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γ-CARBOLINES AND THEIR HYDROGENATED DERIVATIVES. 1. AROMATIC γ-CARBOLINES: METHODS OF SYNTHESIS, CHEMICAL AND BIOLOGICAL PROPERTIES (REVIEW)

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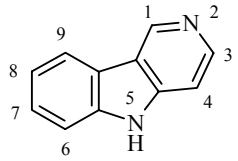
Published data on the methods of synthesis and chemical and biological properties of aromatic γ-carbolines are reviewed.

Keywords: anhydro bases, benzotriazoles, γ-carbolines, pyrido[4,3-*b*]indoles, biological activity, Fischer synthesis, Graebe–Ullman reaction, hetero-Diels–Alder reactions, metal-complex catalysis, microwave radiation.

The γ-carbolines are a less well studied class of compounds than their β-analogs, although their methods of synthesis and chemical characteristics are of undoubted interest. Moreover they are precursors of tetra- and hexahydro-γ-carbolines, the biological activity of which is extremely diverse (e.g., see [2]). For this reason we considered it expedient to devote the first part of this review to 5H-pyrido[4,3-*b*]indoles.

In contemporary literature there are several alternatives for the nomenclature of carbolines and for the numbering of the atoms in these cyclic systems. For simplicity and convenience we will use the numbering employed in [3].



γ-Carboline 5H-pyrido[4,3-*b*]indole

Methods of Synthesis of γ-Carbolines

One of the first methods used for the production of γ-carbolines was the Graebe–Ullman method, which involves thermal cleavage of the respective benzotriazoles and was proposed at one time for the production of various carbazoles [4]. It was by this method that Robinson and Thornley first obtained unsubstituted γ-carboline [5] by thermal decomposition of 1-(4-pyridyl)benzotriazole (**1**).

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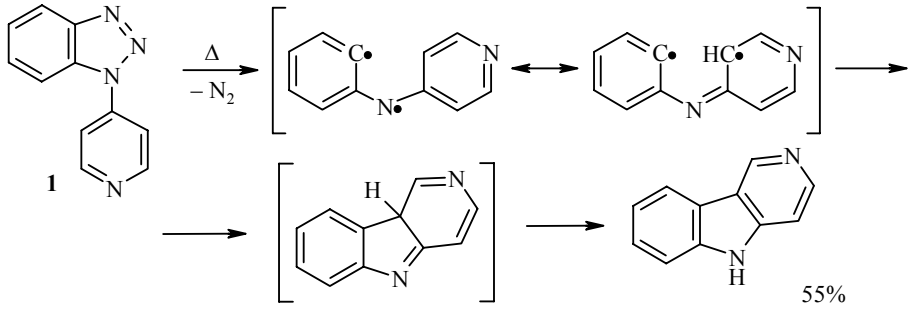
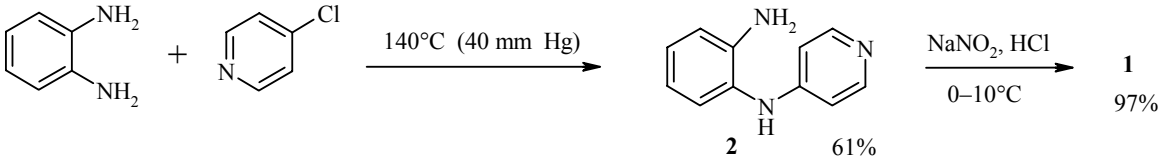


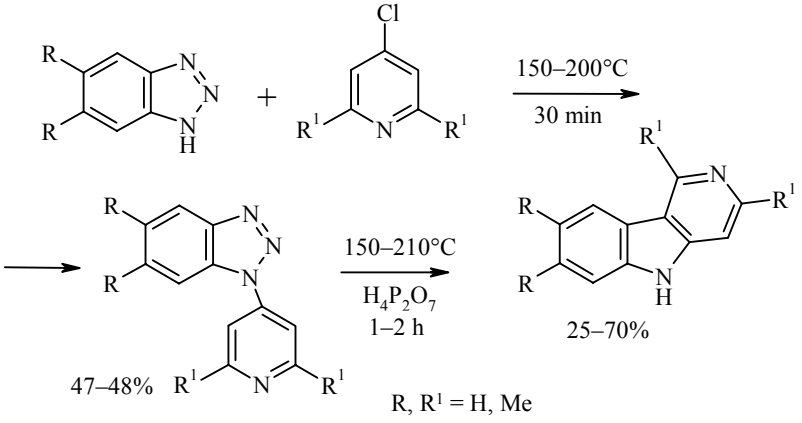
The thermal decomposition of benzotriazole takes place fairly smoothly and easily; in UV light a hydrochloric acid solution of γ-carboline gives a blue-violet fluorescence.

The initial benzotriazole **1** was obtained by baking *o*-phenylenediamine and 4-cloropyridine followed by treatment of the reaction product with nitrous acid.

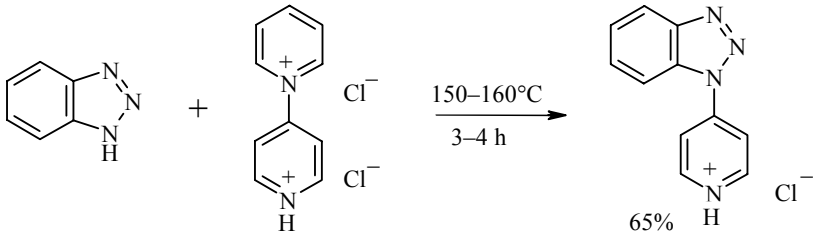


The intermediate aminopyridine **2** can also be synthesized from the same compounds using the Cu (1 equiv.)–K_2CO_3 (1 equiv.)–I_2 (cat.) system [6].

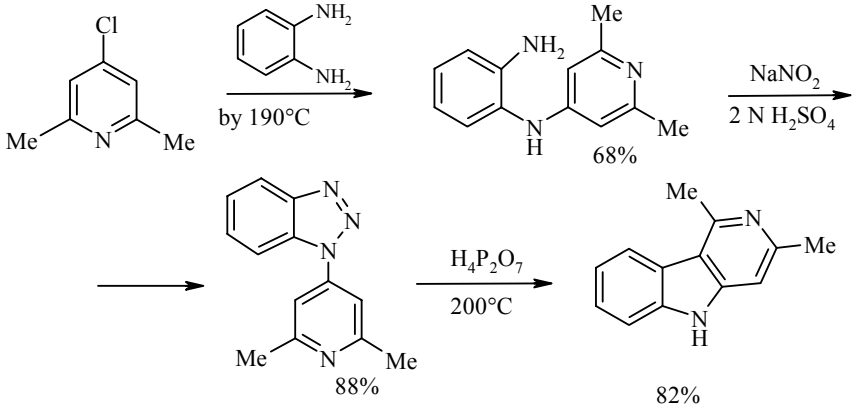
1-(4-Pyridyl)benzotriazoles with a symmetrical arrangement of the substituents in the phenylene fragment can be obtained by direct hetarylation at position 1 of the corresponding N-unsubstituted benzotriazoles by the action of 4-halopyridines or 4-pyridylpyridinium chloride under harsh conditions. As a rule such transformations take place in the presence of copper or its divalent salts as catalyst [7], but in some cases heating alone is sufficient [8, 9].



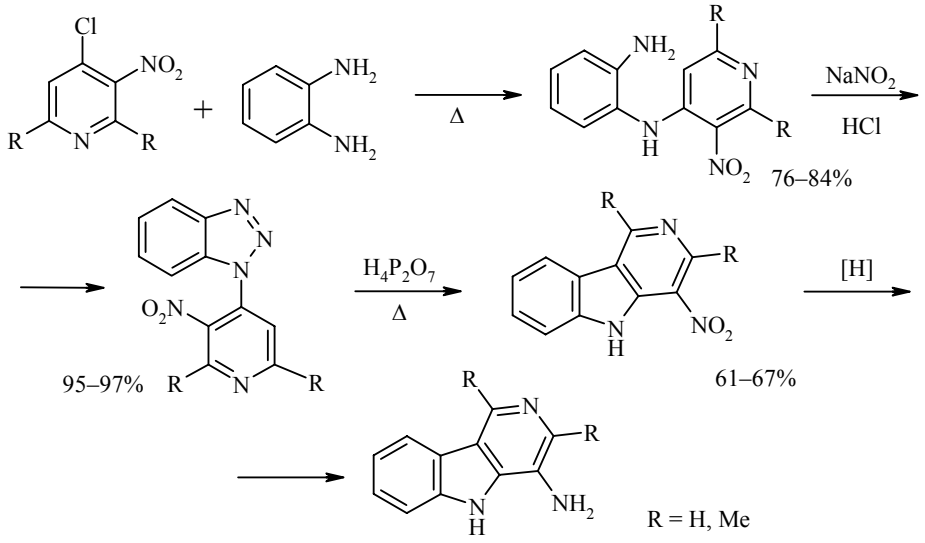
It is significant that the thermal decomposition of benzotriazoles takes place more smoothly and with better yields in hot syrupy phosphoric, pyrophosphoric ($H_4P_2O_7$), and polyphosphoric acids [10] than with zinc chloride, but the role of the acid in this transformation is not at the moment quite clear. The acids are obviously extremely convenient nonoxidizing media for thermolysis. In addition, such transformations are often performed in paraffin wax [9].



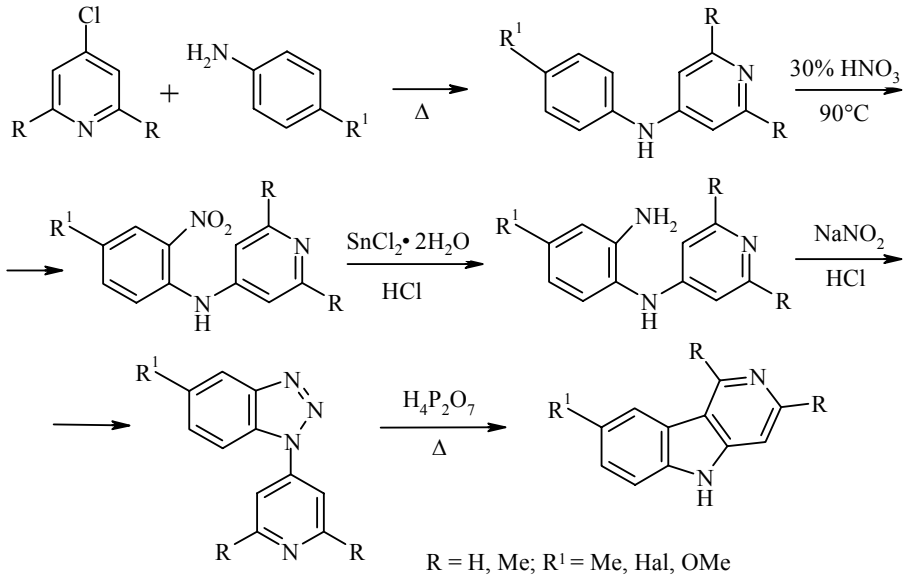
The thermal decomposition of 1-(2,6-dimethyl-4-pyridyl)benzotriazole, the process leading to which is shown in the scheme below, leads to the formation of 1,3-dimethyl-γ-carboline [11]:



If 4-halo-3-nitropyridines are used in a similar transformation it is possible to obtain 4-nitro- and 4-amino-γ-carbolines [11, 12].

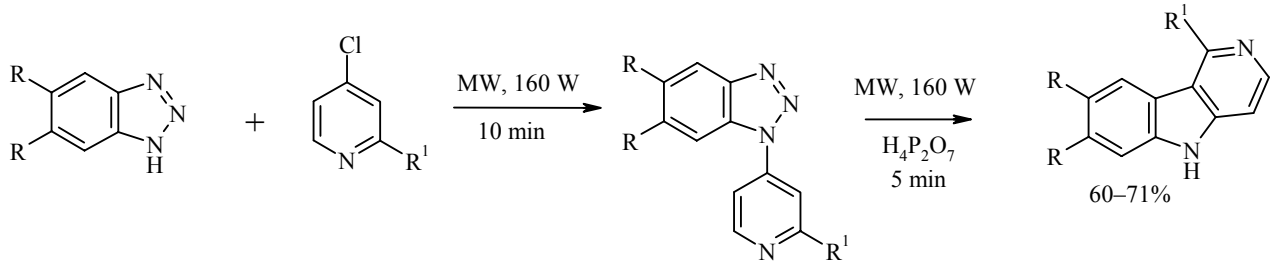


The same scheme can be used for the production of γ-carbolines with identical substituents at positions 6 and 9 or 7 and 8 from the respective *o*-phenylenediamines. In the case where there are different substituents in the *o*-phenylenediamine molecule the formation of a mixture of regioisomers is possible. A scheme based on the use of substituted anilines was proposed for the selective production of only the 8-substituted compounds [13].



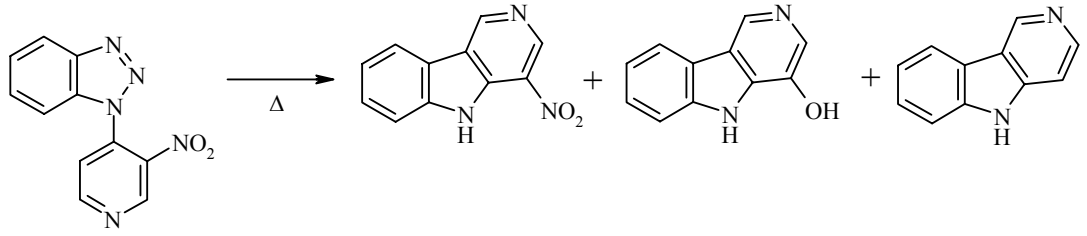
R = H, Me; R[1] = Me, Hal, OMe

The arylation and decomposition of benzotriazoles with the formation of γ-carbolines can be conducted not only under harsh thermal conditions but also under fairly mild conditions – by the action of microwave radiation [14] – and with higher yields.



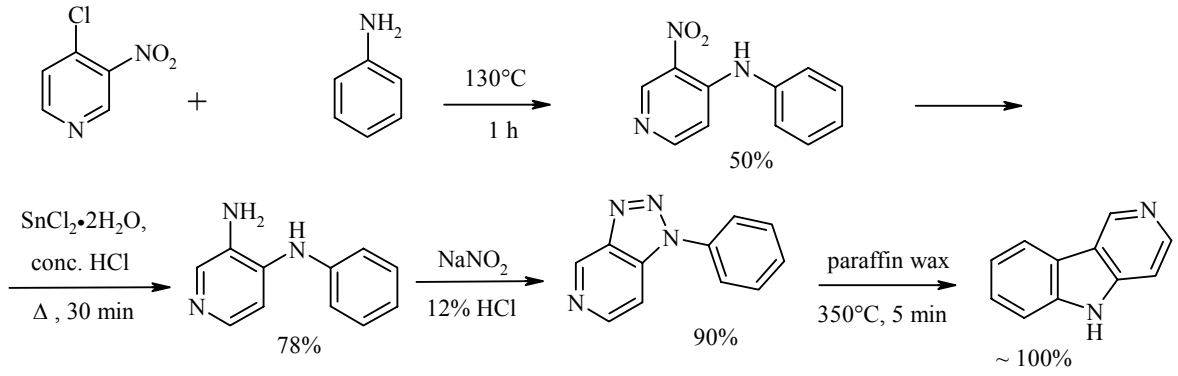
R, R[1] = H, Me

In addition to the decomposition of benzotriazoles under conditions of thermolysis or microwave exposure, there are also the flash-vacuum pyrolysis [15] and photodecomposition [16] techniques, which sometimes lead to compounds that cannot be obtained by the thermal methods. Thus, for example, flash-vacuum pyrolysis of N-(4-pyridyl)benzotriazole, containing a nitro group at the *ortho* position to the benzotriazolyl substituent, leads to the formation of 4-hydroxy-substituted and unsubstituted γ-carbolines [15].

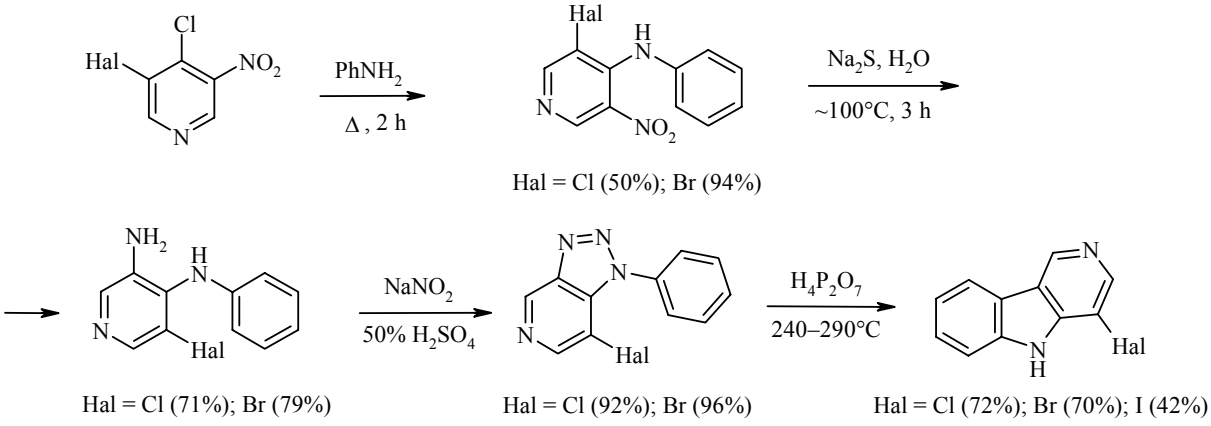


Methods for the production of various benzotriazoles and all sorts of chemical transformations were described in [15, 17].

