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PYRROLO[2,1-*a*]ISOQUINOLINES (REVIEW)

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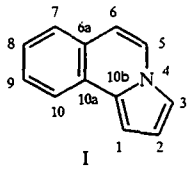
Published data on the synthesis of compounds containing the pyrrolo[2,1-a]isoquinoline system in their structure are reviewed. Examples of substances that have useful properties for practical purposes are given.

Pyrrolo[2,1-*a*]isoquinoline is the benzo analog of indolizine (pyrrocoline):



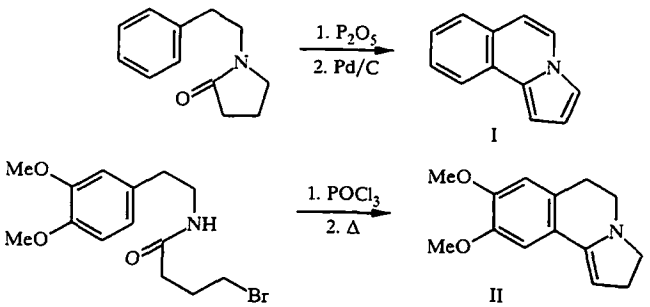
I

The classical chemistry of indolizine has been discussed in a series of reviews [1, 2]. However, there have not so far been any reviews in the literature on the chemistry of the benzo analogs of indolizine. This tricyclic structure forms the basis of certain alkaloids. These are primarily the erythrinanes [3-14] and also, for example, hirsutene [15], cancentrine [16], and lamellar marine molluscs [17]. Synthetic pyrrolo[2,1-*a*]isoquinolines have a wide spectrum of pharmacological activity, including cardiotonic [18-20] and hypotensive [21] effects. Antidepressants were described in [22, 23], and there also substances having antitumor activity [24], inhibitors of the serotonin and dopamine level [25-33], and inhibitors of enzymes [34]. A wide range of the biological activity of these compounds was described in [35-37]. The useful properties of substances having this heterocyclic system in their structure are not restricted to medicine. Thus, the production of pesticides was described in the patent [38], and light-sensitive and photographic materials were described in [39-43]. The diversity in the chemistry of pyrrolo[2,1-*a*]isoquinoline derivatives and the undoubted practical significance of this heterocyclic system make it desirable to review the published data. In the present review the methods for the construction of the pyrrolo[2,1-*a*]isoquinoline system and the reactions of its derivatives are discussed.

I. METHODS FOR THE CONSTRUCTION OF THE PYRROLO[2,1-*a*]-ISOQUINOLINE SYSTEM

1. The Bischler–Napieralski Reaction and Various Types of Cyclization of Butyrolactam Derivatives

Unsubstituted pyrrolo[2,1-*a*]isoquinoline (I) was obtained in 1953 by the Bischler–Napieralski reaction [44]:



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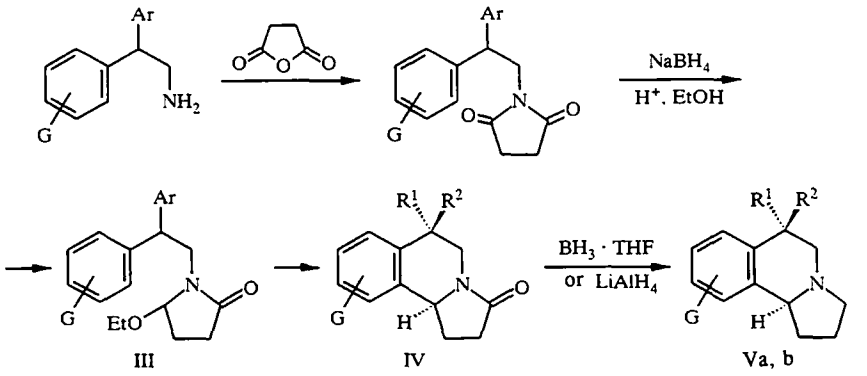
The pyrrolo[2,1-*a*]isoquinoline system (II), obtained by the same classical method, became known as far back as 1931 [45]. The synthesis of the system by the Bischler–Napieralski reaction usually involves two groups of methods, one of which is the direct cyclization of butyrolactam derivatives [44]. In the other the isoquinoline ring is produced first, and the pyrrole ring is then constructed by various methods as, for example, in [45]. There are few examples of the use of the Bischler–Napieralski reaction in its classical form for the synthesis of the pyrrolo[2,1-*a*]isoquinoline system in the literature [46-49].

