with the process leading to *trans*-hexahydrocarbazoles [145].



Thus, the published data covered in the review demonstrate the variety of methods available for the synthesis of hydrogenated derivatives of γ-carbolines; this makes it possible to obtain an enormous range of varied prospective derivatives in the search for biologically active compounds having a broad spectrum of activity. The chemical and biological characteristics of hydrogenated γ-carbolines will be the subject of the third part of our review.

REFERENCES

1. R. S. Alekseev, A. V. Kurkin, and M. A. Yurovskaya, *Khim. Geterotsikl. Soedin.*, 1123 (2009). [*Chem. Heterocycl. Comp*., **45**, 889 (2009)].
2. A. M. Patterson, L. T. Capell, and S. T. Walker, *The Ring Index*, 2nd ed., Am. Chem. Soc., New York (1960).
3. A. N. Kost, M. A. Yurovskaya, and F. A. Trofimov, *Khim. Geterotsikl. Soedin.*, 291 (1973). [*Chem. Heterocycl. Comp*., **9**, 267 (1973)].
4. http://www.prous.com/molecules/default.asp?ID=162
5. D. Bevk, U. Grošelj, A. Meden, J. Svete, and B. Stanovnik, *Helv. Chim. Acta*, **89**, 2774 (2006).
6. R. D. Clark, A. B. Miller, J. Berger, D. B. Repke, K. K. Weinhardt, B. A. Kowalczyk, R. M. Eglen, D. W. Bonhaus, C.-H. Lee, A. D. Michel, W. L. Smith, and E. H. F. Wong, *J. Med. Chem.*, **36**, 2645 (1993).
7. J. Berger, R. D. Clark, US Pat., 5189041; www.espacenet.com
8. S. T. Wrobleski, P. Chen, J. Hynes, Jr., S. Lin, D. J. Norris, C. R. Pandit, S. Spergel, H. Wu, J. S. Tokarski, X. Chen, K. M. Gillooly, P. A. Kiener, K. W. McIntyre, V. Patil-koota, D. J. Shuster, L. A. Turk, G. Yang, and K. Leftheris, *J. Med. Chem.*, **46**, 2110 (2003).
9. G. A. Bahadur, A. S. Bailey, N. W. Middleton, and J. M. Peach, *J. Chem. Soc.*, *Perkin Trans. 1*, 1688 (1980).
10. E. M. Beccalli, G. Broggini, A. Marchesini, and E. Rossi, *Tetrahedron*, **58**, 6673 (2002).
11. T. Okegawa and M. Kawamura, Eur. Pat., 0392663; www.espacenet.com
12. I. H. Coates, A. W. Oxford, and P. G. North, US Pat., 5008272; www.espacenet.com
13. M. Lluïsa Bennasar, T. Roca, M. Monerris, and D. García-Díaz, *J. Org. Chem.*, **71**, 7028 (2006).
14. J. Kebrle, A. Rossi, and K. Hoffmann, *Helv. Chim. Acta*, **42**, 907 (1959).
15. H. Akimoto, A. Kawai, and H. Nomura, *Bull. Chem. Soc. Jpn.*, **58**, 123 (1985).
16. H. Akimoto, A. Kawai, H. Nomura, M. Nagao, T. Kawachi, and T. Sugimura, *Chem. Lett.*, 1061 (1977).
17. N. N. Novikova, I. D. Silenko, N. F. Kucherova, and V. A. Zagorevskii, *Khim. Geterotsikl. Soedin.*, 1630 (1976). [*Chem. Heterocycl. Comp*., **12**, 1340 (1976)].
18. N. V. Koninklijke Pharmaceutische Fabrieken v. h. Brockades Stheeman & Pharmacia BE Pat. 669682; www.espacenet.com
19. N. V. Koninklijke Pharmaceutische Fabrieken v/h Brockades-Stheeman & Pharmacia te Amsterdam, NL Pat. 6512019; www.espacenet.com
20. V. Vecchietti, G. D. Clarke, R. Colle, G. Giardina, G. Petrone, and M. Sbacchi, *J. Med. Chem.*, **34**, 2624 (1991).
