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CHEMISTRY OF INDOLOPYRIDINES WITH A BRIDGEHEAD HETEROATOM. (REVIEW)

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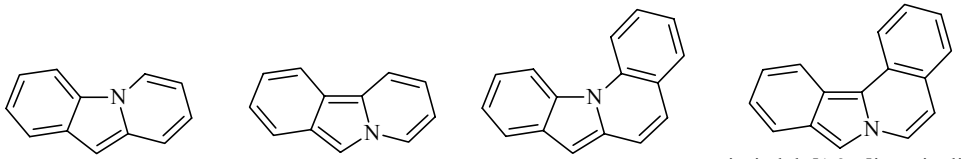
Published data on the synthesis and reactions of indolopyridines with one bridgehead heteroatom and their benzannelated derivatives are reviewed for the first time.

Keywords: indolo[1,2-*a*]pyridines, isoindolo[2,1-*a*]pyridines, indolo[1,2-*a*]quinolines, isoindolo[1,2-*a*]-isoquinolines, indolo[1,2-*b*]isoquinolines, isoindolo[2,1-*b*]isoquinolines, indolo[2,1-*a*]isoquinolines, isoindolo[2,1-*a*]quinolines.

The review literature on the chemistry of indole, pyridine, and their benzo derivatives is extremely comprehensive. At the same time aspects of the synthesis and reactivity of indolopyridines and indoloquinolines (or benzoindolizines) – a group of compounds in which the indole ring is condensed with a pyridine ring in such a way that the nitrogen atom is common (bridgehead) for these rings – have not received sufficient attention. Only one paper [1], published in 1990, contains a small section (16 references) concerning methods for the synthesis of indolopyridines. In the mean time certain natural compounds (e.g., the plant alkaloids cryptaustoline and cryptowoline [2], which exhibit curare-like activity, or fascaplysin [3] – a red pigment of a marine sponge) exhibit antimicrobial activity and are based on partly reduced indoloisoquinoline. Substances with technically useful properties (optical whiteners [4], dyes, luminophors and active laser media [5-7]) and also with biological activity [8-11] have been found among the synthetic derivatives of indolopyridines. Since indolopyridines with a bridgehead heteroatom contain an indolizine fragment, it must be remembered that certain hydroxy derivatives of perhydroindolizine exhibit clearly defined activity against HIV virus [12], anticancer activity [13], and an anesthetic effect (e.g., the alkaloids castanospermine, swainsonine) [13].

The present review covers data on the synthesis and reactions of indolopyridines, their benzo derivatives, and the products from partial hydrogenation of compounds based on the following eight schemes:



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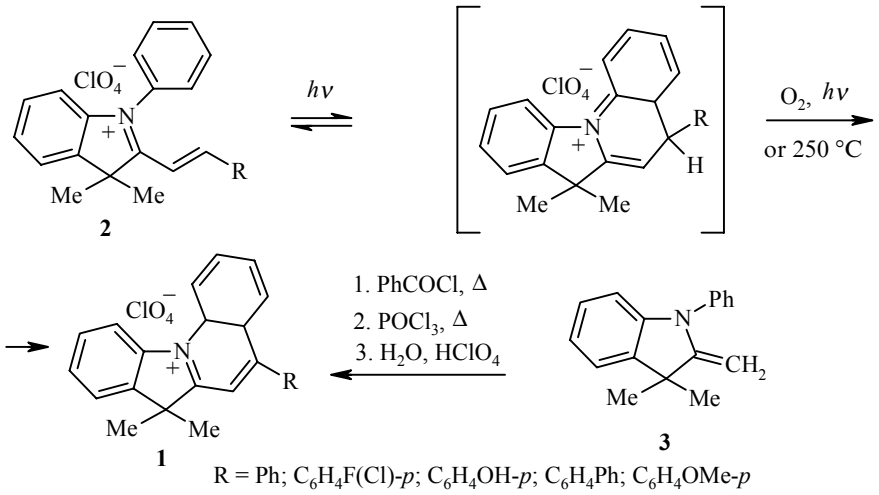
1. METHODS FOR THE SYNTHESIS OF INDOLOPYRIDINES

Currently known approaches to the formation of the indolopyridine system can be grouped as follows: 1) Cyclization of substituted indoles; 2) heterocyclization of α-benzylpyridines and their derivatives; 3) cyclization of pyridinium N-methylides and other zwitterions; 4) other types of formylation of indolopyridines.

1.1. Cyclization of Substituted Indoles

The photochemical and thermal synthesis of indolo[1,2-*a*]quinolinium salts **1** by the dehydrocyclization of 3,3-dialkyl-2-(arylethenyl)-1-phenyl-3H-indolinium perchlorates **2** was described in a series of papers by Polish authors [5, 7, 14]. The salt **1** (R = Ph) was obtained by an alternative synthesis from the 2-methylene derivative of indole **3**.

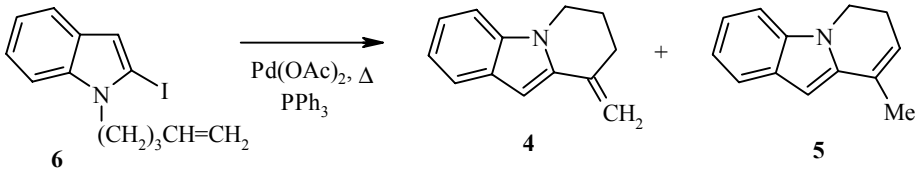


2 **1** **3**

R = Ph; $C_6H_4F(Cl)$-*p*; C_6H_4OH-*p*; C_6H_4Ph; C_6H_4OMe-*p*

The perchlorates **1**, which belong formally to N-arylammonium hemicyanines, are strongly fluorescent materials of interest as laser dyes [6, 7], solvatochromic indicators, and pigments for epoxide resins [14].

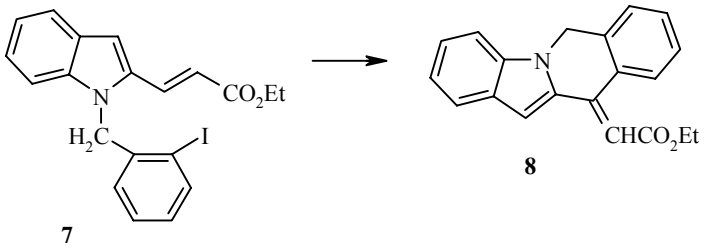
A mixture of indolopyridines **4** and **5** (ratio 3:1, total yield 84%) is formed from 2-iodo-1-(4-pentenyl)indole (**6**) in the Heck reaction [11, 15].



6 **4** **5**

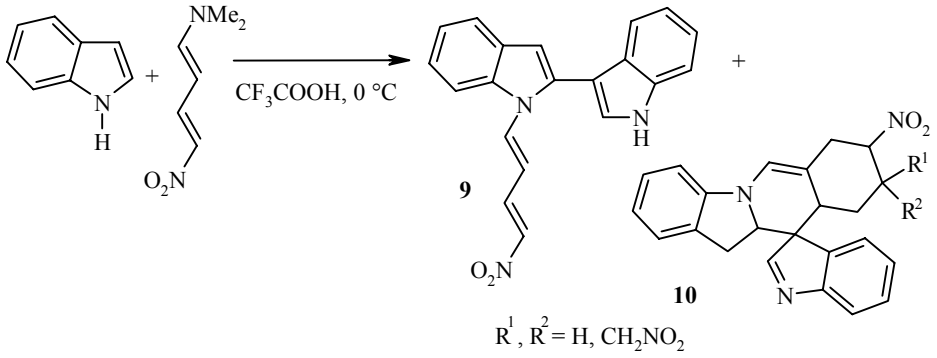
Closure of the pyridine ring is accelerated by the presence of palladium or thallium acetate without significant change in the ratio of the isomers **4** and **5**. If the length of the experiment is increased, the content of the product **4** from kinetic control is reduced.

When a version of the intramolecular Heck reaction was used in the case of the ester **7**, the indoloisoquinoline **8** – a benzannellated analog of indolopyridine – was obtained with a yield of 90% [11, 15].



7 **8**

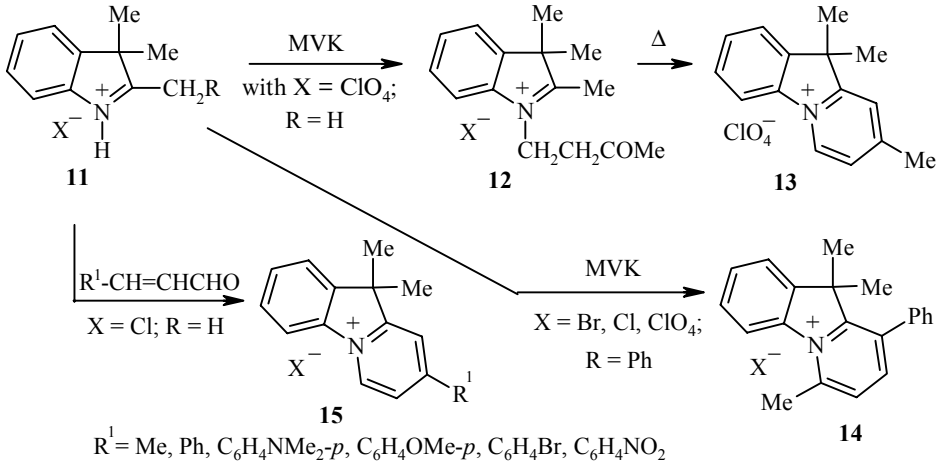
The treatment of indoles with a nitrodienamine in trifluoroacetic acid led to a complex mixture of condensation products, from which the biindole **9** (yield ~10%) and the spiro derivatives of indoloisoquinoline **10** (yield 20%) were isolated [16].



9 **10**

R^1, R^2 = H, CH_2NO_2

2-Methyl-substituted 3H-indolium salts **11** react with α,β-unsaturated ketones or aldehydes with the formation of indolopyridinium derivatives (yields 49-59%) [4, 17-19]. Thus, 2,3,3-trimethyl-3H-indolium perchlorate (**11**) (R = H) adds methyl vinyl ketone (MVK) and is converted into the 1-(3-oxobutyl)-substituted indolium salt **12**, which then undergoes cyclization after heating in pyridine to the trimethyl-substituted indolopyridinium perchlorate **13**. If R = Ph the salt **14** with the methyl group at a different position in the pyridine fragment is formed from compound **11**.

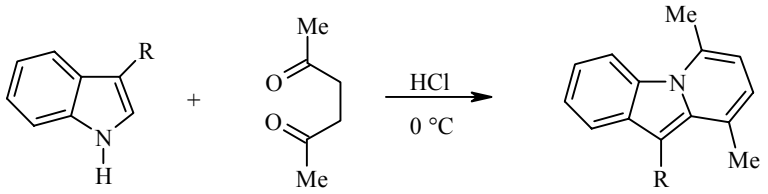


11 **12** **13** **15** **14**

R^1 = Me, Ph, $C_6H_4NMe_2$-*p*, C_6H_4OMe-*p*, C_6H_4Br, $C_6H_4NO_2$

The indolium salt **11** (R = H) undergoes a similar condensation with α,β-unsaturated aldehydes [20, 21]. The indolopyridine derivatives **15** are formed here, and their structures indicate that the condensation takes place through intermediate reaction between the carbonyl carbon atom and the indolium nitrogen atom.

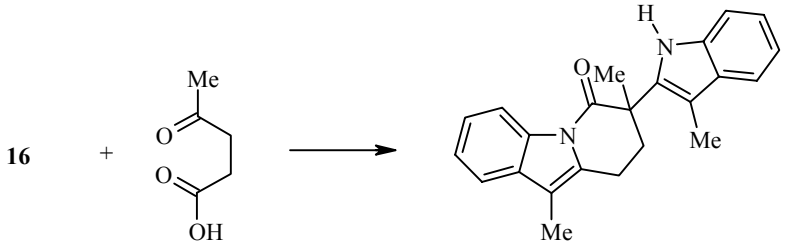
3-Alkylindoles and acetyltryptamine **16** undergo cyclization with acetonylacetone in the presence of HCl and form the indolopyridines **17** [22, 23]. Under these conditions unsubstituted indole is only converted into dimethylcarbazole, while 2-methylindole does not enter into the reaction.



16 **17**

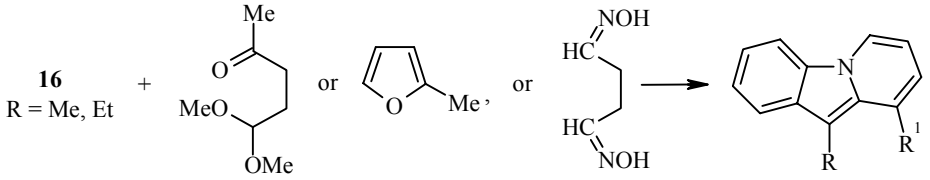
R = Me (47%), Et, CH_2CH_2NHAc (10%)

The condensation of 3-methylindole (**16**) (R = Me) with levulinic acid takes place in a more complicated manner – two molecules of skatole take part in the reaction, and the tetrahydro derivative of indolopyridine **18** is formed with a yield of 15% [22, 23].



18

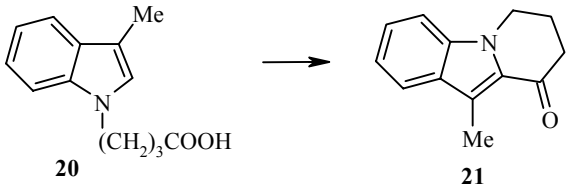
The indolopyridines **19** were obtained during the condensation of 3-substituted indoles **16** with levulinaldehyde dimethyl acetal, 2-methylfuran, or succinaldehyde dioxime [22, 23].



19

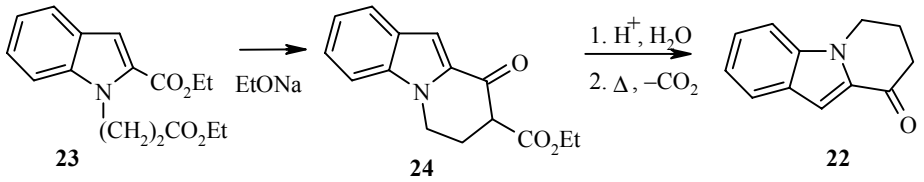
R^1= H, Me

The intramolecular condensation of 4-(3-methyl-1-indolyl)butyric acid (**20**) was realized successfully under the conditions of the Friedel–Crafts reaction. Cyclization takes place mainly at the π-electron-excessive pyrrole ring with the formation of tetrahydroindolopyridinone **21** [24].