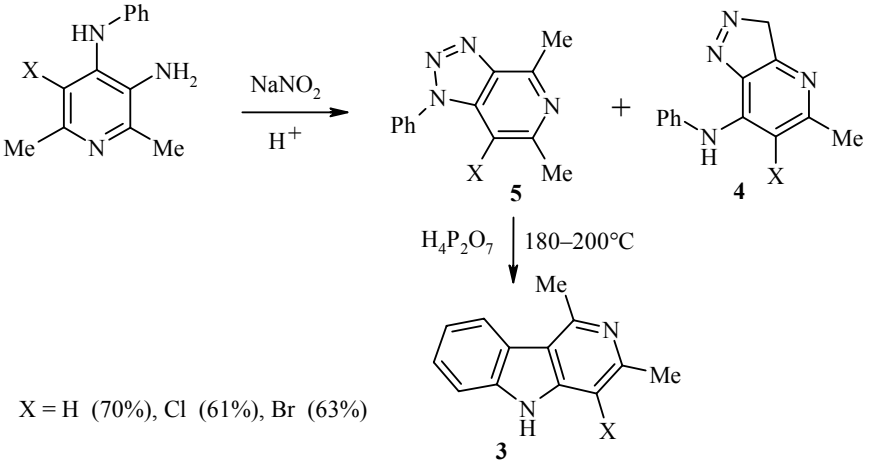
An alternative approach to the synthesis of γ-carbolines is the thermolysis of the corresponding 1-phenylpyrido[3,4-*d*]-*vic*-triazoles at 320-350°C [18]. Compared with the methods described above it gives higher yields of the desired compound:



4-Halo-substituted γ-carbolines were obtained similarly from 4,5-dihalo-3-nitropyridines [12]:

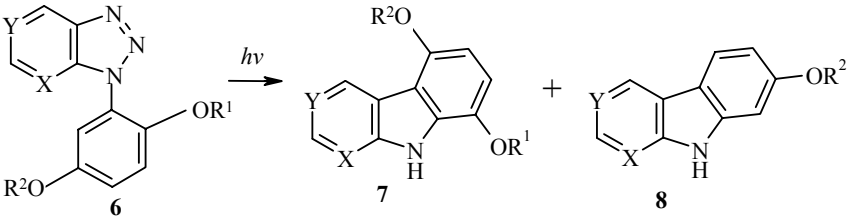


The extension of this method to the synthesis of 4-halo-1,3-dimethyl-γ-carboline revealed a series of peculiarities and limitations [11]. Thus, together with the desired 1,3-dimethyl-4-X-γ-carbolines **3** the formation of 3H-pyrazolo[4,3-*b*]pyridine **4** as side product was observed. During heating one of the tautomeric forms of pyrido[3,4-*b*]-*vic*-benzotriazole **5** probably undergoes recyclization to the pyrazolopyridine **4**, which at 250°C eliminates nitrogen without forming the γ-carboline.



Since this competing process leads to a decrease in the yield of the 1,3-dimethyl-γ-carbolines **3**, for their production it is better to use decomposition of the corresponding 1-(2,6-dimethyl-4-pyridyl)benzotriazoles discussed above.

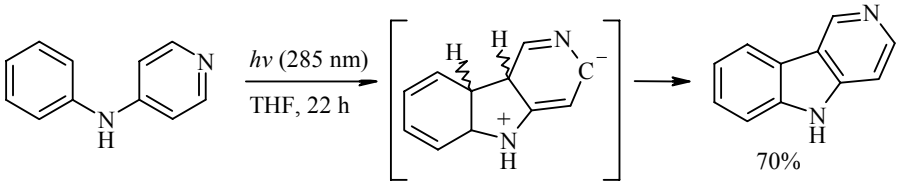
Like the benzotriazoles pyrido-*vic*-triazoles undergo decomposition not only under thermal conditions. During the photolysis of 1-arylpyrido-*vic*-triazoles **6** containing two alkoxy groups in the *para* position in relation to each other cyclization with elimination of the *ortho* substituent can take place alongside the formation of the dialkoxycarboline [16].



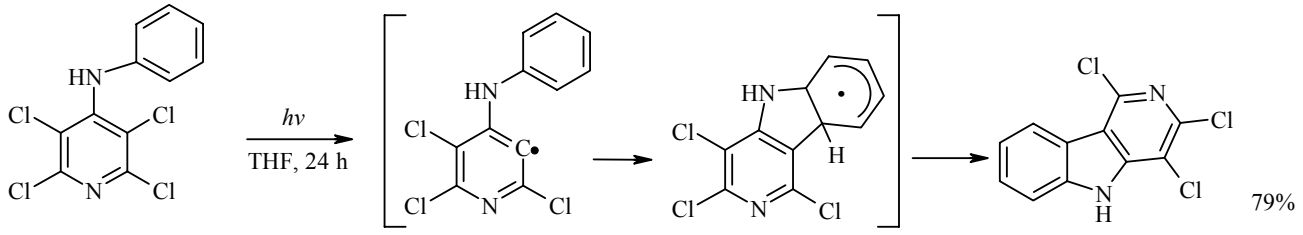
X	Y	R^1	R^2	**7**	**8**
N	CH	*i*-Pr	Me	84%	9%
CH	N	Me	*i*-Pr	30%	15%
CH	N	*i*-Pr	Me	36%	–

As seen from the presented data, increase in the size of the substituent at the *ortho* position leads to an increase in the yield of 6,9-dialkoxycarbolines **7** and prevents the formation of the minor 7-alkoxycarbolines **8**. Thus, the position and size of the substituents in the phenyl fragment and the position of the heteroatom in the pyridine ring of 1-arylpyrido-*vic*-triazole have a significant effect on the structure and yield of the final compound.

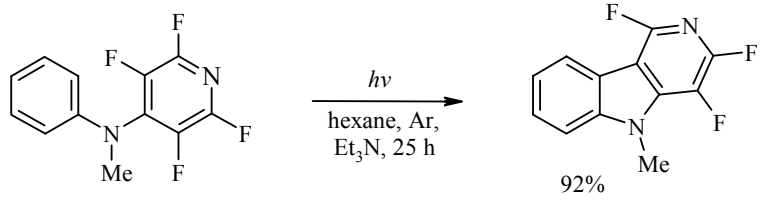
During irradiation in cyclohexane or THF 4-(phenylamino)pyridine undergoes oxidative photocyclization [19] accompanied by the formation of γ-carboline. This was first noticed in diphenylamines, which are converted under these conditions into the corresponding carbazoles [20]. If the process is conducted in methanol or benzene the formation of the carboline is not observed.



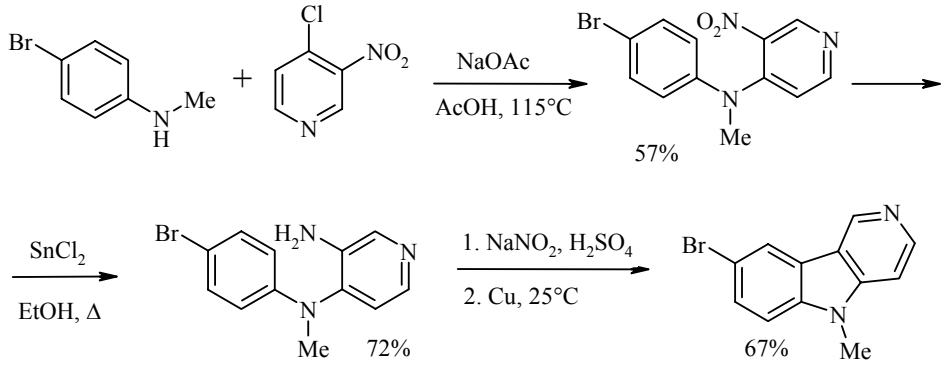
A similar reaction is also typical of polyhalodiarylamines, but it is accompanied not by oxidative dehydrogenation but by elimination of the hydrogen halide. Thus, 1,3,4-trichloro-γ-carboline can be obtained with a good yield during the irradiation of 2,3,5,6-tetrachloro-4-phenylaminopyridine with a quartz lamp [21]. The process is possible as a result of the photolability of the C(3)–Cl bond, as reported earlier for 2,3,4,5,6-pentachloropyridine, which is easily transformed into 2,3,4,6-tetrachloropyridine during UV irradiation [22].



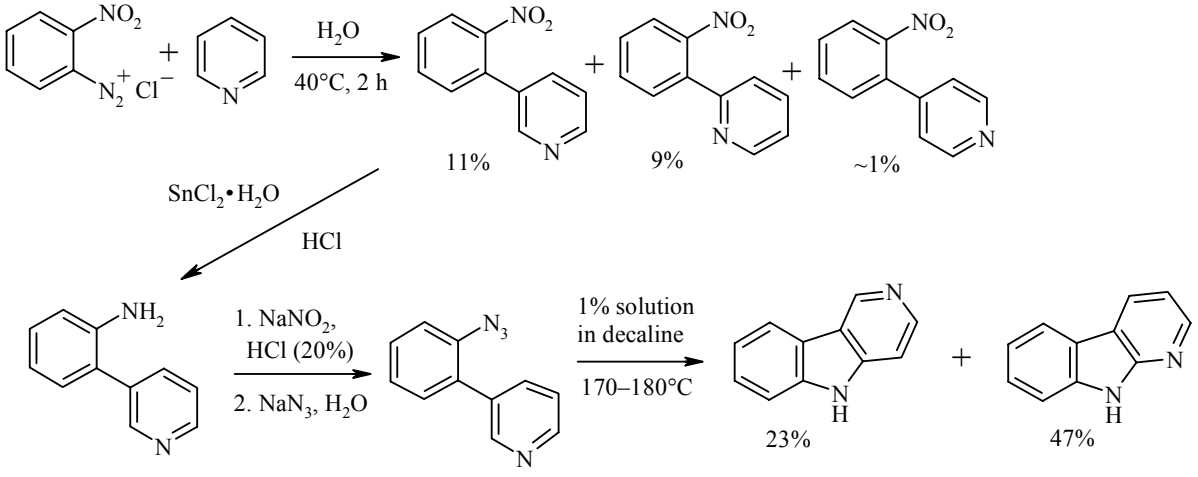
A similar transformation is known for 2,3,5,6-tetrafluoro-4-(phenylmethylamino)pyridine [23]. During UV irradiation in a stream of argon the process is relatively slow, but the addition of an equimolar amount of an amine (Et_3N, $BuNH_2$) leads to the formation of 1,3,4-trifluoro-5-methylpyrido[4,3-*b*]indole with a high yield.



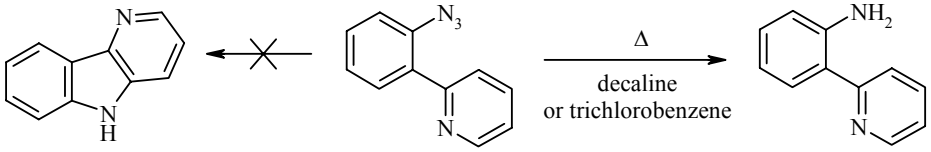
5-Methyl-γ-carbolines can be obtained as a result of an intramolecular process, related to the Gomberg–Bachmann reaction, that takes place at room temperature in the presence of copper powder with closure of a pyrrole ring [24].



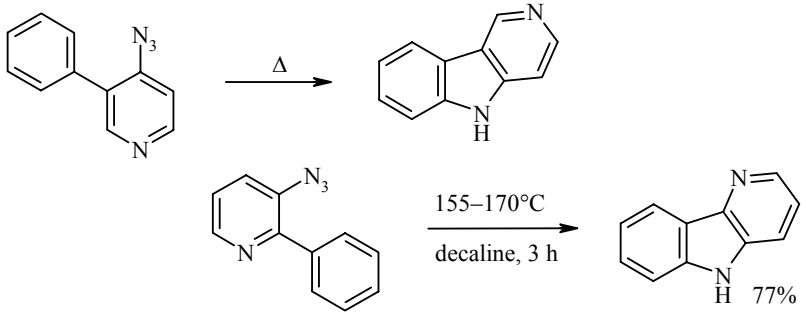
A method is known for the synthesis of γ-carbolines based on the thermal decomposition of 3-(2-azidophenyl)pyridine, the starting compound for the production of which is β-(*o*-nitrophenyl)pyridine, but it does not have preparative value for several reasons. First, during the preparation of the β-(*o*-nitrophenyl)pyridine itself by the reaction of the *o*-nitrophenyldiazonium salt with pyridine a mixture of approximately equal amounts of α- and β-arylpyridines and trace quantities of the γ-isomer is formed with a very low yield [25]. Second, the thermal decomposition of 3-(2-azidophenyl)pyridine, accompanied by ring closure, leads to the formation of a mixture of α- and γ-carbolines [26].



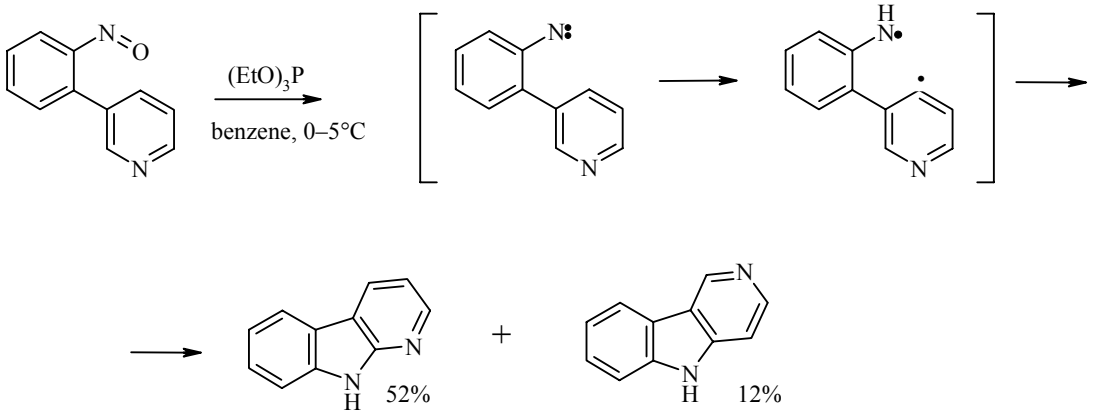
Only the β-isomer of *o*-azidophenylpyridine undergoes thermolysis with ring closure. Instead of the expected δ-carboline the decomposition of α-(*o*-azidophenyl)pyridine leads to 3-(2-aminophenyl)pyridine due, probably, to the removal of two hydrogen atoms either from a molecule of the solvent or from another molecule.



Carboline structures can also be obtained by the decomposition of arylpyridyl azides, and this process takes place with the unequivocal formation of only one cyclization product [27]. A disadvantage of the method is the difficulty of obtaining the initial arylpyridyl azides, and this significantly restricts its use for synthesis purposes.

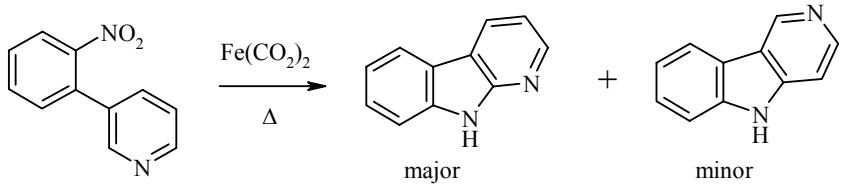


In the presence of triethyl phosphite 3-(*o*-nitrosophenyl)pyridine is converted with a total yield 64% into a mixture of α- and γ-carbolines (81 and 19% respectively) [28]. By analogy with the reduction of 2-nitrosobiphenyls to carbazoles under these conditions it was postulated that nitrenes are formed as intermediates during deoxygenation of the initial nitro compound. Triphenylphosphine can also be used as reducing agent instead of triethyl phosphite [28].



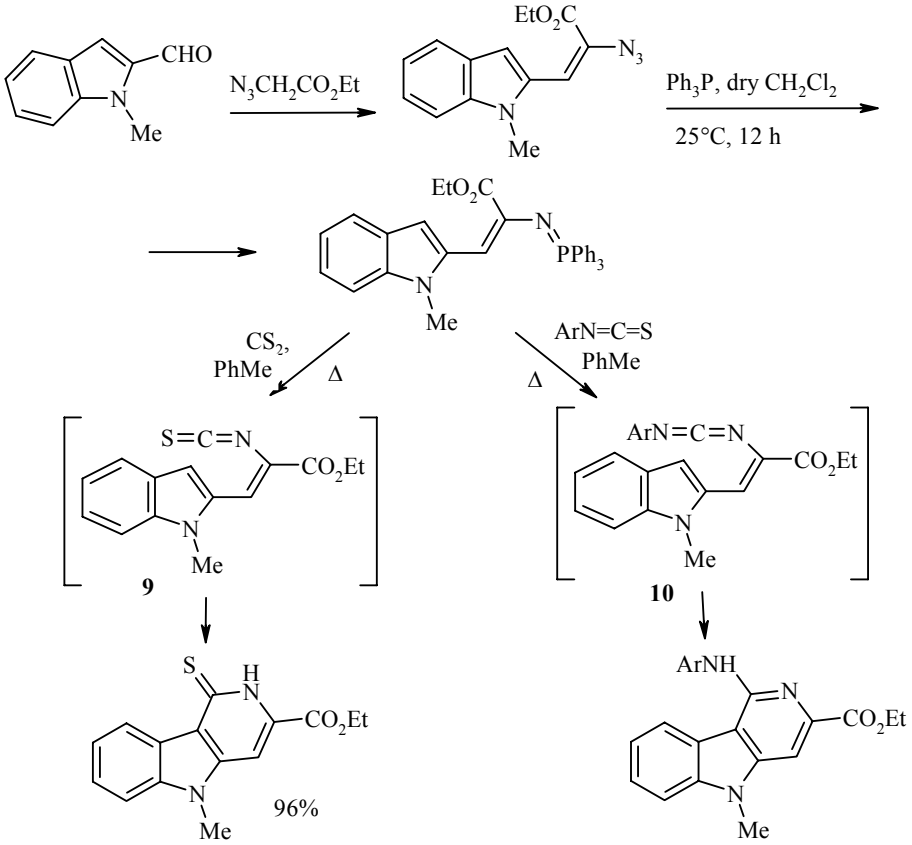
It is quite clear that the method does not have preparative value for the production of γ-carbolines on account of its low selectivity and yields.

In an attempt to extend the method for the synthesis of carbazoles based on the reduction of *o*-nitrobiphenyl with iron oxalate [29] to the production of carbolines it was proposed to use *o*-nitrophenylpyridines as starting compounds. Thus, the cyclization of 4-(*o*-nitrophenyl)pyridine by heating with iron oxalate leads to the formation of β-carboline without any difficulties, but the initial nitro compound is quite difficult to obtain. If 3-(*o*-nitrophenyl)pyridine is used a mixture of reaction products containing α- and γ-carbolines is obtained [30], and by analogy with the reductive cyclization of 3-(2-nitrosophenyl)pyridine the major product of this transformation is the α-carboline.