21. N. N. Komzolova, N. F. Kucherova, and V. A. Zagorevskii, *Zh. Org. Khim.*, **1**, 1139 (1965).
22. V. A. Zagorevskii, N. N. Novikova, N. F. Kucherova, I. D. Silenko, G. N. Artemenko, and S. G. Rozenberg, *Khim. Geterotsikl. Soedin.*, 1387 (1980). [*Chem. Heterocycl. Comp*., **16**, 1054 (1980)].
23. S. P. Hiremath and M. G. Purohit, *Indian J. Chem.*, **10**, 984 (1972).
24. S. P. Hiremath and M. G. Purohit, *J. Indian Chem. Soc.*, **53**, 198 (1976).

25. G. A. Bhat and S. Siddappa, *J. Indian Chem. Soc.*, **52**, 335 (1975).
26. A. V. Butin, A. S. Pilipenko, A. A. Milich, and A. V. Fin'ko, *Khim. Geterotsikl. Soedin.*, 774 (2009). [*Chem. Heterocycl. Comp*., **45**, 613 (2009)].
27. P. Molina, J. Alcántara, and C. López-Leonardo, *Tetrahedron Lett.*, **36**, 953 (1995).
28. P. Molina, J. Alcántara, and C. López-Leonardo, *Tetrahedron*, **52**, 5833 (1996).
29. M. Somei, F. Yamada, and G. Yamamura, *Chem. Pharm. Bull.*, **46**, 191 (1998).
30. G. L. Karrick and N. P. Peet, *J. Heterocycl. Chem.*, **23**, 1055 (1986).
31. A. Monge, J. A. Palop, T. Goni, A. Martinez, and E. Fernandez-Alvarez, *J. Heterocycl. Chem.*, **21**, 381 (1984).
32. R. Robinson and S. Thornley, *J. Chem. Soc.*, **125**, 2169 (1924).
33. A. H. Cook and K. J. Reed, *J. Chem. Soc.*, 399 (1945).
34. N. F. Kucherova and N. K. Kochetkov, *Zh. Obshch. Khim.*, **26**, 3149 (1956).
35. A. Bridoux, L. Goossens, R. Houssin, and J.-P. Hénichart, *J. Heterocycl. Chem.*, **43**, 571 (2006).
36. A. N. Kost, E. V. Vinogradova, Kh. Daut, and A. P. Terent'ev, *Zh. Obshch. Khim.*, **32**, 2050 (1962).
37. R. G. W. Spickett, *J. Med. Chem.*, **9**, 436 (1966).
38. C. J. Cattanach, A. Cohen, and B. Heath-Brown, *J. Chem. Soc.*, *C*, 1235 (1968).
39. N. G. Tsyshkova and F. A. Trofimov, *Khim.-Farm. Zh.*, **5**, No. 9, 14 (1971).
40. V. Boekelheide and C. Ainsworth, *J. Am. Chem. Soc.*, **72**, 2132 (1950).
41. J. Moron, C. Landras, and E. Bisagni, *J. Heterocycl. Chem.*, **29**, 1573 (1992).
42. R. Elderfield (editor), *Heterocyclic Compounds* [Russian translation], Izd. Inostr. Lit., Vol. 7, p. 185 (1965).
43. N. P. Buu-Hoï, O. Roussel, and P. Jacquignon, *J. Chem. Soc.*, 708 (1964).
44. I. J. Pachter, US Pat., 3299078; www.espacenet.com
45. J. Figueroa, E. Caballero, P. Puebla, F. Tomé, and M. Medarde, *Molecules*, **11**, 929 (2006).
46. N. N. Komzolova, N. F. Kucherova, and V. A. Zagorevskii, *Zh. Obshch. Khim.*, **34**, 2383 (1963).
47. L. Zhang, W. Meier, E. Wats, T. D. Costello, P. Ma, C. L. Ensinger, J. M. Rodgers, I. C. Jacobson, and P. Rajagopalan, *Tetrahedron Lett.*, **36**, 8387 (1995).