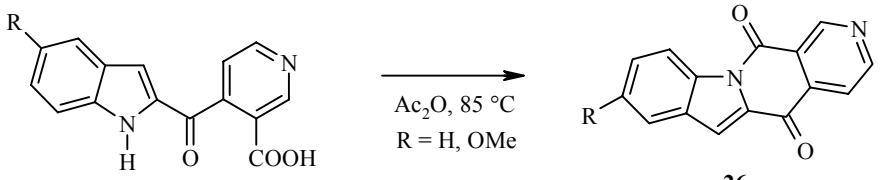
20 **21**

The unsubstituted product **22** was obtained by the Dieckmann condensation of the indole-2-carboxylate **23** followed by hydrolysis and decarboxylation of the intermediate ester **24** [25].



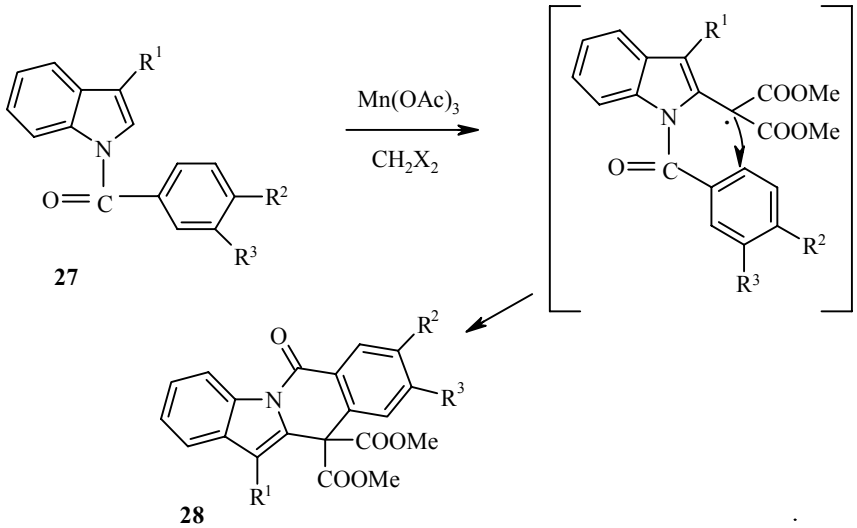
23 **24** **22**

During the synthesis of a series of pyridocarbazole alkaloids it was established that the action of heat on 2-(3-carboxypyridine-4-carbonyl)indoles **25** in acetic anhydride leads not only to carbazole systems (through condensation of the carboxyl group at the β-position of the indole) but also to the formation of the indolonaphthiridines **26** on account of the competing condensation at the pyrrole nitrogen atom [26].



25 **26**

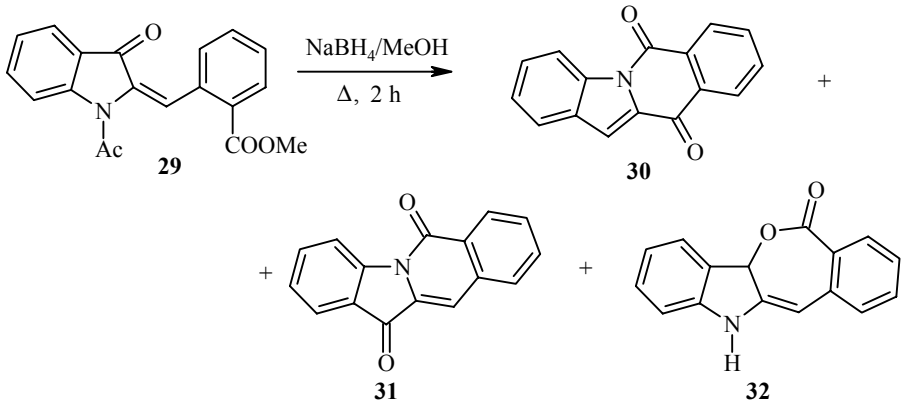
The recently studied oxidative cocondensation of dimethyl malonate with N-benzoylindoles **27** made it possible to develop a new effective method for the synthesis of indolo[1,2-*b*]isoquinolines **28** [27, 28]. The oxidizing agent was Mn(III) acetate, which initiates the formation of the malonyl radical, its electrophilic addition at the α position of the pyrrole ring, and subsequent oxidative intramolecular annellation to the tetracyclic product **28**.



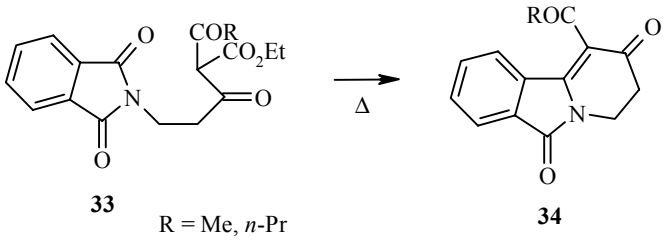
27 **28**

X = COOMe, R[1]= X, CN, COMe; R[2] = H, Me, OMe, Ph; R[3] = H, Me, Br, Cl

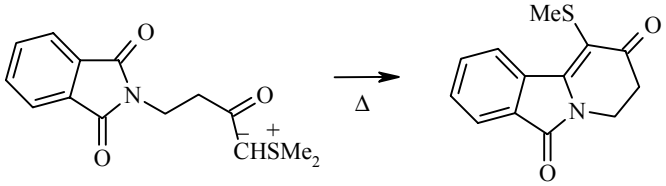
Study of the reduction of 2-(*ortho*-methoxycarbonyl)arylideneindoxyl **29** demonstrated the possibility of intramolecular cyclization to derivatives of indolo[1,2-*b*]isoquinolines **30**, **31** and the lactone **32** (with yields of 15.5 and 54% respectively) [29].



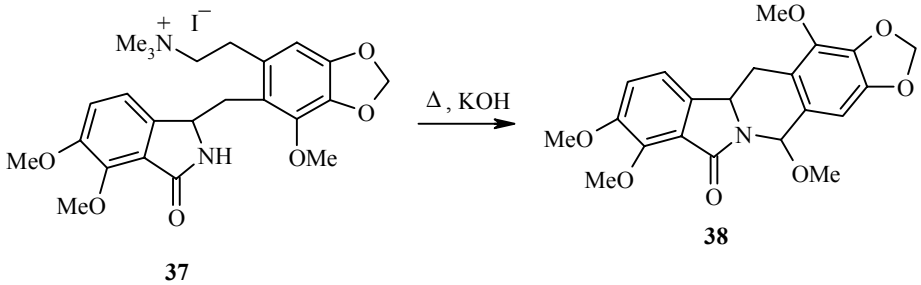
When heated in pyridine the esters of the phthalimido-substituted keto acids **33**, which have a β-keto acid residue at the nitrogen atom, undergo cyclization to derivatives of isoindolopyridinediones **34** with yields of 43-78% [30].



The analogous tricyclic system **35** is formed as a result of thermally initiated intramolecular cyclization of 1,3-dioxoindolyl-substituted ketostabilized sulfur ylides **36** [30-33], while the presence of an equimolar amount of benzoic acid significantly increases the yield of the product **35** (from 27 to 86%) [32, 33].

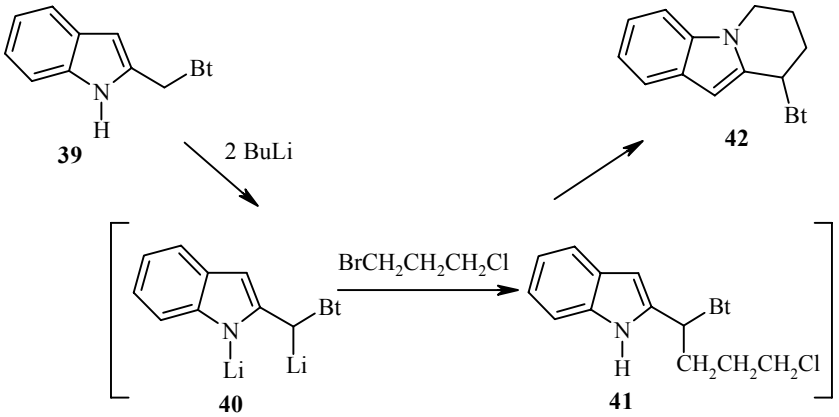


The dependence of the regioselectivity of the cyclization of the ylides on the position and nature of substituents in the benzene fragment was studied. A limitation of this method is the absence of cyclization products in the case of ylides containing a hydrogenated phthalimide fragment [33].

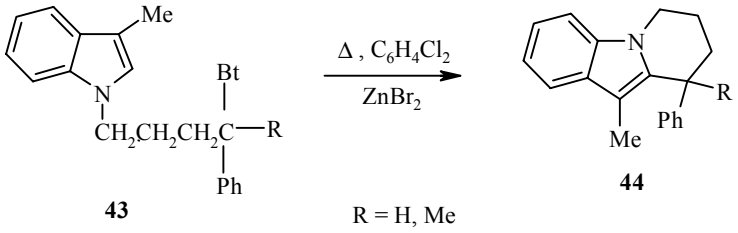


The thermal alkaline treatment of the methiodide of the alkaloid narceine imide (**37**) leads to a small yield of the cyclization product isoindoloquinoline **38** [34].

It was noted that 1- and 2-(1-benzotriazolyl)alkylindoles are effective as intermediate compounds for the synthesis of indolopyridine systems [35, 36]. Thus, the lithiation of 2-benzotriazolylindolylmethane (**39**) with two equivalents of butyllithium followed by treatment of the intermediate dianion **40** with 1-bromo-3-chloropropane leads to the product from regioselective [3+3] alkylation **41** with a yield of 92%. The tetrahydroindolopyridine **42** is formed through the monoalkylated derivative **41**, as demonstrated by the isolation of the latter and its conversion into compound **42** by the action of sodium hydride [35].

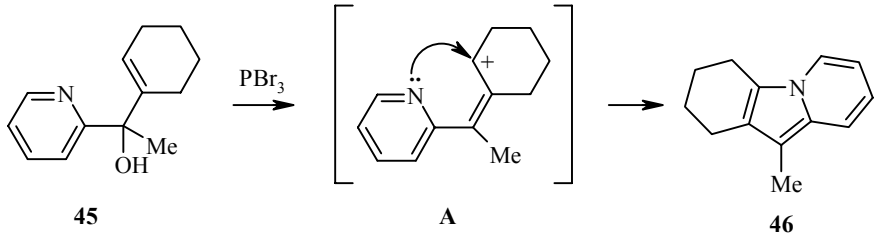


When the indoles **43** are heated in dichlorobenzene (120-150°C, $ZnBr_2$), the benzotriazolyl substituent (Bt) is eliminated, and regioselective electrophilic attack by the obtained carbocation on the pyrrole ring occurs. If the carbocation is stabilized (with R = Me), the yield of the indolopyridine **44** is tripled (to 97%) [36].

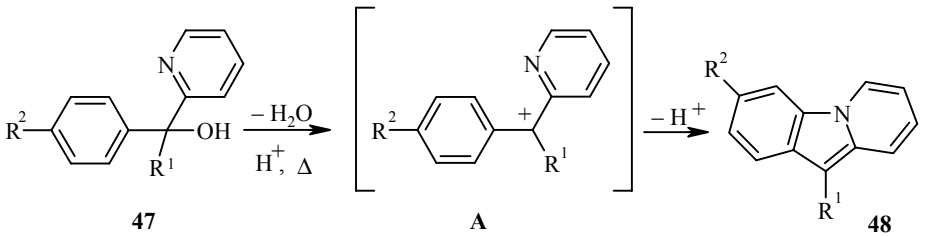


1.2. Heterocyclization of α-Benzylpyridines and their Derivatives

1.2.1. Cyclization of 2-Pyridylcarbinols. 1-(2-Pyridyl)-1-(1-cyclohexenyl)ethanol (**45**) was used in the first paper on the intramolecular C–N cyclization of 2-pyridylcarbinols. This carbinol readily eliminates water under the influence of phosphorus tribromide and is converted through the carbocation **A** into the tetrahydroindolopyridine **46** even at 20°C [37].



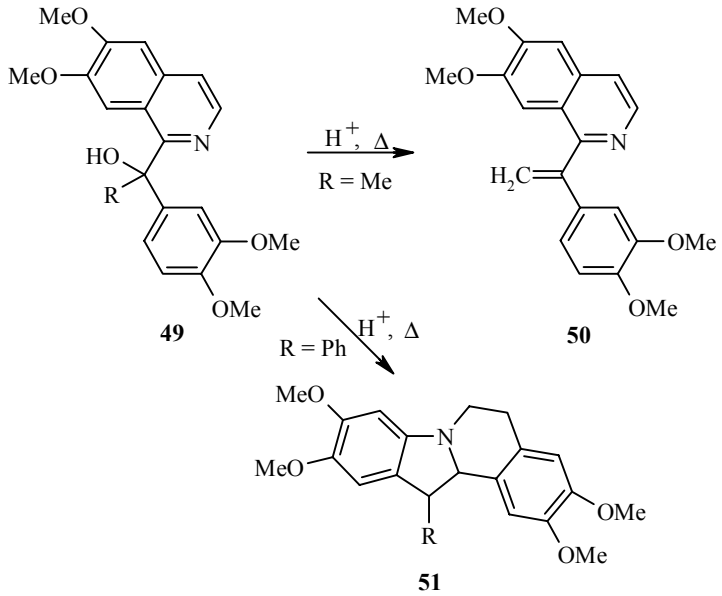
The fully aromatic α-pyridylcarbinols **47** undergo acid-catalyzed cyclization to the indolopyridines **48** with yields that depend largely on the nature of the substituents [38]. If R^1 = H cyclization does not take place at all, and this is explained by the instability of the secondary carbocation **A** on account of the impossibility of delocalization of the positive charge at R^1 and its susceptibility to polymerization [39].