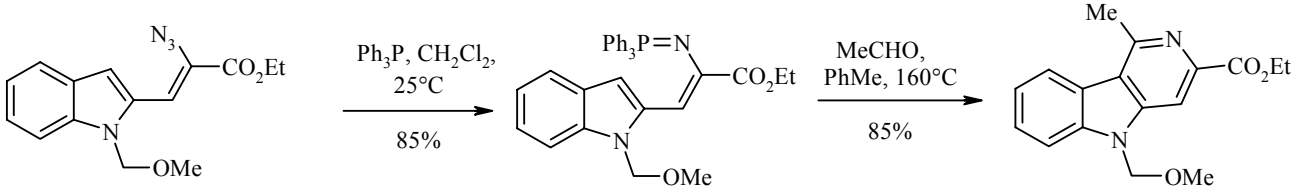
The methods examined above involve closure of the pyrrole ring of the γ-carboline aromatic system, but annelation of the pyridine ring to the indole fragment is often used for the synthesis of γ-carbolines.

One such method is based on the aza-Wittig reaction of the iminophosphorane derivative of α-azido-β-(1-methylindolyl)acrylate. Pyridoannelation takes place through the formation of the adducts **9** and **10** containing a heterocumulene fragment, which ensures that the electrocyclic closure of the pyridine ring occurs [31]. The 1-arylamino-3-ethoxycarbonyl-5-methylpyrido[4,3-*b*]indole and, accordingly, its 1-thio analog were produced according to the following scheme:

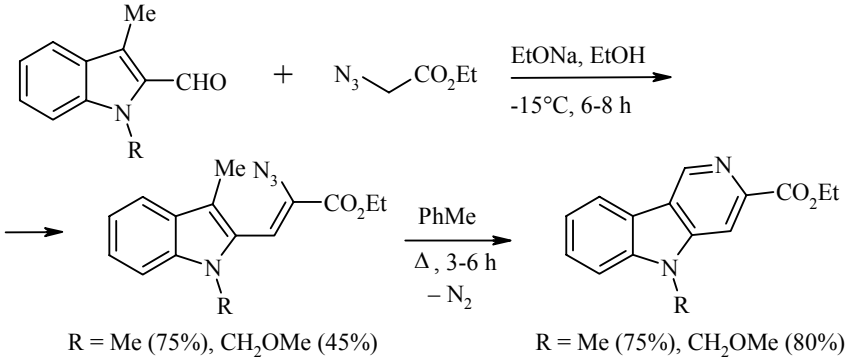


Ar = Ph (94%), 4-MeC$_6$H$_4$ (81%), 4-MeOC$_6$H$_4$ (89%), 4-ClC$_6$H$_4$ (93%)

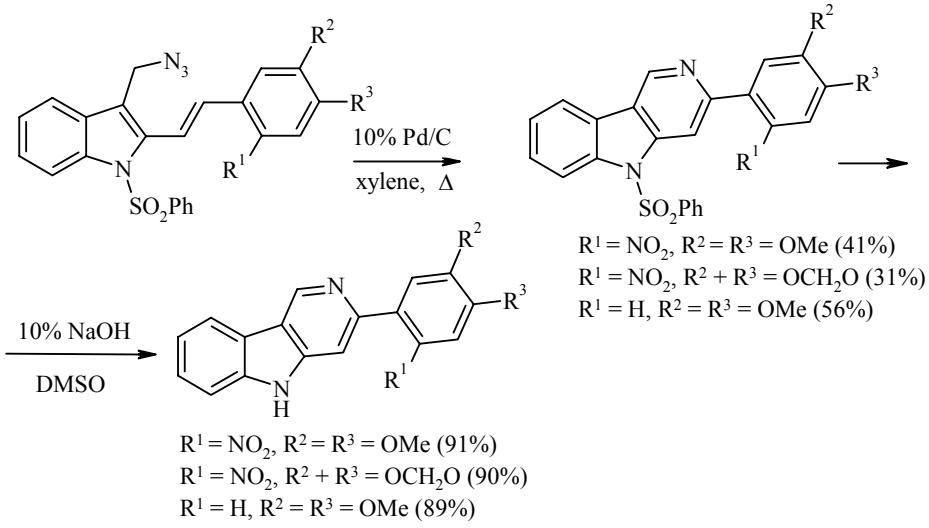
If various aldehydes are used instead of carbon disulfide or aromatic isothiocyanates it is possible to obtain the corresponding 1-alkyl- or 1-aryl-γ-carbolines by heating in a sealed ampule [32].



1-Unsubstituted 3-ethoxycarbonyl-γ-carboline can be synthesized on the basis of 2-formyl-3-methylindole [33, 34].

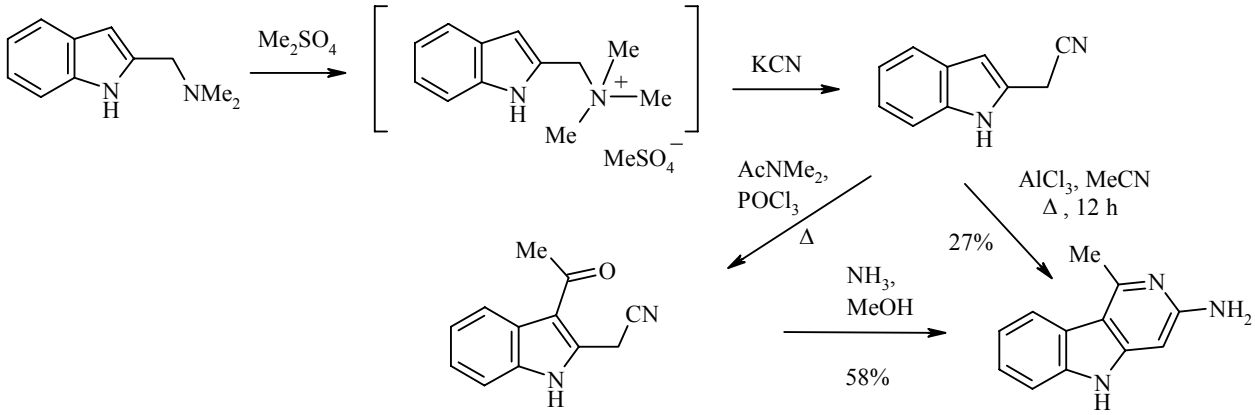


The intramolecular addition of nitrene at a carbon–carbon double bond can also lead to the formation of the γ-carboline skeleton. For example, 3-aryl-5H-pyrido[4,3-*b*]indoles can be obtained with moderate yields during the catalytic thermolysis of 2-(β-arylvinyl)-3-azidomethyl-1-phenylsulfonylindoles [35].

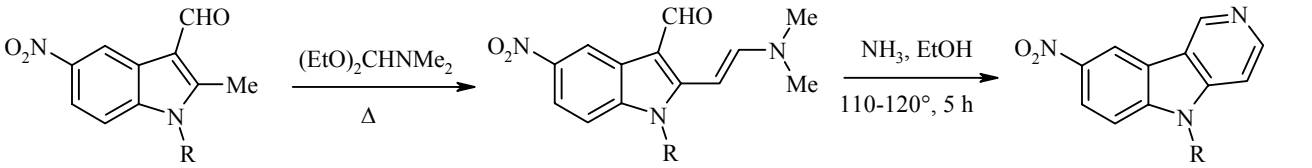


In the case of $R^1 = NO_2$ the 2-(β-arylvinyl)-3-cyanomethyl-1-phenylsulfonylindole is also formed with a yield of 26-32% in addition to the 3-aryl-γ-carboline.

A completely different approach to closure of the pyridine fragment of γ-carboline is based on the cyclization of 3-acyl-2-cyanomethylindole with ammonia [36, 37]. In this case isogramine methyl sulfate enters into nucleophilic substitution with the cyanide ion to form 2-cyanomethylindole, which is readily transformed into 3-acetyl-2-cyanomethylindole by a Vilsmeier–Haack reaction. The reaction of 3-acetyl-2-cyanomethylindole with ammonia leads to 3-amino-1-methyl-γ-carboline, which can also be obtained by the acylation of 2-cyanomethylindole with acetonitrile in the presence of $AlCl_3$ [38]. During the reaction with acetonitrile in a mixture of acetic acid and methanol the yield of the γ-carboline derivative can be increased to 40% [39].



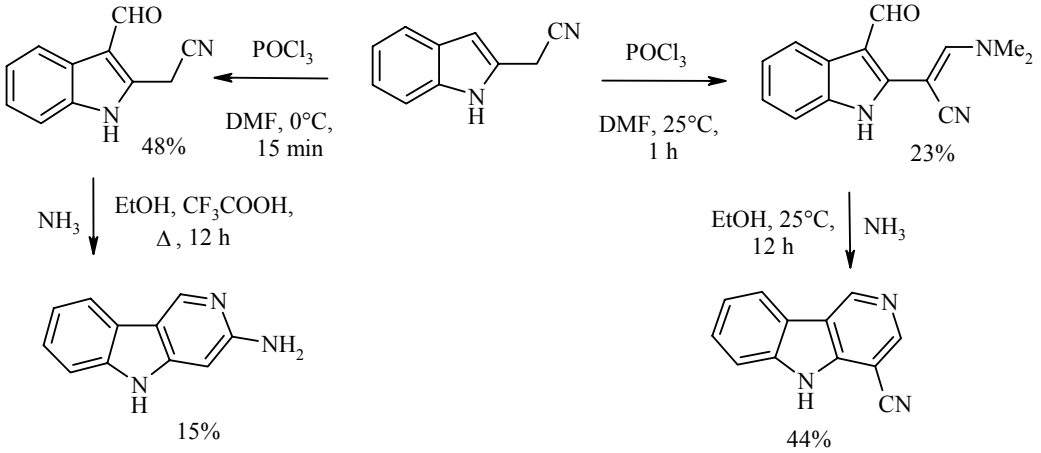
The dienaminocarbonyl structural fragment is a convenient five-carbon component for the construction of the pyridine ring by reaction with ammonia or primary amines. The use of the dienaminocarbonyl fragment, often contained in a substituted indole ring, leads to γ-carboline structures [40].



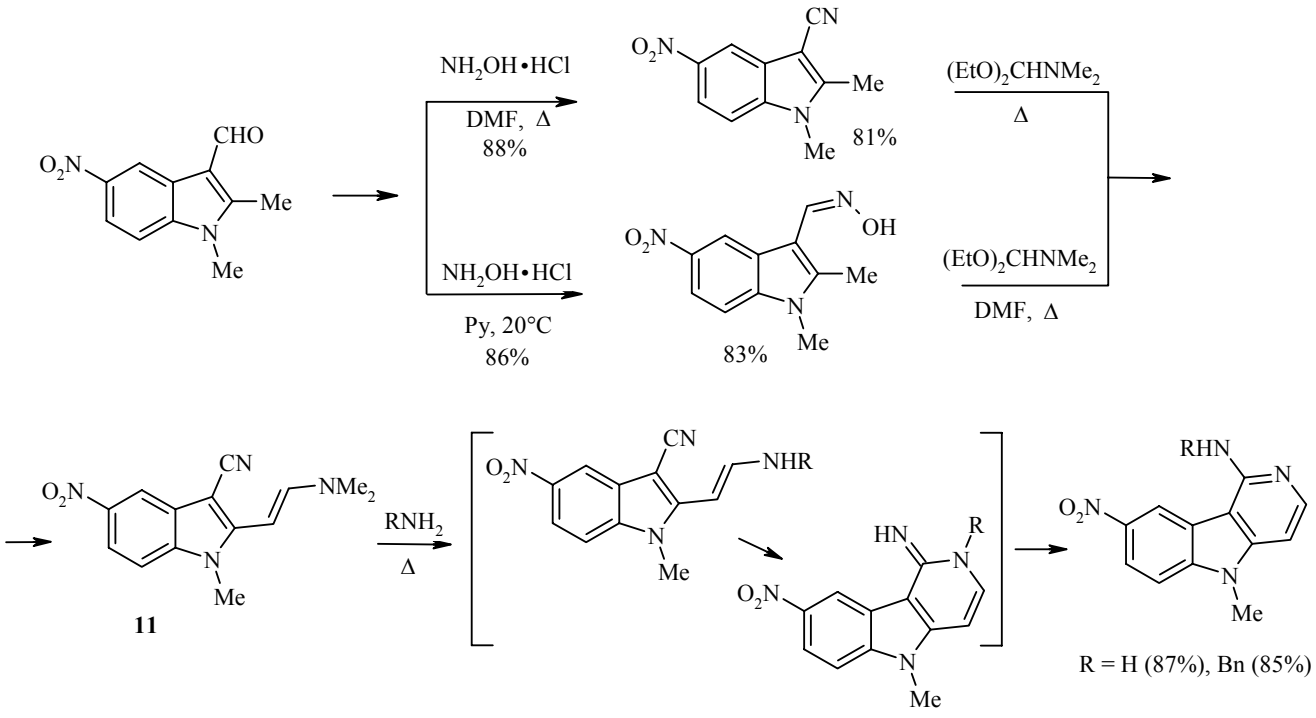
R = Me (78%), Et (80%), Bn (74%)

R = Me (85%), Et (79%), Bn (81%)

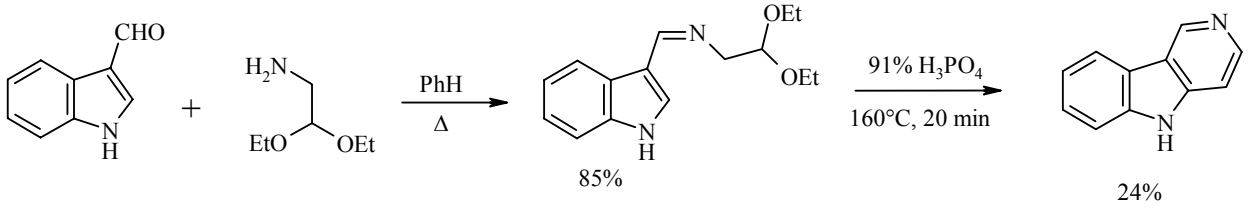
Depending on the temperature, Vilsmeier formylation of 2-cyanomethylindole leads to the formation of 2-(1-cyano-2-dimethylaminovinyl)-3-formyl- and 2-cyanomethyl-3-formyl-indoles, which in reaction with ammonia are converted into 4-cyano- and 3-amino-γ-carbolines respectively [38].



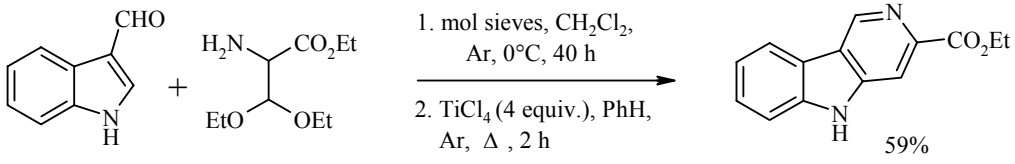
On the basis of the 2-(β-2-dimethylaminovinyl)indole derivative **11** it is possible to synthesize various 1-amino derivatives of 5-methyl-8-nitro-γ-carboline [41].



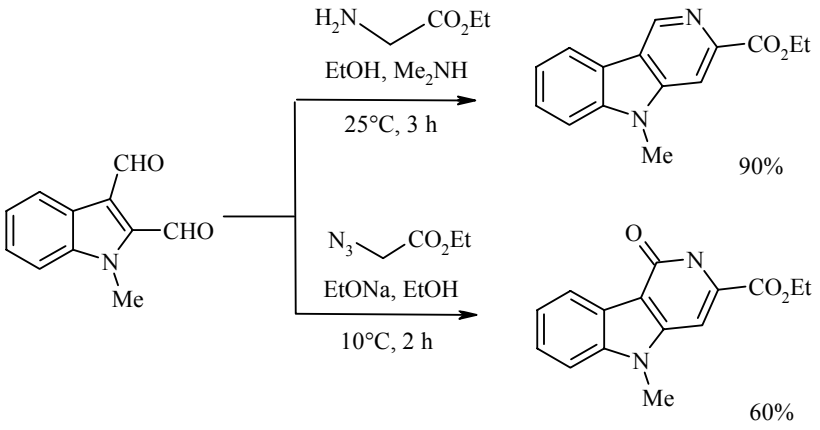
γ-Carbolines can also be synthesized during cyclization of the azomethines obtained from 3-formylindole and aminoacetal with orthophosphoric as condensing agent [42].



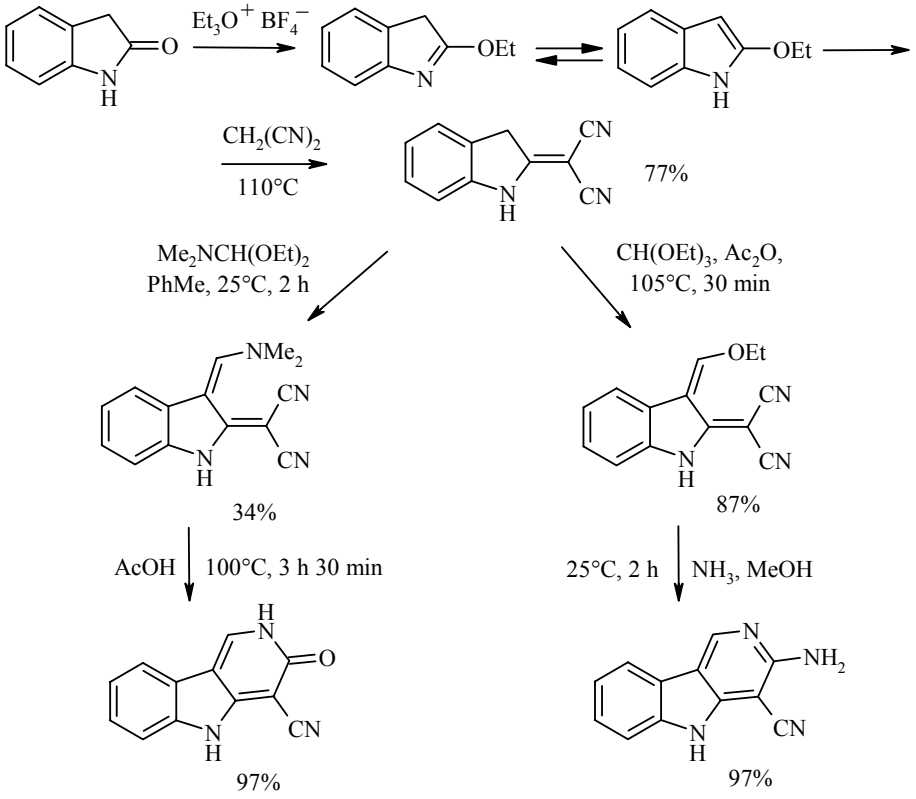
If ethyl α-amino-β,β-diethoxypropionate is used as amino component, by using $TiCl_4$ it is possible to increase the yield of the final γ-carboline substantially [43].