48. M. E. Lizarzaburu and S. J. Shuttleworth, *Tetrahedron Lett.*, **45**, 4781 (2004).
49. L. A. Aksanova, N. M. Sharkova, M. A. Baranova, N. F. Kucherova, and V. A. Zagorevskii, *Zh. Org. Khim.*, **2**, 163 (1966).
50. L. A. Aksanova, I. N. Pidevich, L. M. Sharkova, and N. F. Kucherova, *Khim.-Farm. Zh.*, **2**, No. 7, 3 (1968).
51. W. M. Welch, *Synthesis*, 645 (1977).
52. W. M. Welch, Jr., US Pat. 4014890; www.espacenet.com
53. D. J. Kyle, B. J. Mavunkel, S. Chakravarty, and Z. Lu, US Pat. 5817756; www.espacenet.com
54. C. A. Harbert, J. J. Plattner, and W. M. Welch, *J. Med. Chem.*, **23**, 635 (1980).
55. U. Hörlein, US Pat. 2786059; www.espacenet.com
56. N. Bărbulesku, C. Bornaz, and C. Greff, *Rev. Chim.*, **22**, 269 (1971).
57. V. A. Zagorevskii, N. F. Kucherova, N. M. Sharkova, T. I. Ivanova, and S. M. Klyuev, *Khim. Geterotsikl. Soedin.*, 1353 (1975). [*Chem. Heterocycl. Comp*., **11**, 1156 (1975)].
58. U. Hörlein, *Chem. Ber*., **87**, 463 (1954).
59. N. K. Kochetkov, N. F. Kucherova, L. P. Pronina, and M. I. Petruchenko, *Zh. Obshch. Khim.*, **29**, 3620 (1959).
60. A. N. Kost, S. I. Suminov, E. V. Vinogradova, and V. Kozler, *Zh. Obshch. Khim.*, **33**, 3606 (1963).
61. W. E. Hahn, R. Bartnik, and H. Zawadzka, *Acta Chim.* (Łódź), **11**, 83 (1966); *Chem. Abstr.*, **66**, 75925 (1967).

62. M. K. Eberle, G. G. Kahle, and S. M. Talati, *Tetrahedron*, **29**, 4045 (1973).
63. E. K. Orlova, N. M. Sharkova, L. M. Meshcheryakova, V. A. Zagorevskii, and N. F. Kucherova, *Khim. Geterotsikl. Soedin.*, 1262 (1975). [*Chem. Heterocycl. Comp*., **11**, 1099 (1975)].
64. T. Lee, A. J. Robichaud, K. E. Boyle, Y. Lu, D. W. Robertson, K. J. Miller, L. W. Fitzgerald, J. F. McElroy, and B. L. Largent, *Bioorg. Med. Chem. Lett.*, **13**, 767 (2003).
65. H. Yamamoto, *J. Org. Chem.*, **32**, 3693 (1967).
66. C. Rosenbaum, P. Baumhof, R. Mazitschek, O. Müller, A. Giannis, and H. Waldmann, *Angew. Chem.*, **116**, 226 (2004).
67. S. R. Prakash, K. M. Cable, I. D. Correa, I. Fellows, S. Montgomery, J. J. Newman, I. Waterhouse, G. N. Wells, and D. R. Sutherland, *J. Labell. Comp. Radiopharm.*, **36**, 993 (1995).
68. N. N. Novikova, I. D. Silenko, N. F. Kucherova, C. G. Rozenberg, and V. A. Zagorevskii, *Khim. Geterotsikl. Soedin.*, 1070 (1971). [*Chem. Heterocycl. Comp*., **7**, 1002 (1971)].