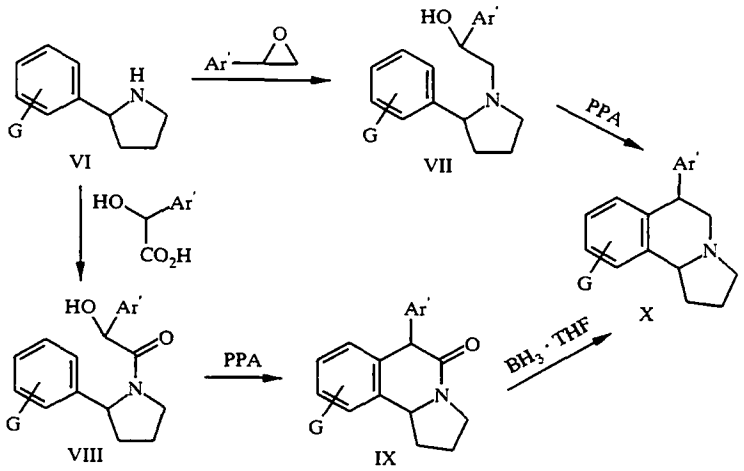
In addition to the Bischler–Napieralski reaction, other methods for the cyclization of N-(β-phenylethyl)pyrrolidines, leading to the pyrrolo[2,1-*a*]isoquinoline system, are known. Two main methods have been used for the production of the compounds [50-52]. The first of them is the acyliminium cyclization of the lactam (III) or of lactams close to it in structure. Investigations of the stereochemistry showed that with R^1/R^2 = Ar or H, the acyliminium path is highly selective and gives the *cis* isomer [6α, 10*b*α, compound (Va)]. The *trans* diastereomers (Vb) (6α, 10*b*β) were obtained by the base-catalyzed epimerization of the lactam, enriched in the *cis* isomer, or of the corresponding amine (after reduction):



Va (cis) R^1 = Ar, R^2 = H; b (trans) R^1 = H, R^2 = Ar

In the case where R^1/R^2 = Ph and Me, cyclohexyl, and hydrogen, a mixture of the diastereomers of the lactams in an approximate ratio of 1:1 was obtained [51]. The stereoselectivity changed abruptly for the case where R^1/R^2 = H and cyclohexyl, and a mixture of lactams with a preference for the *trans* isomer in a ratio of 88:12 was obtained [52]. The described cyclization through the acyliminium ion was successful and selective in the case of the synthesis of structures similar to the erythrine alkaloids [53].

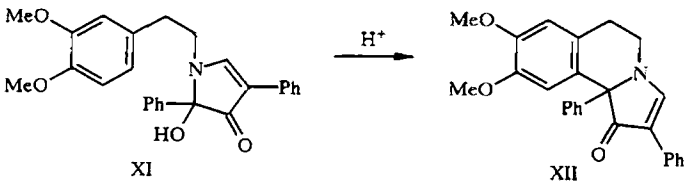
The second path [50] is the cyclization of mandelic acid or styrene oxide. In this method the respective 2-arylpyrrolidine (VI) and styrene oxide are boiled in ethanol, DMFA, or sulfolane to produce the intermediate amino alcohols (VII). The latter then undergo cyclization with polyphosphoric acid with the formation of a mixture of isomers in a ratio of 3:1 with a preference for the *cis* isomer. In the method with the derivatives of mandelic acid, the respective 2-arylpyrrolidine (VI) and mandelic are submitted to high-temperature condensation in boiling xylene with the formation of the intermediate hydroxyamides (VIII). The latter are cyclized like the amino alcohols at 100°C with the formation of the lactams (IX), rich in the *cis* isomer:



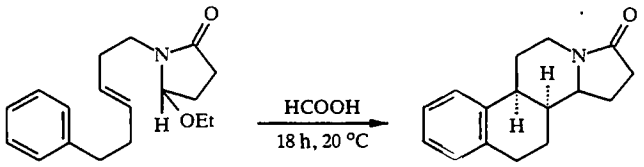
This method was used to obtain substances containing the furan or thiophene residue at position 6 [54]. The lactams (IV) or (IX) in the case where R^1/R^2 = Ar or H were submitted to epimerization in aqueous DMSO by the action of potassium carbonate in order to produce the required ratio of *cis* and *trans* isomers and were then reduced.