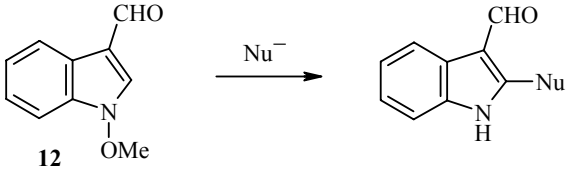
The γ-carboline system can be constructed chemoselectively from 2,3-diformylindole and glycine ethyl ester [44]; the use of azidoacetic ester leads to the chemoselective formation of the 1-oxo-γ-carboline derivative [44].



2-Ethoxy-3H-indole, which is in tautomeric equilibrium with 2-ethoxy-1H-indole, is capable of reacting with a series of CH-acids (e.g., malononitrile) and provides the basis for the production of 4-cyano-γ-carboline derivatives [45].



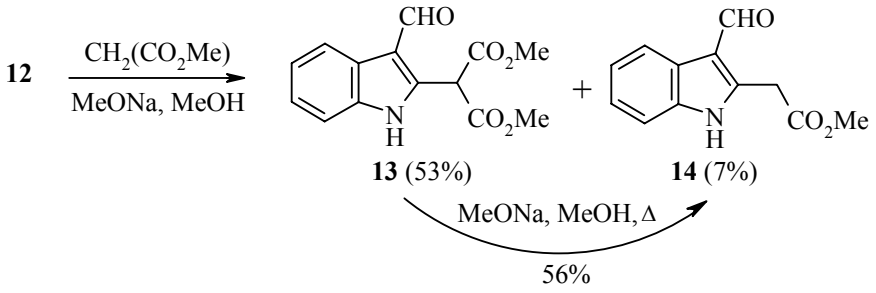
An extremely interesting method for the synthesis of γ-carbolines was proposed on the basis of 3-formyl-1-methoxyindole (**12**) [46], which has the ability to enter into substitution with nucleophilic agents with the formation of 2-substituted 3-formylindoles [47].



12

Nu = OR, NRR[1], SR; heteroaromatic compounds, CH-acid compounds

This property of 3-formyl-1-methoxyindole makes it possible to introduce a malonic acid residue at position 2 with the formation of the esters **13** and **14**.



When compound **14** is boiled with ammonium acetate in alcohols for several hours a mixture of carbolines **15** and **16** is formed. In the opinion of the authors the indole derivative **14** in this reaction acts as catalyst for the oxidation of the alcohol by atmospheric oxygen to the corresponding aldehyde, but the mechanism of the process has not yet been established. The direct use of the aldehydes in the condensation reaction substantially reduces the reaction time, leads to an increase in the yield of the desired compound **15**, and prevents the occurrence of side processes (Table 1).

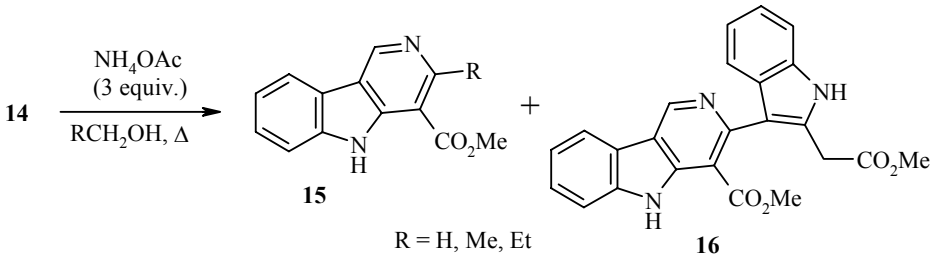


TABLE 1. The Production of γ-Carbolines **15** and **16** from the Ester **14**

Reaction conditions			R	Composition of reaction mixture, %		
Reagent	Solvent	Time, h		**15**	**16**	**14**
MeOH	MeOH	10	H	28	59	—
EtOH	EtOH	10	Me	19	69	—
PrOH	PrOH	2	Et	14	39	20
$(CH_2O)_n$ (1 equiv.)	MeOH	1	H	42	—	—
MeCHO (1 equiv.)	EtOH	1	Me	45	29	20
EtCHO (3 equiv.)	PrOH	1	Et	55	—	—

Boiling of the ester **13** with an excess of primary amines, hydrazine, or hydroxylamine in alcohol leads to cyclization with the formation of several reaction products (Table 2).

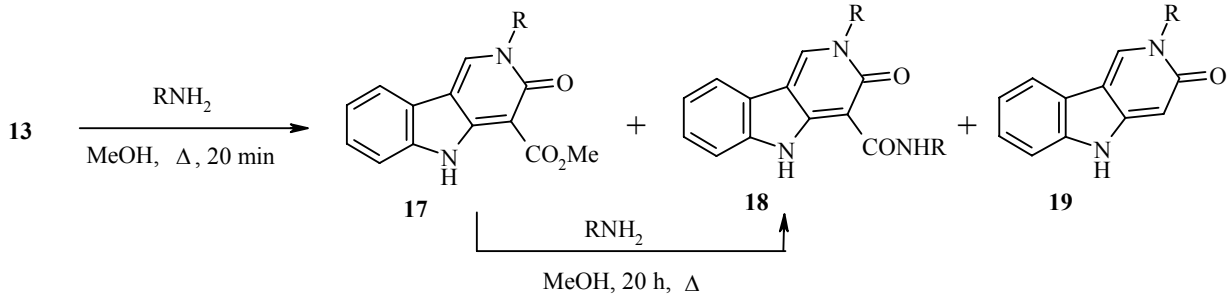
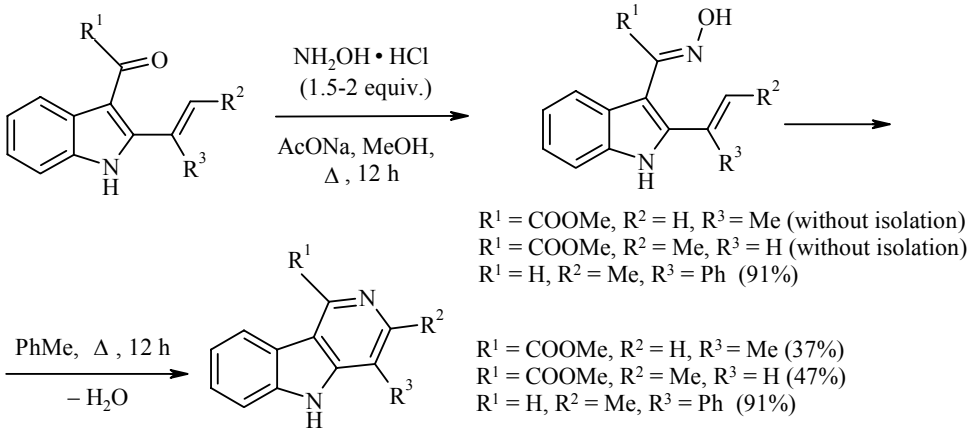


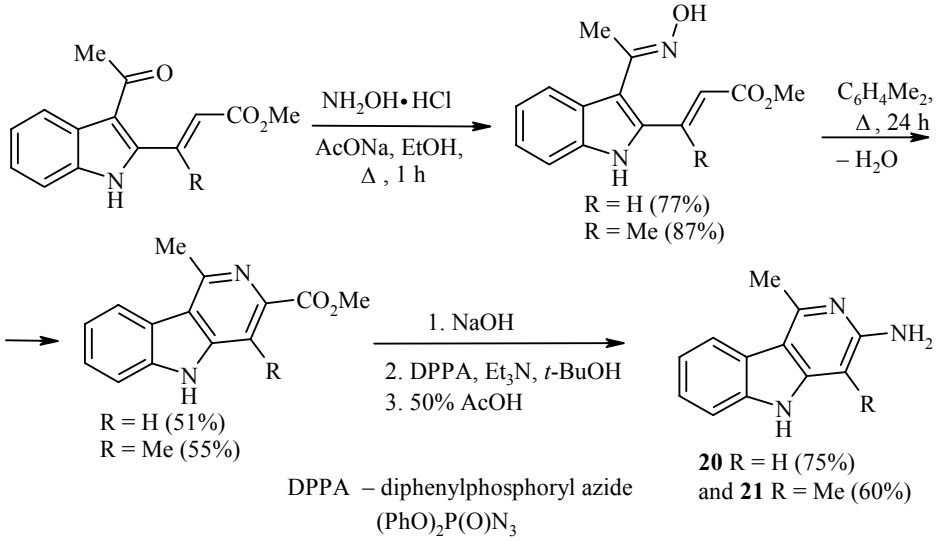
TABLE 2. Reaction of the Ester **13** with Nitrogen Nucleophiles

Reaction conditions		Yields of reaction products, %		
R	Time, min	**17**	**18**	**19**
Me	30	72	22	5
4-$MeOC_6H_4CH_2CH_2$	60	73	17	—
$CH_2CH_2NH_2$	60	75	22	—
4-MeC_6H_4	60	98	—	—
Pr	60	96	—	—
CH_2CH_2OH	60	98	—	—
CH_2CO_2Me	30	98	—	—
NH_2	5	41	—	—
OH	15	89	—	—
OMe	20	84	—	—
H	300	24	—	—

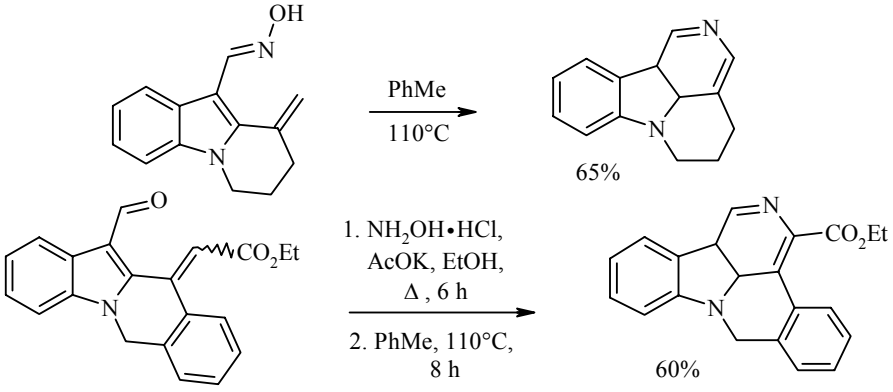
Another approach to synthesis of γ-carbolines from indoles was based on the intramolecular thermal cyclization of a 1-azahexa-1,3,5-triene system [48].



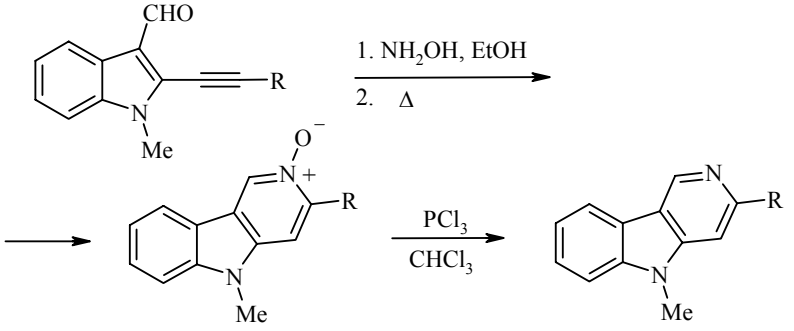
The cyclization of 1-azatrienes was also used for the production of γ-carbolines **20** and **21**, which have mutagenic properties [49, 50].



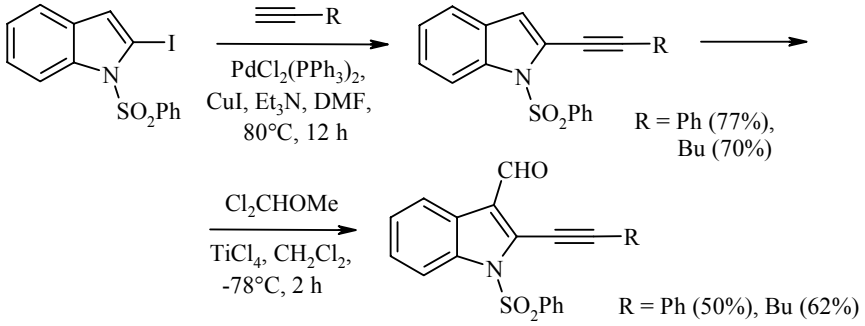
The method can also be used for the production of tetra- and pentacyclic γ-carboline structures [51].

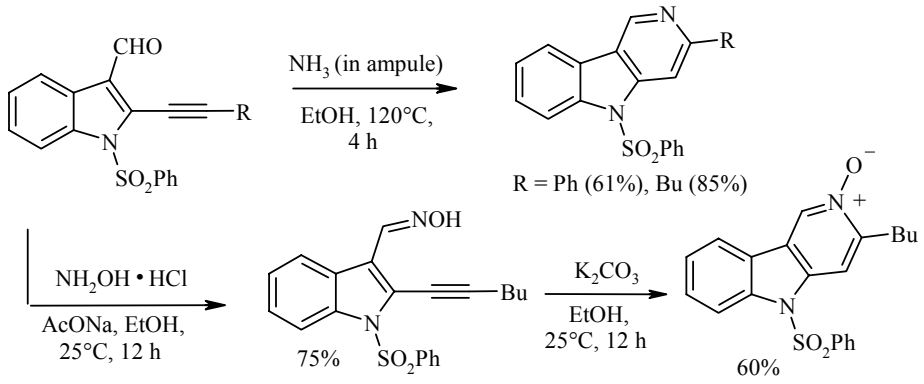


During the intramolecular electrocyclic (in the opinion of the authors) reaction of the oximes of various 2-ethynyl-3-formylindoles the N-oxides of the corresponding γ-carbolines, which can easily be reduced to the corresponding γ-carbolines, are formed. The addition of KOH or Cu(I) salts does not have a significant effect on the yield of the cyclization product [52].

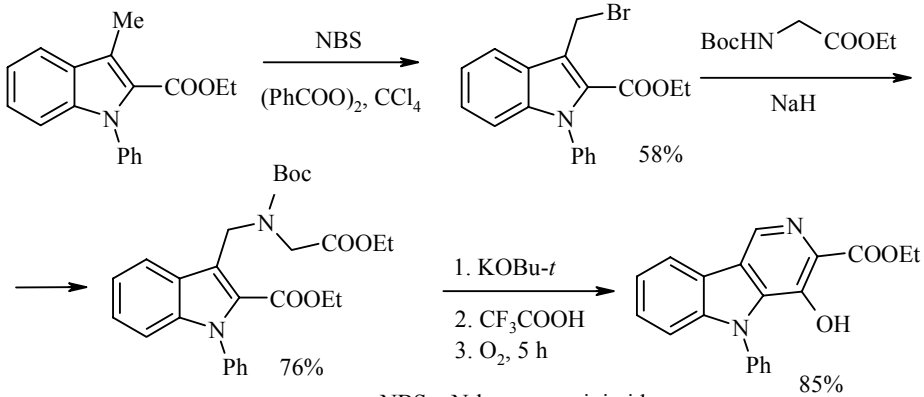


A similar synthesis scheme was put forward by Japanese authors [53] without reference to the previous work of Russian scientists [52], and they used the method to produce the N-oxides of both γ- and β-carbolines. The products from the condensation of the 2-ethynyl-3-formylindoles themselves with ammonia were γ-carbolines [53].



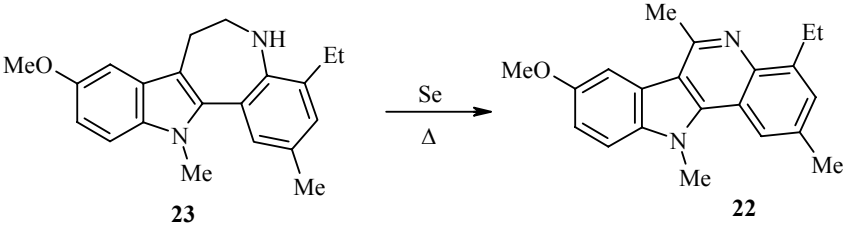


A derivative of 3-ethoxycarbonyl-4-hydroxy-γ-carboline can be obtained from 1-substituted 3-(bromoethyl)-2-ethoxycarbonylindole and N-Boc-glycine ethyl ester [54].



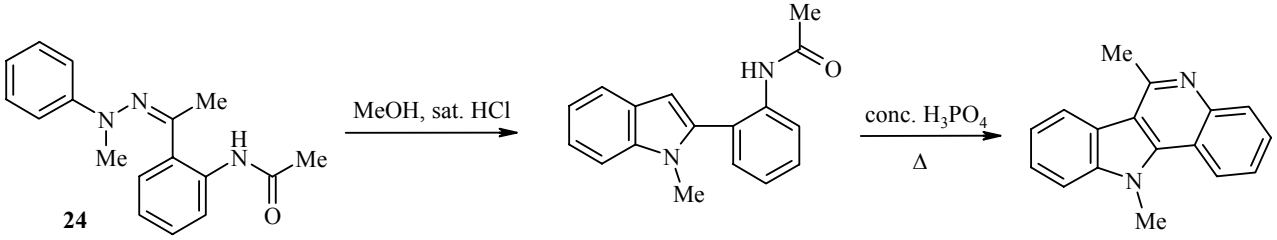
NBS – N-bromosuccinimide

Benzo-γ-carbolines are of particular interest (especially in the chemistry of alkaloids). In one of the first methods for the synthesis of benzo-γ-carboline **22** an original approach based on contraction of the seven-membered ring of compound **23** by heating in the presence of selenium was used [55].



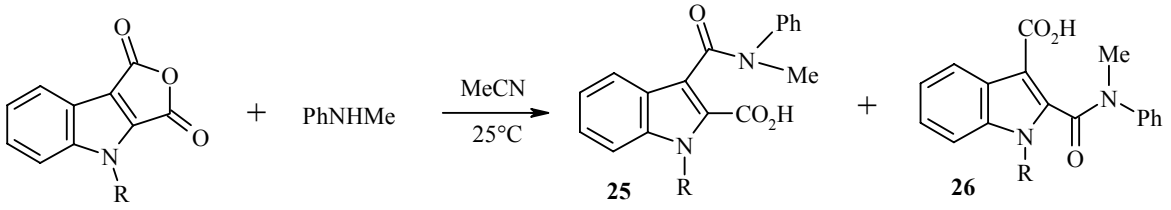
23 **22**

In most cases, however, classical methods of annelation of the isoquinoline fragment to indole are used to form the benzo[*c*]-γ-carboline structure. Thus, the initial formation of indole from the methylphenylhydrazone of *o*-acetamidoacetophenone (**24**) by the Fischer reaction creates the possibility of subsequent cyclization to 1,7-dimethylbenzo[*c*]-γ-carboline by the Bischler–Napieralski method [56].