69. E. Ebnöther, P. Niklaus, and R. Süess, *Helv. Chim. Acta*, **52**, 629 (1969).
70. C. J. Cattanach, A. Cohen, and B. Heath-Brown, *J. Chem. Soc.*, *C*, 359 (1971).
71. V. Padmavathi, T. V. R. Reddy, K. A. Reddy, A. Padmaja, and D. B. Reddy, *Indian J. Chem.*, **44B**, 2527 (2005).
72. R. E. Mewshaw, L. S. Silverman, R. M. Mathew, C. Kaiser, M. Bailey, and E. W. Karbon, *J. Med. Chem.*, **36**, 343 (1993).
73. R. E. Mewshaw, L. S. Silverman, R. M. Mathew, C. Kaiser, R. G. Sherrill, M. Cheng, C. W. Tiffany, E. W. Karbon, M. Bailey, S. A. Borosky, J. W. Ferkany, and M. E. Abreu, *J. Med. Chem.*, **36**, 1488 (1993).
74. V. L. Kudzma, *Synthesis*, 1661 (2003).
75. C. Chen, D. R. Lieberman, R. D. Larsen, T. R. Verhoeven, and P. J. Reider, *J. Org. Chem.*, **62**, 2676 (1997).
76. E. H. Ruediger, D. H. Deon, and J. F. Kadow, US Pat., 2005/0267130; www.espacenet.com
77. J. Maruyama, H. Yamashita, T. Watanabe, S. Arai, and A. Nishida, *Tetrahedron*, **65**, 1327 (2009).
78. M. E. Kuehne, *J. Am. Chem. Soc.*, **84**, 837 (1962).
79. N. Moskalev, M. Barbasiewicz, and M. Mąkosza, *Tetrahedron*, **60**, 347 (2004).
80. T. A. Engler and J. Wanner, *Tetrahedron Lett.*, **38**, 6135 (1997).
81. F. Barbot and P. Miginiac, *Helv. Chim. Acta*, **62**, 1451 (1979).
82. T. A. Engler and J. Wanner, *J. Org. Chem.*, **65**, 2444 (2000).
83. J.-C. Blazejewski and C. Wakselman, *J. Chem. Soc.*, *Perkin Trans. 1*, 2845 (1980).
84. N. N. Komzolova, N. F. Kucherova, and V. A. Zagorevskii, *Khim. Geterotsikl. Soedin.*, 668 (1968). [*Chem. Heterocycl. Comp*., **4**, 490 (1968)].
85. F. A. Trofimov, V. I. Garnova, A. N. Grinev, and N. G. Tsyshkova, *Khim. Geterotsikl. Soedin.*, 72 (1979). [*Chem. Heterocycl. Comp*., **15**, 63 (1979)].