47 **A** **48**

R^1 = Me, Ph, C_6H_4OMe-*p*; R^2 = H, Me

With the introduction of a methyl group (R^1 = Me) cyclization occurs, but the yield of the product **48** with R^2 = H is very low. With R^1 = Ph the stability of the tertiary carbocation is increased significantly, and this leads to the formation of the indolopyridine **48** (R^2 = H) with a yield of up to 30%. Finally, in the case of the di(*para*-anisyl)-substituted carbinol **47** (R^1 = C_6H_4OMe-*p*, R^2 = OMe) the yield of the product **48** is increased to 70%. It was found that the yields of the indolopyridines **48** depend little on the nature of the acid center (HCOOH, PPA, Lewis acids). These products were also obtained by an alternative synthesis, i.e., by the condensation of 3-methyl- or 3-arylindoles with succinaldehyde dioxime (see the previous section [22, 23]).

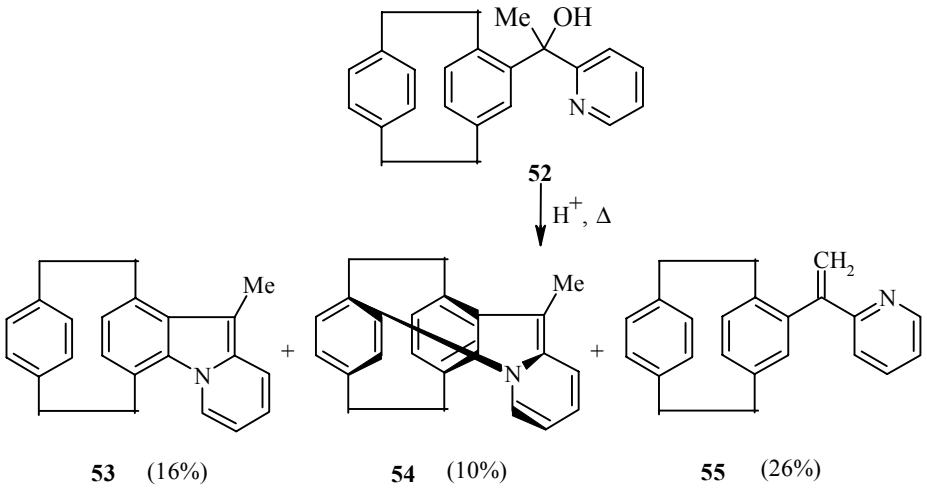


49 **50**

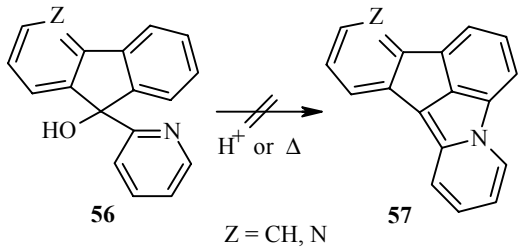
51

A similar method with heating in formic acid was used for the cyclization of derivatives of papaverinol (**49**) [40]. Here it was found that cyclization does not occur in the case of R = H. The introduction of a methyl group into compound **49** leads to the alkene **50** with a high yield. (The cyclization product was not identified.) Finally, the presence of a phenyl substituent in the carbinol **49** (R = Ph) secures the rapid formation of only one isomer of indoloisoquinoline **51** with a quantitative yield, although it was possible to expect cyclization in two directions, i.e., at the phenyl and at the dimethoxyphenyl substituents with the formation of a mixture of at least two indoloisoquinolines.

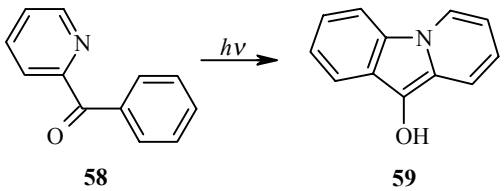
The indolopyridine structure **53**, containing a paracyclophane fragment, was synthesized starting from the carbinol **52** [41]. Together with this the formation of the product from transannular cyclization **54** and the alkene **55** was also observed. Replacement of the methyl substituent in the initial carbinol by phenyl significantly increases the yield of the heterocyclization products [42].



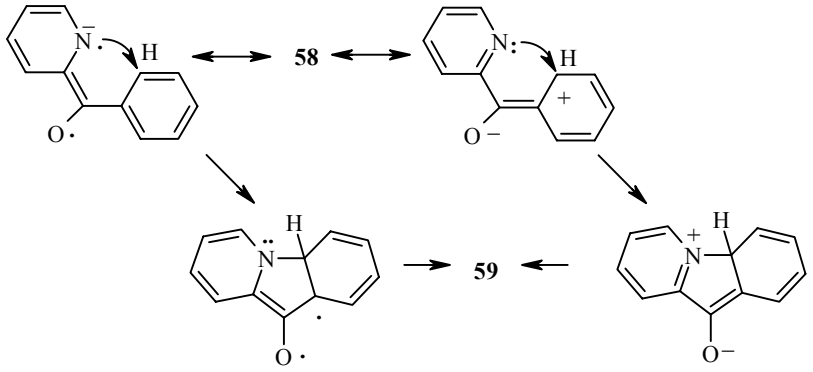
Whereas the diaryl-2-pyridyl- and 1-isoquinolylcarbinols are readily transformed with good yields under the conditions of acid-catalyzed dehydration into indolopyridines containing a bridgehead heteroatom, their condensed analogs **56** containing fluorene or 4-azafluorene fragments do not undergo cyclization to indolopyridines of the **57** type under analogous conditions (at 100-230°C) or under the conditions of vapor-phase heterogeneous catalysis (metal oxides, 600°C) [43]. In the first case the initial the initial carbinols are largely recovered, while in the second their thermolysis mainly to fluorenes is observed.



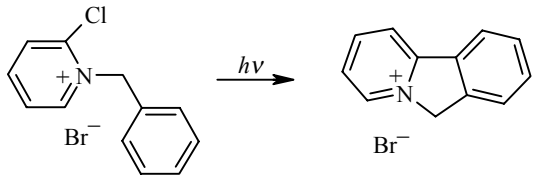
1.2.2. Cyclization of α-Benzoyl- and α-Benzylpyridines and Isoquinolines. Hydroxy-substituted indolopyridine is formed during the photolysis of aqueous solutions of 2-benzoylpyridine **58** [44].



The authors of this paper suppose that the isomerization rearrangement **58** → **59** can take place through resonance radical or dipolar forms in the $n \rightarrow \pi^*$ excited state, which has sufficient energy to remove a proton or H· and transfer it to the oxygen atom.

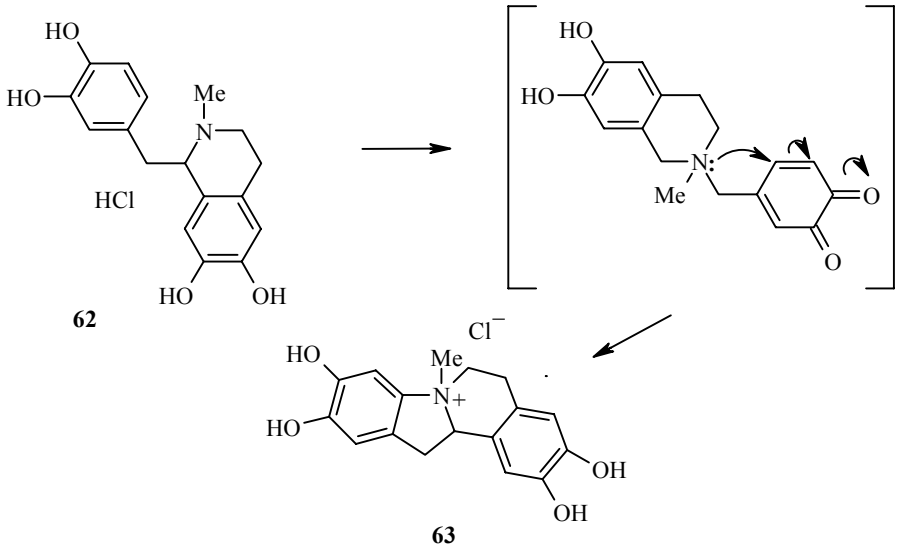


Photolysis of 1-benzyl-2-chloropyridinium bromide (**60**) leads to radical heterocyclization with cleavage of the C–Cl bond and the formation of indolopyridinium bromide (**61**) [41].



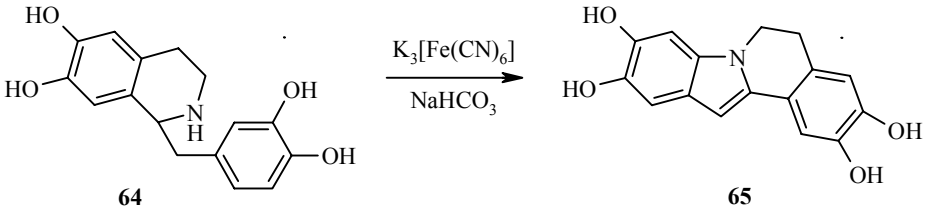
60 **61**

In one of the first papers on oxidative cyclization [46] the starting compound was the alkaloid laudanosoline (**62**). It is oxidized relatively easily by chloranil in ethanol in the presence of potassium acetate (or oxygen at platinum) with the formation of the dehydrocyclization product **63**. It is interesting that NH- and N-acetyl derivatives like **62** do not undergo cyclization under analogous conditions [46, 47].

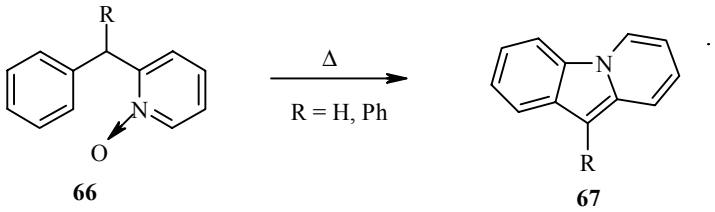


62 **63**

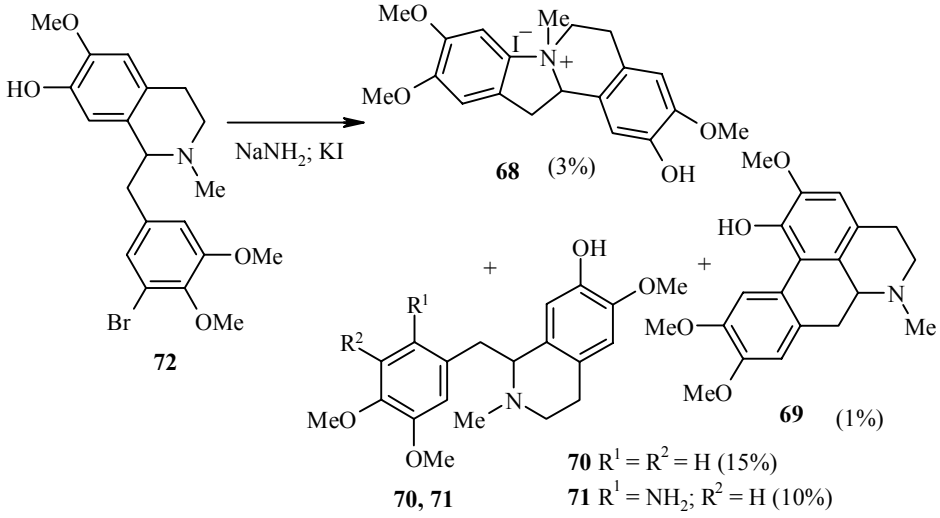
At the same time norlaudanosoline (**64**) undergoes cyclization under the influence of potassium ferricyanide with the formation of dihydroindoloisoquinoline **65** [48].



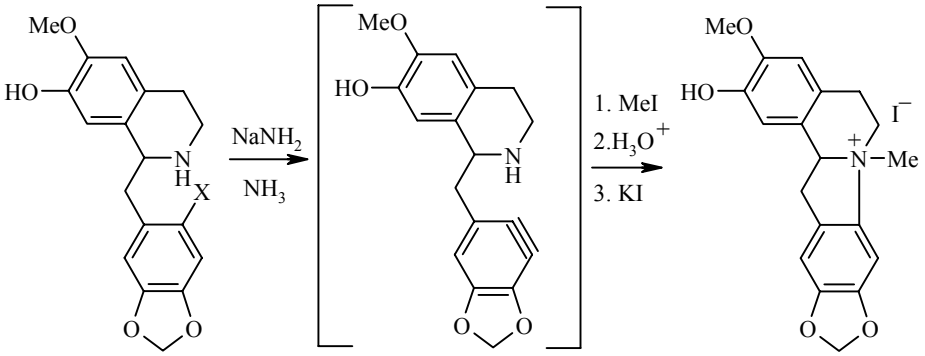
Intramolecular oxidative heterocyclization was observed when 2-benzylpyridinium N-oxides **66** were heated. The respective indolopyridines **67** are formed with yields of 10-65%, depending on the temperature [49-51].



The alkaloid cryptaustoline (**68**) was obtained together with the side products **69-71** by cyclization of the 5-bromobenzyl-substituted isoquinoline **72** with sodium amide [52, 53]. It was considered that the formation of compounds **70** and **71** indicates the intermediate formation of a dehydrobenzene derivative.

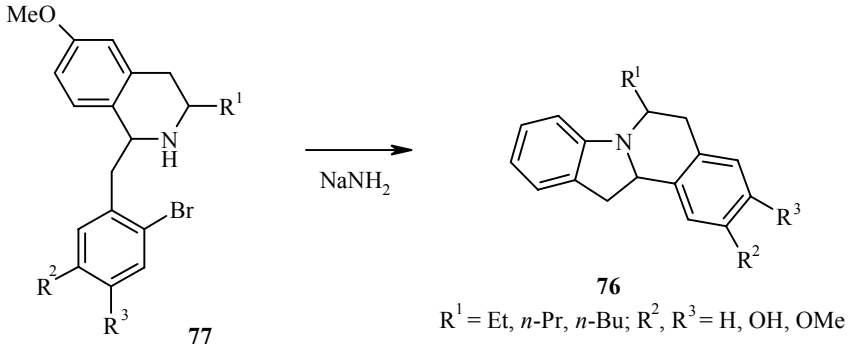


Somewhat earlier (simultaneously and independently) analogous syntheses of the alkaloid cryptowoline (**73**) from 2-(*ortho*-chlorobenzyl)- or 2-(*ortho*-bromobenzyl)isoquinolines **74** were announced [54, 55]. They probably also take place through the dehydrobenzene derivative **75**. It was established that the optically active compound **74** epimerizes to the racemic product **73** during cyclization [55].