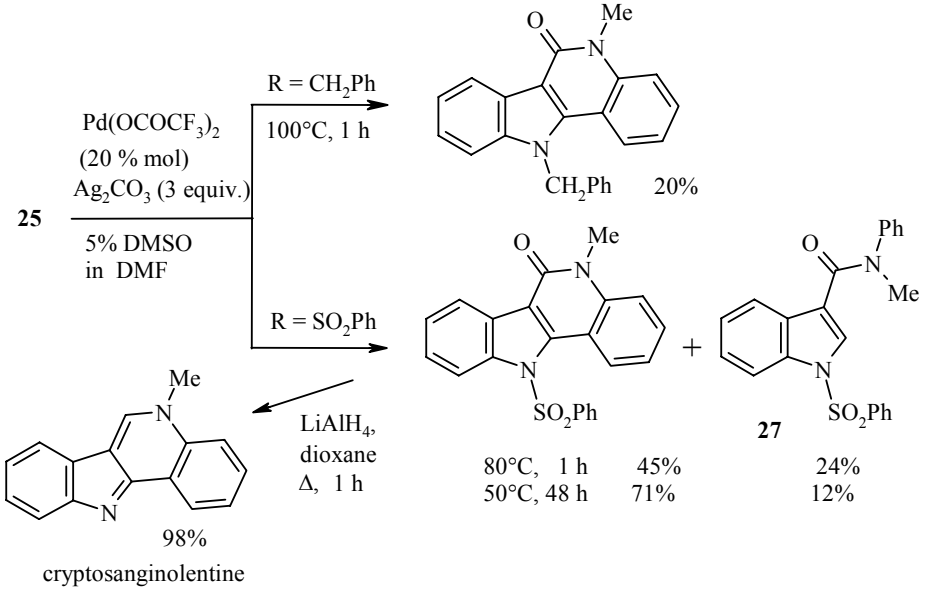
24

Not a simple task of synthesis of the alkaloid cryptosanginolentine, which belongs to the class of benzo[*c*]-γ-carbolines, was solved successfully by the authors of [57]. At the first stage the reaction of indole-2,3-dicarboxylic anhydride with N-methylaniline leads to the formation of derivatives of indole-2-carboxylic and indole-3-carboxylic acids **25** and **26**, and the formation of compound **25** is favored by conducting the reaction in acetonitrile.

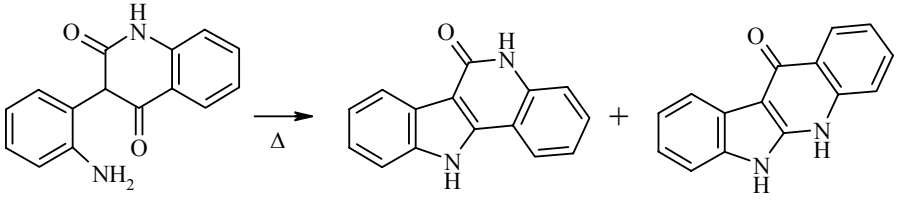


R = SO_2Ph, **25** (73%) , **26** (22%); R = CH_2Ph, **25** (78%), **26** (5%)

The cyclization of 1-benzenesulfonylindole-2-carboxylic acid **25** (R = SO_2Ph) in a reaction of the Heck type, catalyzed by a salt of Pd(II) and accompanied by decarboxylation, leads to the formation of a mixture of the derivative **27** and 11-benzenesulfonyl-5-methylindolo[3,2-*c*]quinolone, the reduction of which leads to the required cryptosanginolentine.

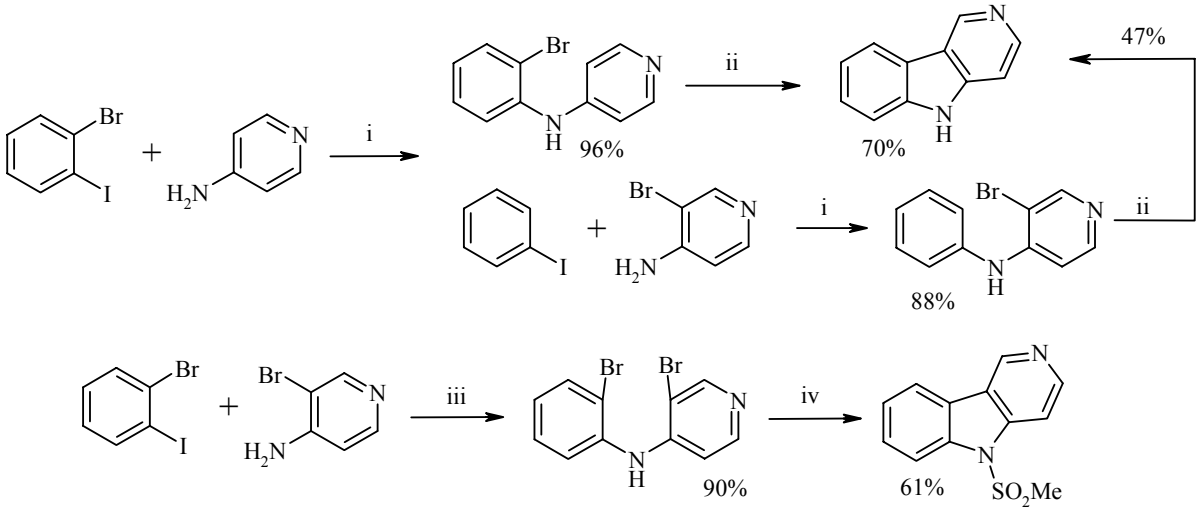


During the pyrolysis of 3-(2-aminophenyl)-2,3-dioxo-1,2,3,4-tetrahydroquinoline intramolecular cyclization, accompanied by the formation of a mixture of benzo-α- and benzo-γ-carboline derivatives, occurs [58].

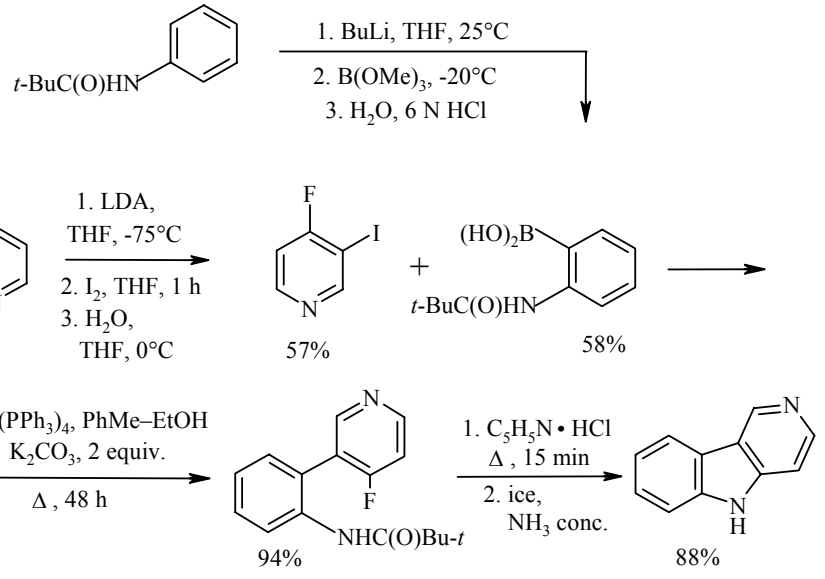


By using palladium-catalyzed transformations it is possible to construct the γ-carboline skeleton with the formation of both the pyrrole and the pyridine fragments. The pyrrole ring can be constructed in two ways. The first path involves the cyclization of an anilinopyridine derivative, whereas the second involves cyclization of a derivative of phenylpyridine having a nitrogen-containing substituent in the *ortho* position.

Production of the γ-carboline by the first method involves the combination of two palladium-catalyzed cross-coupling reactions: amination of iodobenzene with 4-aminopyridine and intramolecular arylation of the *o*-bromine-substituted phenylaminopyridine, and here the cross-coupling process with the formation of γ-carboline takes place most effectively for N-(2-bromophenyl)pyridine-4-amine [59]. It was also shown that cross coupling in the case of N-(2-bromophenyl)-3-bromopyridine-4-amine leads to the γ-carboline with a lower yield. The required *o*-bromine-substituted compound can also be obtained by the reaction of 4-halopyridine and a small excess of *o*-bromoaniline in the presence of palladium compounds.

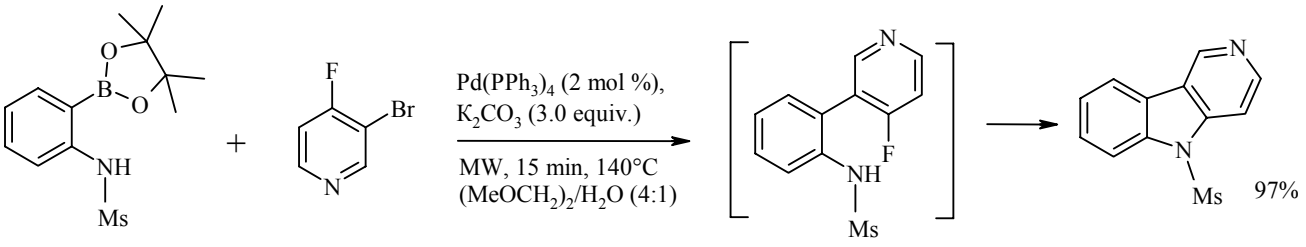


i – $Pd_2(dba)_3$, DPPF, *t*-BuONa, PhMe, 100°C; ii – $Pd(OAc)_2$, Na_2CO_3, DMF, Δ;
iii – NaH, MsCl, THF, ~20°C; iv – $PdCl_2(Ph_3P)_2$, $(Bu_3Sn)_2$, Li_2CO_3, $Et_4N^+I^-$, DMF, Δ
dba - dibenzylideneacetone, DPPF - 1,1'-bis(diphenylphosphino)ferrocene



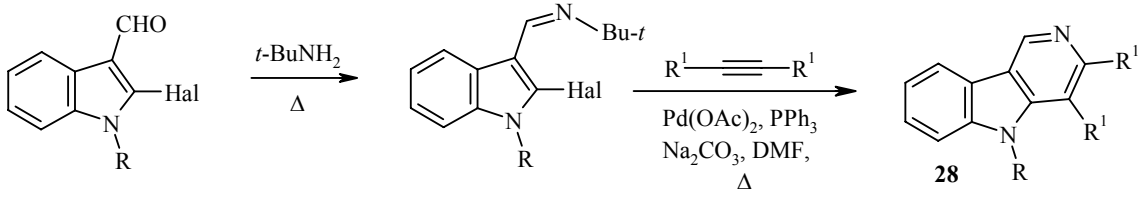
An example of the synthesis of γ-carboline with a high yield by the second method was presented in [60], where successive cross coupling of 4-fluoro-3-iodopyridine with *o*-aminophenylboric acid, catalyzed by palladium complexes, and intramolecular nucleophilic substitution of the fluorine by the amino group in the pyridine ring were used for this purpose.

A variant of such a scheme for the one-pot production of γ-carboline is found in tandem cross coupling according to Suzuki and aromatic nucleophilic substitution [61].



Ms = $MeSO_2$

The γ-carboline skeleton can also be constructed by means of the reaction of 3-formylindoleimines with disubstituted alkynes (Table 3) catalyzed by palladium complexes [62, 63]. The initial *tert*-butylimines entering into the Pd(0)-catalyzed cyclization with the formation of 3,4-disubstituted γ-carbolines are obtained by the reaction of 3-formyl-2-haloindoles with *tert*-butylamine.



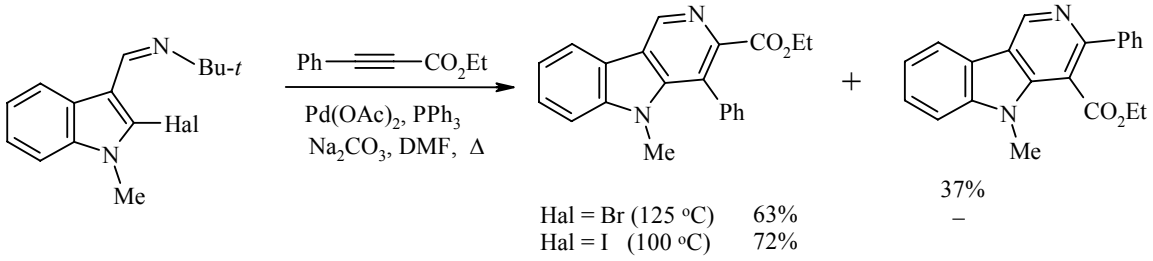
R = H, Me, CH_2OMe

Earlier it was reported that aryl halides and indoles readily enter into reaction in the presence of palladium with the formation of N-arylindoles [64]. Such a small yield (28%) of the 5H-carboline in the case of diphenylacetylene can therefore be explained by N-arylation of the initial indole by its second molecule. In order to avoid such a side process it is better to realize the annelation process with 1-substituted indoles.

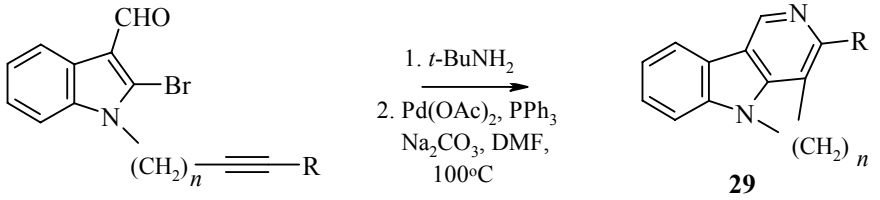
If ethyl 3-phenylpropyn-2-oate is used at 100°C only one regioisomer with the phenyl substituent at position 4 is formed, whereas both regioisomers are formed if the reaction temperature is increased to 125°C.

TABLE 3. The Yields of 5-Substituted Carbolines **28** and the Reaction Conditions

Reaction conditions					Yield, %
Hal	R	R^1	Reaction time, h	Temperature, °C	
I	H	Ph	—	100	28
I	Me	Pr	50	100	78
Br	Me	Ph	96	100	58
Br	Me	Ph	18	125	70
Br	Me	Pr	16	125	67
Br	Me	CH_2OH	20	125	65
Br	CH_2OMe	Ph	72	125	70

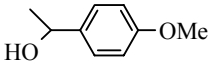
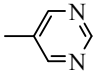


On the basis of their previous work the same team of authors proposed a method for the production of tetracyclic γ-carbolines **29** (Table 4) [65].

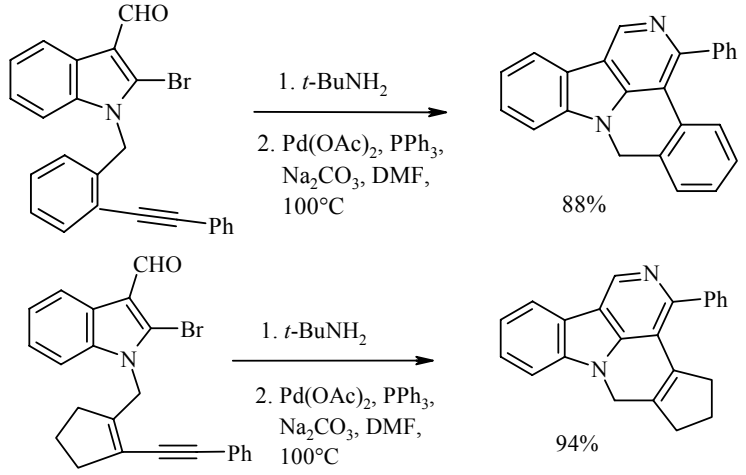


29

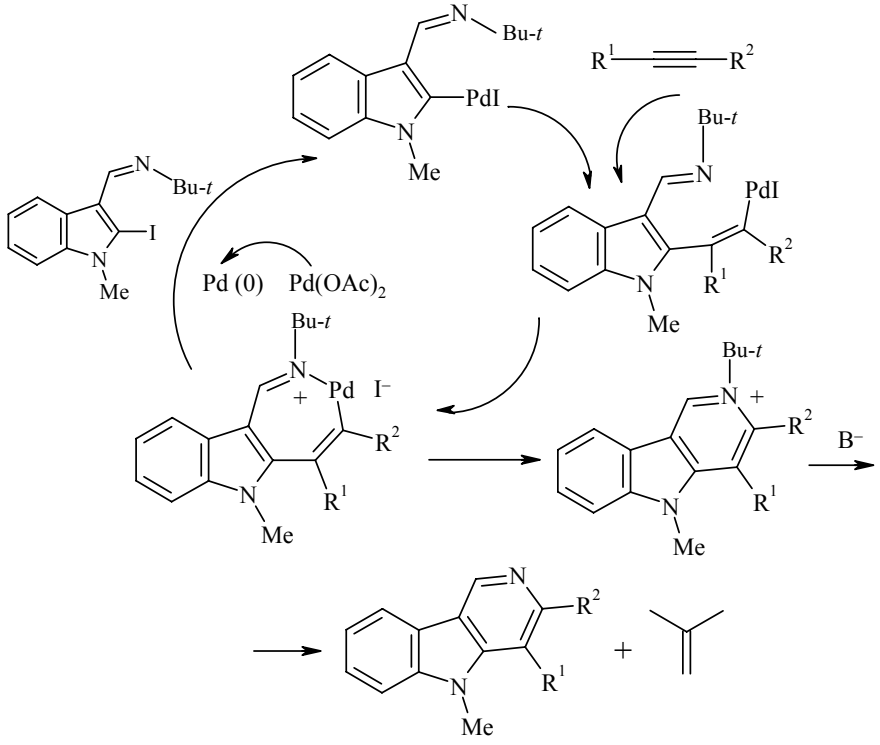
TABLE 4. Tetracyclic γ-Carbolines **29**

Compound		Reaction time, h	Yield, %
R	*n*		
Ph	3	10	93
c-Hex	3	24	95
	3	18	95
	3	40	99
Ph	4	10	90
c-Hex	2	12	91

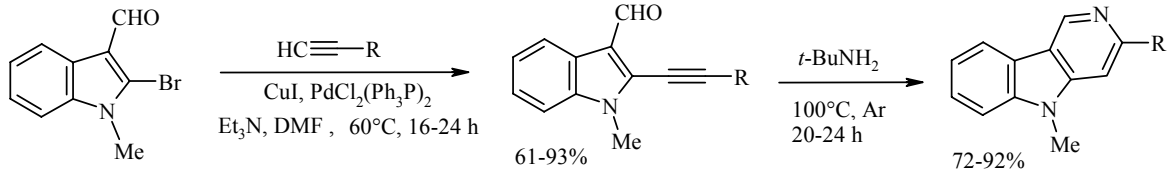
With a cyclic fragment containing an ethynyl substituent at the nitrogen atom of 2-bromo-3-formyl-indoles it becomes possible to synthesize the corresponding pentacyclic γ-carboline systems with high yields.