86. K. Bhandari, V. A. Murti, P. C. Jain, and N. Anand, *Indian J. Chem.*, **17B**, 246 (1976).
87. N. Valls, V. M. Segarra, X. López, and J. Bosch, *Heterocycles*, **29**, 231 (1989).
88. F. Reis, H.-P. Husson, P. Potier, and M.-M. Janot, *Anales de Quimica*, **70**, 1052 (1974).
89. D. A. Shirley and P. A Roussel, *J. Am. Chem. Soc.*, **75**, 375 (1953).
90. J. Kebrle, A. Rossi, and K. Hoffmann, *Helv. Chim. Acta*, **42**, 907 (1959).
91. R. J. Sundberg and J. D. Bloom, *J. Org. Chem.*, **46**, 4836 (1981).
92. J. Kraxner and P. Gmeiner, *Synthesis*, 1081 (2000).
93. S. Cutri, A. Diez, M. Bonin, L. Micouin, and H.-P. Husson, *Org. Lett.*, **7**, 1911 (2005).
94. K. T. Potts and H.-G. Shin, *Chem. Comm.*, **23**, 857 (1966).
95. M. Salas, I. K. Al-Khawaja, M. J. Thomas, and J. A. Joule, *J. Chem. Res.*, *Synop.*, **7**, 218 (1988).
96. R. Grigg, V. Sridharan, and D. A. Sykes, *Tetrahedron*, **64**, 8952 (2008).

97. M.-L. Bennasar, E. Zulaica, and S. Alonso, *Tetrahedron Lett.*, **46**, 7881 (2005).
98. F. A. Trofimov, V. I. Ryabchenko, and A. N. Grinev, *Khim. Geterotsikl. Soedin.*, 1343 (1975). [*Chem. Heterocycl. Comp*., **11**, 1147 (1975)].
99. T. Dahlgren, D. R. Deardorff, and A. R. Martin, *Heterocycles*, **20**, 641 (1983).
100. J. Thesing and G. Semler, *Liebigs. Ann. Chem.*, **680**, 52 (1964).
101. A. Padwa, S. M. Lynch, J. M. Mejía-Oneto, and H. Zhang, *J. Org. Chem.*, **70**, 2206 (2005).
102. J. M. Bobbitt, C. L. Kulkarni, C. P. Dutta, H. Kofod, and K. N. Chiong, *J. Org. Chem.*, **43**, 3541 (1978).
103. M. Abou-Gharbia, U. R. Patel, M. B. Webb, J. A. Moyer, T. H. Andree, and E. A. Muth, *J. Med. Chem.*, **30**, 1818 (1987).
104. G. N. Walker and M. A. Moore, *J. Org. Chem.*, **26**, 432 (1961).
105. M. Decker, R. Faust, M. Wedig, M. Nieger, U. Holzgrabe, and J. Lehmann, *Heterocycles*, **55**, 1455 (2001).
106. R. S. Kusurkar, N. A. H. Alkobati, A. S. Gokule, and V. G. Puranik, *Tetrahedron*, **64**, 1654 (2008).
107. J. H. Wynne and W. M. Stalick, *J. Org. Chem.*, **68**, 4845 (2003).
108. M. Bandini, A. Melloni, F. Piccinelli, R. Sinisi, S. Tommasi, and A. Umani-Ronchi, *J. Am. Chem. Soc.*, **128**, 1424 (2006).
109. H. Ohno, A. Aso, Y. Kadoh, N. Fujii, and T. Tanaka, *Angew. Chem.*, *Int. Ed.*, **46**, 6325 (2007).
110. R. Grigg and T. Coulter, *Tetrahedron Lett.*, **32**, 1359 (1991).
111. Y. Shimoji, T. Hashimoto, and H. Yanagisawa, *Heterocycles*, **36**, 123 (1993).
112. L. K. Dalton, S. Demerac, and T. Teitei, *Aust. J. Chem.*, **22**, 185 (1969).
113. N. N. Smolyar, A. S. Volchkov, and Yu. M. Yutilov, *Khim.-Farm. Zh.*, **35**, No. 9, 46 (2001).
114. B. W. Cue, Jr., US Pat. 4451655; www.espacenet.com
115. Yu. M. Yutilov, N. N. Smolyar, and A. S. Volchkov, *Khim.-Farm. Zh.*, **34**, No. 12, 33 (2000).
116. V. Rosnati and G. Palazzo, *Gazz. Chim. Ital.*, **84**, 644 (1954).
117. B. Robinson, *Chem. Rev.*, **69**, 785 (1969).
118. L. J. Dolby and G. W. Gribble, *J. Heterocycl. Chem.*, **3**, 124 (1966).
119. N. K. Kochetkov, N. F. Kucherova, and I. G. Zhukova, *Zh. Obshch. Khim.*, **31**, 924 (1961).
120. N. K. Barkov, N. F. Kucherova, N. K. Kochetkov, and I. G. Zhukova, US Pat. 3657254; www.espacenet.com
121. N. N. Komzolova, N. F. Kucherova, and V. A. Zagorevskii, *Khim. Geterotsikl. Soedin.*, 696 (1967). [*Chem. Heterocycl. Comp*., **3**, 556 (1967)].