74 **75** **73** X = Cl, Br

A series of hydroindoloisoquinolines **76**, derivative of which inhibit the growth of malignant cells in breast cancer, were synthesized under mild conditions by the action of sodium hydride in DMSO on 2-(*ortho*-bromoaryl)methyltetrahydro derivatives of isoquinoline **77** [10].

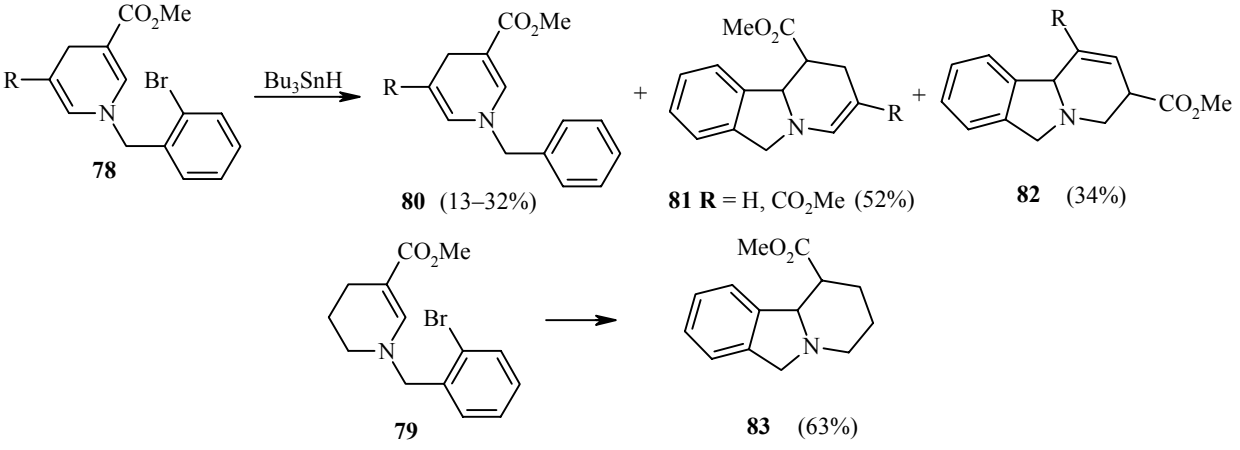


77

76

R^1 = Et, *n*-Pr, *n*-Bu; R^2, R^3 = H, OH, OMe

The methodology for the radical cyclization of N-(*ortho*-halogenobenzyl)- or N-(*ortho*-halogenobenzoyl)pyridines and their derivatives by the action of tributyltin hydride and radical initiators has been developed in a series of investigations [56-61]. Dihydropyridines or tetrahydropyridines **78**, **79** are debrominated by Bu_3SnH when heated in benzene, undergoing cyclization to the tetrahydro or hexahydro derivatives of isoindolopyridines **80**-**82** or **83** with good yields [56]. These compounds have *trans* fusion of the two heterocyclic fragments, as demonstrated by the diagnostic Boltzmann absorption bands at 2700 cm^{-1} in their IR spectra. (These bands appear when two or more C–H bonds are in the *trans*-diaxial position in relation to the unshared electron pair of the bridgehead nitrogen.)



78

80 (13–32%)

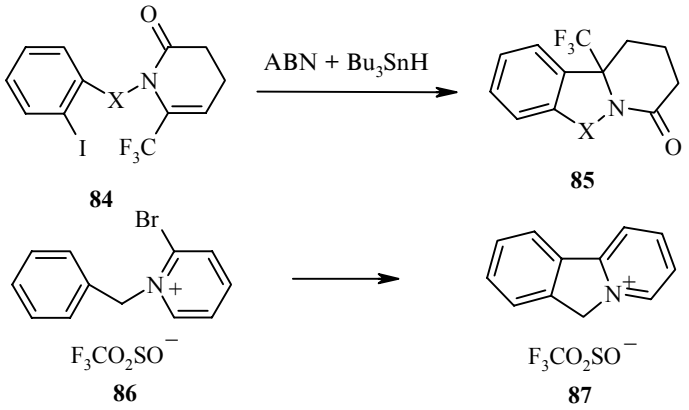
81 R = H, CO_2Me (52%)

82 (34%)

79

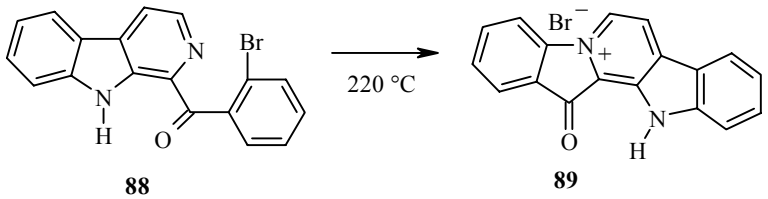
83 (63%)

The tetrahydropyridinones **84** enter readily into radical cyclization under the influence of a mixture of Bu_3SnH with azobisisobutyronitrile (ABN).

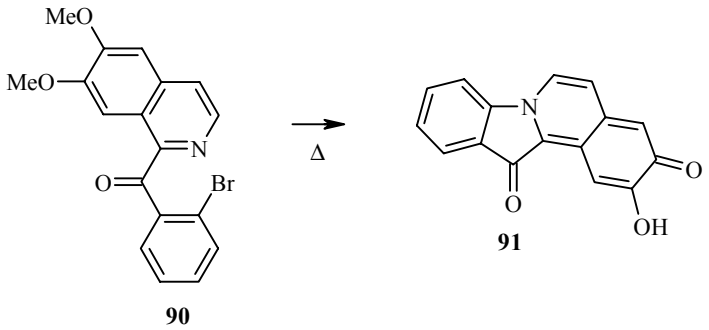


It is possible to avoid simple reduction of the initial iodides by the slow addition (8-10 h, 80°C) of a benzene solution of Bu_3SnH and ABN. The yield of the isoindolopyridinones here amounts to 92-97% [59]. an analogous system was used successfully for the radical condensation of 1-benzylpyridinium triflate **86** to the isoindolopyridinium salt **87** (yield 60%) [58, 61].

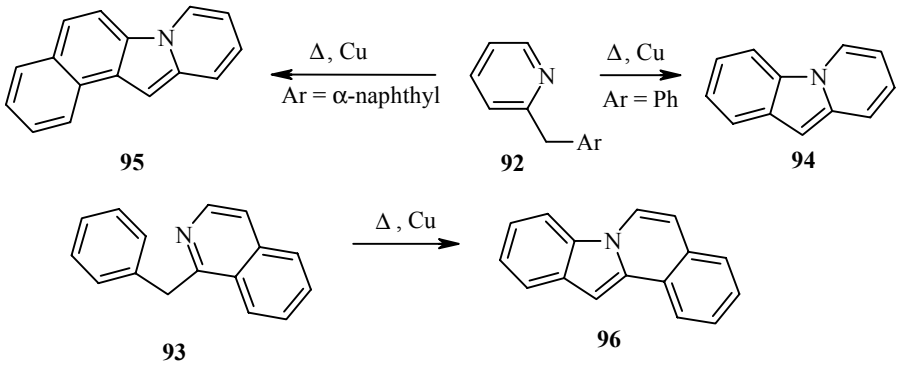
The quaternary diindolopyridinium salt **89** was obtained with a yield of 90% by briefly heating α-(*ortho*-bromobenzoyl)-substituted β-carbolin **88** [3].



Subsequent replacement of the Br^- by Cl^- in the salt **89** by the action of HCl/MeOH led to the natural pigment fascaplysin, which has antimicrobial and cytotoxic activity. 1-(2-Bromobenzoyl)-6,7-dimethoxyisoquinoline (**90**) undergoes similar cyclization (200°C, 20 min), but in this case methyl bromide is readily eliminated, and the indoloisoquinolinedione **91** is formed quantitatively instead of a quaternary salt of the **89** type. The quinonoid system of **91** is converted by treatment with trifluoroacetic acid into a dihydroxyindoloisoquinolinium quaternary salt.

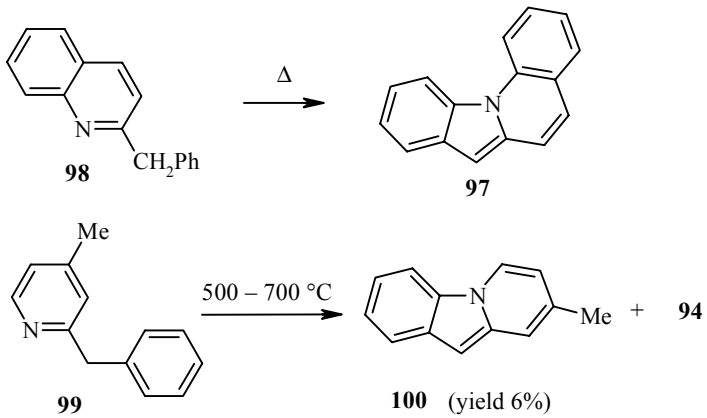


The high-temperature heterocyclization of α-benzyl-substituted pyridines and (iso)quinolines was first realized in [62]. It was found that the indolopyridine structures **94-96** are formed from the α-benzylazines **92**, **93** when they are passed over a copper catalyst in the vapor phase. The yields of the products did not exceed 40%.



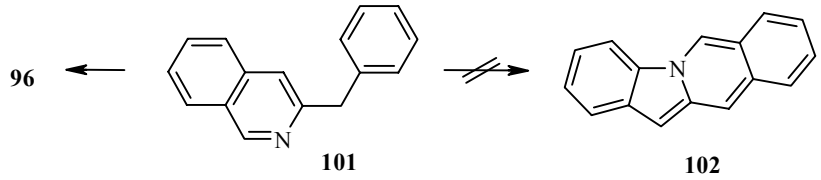
95 **92** **94** **93** **96**

More recently [63, 64] it was shown that a similar radical transformation of α-benzylazines also takes place purely thermally in the absence of catalysts, and the indolopyridine **94** and indoloquinoline **97** (from α-benzylquinoline **98**) are formed at 650°C with yields of up to 42%, and the indoloisoquinoline **96** is formed with yields of up to 70%. Thus, the use both of the copper catalyst [62] and of oxide catalysts leads only to some decrease in the optimum temperature for the synthesis (590-600°C). The noncatalytic formation the indolopyridines **92** and **95** is already observed at 500°C (yields 3% and 7% respectively) [64]. In the case of the pyrolysis of the 4-methyl-substituted 2-benzylpyridine **99** at 650°C the formation of 2-methylbenzoindolizine **100** with a 22% yield is observed (with 50% conversion), and its demethylation product **94** is isolated from the reaction mixture (yield 6%).



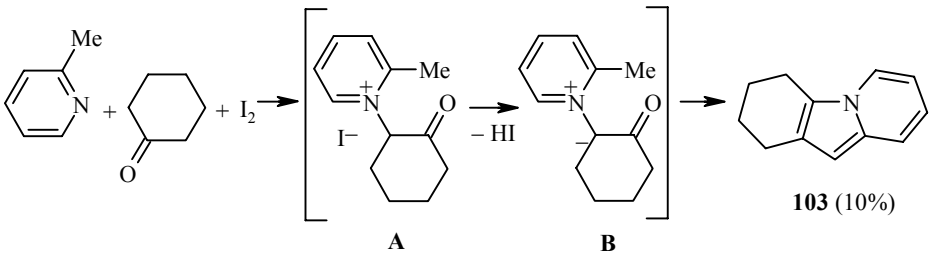
98 **97** **99** **100** (yield 6%) **94**

During study of the possibility of cyclization of 3-benzylisoquinoline (**101**) to the linear indolo[1,2-*b*]isoquinoline **102** it was established that even in the range of 400-500°C it is transformed almost entirely by a different path with the formation of isoquinoline, diphenylethane, 1-benzylisoquinoline (**93**) (through radical debenzylation), and the angular indoloisoquinoline **96**. (The yield of the latter amounted to 60%; we note that its yield at 500°C direct from compound **93** amounted to only 3%.) It was not possible to detect the formation of the linear indoloisoquinoline **102** here, and this was probably due to the thermodynamic instability of its *ortho*-quinonoid structure at high temperatures. Unlike the α-benzyl-substituted isoquinolines **93** and **101**, the isomeric β-benzylisoquinoline is stable under analogous pyrolysis conditions and does not enter into cyclization.

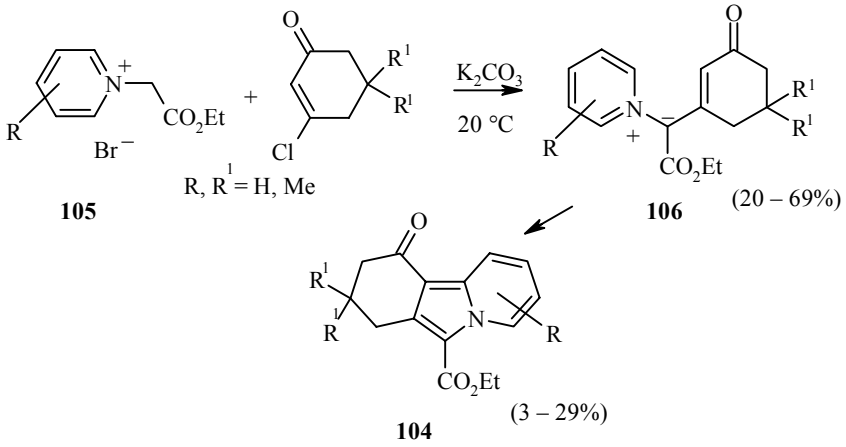


1.3. Cyclization of Pyridinium N-Methylides and Other Zwitterions

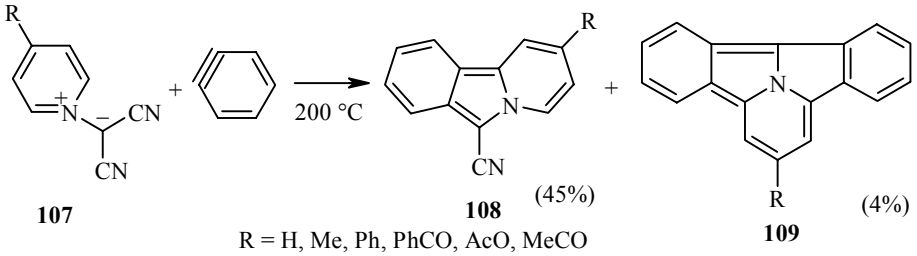
A synthesis of the tetrahydroindolopyridine **103**, for which a combination of the King and Chichibabin reactions was used, was described in [66-68]. For this purpose 2-methylpyridine was added to a solution of the halogen-substituted cyclohexanone produced by treatment of cyclohexanone with iodine or bromine. Without isolation of the quaternary salt **A** the reaction mixture was then treated with sodium bicarbonate or calcium carbonate. Intramolecular cyclization takes place through the intermediate ylide **B**:



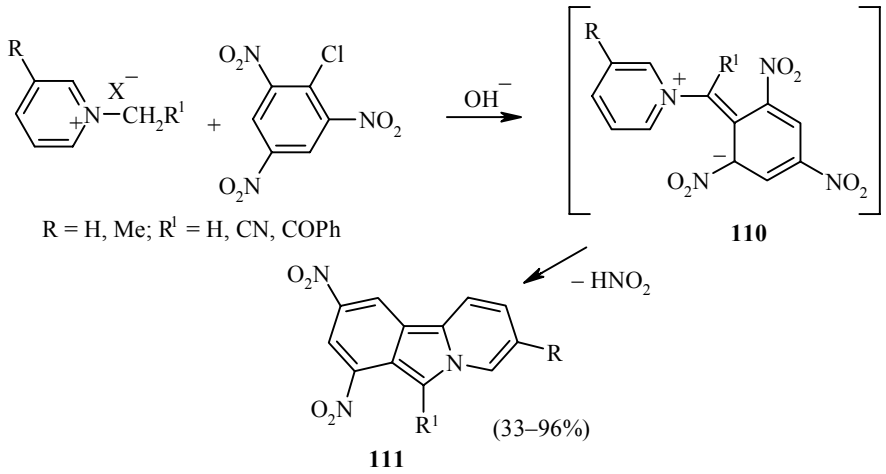
The tetrahydro derivatives of isoindolopyridine **104** were obtained from the substituted pyridinium bromides **105** and chlorocyclohexanes through the ylides **106** [69].