Papers by the same authors [55-60] were devoted to the stereochemistry of the compounds obtained by the discussed methods and to the development of HPLC methods to monitor the course of the reactions and optimize the conditions for the production of enantiomerically pure compounds [61]. Aspects of the pharmacology of the compounds were touched upon in a series of papers [22, 23, 50, 62, 63].

In addition to the methods discussed above, there are other methods for the construction of the pyrrolo[2,1-*a*]isoquinoline system based on the aryl derivatives of butyrolactam in the literature, e.g., the cyclization of the hydroxylactams (XI) and their derivatives [64-67]. The acylimminium cyclization of compounds (XIII) is accompanied by the simultaneous stereospecific formation of C–C bonds [67].

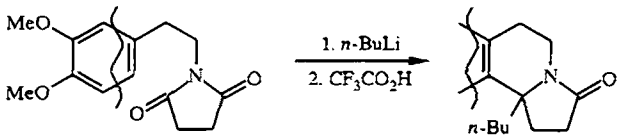


XI XII

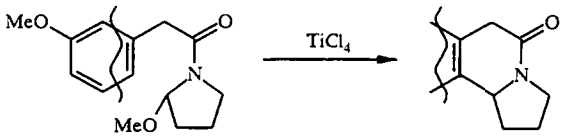


XIII XIV

The method involving the cyclization of hydroxy lactams, obtained by means of organolithium compounds, merits attention. Thus, the treatment of the succinimide (XV) with *n*-butyllithium (−78°C) followed by the addition of trifluoroacetic acid leads to compound (XVI) [68]:

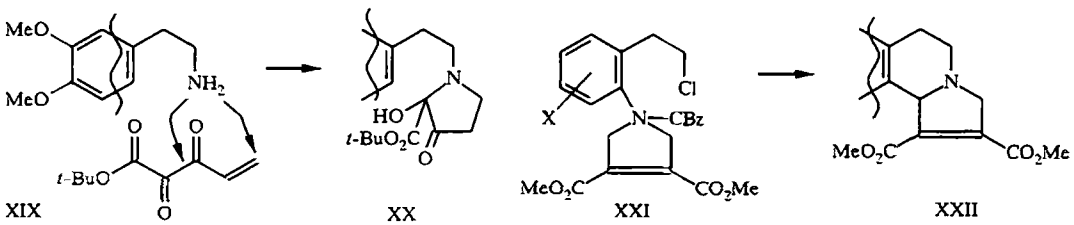


XV XVI



XVII XVIII

The cyclization of such derivatives of pyrrolidine is possible under the influence both of Lewis acids such as $TiCl_4$ [the amide (XVII)] [69] and of protic acids [70]. A convenient method for the production of the hydroxy lactones required for such cyclization proposes the use of vicinal tricarbonyl compounds [71, 72], like compound (XIX):



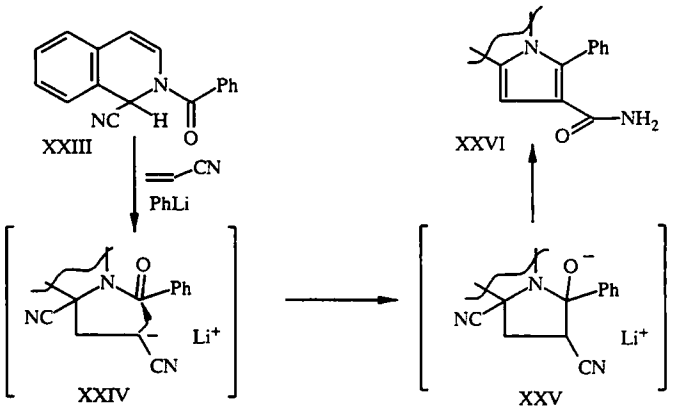
XIX XX XXI XXII

The originality of the method in [73], in which the cyclization of compound (XXI) to the ester (XXII) takes place with the simultaneous removal of the benzyloxycarbonyl group (CBz), is undoubted.