122. Y. Nagai, A. Irie, Y. Masuda, M. Oka, and H. Uno, *J. Med. Chem.*, **22**, 677 (1979).
123. G. W. Gribble, *Chem. Soc. Rev.*, **27**, 395 (1998).
124. N. F. Kucherova, N. N. Novikova, N. M. Sharkova, I. D. Silenko, and V. A. Zagorevskii, *Khim. Geterotsikl. Soedin.*, 995 (1977). [*Chem. Heterocycl. Comp*., **13**, 809 (1977)].
125. N. F. Kucherova, N. M. Sipilina, N. N. Novikova, I. D. Silenko, C. G. Rozenberg, and V. A. Zagorevskii, *Khim. Geterotsikl. Soedin.*, 1383 (1980). [*Chem. Heterocycl. Comp*., **16**, 1051 (1980)].
126. G. W. Gribble, *Chem. Soc. Rev*., **27**, 395 (1998).
127. G. W. Gribble and J. H. Hoffman, *Synthesis*, 859 (1977).
128. J. G. Berger, A. Davidson, and G. E. Langford, *J. Med. Chem.*, **20**, 600 (1977).
129. B. E. Maryanoff and D. F. McComsey, *J. Org. Chem.*, **43**, 2733 (1978).
130. B. E. Maryanoff, D. F. McComsey, and S. O. Nortey, *J. Org. Chem.*, **46**, 355 (1981).
131. J. G. Berger, *Synthesis*, 508 (1974).
132. B. Heath-Brown, *Chem. Ind.*, 1595 (1969).

133. J. G. Berger, S. R. Teller, C. D. Adams, and L. J. Guggenberger, *Tetrahedron Lett.*, 1807 (1975).
134. W. M. Welch, C. A. Harbert, A. Weissman, and B. K. Koe, *J. Med. Chem.*, **29**, 2093 (1986).
135. A. E. Lanzilotti, R. Littell, W. J. Fanshawe, T. C. McKenzie, and F. M. Lovell, *J. Org. Chem.*, **44**, 4809 (1979).
136. V. A. Zagorevskii, C. G. Rozenberg, N. M. Sipilina, L. U. Bykova, and A. P. Rodionov, *Zh. Vses. Khim. Obshch.*, **27**, 102 (1982).
137. G. E. Ryschkewitsch, *Adv. Chem. Ser*., **42**, 53 (1964).
138. A. J. Elliott and H. Guzik, *Tetrahedron Lett.*, **23**, 1983 (1982).
139. O. Repič and D. J. Long, *Tetrahedron Lett*., **24**, 1115 (1983).
140. V. A. Zagorevskii, N. M. Sipilina, C. G. Rozenberg, L. U. Bykova, and N. Ya. Pokin-boroda, in: *Proceedings of Third Moscow Conference on Organic Chemistry and Technology* [in Russian], Moscow (1982), p. 147.
141. J. C. Tomesch, P. Li, W. Yao, Q. Zhang, J. D. Beard, A. S. Thompson, and H. Cheng, Int. Pat. WO2008/112280; www.espacenet.com
142. J. G. Berger, Ger. Pat., 2715355; www.espacenet.com
143. R. M. Salimov, G. I. Kovalev, M. N. Preobrazhenskaya, S. N. Lavrenov, and S. A. Lakatosh, US Pat. 2008/0262019; www.espacenet.com
144. R. Sarges, H. R. Howard, K. M. Donahue, W. M. Welch, B. W. Dominy, A. Weissman, B. K. Koe, and J. Bordner, *J. Med. Chem.*, **29**, 8 (1986).
145. O. L. Chapman, G. L. Eian, A. Bloom, and J. Clardy, *J. Am. Chem. Soc.*, **93**, 2918 (1971).