The following mechanism was proposed for the reaction of 3-formylindoles with alkynes catalyzed by palladium compounds [63].

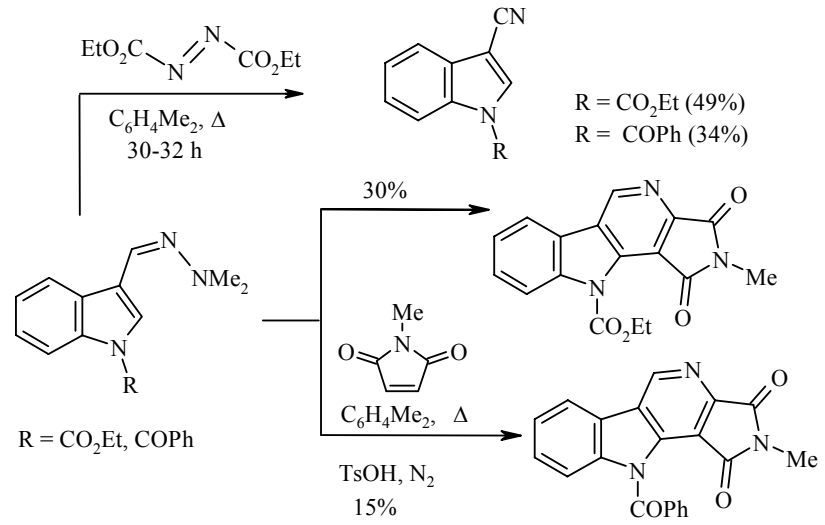


Terminal alkynes can also enter into such transformations, but it is necessary to use copper(I) besides palladium as catalyst [66]. The production of 3-substituted γ-carbolines is accompanied by successive palladium/copper-catalyzed cross-coupling of the 2-haloindole and terminal alkyne (according to a reaction of the Sonogashir type) and thermal cyclization of the obtained compound in the presence of *tert*-butylamine.

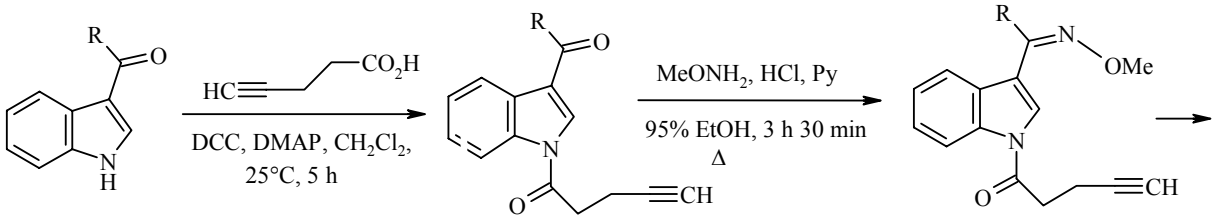


R = Ph, *n*-C_8H_{17}, $(CH_2)_9OH$, $(CH_2)_8CO_2Me$

The hetero-Diels–Alder reaction is a powerful tool for the creation of six-membered heterocycles [67]. Of the many dienes used in synthesis 1-azadienes constitute an important class of compounds, among which 1-aza-1,3-dienes with a C=C bond that is part of a heteroarene are of particular interest for the production of condensed heterocyclic systems [68, 69]. An example of such a structure is the N,N-dimethylhydrazone of 1-ethoxycarbonyl-3-formylindole, which readily enters into [4+4] cycloaddition with such a electron-deficient dienophile as N-methylmaleimide [70]. The formation of the γ-carboline is accompanied by the successive elimination of a dimethylamine molecule and dehydrogenation. The analogous transformation but with a smaller yield takes place for 1-benzoyl-3-formylindole N,N-dimethylhydrazone in the presence of catalytic amounts of *p*-toluenesulfonic acid [71]. It is interesting to note that the hetero Diels–Alder reaction does not occur if diethyl azodicarboxylate is used as electron-deficient dienophile, but 3-cyano-1-ethoxycarbonylindole is formed as a result of the elimination of a dimethylamine molecule from the initial compound participating in the reduction of the azodicarboxylate to N,N′-diethoxycarbonylhydrazine [70].

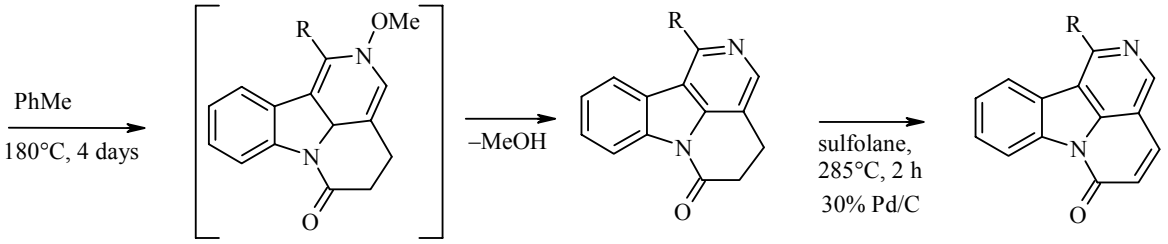


There are examples of the use of an intramolecular hetero-Diels–Alder reaction for the production of analogs of γ-carboline alkaloids **30** and **31** [72].



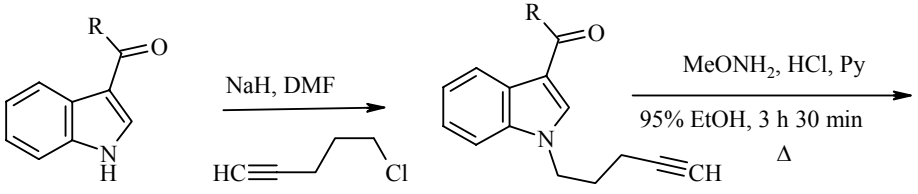
R = H (96%), R = Me (88%) R = H (94%), R = Me (96%)

DCC – dicyclohexylcarbodiimide, DMAP – 4-(dimethylamino)pyridine

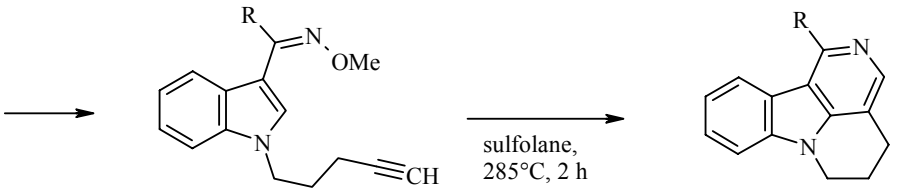


R = H (55%), R = Me (66%)

isocanthin-6-one (**30**, R = H, 86%)
1-methylcanthin-6-one (R = Me, 78%)



R = H (100%), R = Me (75%)



R = H (98%), R = Me (76%)

isocanthine (**31**, R = H, 8%)
1-methylcanthine (R = Me, 0%)

Such low yields for the isocanthine (**31**) and its 1-methyl-substituted analog are explained by the absence of the acyl fragment at the indole nitrogen atom. The presence of the planar amide π-system leads to a better orientation of the ethynyl fragment in relation to the 1-aza-1,3-diene system of the indole ring, and this favors the successful realization of cycloaddition. In addition, the amide fragment facilitates the cyclization process on account of delocalization of the electron pair of the indole nitrogen atom, and this favors retention of the 1-aza-1,3-diene structure [72].

The γ-carboline system can be created on the basis of a Diels–Alder reaction with reversed electron demands during the reaction of indoles with 1,2,4-triazines, which can take place in several directions [73]. If path **A** is realized the γ-carboline derivative **32** and the 2,3-disubstituted 6H-benzo[*f*][1,7]naphthiridin-5-one **33** (the product of rearrangement in the case where there is an ester group at the C-3 atom of 1,2,4-triazine) are formed. Path **B** is characterized by the formation of the adduct **34** as a result of nucleophilic addition of the indole fragment at the C-5 atom of the triazine ring, while in the case of path **C** cycloaddition with the formation of the β-carboline derivative **35** isomeric with compound **32** occurs.

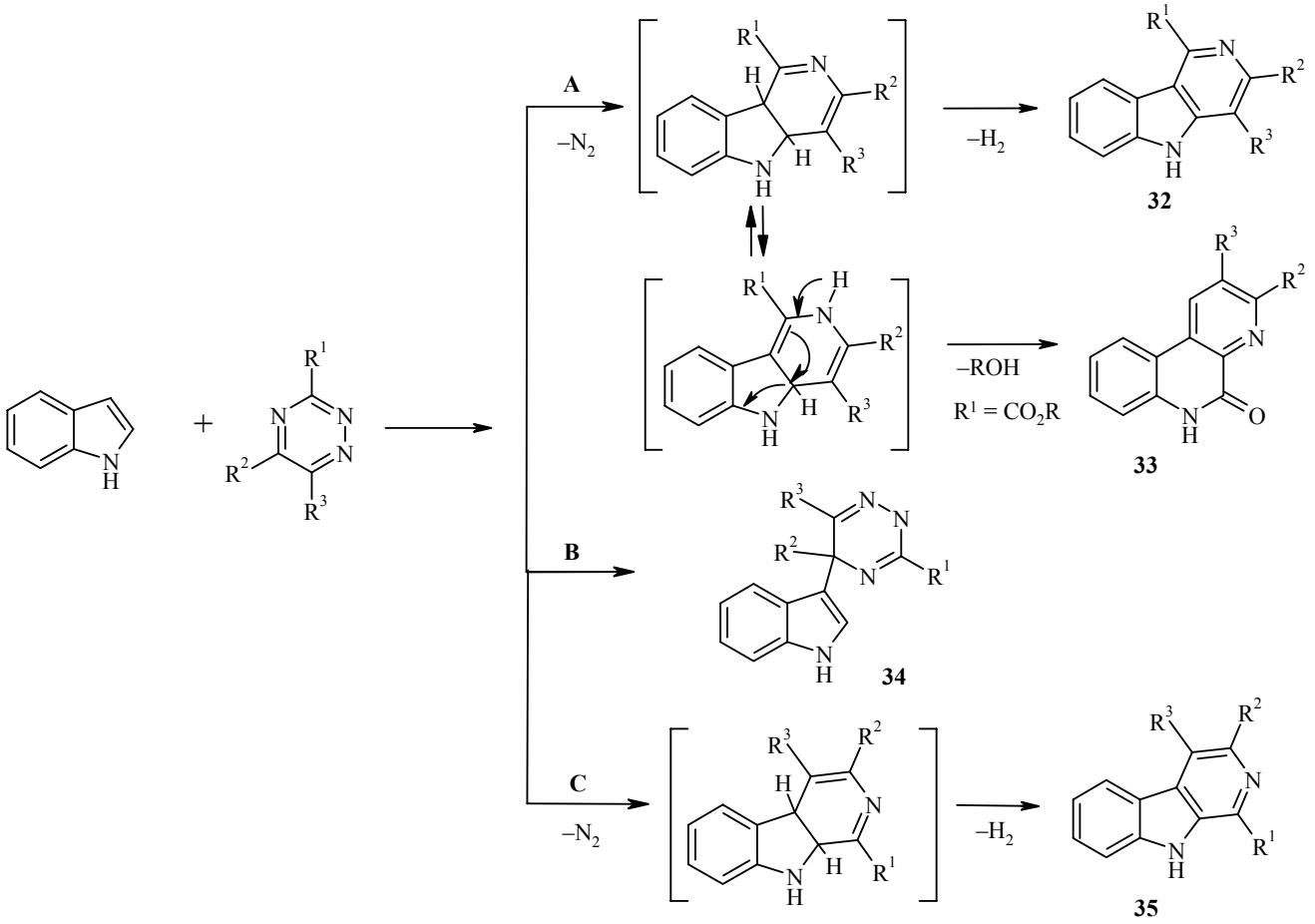


TABLE 5. Reaction of Various Indoles with 3-Ethoxycarbonyl-5,6-dimethoxycarbonyl-1,2,4-triazine*

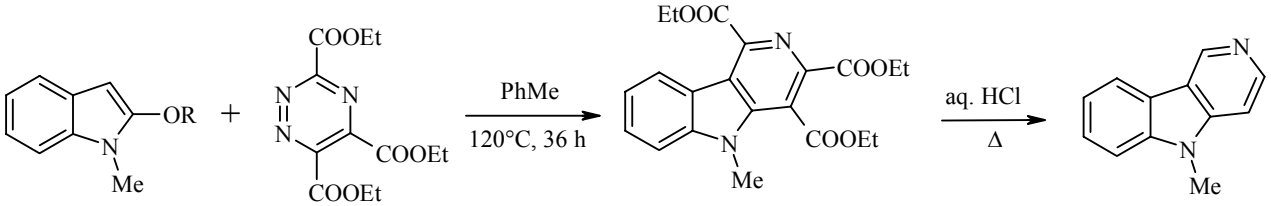
Reaction conditions				Yield of reaction products, %	
Indole	Solvent	Temperature, °C	Time, h	**32**	**33**
Indole	Diglyme	120	16	89	6
3-Acetoxyindole	Dioxane	80	16–20	—	—
	—	120	18	15	—
5-Methoxyindole	Dioxane	80	19	72	20
1-Methylindole	Dioxane	80	19	42	49

*The reaction was carried out in an atmosphere of Ar using 1.8 equiv. of 1,2,4-triazine.

It was shown that the direction of the reaction and the ratio of the reaction products depend both on the substituents in the 1,2,4-triazine ring and on the conditions. The γ-carboline skeleton is formed when the 1,2,4-triazine-3,5,6-tricarboxylates are used, and the largest yield of the γ-carboline **32** here is obtained at a moderate temperature (80-120°C) with the use of 1.8 equiv. of the 1,2,4-triazine, which acts simultaneously as dehydrogenating agent. Under harsher conditions 6H-benzo[*f*][1,7]naphthiridinone **33** is mostly formed. As a rule cycloaddition with other 1,2,4-triazines goes along several paths and leads to a complex mixture of products [73].

The presence of substituents in the indole system also has a significant effect on its reactivity and, consequently on the yield of the γ-carboline and the ratio of the reaction products **32** and **33** (Table 5). This can be explained by an increase in the energy level of the HOMO of the dienophile during the introduction of electron-donating groups into the aromatic skeleton of indole.

The use of 2-alkoxy-1-alkylindoles as dienophile in the reaction with 3,5,6-triethoxycarbonyl-1,2,4-triazine leads to 1,3,4-triethoxycarbonyl-γ-carbolines, from which 5-alkyl-substituted γ-carbolines can be obtained [74].



R = Me (74%), Et (74%)

Apart from the methods described above the Fischer method is widely used for the construction of indole structures. This method is usually employed for the production of 1,2,3,4-tetrahydro-γ-carbolines based on the arylhydrazones of N-substituted 4-piperidones, but there is an example of the use of the reaction for a single-stage synthesis of an aromatic γ-carboline both under thermal conditions and by the action of microwave radiation [75]. Such a transformation became possible on account of the presence in the initial N-acetyl-3-bromo-4-piperidone of two fragments (acetyl and a bromine atom) that are eliminated during cyclization in the form of acetic acid and hydrogen bromide.

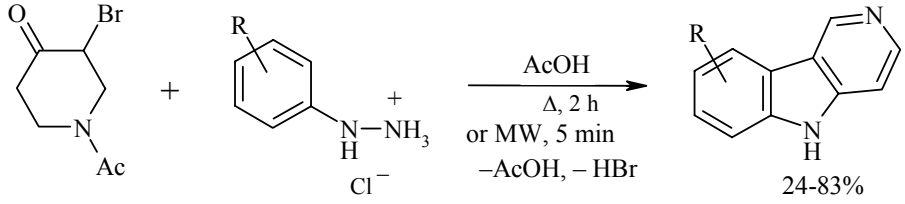
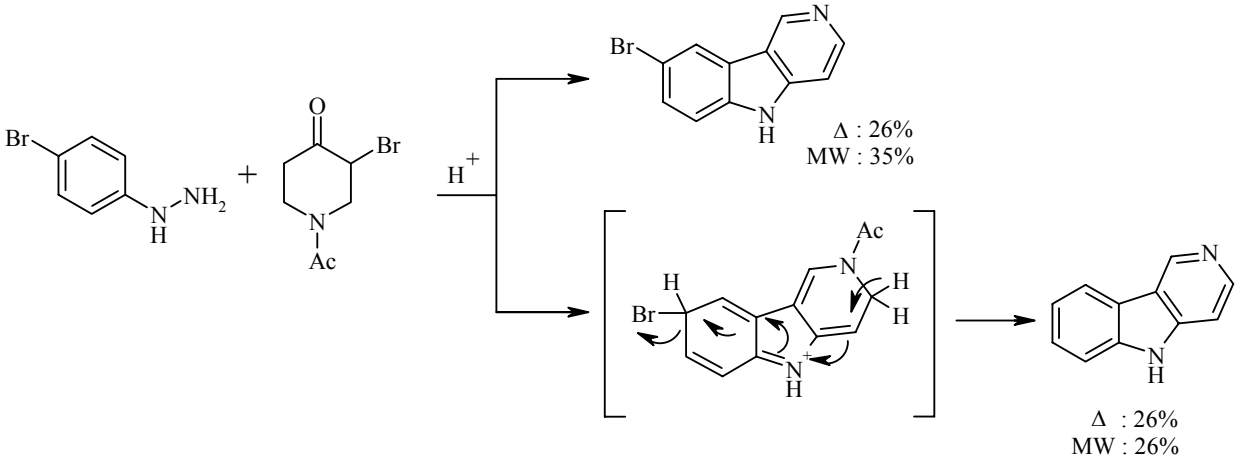


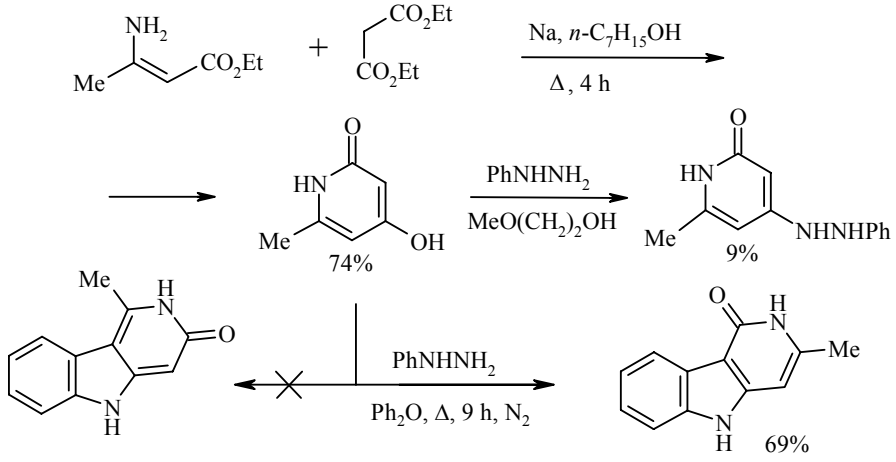
TABLE 6. The Yields of γ-Carbolines under Various Reaction Conditions

R (hydrazine)	R (γ-carboline)	Yield, %	
		Δ	MW
H	H	71	83
4-MeO	8-MeO	49	54
4-Me	8-Me	50	59
4-F	8-F	60	76
4-Cl	8-Cl	31	54
2-MeO	6-MeO	20	24
2-Me	6-Me	38	59

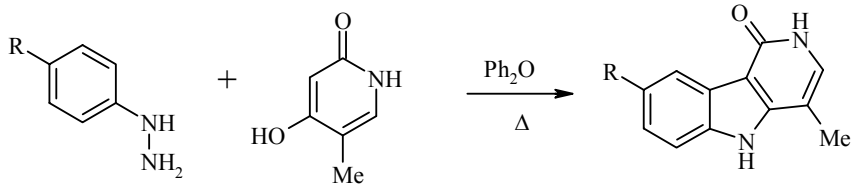
In the case of 4-bromophenylhydrazine the Fischer reaction results in the formation of a mixture of 6-bromo-γ-carboline and the γ-carboline resulting from elimination of the halogen atom.