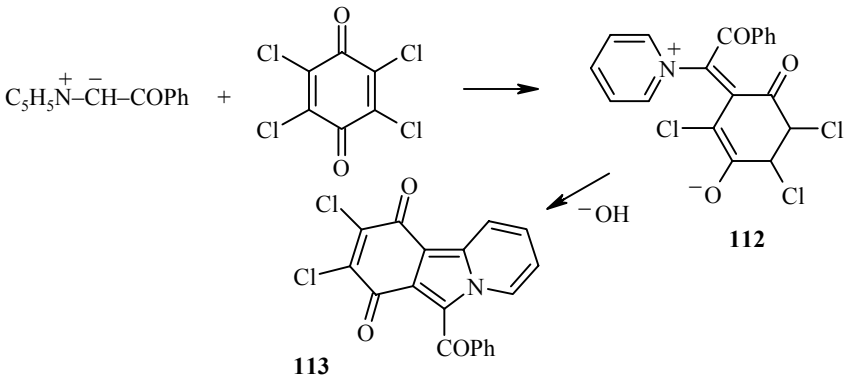
During the thermal reaction of pyridinium dicyanomethylides **107** with dehydrobenzene 1,3-dipolar cycloaddition with the elimination of one CN group occurs, and 6-cyanoisoindolo[2,3-*a*]pyridine (**108**) is formed [70]. The products from subsequent analogous cyclocondensation of dehydrobenzene with compound **108**, i.e., dibenzopyridoazapentalenes **109**, were also isolated:



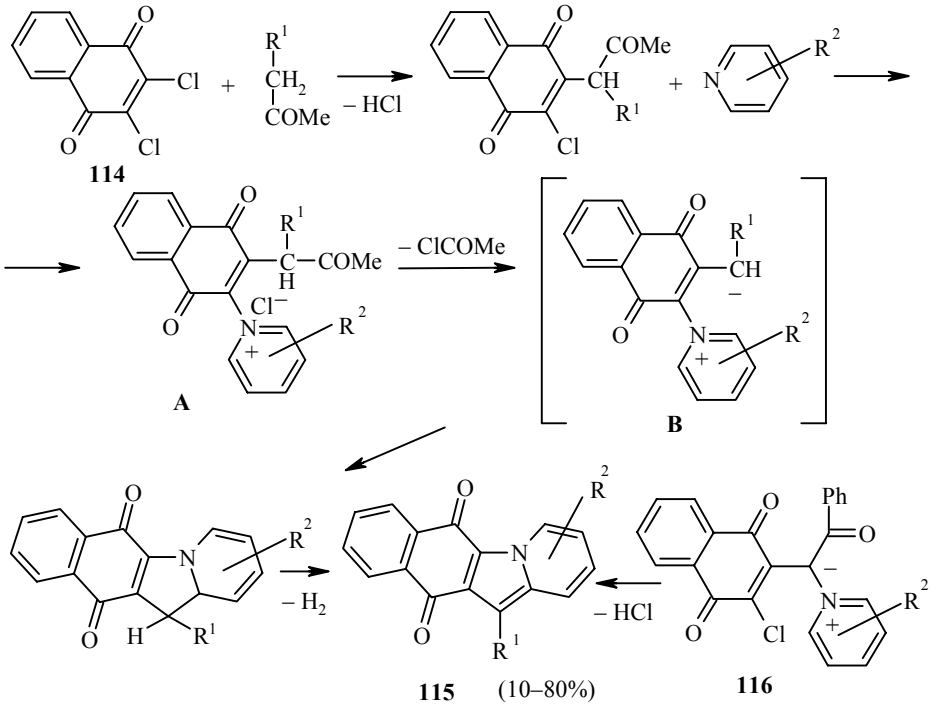
The ylides **110** readily undergo cyclization to the dinitroisoindolopyridines **111** as a result of 1,5-dipolar intramolecular interaction, which take place with the elimination of nitrous acid [71-74]. The ylides are generated from a mixture of quaternary salts and picryl chloride in the presence of bases or alkalis. Analogous transformations are observed in the case of isoquinolinium derivatives.



The derivative of indolopyridine **113** was obtained from pyridinium benzoylmethylide and chloranil through the zwitterion **112** [71].

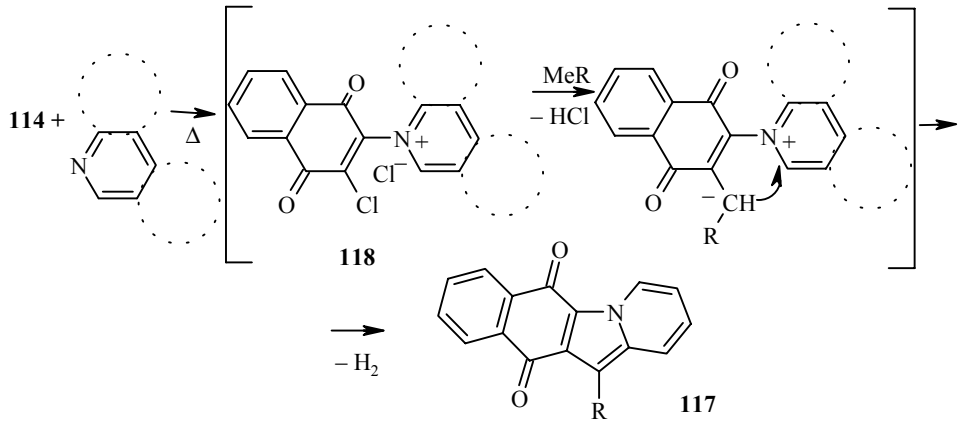


The reaction of 2,3-dichloronaphthoquinone **114** with azines and compounds containing active methylene groups takes place in a more complicated way [75-79].



R^1 = H, Me, COMe, COPh, CO_2Alk, CN; R^2 = H, Me, Ph

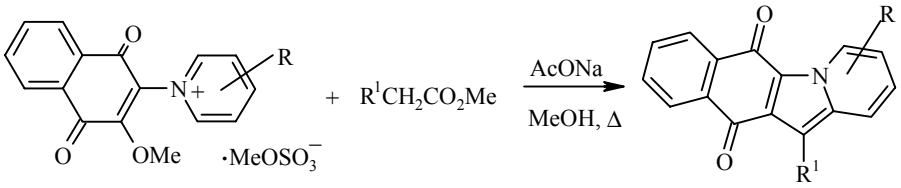
Condensation to the polycycles **115** was conducted in one reactor by boiling a mixture of the dichloride **114** with the azine and ketone RCH_2COR^1 (where R^1 is an electron-withdrawing group: Ph, COMe, CO_2Alk, $CONH_2$, CN) in alcohol. In the course of the reaction, the sequence of which is shown above, the zwitterion **B** is formed as a result of the elimination of the ClCOMe group from the salt **A**. Pyridine, picolines, collidines, phenylpyridines, and isoquinoline (but not quinoline!) act as azine in the reaction. Compounds of the **115** type represent an important class of dye [75], and some of them have been obtained by an alternative method – 1,5-cyclization of the ylides **116** [80].



R = NO_2, CN, NH_2; $C_6H_3(NO_2)_2$-*o*, *p*; $C_6H_2(NO_2)_3$-*o*, *o'*, *p*; $C_6H_3NO_2$-*p*-CN-*o*

The analogous reaction of the dichloride **114** with the azines in the presence of such CH acids as nitromethane or di- or trinitrotoluene leads to the formation of nitro- or nitroaryl-substituted benzindolopyridines **117**, which are of interest as quinonoid chromophoric systems for industrial dyes [81].

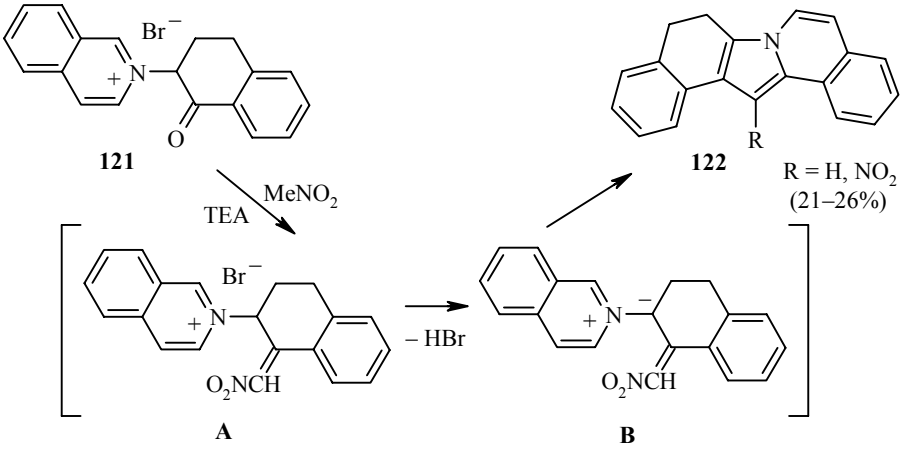
Condensation here takes place with lower yields than in the previous case (30-35% with pyridine, 9-20% with isoquinoline, and only 6% with quinoline). This reaction takes place in benzene, toluene, chlorobenzene, xylene, and dioxane and does not take place in DMFA, DMSO, and ethanol. In the case of ethyl isonicotinate and 4-amino- or 4-acetamidopyridine the yields of the compounds **117** are reduced to 2-5%. The intermediate formation of the salt **118**, followed by attack by the nitrocarbanion formed from nitromethane or nitrotoluene, was established. The anion is deactivated if triethylamine or sodium amide is used. In [82] the quaternary salts N-(1,4-dioxo-2-methoxy-3-naphthyl)pyridinium methylsulfates **119** were brought into condensation with various CH acids. The reaction took place successfully when the mixtures were boiled in methanol (sodium acetate). Derivatives of malonic and acylacetic acids, nitromethane, 2,4-pentanedione, and 2- and 4-picolines were used as CH acids. At the initial stage the methoxy group in compound **119** is substituted by the anion generated from the CH acid. A betaine is then formed by the action of the base and then undergoes cyclization with the elimination of the methoxy group and is converted into the product **120** according to the previously examined scheme of transformations **114** → **115**.



119 **120**

R = H, Me; R = CO_2Alk, $CONH_2$, CN, Ac, COPh, $C_6H_3NO_2$-*p* и др.

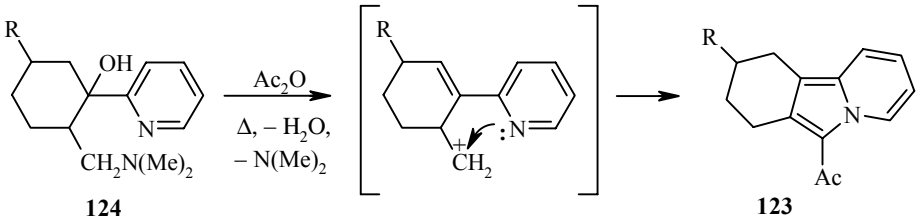
To conclude this section it is necessary to mention the paper [69], in which derivatives of indolo[1,2-*a*]pyridines **122** were obtained by treating 2-(1-oxo-2-tetralinyl)isoquinolinium bromide with triethylamine in nitromethane. In this case the nitrocarbanion did not substitute but added to the keto group with the formation of the nitromethylene derivative **A**, which then entered into intramolecular 1,5-dipolar cycloaddition through the ylide **B**.



1.4. Other Methods of Synthesis of Indolopyridines

Closure of the pyrrole ring with the formation of derivatives of isoindolopyridine **123** is also possible through the formation of a C–N bond between two rings already linked by the C–C bond of compound **124** [83]. Intramolecular cyclization becomes possible on account of the elimination of the readily leaving dimethylamino

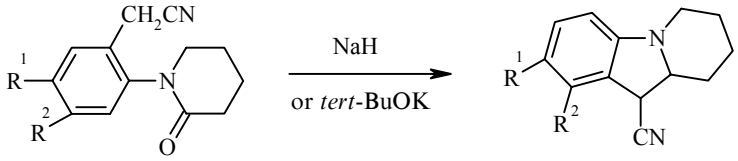
group, which must be situated at the $C_{(2)}$ atom of the homocycle, from the Mannich base. The carbocation generated here attacks the pyridine nitrogen atom electrophilically, and the pyrrole ring formed here is acylated, since the cyclization is conducted in acetic anhydride.