3-Methyl-1-oxo-1,2-dihydro-γ-carboline was also obtained by the Fischer method from 2,4-dihydroxy-6-methylpyridine and phenylhydrazine [76]. The individual oxo-γ-carboline regioisomer is formed as a result of the reaction.

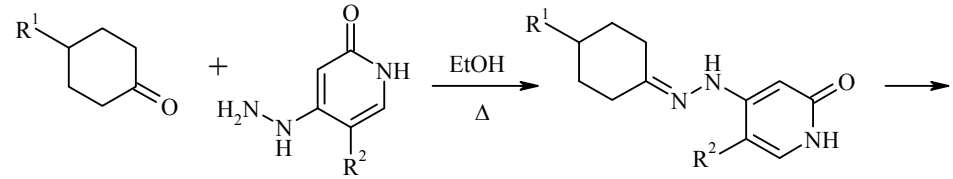


The use of 4-hydroxy- [77] and 4-hydroxy-5-methyl-1H-pyrid-2-ones [78, 79] under the thermal conditions of the Fischer reaction leads to the corresponding 1-oxo- and 4-methyl-1-oxo-γ-carboline derivatives.

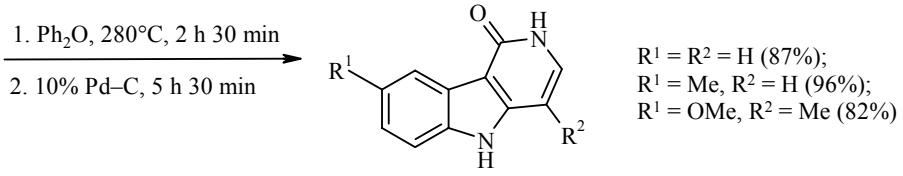


R = H (88%), OMe (17%)

1-Oxo-γ-carboline structures can also be obtained by the Fischer reaction from 4-hydrazino-1H-pyrid-2-ones and substituted cyclohexanones with subsequent aromatization [80, 81].

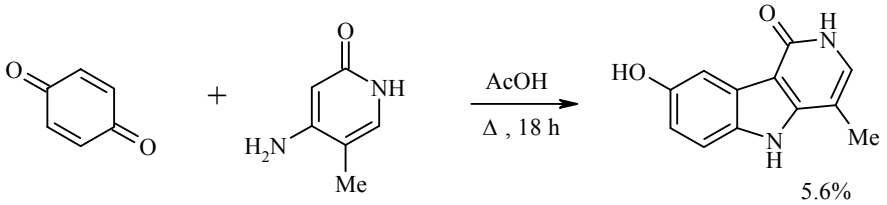


$R^1 = R^2 = H$ (80%); R^1 = Me, R^2 = H (66%);
R^1 = OMe, R^2 = Me (86%)



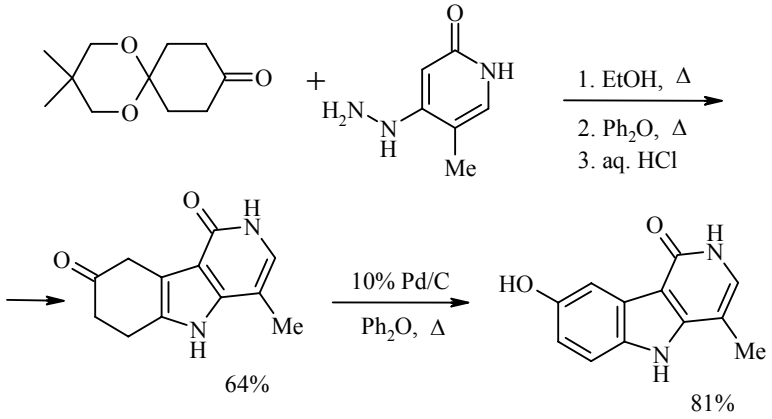
$R^1 = R^2 = H$ (87%);
R^1 = Me, R^2 = H (96%);
R^1 = OMe, R^2 = Me (82%)

8-Hydroxy-1-oxo-γ-carboline derivatives can be obtained in the Nenitzescu reaction, but the yield is small (~6%) [79].



5.6%

For the production of 8-hydroxy-γ-carboline derivatives it is much more efficient to use the scheme presented above with 3,3-dimethyl-1,5-dioxaspiro[5,5]undecan-9-one as carbonyl component [79, 80].

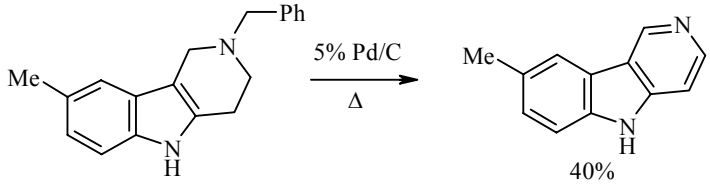


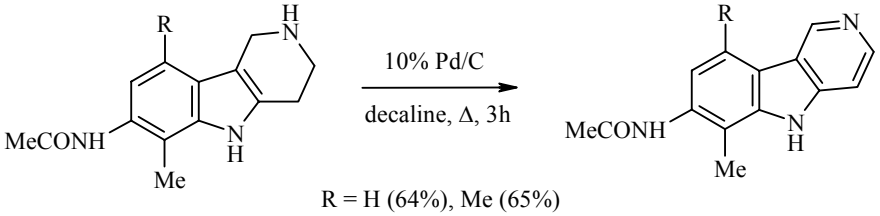
64%

81%

One of the most widely used methods for the production of γ-carbolines is aromatization of their hydrogenated analogs such as 1,2,3,4-tetrahydro-γ-carbolines and also reduction of the corresponding oxo-γ-carbolines accompanied by the elimination of a water molecule.

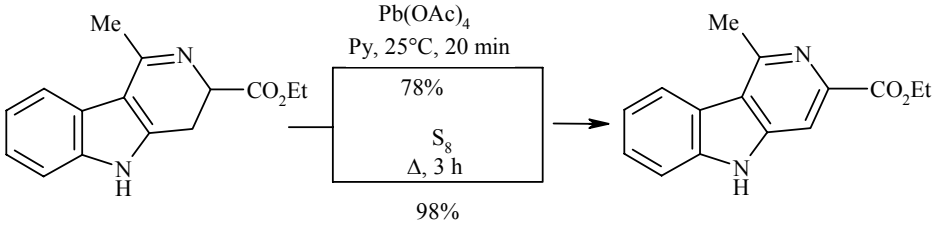
Aromatization is most often realized by heating the respective γ-carboline derivative over metallic palladium [82, 83]. Thus, 8-methyl-γ-carboline was first obtained from 2-benzyl-8-methyl-1,2,3,4-tetrahydro-γ-carboline by joint dehydrogenation and debenzylation.



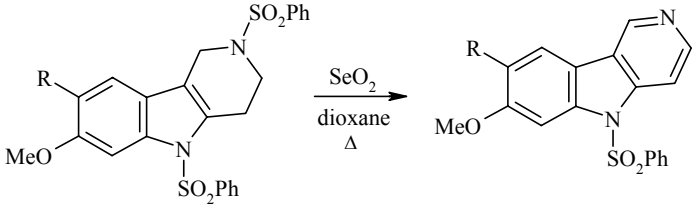


R = H (64%), Me (65%)

Another example is aromatization with lead tetraacetate or elemental sulfur [36].

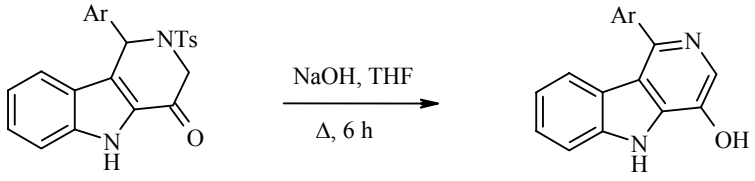


Dehydrogenation can also be realized with selenium(IV) oxide [84].

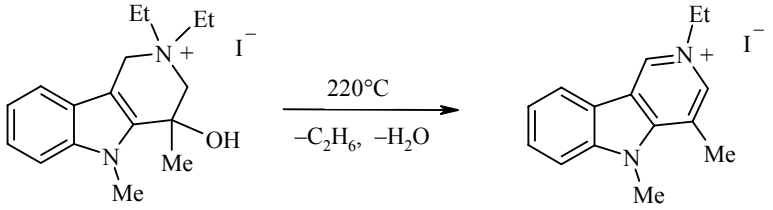


R = H (90%), Me (84%)

When 1-aryl-4-oxo-2-tosyl-1,2,3,4-tetrahydro-γ-carboline is boiled with alkali aromatization leading to the formation of 1-aryl-4-hydroxy-γ-carboline occurs [85].

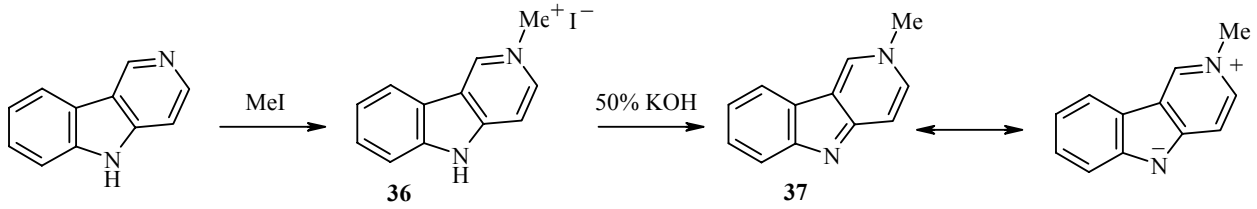


The thermolysis of tetrahydro-γ-carboline salts sometimes leads to aromatic γ-carboline derivatives [86].

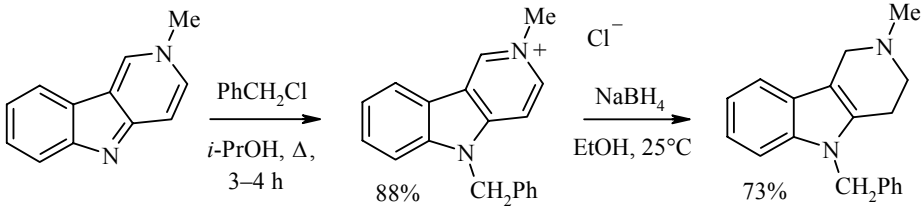


The Chemical Properties of γ-Carbolines

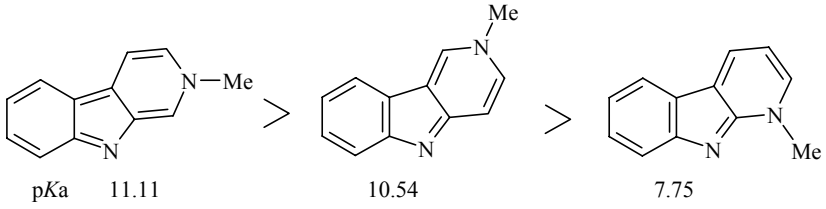
The γ-carboline cyclic system has clearly defined aromatic character and is extremely stable; unsubstituted γ-carboline is stable during distillation over zinc dust in a stream of hydrogen. On account of the presence of the pyridine nitrogen carbolines have basic characteristics and behave as monobases giving easily isolated salts with mineral acids. With methyl iodide and dimethyl sulfate they form quaternary salts **36** [1], which can be converted into the anhydro bases **37** by the action of a large excess of a hot concentrated solution of potassium hydroxide [5].



2-Methyl-γ-isocarboline (the anhydro base **37**) can be present in two resonance forms and exhibits basic characteristics; it dissolves in water, and the solution has an alkaline reaction. The action of alkylating agents on the anhydro bases gives 5-alkyl-γ-carbolinium quaternary salts, which can be reduced to tetrahydro-γ-carbolines [9, 42, 87].

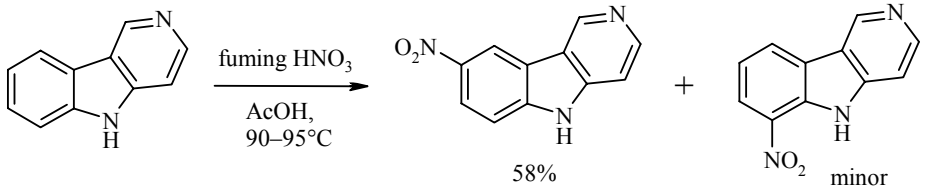


An interesting investigation into the comparative basicity of α-, β-, and γ-carboline anhydro bases was published by Gray [88]. The pK_a values for the anhydro bases of 1-methyl-α-carboline, 2-methyl-β-carboline, and 2-methyl-γ-carboline, determined by potentiometric titration in 60% ethanol at 25°C, amounted to 7.75, 11.11, and 10.54.

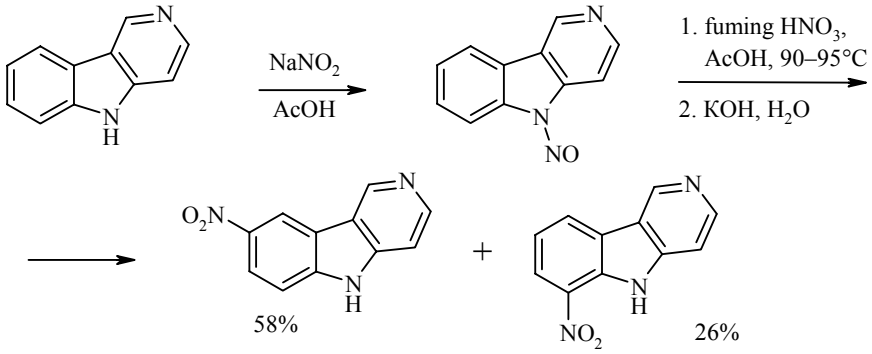


The increased basicity of the β-derivative can be attributed to the lower stabilization energy of the β-carboline anhydro base. During examination of the resonance structures of the anhydro bases it is seen that the aromaticity of the benzene ring is destroyed in the β-derivative, indicating a higher energy for the structure. As a consequence the formation of the β-anhydro base will be less favorable energetically.

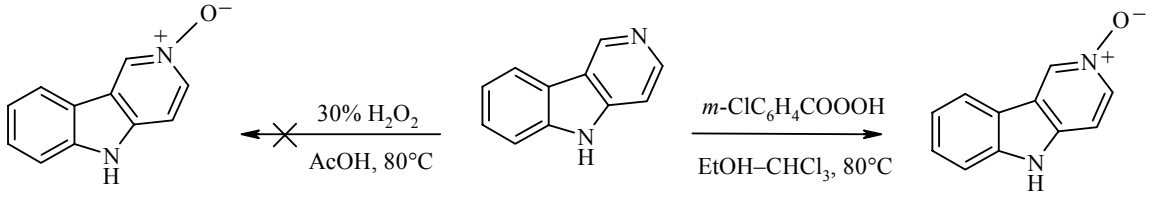
Like their reduced analogs, the γ-carbolines enter into electrophilic substitution in the benzene ring mostly at position 8 and also at position 6, but such reactions have been used extremely rarely for preparative purposes. Thus, the nitration of γ-carboline with fuming nitric acid gives a moderate yield of 8-nitro-γ-carboline with 6-nitro-γ-carboline as impurity [89].



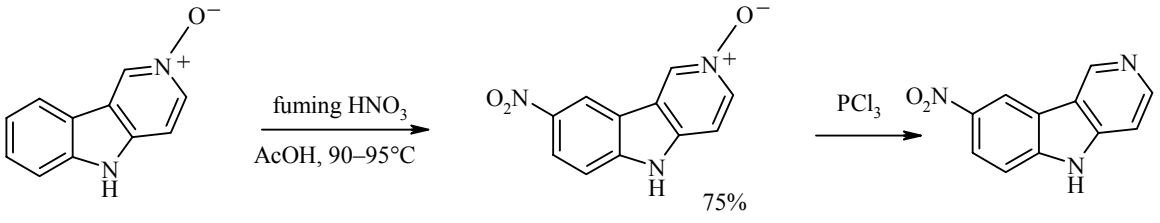
By nitrating 5-nitroso-γ-carboline it is possible to increase the content of the 6-nitro derivative substantially; this method was initially used for the nitration of carbazoles [90].