124 **123**

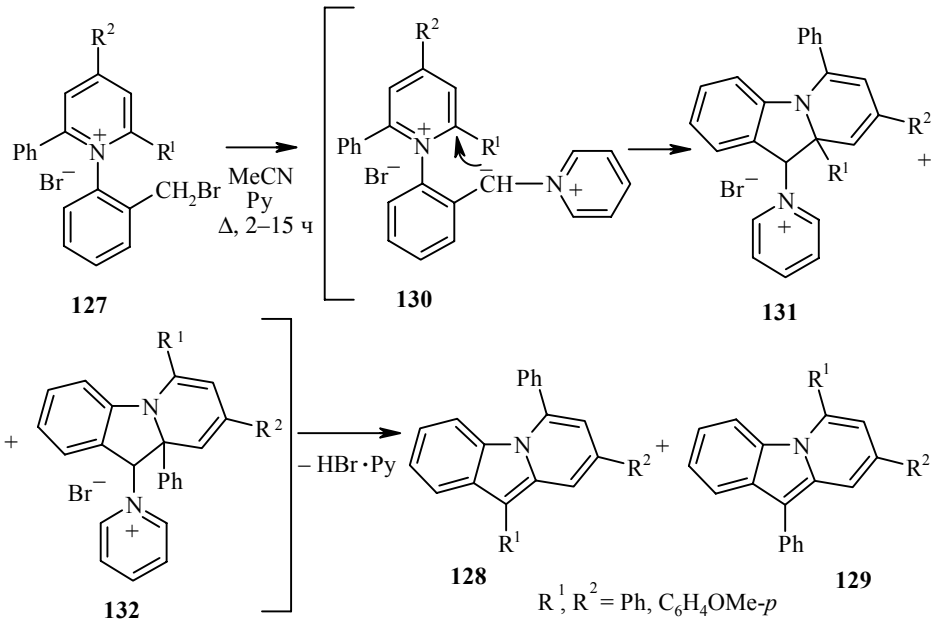
R = H, CH_2Me_2, CH_2OAc

Of specific interest is the path for the synthesis of the indolopyridines **125** according to which it is possible to bring the carbonyl group of the lactam **126**, which has an aryl substituent with an active methylene group at the *ortho* position, into cyclization (the Madelung cyclization) [8]. The authors of this paper synthesized these indolopyridines for trials on antitumor activity and as synthons for the production of antibiotic analogs (through oxidation to quinones).



126 **125**

Recently [84] a new type of cyclization involving nucleophilic *ipso* substitution and 1,2-migration of the phenol radical was discovered. The substituted indolopyridines **128**, **129** were obtained by heating 2,4,6-triaryl-1-(2-bromomethylphenyl)pyridinium bromides **127** in a mixture of acetonitrile and pyridine. The number and position of the aryl substituents in the products indicate migration of one α-aryl radical from the pyridine ring to the pyrrole ring that forms. (The structure of these indolopyridines was proved by X-ray crystallographic analysis.)

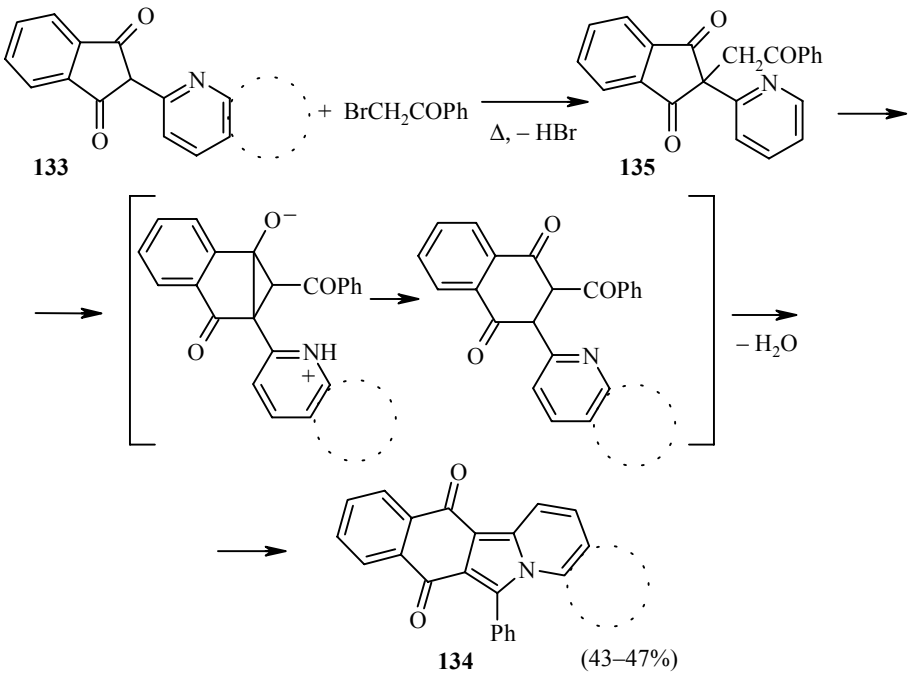


127 **130** **131**

132 **128** **129**

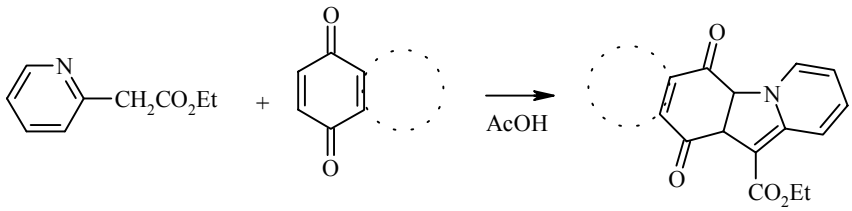
R^1, R^2 = Ph, C_6H_4OMe-*p*

This reaction only takes place in the presence of pyridine, which probably leads to the formation of the salt **130**. Intramolecular nucleophilic attack at one of the α positions of the trisubstituted pyridinium with the formation of the intermediate polycycles **131**, **132**, which are aromatized (with the removal of pyridinium hydrobromide) by undergoing a 1,2-shift of the α-aryl group in the pyrrolidine ring, leads to the final stable indolopyridines **128**, **129** (ratios of yields ~1:1 in all cases). The latter exhibit the characteristics of luminophors.



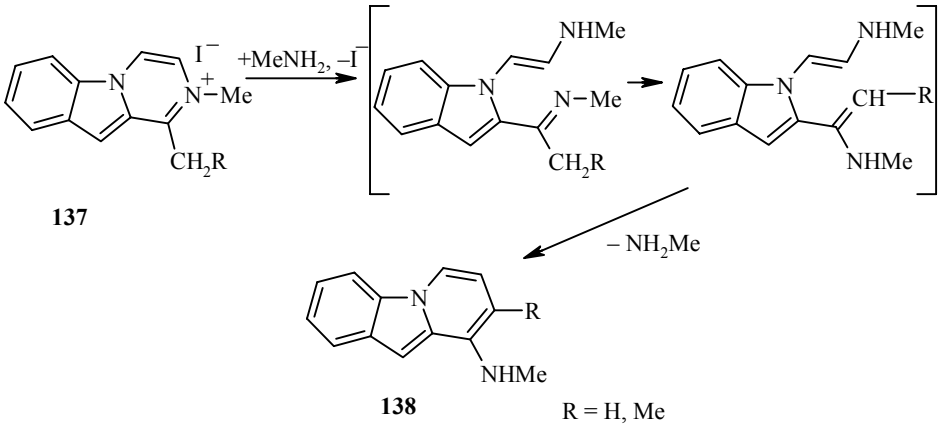
The isoindolopyridines **134** are formed when substituted pyridines or quinolines (pyro- or quinophthalones) **133** are heated for a long time (240°C, 3-12 h) with bromoacetophenone [85]. This method cannot be attributed to the Chichibabin reaction in spite of the formal analogy, since it requires high temperature and goes through the stage of C-alkylation of indane. [An intermediate product of the **135** type was isolated during the reaction of pyrophthalone with benzyl chloride.] It is necessary to note that the scope of this method is limited by the inertness of such alkylating agents as halogen-substituted acetates, acetonitrile, and acetone.

It was established in [86] that benzo- and naphthoquinones react with ethyl (2-pyridyl)acetate and form derivatives of indolopyridines **136**.



Isomerization recyclization (the Kost–Sagitullin reaction) of 1-alkyl-substituted indolo[1,2-*a*]pyrazinium methiodides **137** led to the 9-aminoindolo[1,2-*a*]pyridines **138**, which proved extremely unstable and were characterized in the form of their acetyl derivatives [87]. The reaction was conducted by heating the salts **137** (100°C, 10-15 h) in sealed tubes with a 40% alcohol solution of methylamine. The low yield of compounds **138**

was due not only to their low stability but also probably to the fact that the Kost–Sagitullin rearrangement takes place along different paths. Thus, it is not impossible that the indolopyridine **138** may undergo recyclization to carbazole, while the initial methiodide **137** undergoes cyclization to carbolin.

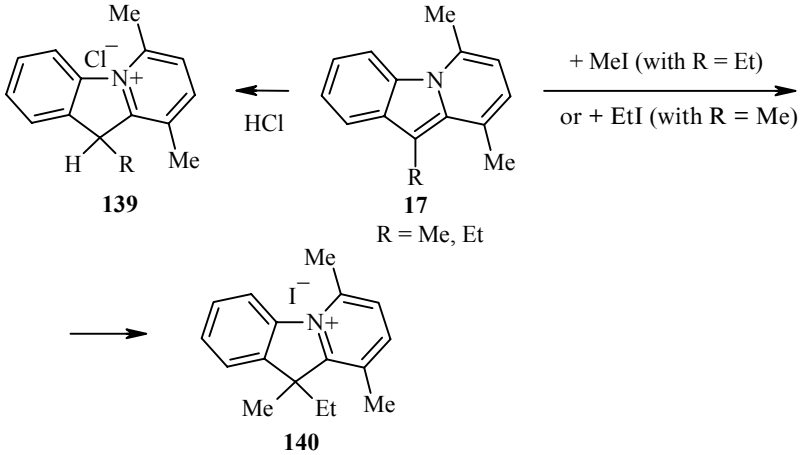


137 **138** R = H, Me

2. REACTIVITY OF INDOLOPYRIDINES

Most publications on the chemistry of indolopyridines are concerned mainly with the development of methods for their synthesis. Information on the chemical behavior of these compounds is fragmentary, and a systematic study of their reactivity has only been reported recently. Nevertheless, the material that has accumulated in this region can be presented in the form of a short section giving some idea of the reactivity of this interesting group of compounds that link in their structure benzene, π-excessive pyrrole, and π-deficient pyridine.

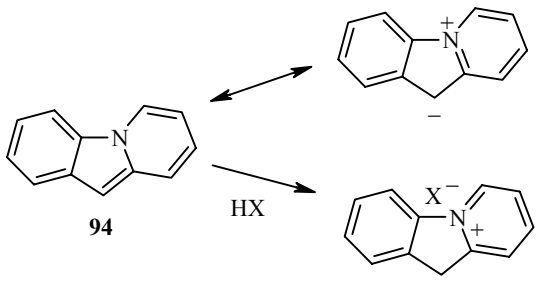
2.1. Quaternization



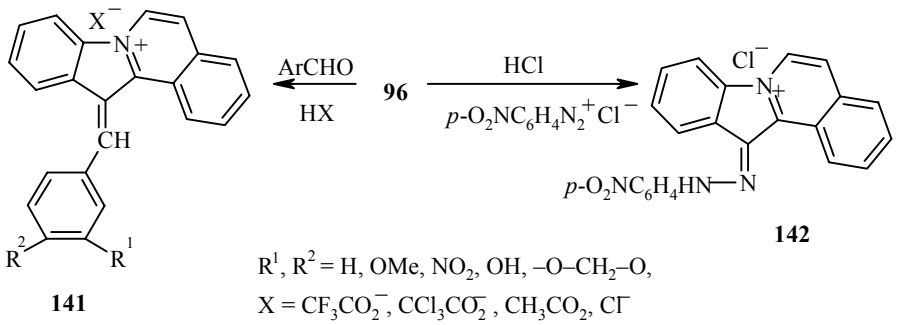
139 **17** R = Me, Et **140**

Indolo[1,2-*a*]pyridines and their benzannellated derivatives form picrates, methiodides, and hydrochlorides [23, 44, 62]. For example, compounds **17** formed the hydrochlorides **139** under normal conditions and were converted by heating with the corresponding alkyl iodides in sealed tubes (100°C, 3 h) into

the 10-alkylated indolopyridinium iodides **140** [23]. It was established on the basis of the ^{1}H NMR spectra of indolo[1,2-*a*]isoquinoline, recorded in trifluoroacetic acid and in deuterochloroform [63], and the spectrum of 9-hydroxyindolo[1,2-*a*]pyridine hydrochloride in DMSO-d_6 [44] that quaternization takes place through protonation of the β-position of the pyrrole ring, irrespective of whether or not it is substituted. Examination of the structure of indolopyridines with a bridgehead heteroatom in the polar canonical form makes such a direction of electrophilic addition and, consequently, orientation of electrophilic monosubstitution obvious.



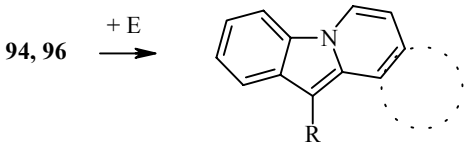
It was established experimentally that indolo[2,1-*a*]isoquinoline **96** and its 5,6-dihydro analog readily condense with aromatic aldehydes or with a *para*-nitrobenzenediazonium salt in an acidic medium to form 12-arylideneindoloisoquinolinium salts **141** or the corresponding hydrazones **142**, which exhibit strong fluorescence [88, 89]:



Such condensation can only take place in an acidic medium through the intermediate formation of quaternary salts protonated at the free position of the pyrrole ring.

2.2. Electrophilic Substitution

The fully aromatic substrates indolopyridine **94** and indoloisoquinoline **96** enter readily into electrophilic substitution, which in neutral or weakly acidic medium takes place at the free position of the electron-excessive pyrrole fragment. Formylation (Vilsmeier), acylation (carboxylic acid chlorides), halogenation, hydroxymethylation (formaldehyde in acetic acid), azo coupling, and nitration take place in this way and give good yields of compounds **143** [10, 11, 64, 89, 90]. Some of the acyl derivatives exhibited antibacterial and fungicidal activity [9] and also antitumor activity [10]. During Mannich aminomethylation the corresponding amine can only be isolated in the form of a quaternary salt. Its hydrochloride is cleaved during treatment with alkali with the formation of the hydroxymethyl derivative.