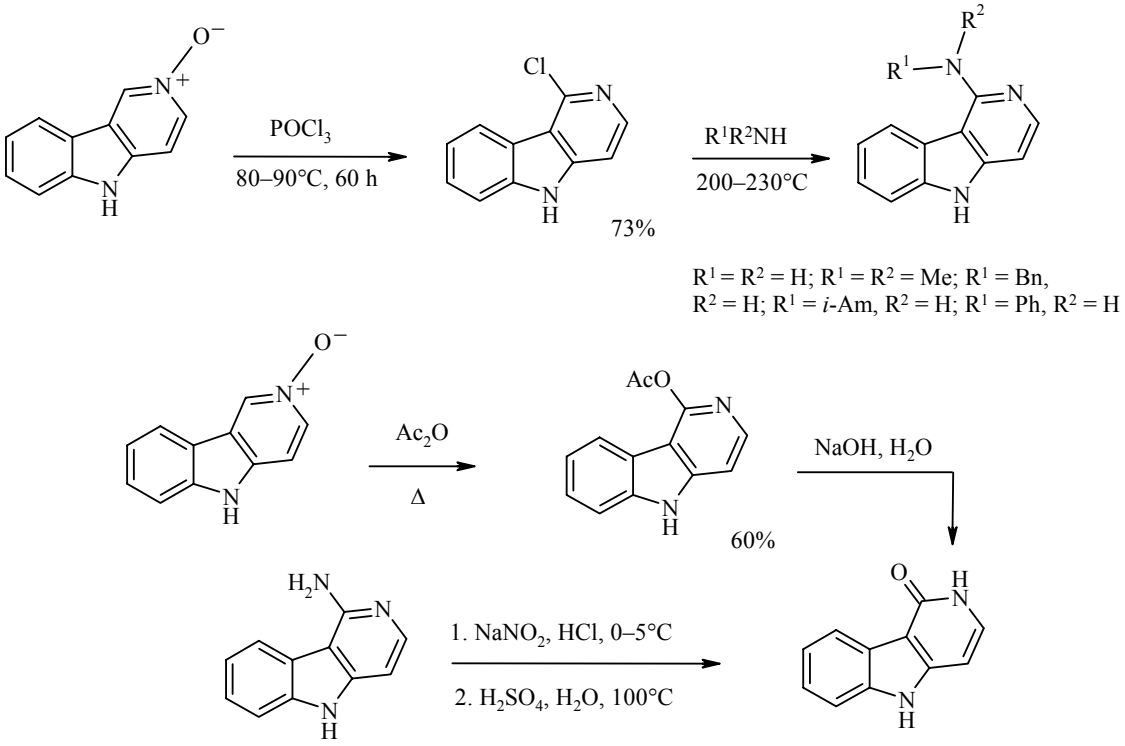
γ-Carbolines can be oxidized to 2-oxides by the action of *m*-chloroperbenzoic acid; the formation of the corresponding N-oxide was not observed [89] in the case of 30% aqueous hydrogen peroxide in acetic acid at 80°C, but with this oxidizing agent at 95°C 5-methyl-8-nitro-γ-carboline N-oxide was obtained with a yield of 85% [41].



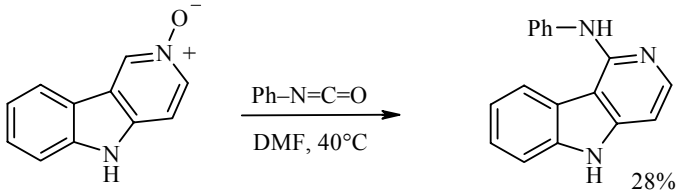
8-Nitro-γ-carboline is mostly formed during the nitration of γ-carboline 2-oxide [89].



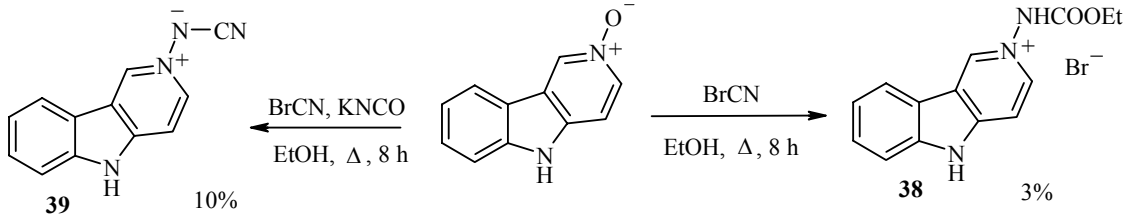
Heating of γ-carboline 2-oxide with phosphorus oxychloride at 80-90°C leads to the formation of 1-chloro-γ-carboline, the chlorine in which can be substituted by a primary, secondary, or tertiary amino group. Boiling the N-oxide in acetic anhydride leads to 1-acetoxy-γ-carboline, the hydrolysis of which gives 1-hydroxy-γ-carboline [83, 89].



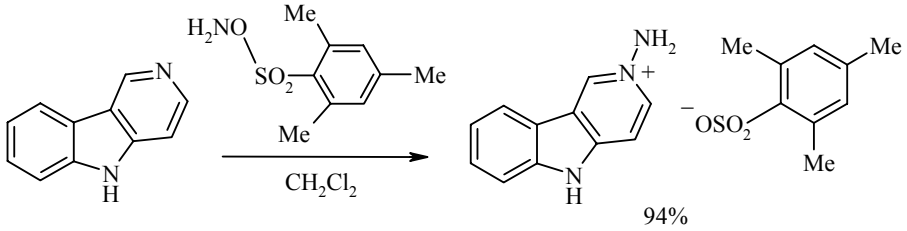
The reaction of γ-carboline 2-oxide with phenyl isocyanate at 40°C only leads to the formation of 1-phenylamino-γ-carboline; the process presumably takes place as 1,3-addition of the isocyanate to the N-oxide [91].



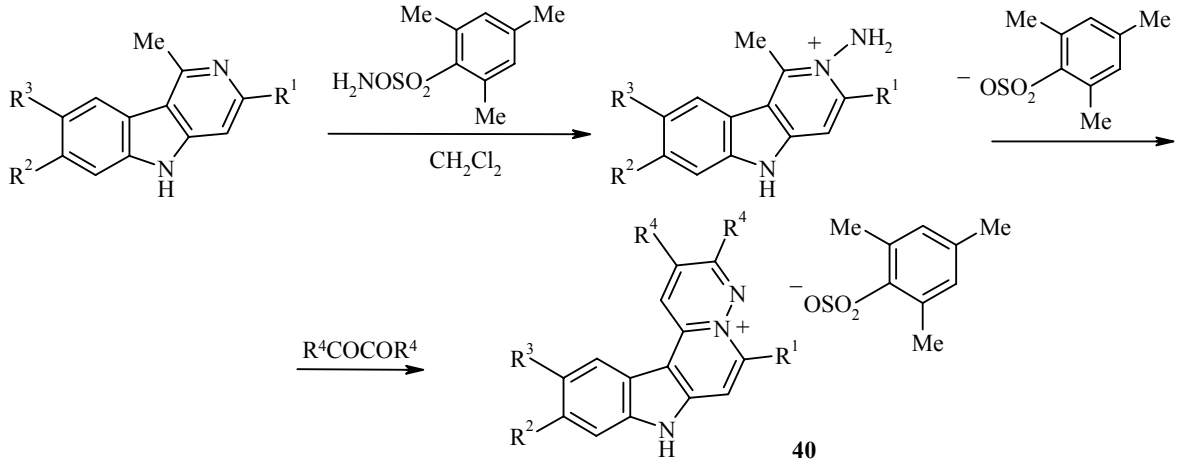
When γ-carboline N-oxide is boiled with cyanobromide in ethanol a small yield (3%) of 2-(ethoxy-carbonylamino)-γ-carbolinium bromide (**38**) is obtained (15% of the γ-carboline and 15% of the N-oxide). If the reaction is carried out with the addition of potassium isocyanate the 2-(cyanoaminato)-γ-carbolinium (**39**) is formed [89].



The amination of γ-carboline with O-(mesitylenesulfonyl)hydroxylamine leads to the formation of 2-amino-γ-carbolinium mesitylenesulfonate.

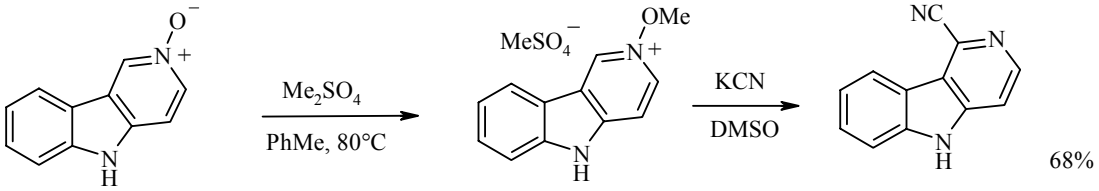


2-Amino-1-methyl-γ-carbolinium salts are capable of entering into condensation with 1,2-dicarbonyl compounds (the Westphal reaction) with the formation of compounds **40** [92].

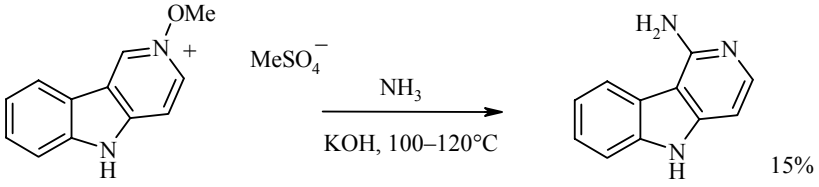


$R^1 = R^2 = R^3 = H$, $R^4 = Me$ (75%); $R^1 = R^4 = Me$, $R^2 = R^3 = H$ (63%);
$R^1 = R^2 = R^3 = H$, $R^4 = Et$ (82%); $R^1 = Me$, $R^2 = R^3 = H$, $R^4 = Et$ (76%);
$R^1 = R^2 = R^3 = Me$, $R^4 = Et$ (72%)

γ-Carboline 2-oxide can be converted by the action of dimethyl sulfate into 2-methoxy-γ-carbolinium methyl sulfate, the addition of potassium cyanide to which leads to the formation of 1-cyano-γ-carboline (68%). When the reaction is carried out in dioxane γ-carboline (30%) and the 1-cyano derivative (32%) are formed [89].

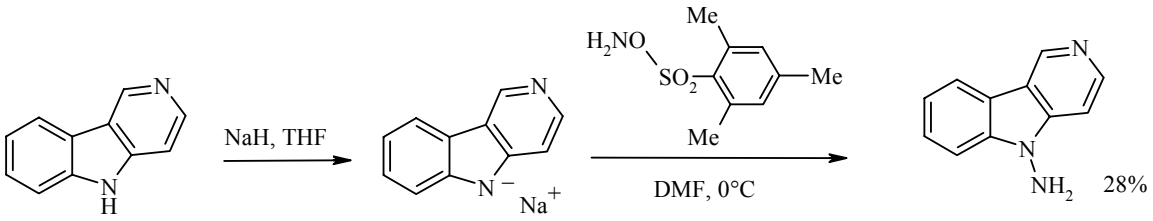


During treatment with ammonia 2-methoxy-γ-carbolinium salts are converted into 1-amino-γ-carbolines, and the formation of 3-amino-γ-carbolines even in trace amounts is not observed [89].

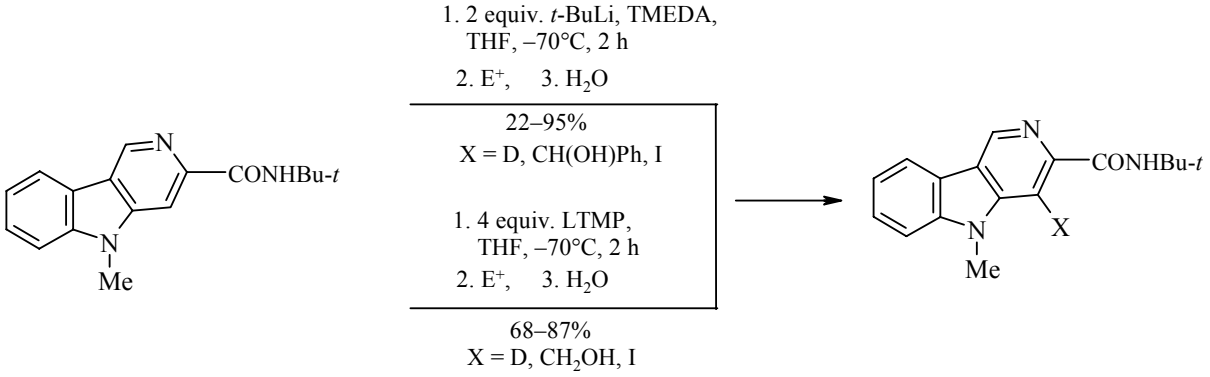


The introduction of an amino group into the γ-carboline skeleton through an N-alkoxy-γ-carbolinium salt is extremely unusual since such transformations have previously only been found in the N-alkoxy derivatives of α-carbolines [93].

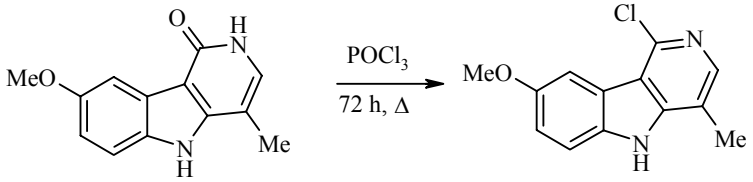
γ-Carboline is a weak NH acid the anion of which adds at an activated multiple bond (the Michael reaction) [94], and it is also alkylated and acylated by the appropriate reagents [8, 95, 96]. During the treatment of the γ-carboline anion with O-(mesitylenesulfonyl)hydroxylamine 5-amino-γ-carboline is formed [89].



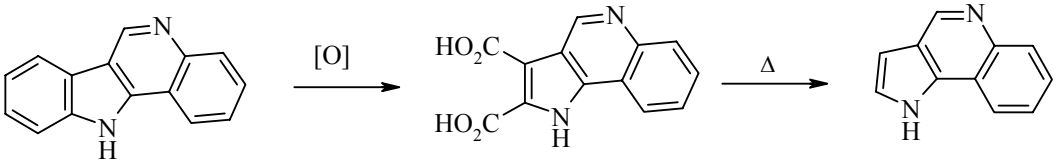
By the metallation of secondary γ-carbolinecarboxamides, realized at position 4 by the action of *t*-BuLi, it is possible to insert various electrophiles at this position. Similar behavior is observed for tertiary amines, but metallation here is achieved by the action of lithium 2,2,6,6-tetramethylpiperidide (LTMP) [97].



Various 2H,5H-pyrido[4,3-*b*]indol-1-ones can be easily transformed into 1-chloro-5H-pyrido[4,3-*b*]indoles by the action of phosphorus oxychloride [41, 98].



The oxidation of γ-carboline and its derivatives is accompanied by destruction of the benzene ring with the formation of a dicarboxylic acid, which on heating undergoes decarboxylation [99].



The Biological Properties of γ-Carbolines

The interest of both chemists and biologists in the various derivatives of carbolines was aroused a long time ago [100]. γ-Carbolines were no exception. Compounds of this group have mainly attracted interest in connection with their ability to inhibit the activity of monoamine oxidase (MAO) and to influence the effects caused by such important neurotransmitters as histamine and serotonin [12].

Such derivatives of aromatic γ-carboline as 3-amino-1,4-dimethyl-5H-pyrido[4,3-*b*]indole (Trp-P-1, **21**) and 3-amino-1-methyl-5H-pyrido[4,3-*b*]indole (Trp-P-2, **20**) are present in fried foods and tobacco smoke and exhibit carcinogenic characteristics, inhibiting the enzyme DNA topoisomerase that participates in the replication of DNA [8, 101] and also give rise to neuroblast apoptosis in humans [102]. γ-Carboline N-oxide **20** is widely used as a source of active oxygen in the study of mutagenesis and in the search for effective antioxidants [103]. Compounds **40** with a nodal quaternary nitrogen atom, produced by the condensation of 2-amino-1-methyl-γ-carbolinium salts with 1,2-dicarbonyl compounds (see above), exhibit the properties of DNA intercalators and can be used in anticancer therapy [104].

It should be noted that replacement of the pyrrole ring of the γ-carboline system by benzene, leading to a benzo[*h*]isoquinoline structure, gives rise to a marked decrease in the cytotoxicity and anticancer activity [104].

1-Alkylamino-8-hydroxy-γ-carbolines exhibit anticancer activity toward proliferating tumor cells in leukemia and also in melanoma, reticulosarcoma, adenocarcinoma, and their metastases [78]. Likewise 1-amino-γ-carboline derivatives can exhibit the characteristics of subtype II receptors of urotensin, which is involved in the etiology of a series of cardiorenal diseases and metabolic disorders, including arterial hypertension, heart failure and impaired renal function, atherosclerosis, and diabetes [77].

Functionalized derivatives of 4-hydroxy-5-phenyl-γ-carboline-3-carboxylic acid are capable of modulating the stability and activity of the hypoxia-induced factor (HIF), which has a cytoprotecting effect during hypoxia and ischemia, increasing the erythropoiesis and adapting the cell or organ physiology to the hypoxic state [54].

Aromatic 1-amino- and 1-hydroxy-γ-carbolines can exhibit inhibiting activity with respect to kinases and can be used for the treatment of myeloproliferative diseases and cancer [105]. Functionalized γ-carbolines can also have an inhibiting effect on cGMP phosphodiesterase, which would make it possible to use these compounds for the treatment of hypertonia, ischemic heart disease, erectile dysfunction (impotence), sexual dysfunction in women, and a series of other disorders [106].

Derivatives of aromatic γ-carbolines are capable of exhibiting antimicrobial activity as, for example, in isocanthin-6-one (**30**) and isocanthine (**31**) [72]. In addition, 5-methyl-γ-carboline has antiviral properties toward bovine diarrhea virus (EC_{50} = 0.26 μmol/liter), the related human hepatitis C virus, and yellow fever virus, while possessing comparatively low cytotoxicity [107]. The similarity of the bovine diarrhea and human hepatitis C viruses makes it possible to hope that promising agents for the prophylaxis and effective therapy of viral hepatitis C may be found among the derivatives of aromatic γ-carbolines.

There are also data [108] indicating that derivatives of γ-carboline-3-carboxylic acid exhibit the properties of benzodiazepine receptor inverse agonists. It is important to mention that the inverse agonists of benzodiazepine receptors not having proconvulsant/convulsant activity may stimulate cognitive powers [109].

Thus, in chemical and pharmaceutical respects aromatic γ-carbolines represent an interesting and challenging class of annelated derivatives of indole.

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