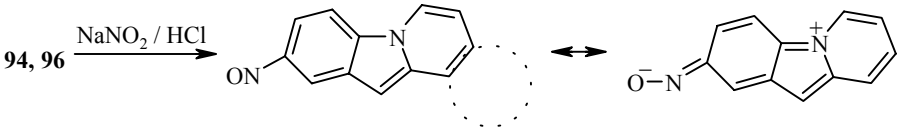


143

R = CHO, COMe, COPh, COC_6H_4Cl–*p,* Br, I, CH_2OH, N_2Ph, $N^+(Et)_3Cl^-$, NO_2

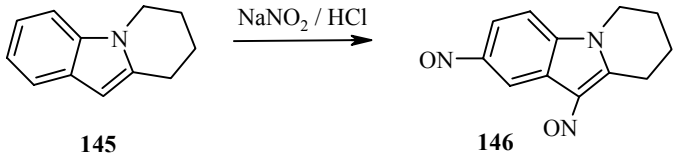
E = electrophile

It should, however, be noted that treatment of the indolopyridines **94** and **96**with sodium nitrite in concentrated hydrochloric acid led to nitrosation not in the pyrrole ring but in the benzene ring with the formation (after neutralization) of the deeply colored mononitroso derivatives **144** [62, 90], the intense color of which can be explained by a large contribution from the polar form **A**.



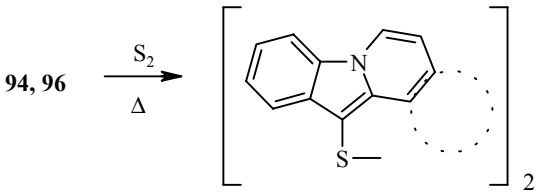
144 **A**

Protonation of the pyrrole ring to its β-H derivative clearly occurs initially under the strongly acidic conditions, and this hinders electrophilic substitution in this ring and directs electrophilic attack at the benzene ring of the indole part. Nevertheless a good yield of the 5,7-dinitro derivative **146** is obtained during the nitrosation of the indole **145** with a fully hydrogenated pyridine ring [62]. In this case the protonation rate probably becomes significantly lower than the nitrosation rate of the 1,2-tetramethylene-substituted indole.



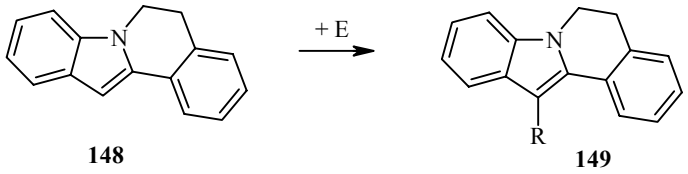
145 **146**

The indolopyridines **94** and **96** react readily with sulfur with relatively mild heating (150°C) [91]. The disulfides **147** are formed with yields of up to 20% as a result of radical substitution in the pyrrole ring.



147

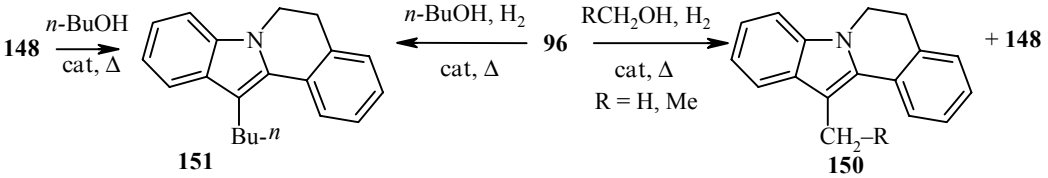
The direction of formylation, acylation, halogenation, azo coupling, and aminomethylation does not change in the transition from the fully aromatic indoloisoquinoline **96** to its 5,6-dihydro derivative [89, 92]. As a result good yields of compound **149** were obtained. The unquaternized Mannich base can be isolated and characterized, but these analogs of biogenic amines are converted after storage for 1-2 months with access to atmospheric moisture into 12-hydroxyindoloisoquinoline, characterized in the form of the O-acetyl derivative.



148 **149**

R = CHO, COMe, COPh, Br, I, CH_2R^1 (R^1 = NMe_2, piperidyl, morpholyl, N_2Ph, NO_2)

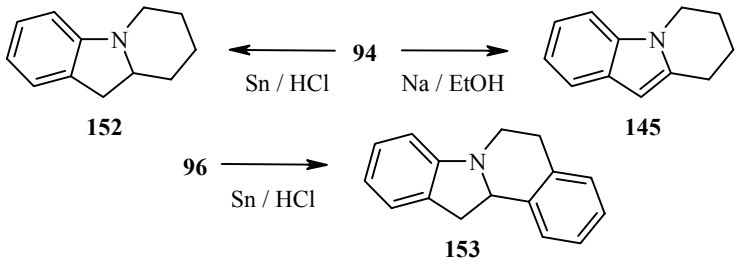
The alkylation of the indoloisoquinoline **96** and its dihydro derivative **148** under the conditions of hydrogenation over rhenium heptasulfide (140 atm, 250°C) in alcohol methanol, ethanol, and butanol takes place by an electrophilic substitution mechanism [9, 93]. The catalyst probably has the characteristics of a Lewis acid, since the yield of the alkylated compounds **150** and **151** increases with decrease in the acidity of the employed alcohols. Amino alcohols and secondary aliphatic alcohols, like phenols, do not alkylate indoloisoquinoline under these conditions.



151 **150**

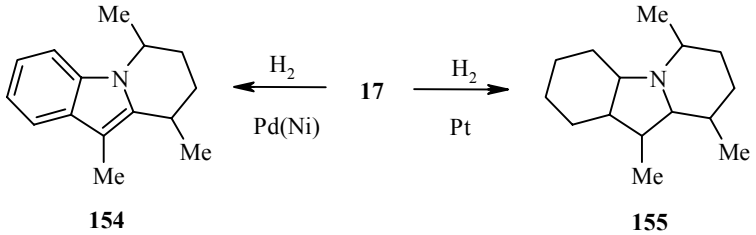
2.3. Reduction

The pyridine ring in the indolopyridine **94** is reduced to the tetrahydro derivative **145** by the action of sodium in alcohol. Tin in hydrochloric acid reduces both heterocyclic fragments in the indolopyridine **94** and indoloisoquinoline **96** to the hexahydro **152** and tetrahydro **153** derivatives respectively [62].



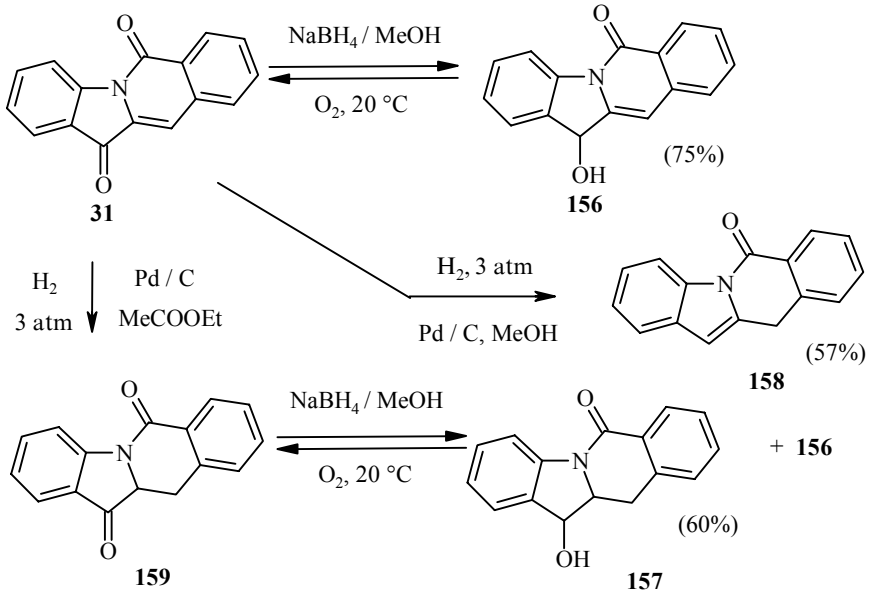
152 **145** **153**

Hydrogenation with hydrogen over palladium or nickel affects only the pyridine ring [22, 23], while the use of a platinum catalyst leads to full hydrogenation of substituted indolopyridines of type **17** [6, 37], including the benzene ring [22, 23]. As a result good yields of compounds **154** and **155** are formed.



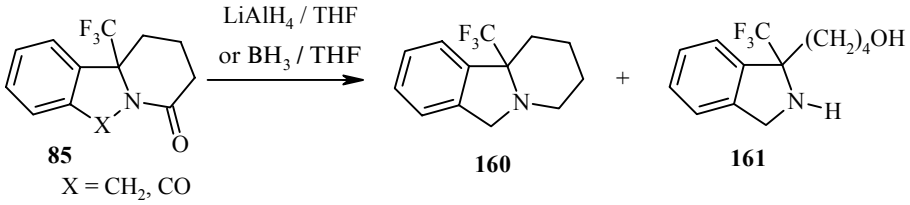
154 **155**

The reduction of diketones of type **31** by sodium borohydride to the alcohols **156** and **157** does not affect the amide carbonyl or the C=C bond in the pyridine fragment [53]. The C=C bond undergoes catalytic hydrogenation with the formation of the ketones **158** and **159**.

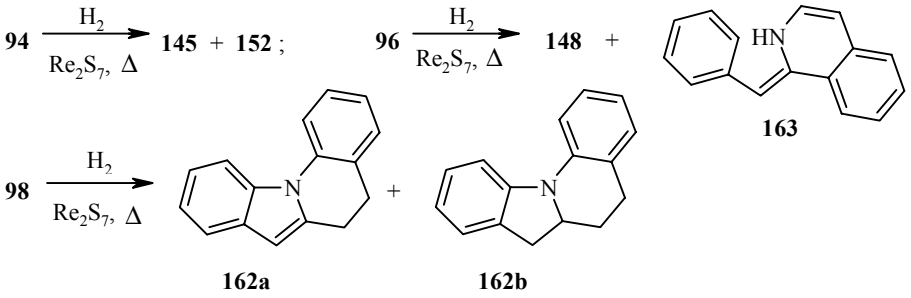


The alcohols **156** and **157** are unstable and are oxidized in air to the initial compounds **31** and **159**.

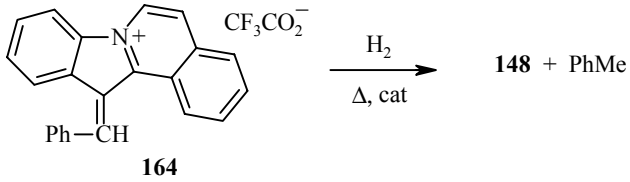
The amide and imide functions can be reduced to the tricycles **85** by lithium aluminum hydride. The formation of the hexahydroisoindolopyridine **160** is accompanied by a side process with decyclization of the piperidine ring, leading to the alcohol **161** (28-39%) [59]. The undesirable reaction can be suppressed if the BH_3–tetrahydrofuran complex is used. This increases the yields of the product **160** from 23-62% to 86-93%.



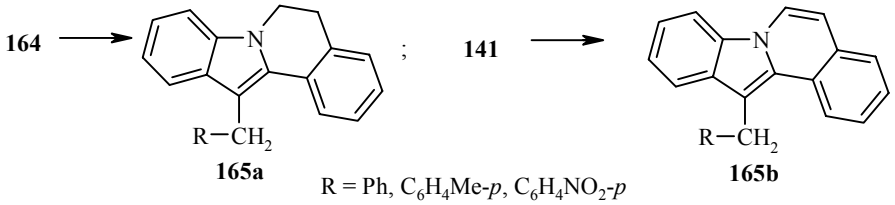
It was established that the degree of saturation of the indolopyridines **96** and **98** with hydrogen during rigorous hydrogenation (250°C, 140 atm, 4 h) depends on their structure (the point of annellation) [94]. In the case of the indolopyridine **94** the tetrahydro and hexahydro derivatives **145** and **152** were obtained in a ratio of ~2:1 with an overall yield of 66%. As a result of hydrogenation of the indoloquinoline **98** under comparable conditions the 5,6-dihydro **162a** and 5,6,6a,7-tetrahydro **162b** derivatives were isolated in a ratio of 3:1. When the coupling of the benzene ring was changed (in the case of the indoloisoquinoline **96**) hydrogenation under these conditions almost stopped at the stage of the formation of the 5,6-dihydro derivative **148** and an insignificant amount of the hydrogenolysis product **163**. The higher degree of hydrogenation of the indole **98** indicates that the dihydro derivative **162a** has higher basicity than the corresponding indole **148**, favoring chemisorption of the former at the acidic centers of the catalyst [94].



Replacement of benzene as solvent by an aliphatic alcohol leads to a decrease in the yield of the dihydroindoloisoquinoline **148** on account of alkylation at the $C_{(12)}$ atom [93]. During an attempt at analogous catalytic hydrogenation of the salt **164** only its hydrogenolysis to compound **148** was observed [89]:

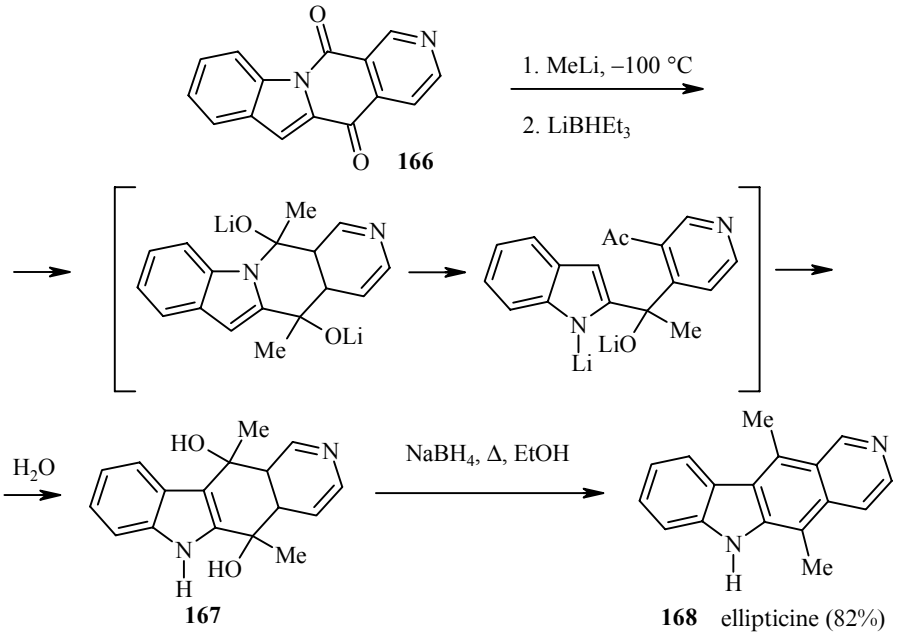


The dihydroindoloisoquinoline **148** was obtained with a yield of 28% when the $NaBH_4/CF_3COOH$ system was used during an investigation of the possibility of noncatalytic reduction of the derivative **96** [89]. In an analogous system the trifluoroacetates **164** and **141** are reduced not to the expected tetrahydro derivatives but to the stable 12-benzyl-substituted indoloisoquinolines **165a** and **165b** respectively with partial hydrogenolysis to the unsubstituted heterocycles **148** and **96** [88, 89].

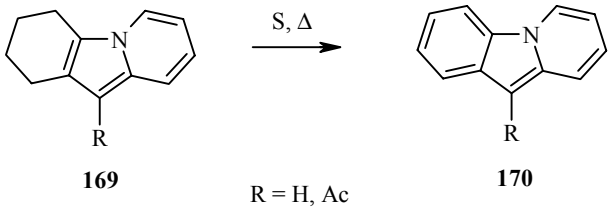


Compound **148** has fungicidal activity, suppressing by ~30% the development of certain pathogenic fungi both *in vitro* and on green plants [9].

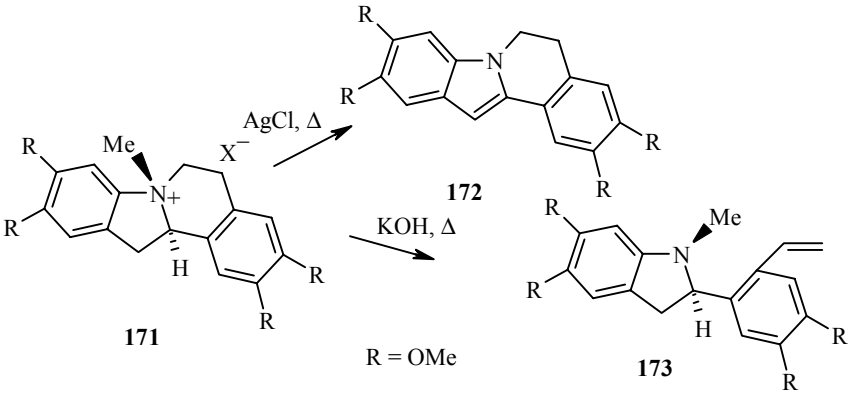
Treatment of the keto lactam **166** with methyllithium and then with superhydride ($LiBHEt_3$) led to the recyclization product, the diol **167**, which underwent reductive dehydroxylation when its alcohol solution was heated in the presence of $NaBH_4$ with the formation of the alkaloid ellipticine (**168**) [26].



2.4. Dehydrogenation and Oxidation

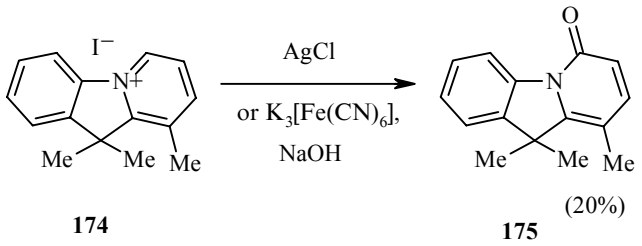


The tetrahydroindolopyridine **169** is readily aromatized when heated with sulfur with the formation of the product **170** [67]. The halomethylate of tetrahydroindoloisoquinoline **171** was converted into the dihydro derivative **172** by the action of AgCl when heated. This indicates greater stabilization by conjugation in the indole fragment than in the isoquinoline fragment [46].



The analogs of compound **172** can be aromatized completely smoothly by the action of various oxidizing agents [48] or palladium on charcoal [69]. The action of heat on the salt **171** in the presence of alkalis leads to its dehydrohalogenation and to cleavage of the piperidine N–C bond with the formation of the 2-aryl-substituted indoline **173** with a yield of up to 69% [46].

The oxidation of indolopyridines with the introduction of oxygen has hardly been studied at all. Indolopyridinium iodide **174** can be oxidized in the presence of AgCl or ferricyanide to a small yield of indolopyridin-4-one (**175**) [23].

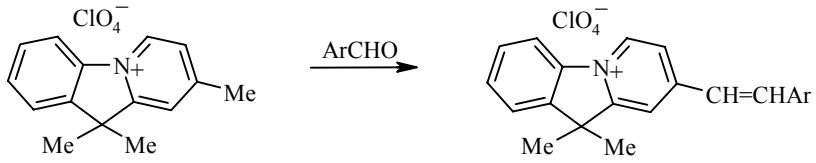


174 **175**

2.5. Chemical Transformations of Substituents

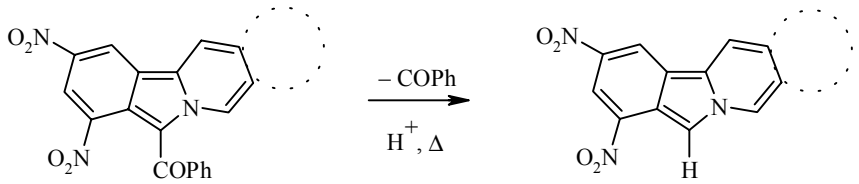
As a rule the alkyl groups in indolopyridines are eliminated under the conditions of pyrolysis. Thus, during an attempt to obtain methyl-substituted indolopyridines by this method the significant or even exclusive formation of unsubstituted polycycles was observed [24-26].

Methyl groups at the α- and γ-positions of the pyridine ring have fairly high CH-acidity, and the corresponding indolopyridines enter readily into condensation with aromatic aldehydes, forming good yields of stilbenes such as **176** [21-23].



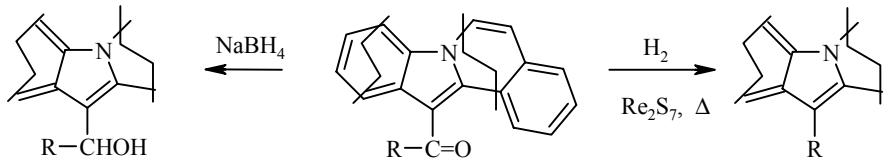
13 **176**

With moderate heating in an acidic medium dinitro- or dichloro-substituted 6-benzoylisoindolopyridines and the corresponding quinolines readily eliminate the benzoyl group and form the isoindolopyridines **177** [71-73].

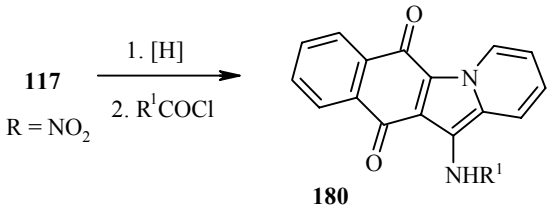


177

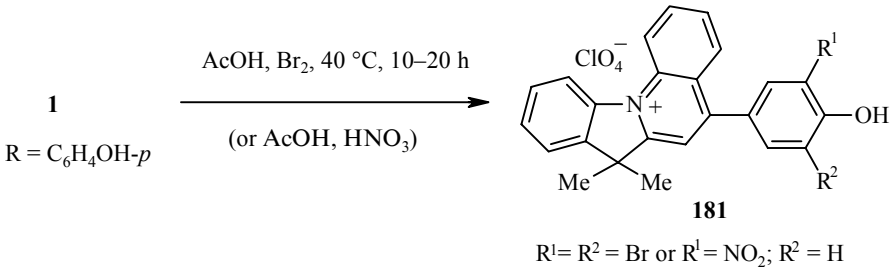
Acyl-substituted indoloisoquinolines **143a** are transformed with high yields into the alcohols **178** by the action of sodium borohydride [90], while their hydrogenation at a catalyst (rhenium heptasulfide) leads to complete reduction of the acyl groups to alkyl groups and the production of compounds **179** [89, 93]. This fact indicates preferential chemisorption of the molecule of **143a** through the C=O group at the acid centers of the catalyst and not through the bridgehead nitrogen.



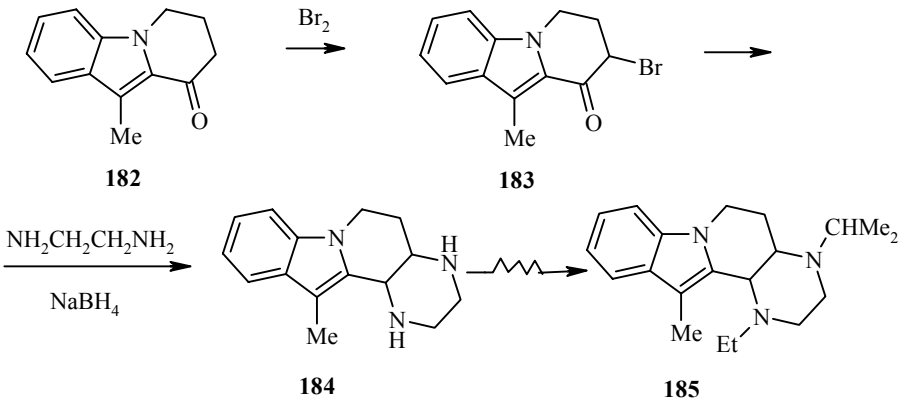
The nitro groups in compound **117** were reduced by sodium sulfide or hydrazine hydrate to amino groups, which were then acylated in order to increase the coloring properties of the chromophoric substrates **180** [81]. The latter were used to confer colors ranging from red to yellow onto polyester fibers with good resistance to the action of oxidizing agents. However, the dyes produced in this way had moderate resistance to the action of light.



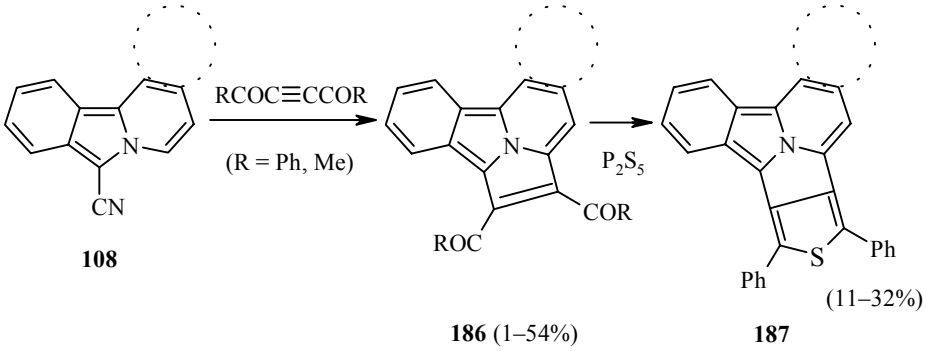
The action of bromine or nitric acid on a solution of 5-(4-hydroxyphenyl)indoloquinolinium perchlorate **1** leads to the products **181** from electrophilic substitution in the phenyl radical without participation of the benzene rings condensed with the heterocyclic fragments [14]. The indolopiperidone **182** is brominated at the α position to the keto group.



The obtained bromo ketone **183** condenses readily with ethylenediamine in the presence of a metal borohydride with the formation of a piperazine ring – compound **184**. The N,N'-dialkyl derivative **185** of the latter exhibits antihypertensive activity [24, 95].

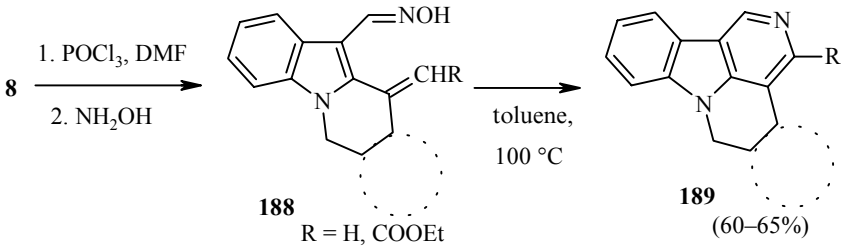


Diacylacetylenes enter into 1,3-dipolar cycloaddition with 6-cyanoisoindolopyridines of type **108** (with elimination of the CN) [70]. 1,2-Diacyl-substituted indolizino[3,4,5-*a,b*]isoindoles **186** are formed. Compounds **108** having other substituents enter into this reaction with difficulty. The interesting possibility of further annellation of the polycycle **186** by its treatment with phosphorus pentasulfide in pyridine, leading to the production of the 18π-electron system **187**, was demonstrated [70].



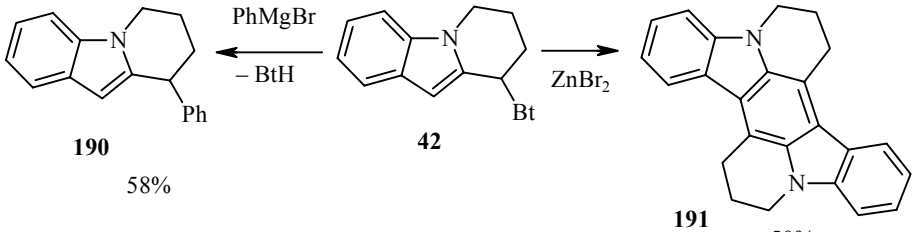
108 **186** (1–54%) **187**

Indolopyridines **8** are easily transformed by means of standard formylation reagents and subsequent oximation into the azatrienes **188**. The latter undergo electrocyclization when heated in toluene and form the indolonaphthiridine system **189**, which forms the basis of antagonists of histamine receptors [11, 15].



8 **188** R = H, COOEt **189** (60–65%)

The benzotriazole substituent in the indolopyridine **42** undergoes nucleophilic substitution by the Grignard reagent (but not sodium cyanide and not thiophenolate) [35]. The phenyl-substituted indolopyridine **190** was isolated with a yield of 58%. Compound **42** dimerizes under the influence of zinc bromide with the elimination of benzotriazole followed by oxidation by atmospheric oxygen. As a result the polycondensed system **191** is formed with a 50% yield.



190 58% **42** **191** 50%

Bt = 1-benzotriazolyl

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