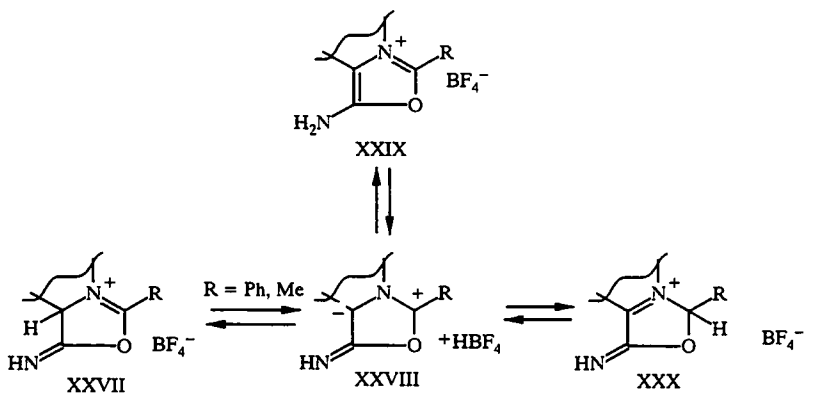
The pyrrolo[2,1-*a*]isoquinoline system can be produced by intramolecular Friedel–Crafts cyclization of 2-phenylpyrrolidine substituted at the nitrogen atom by hydroxyethyl or bromoethyl groups [74]. (The stereochemistry of the reaction was examined.) An example of the production of the tricyclic system by the Pictet–Spengler reaction in its classical form is also known [75].

2. Syntheses by Means of Reissert Compounds and Dipolar Addition

A general method for the synthesis of the pyrrolo[2,1-*a*]isoquinoline ring system is the Michael reaction of Reissert compounds (XXIII) [44]:

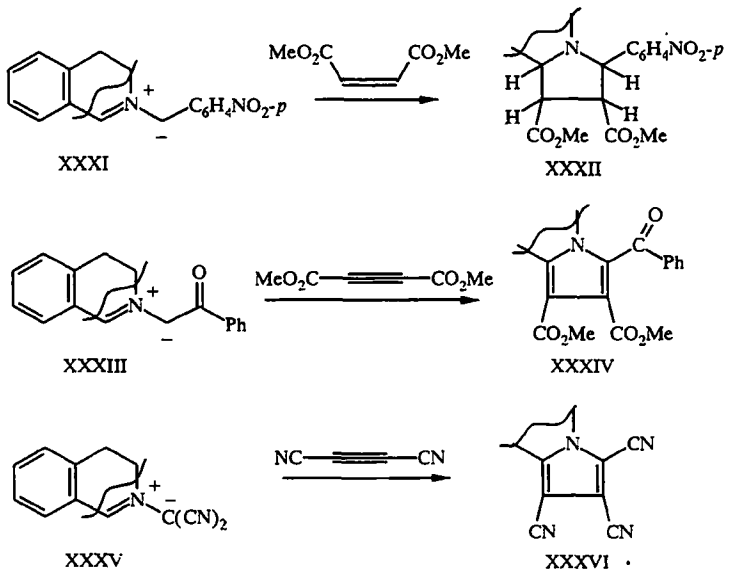


The final product during the addition of the anion of compound (XXIII) to acrylonitrile is compound (XXVI), which is probably formed through the intermediate compounds (XXIV) and (XXV) [44, 76]. Further investigations demonstrated the wide possibilities of using Reissert compounds as synthons. Thus, acrylonitrile was used in this reaction [77], and syntheses using various alkenes [78-81], such as acrylic, fumaric, and maleic esters [78, 80], were examined. Syntheses were conducted successfully with alkynes [82-84]. Investigation of the equilibrium of Reissert compounds in solution showed that the reaction path and the structure of the obtained substances are related to one or the other tautomeric form. There is a view [81] that solutions of the hydrofluoroborates of 2-acyl-1,2-dihydroisoquinaldonitriles (Reissert compounds) consist of mixtures of forms (XXVII-XXX) with a preference for form (XXX). The "true Reissert compound" is considered to be form (XXVIII), which is a mesoionic compound:



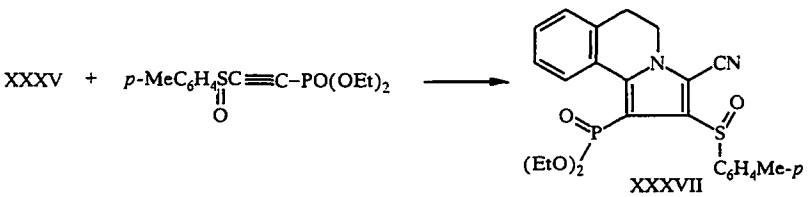
In [83] the kinetic and thermodynamic factors associated with the equilibrium are examined, and mechanisms for the processes leading to the formation of the pyrrolo[2,1-*a*]isoquinoline system are suggested.

The synthesis of the pyrrolo[2,1-*a*]isoquinoline system by 1,3-dipolar cycloaddition was first realized in 1963 by the reaction of the azomethine ylide (XXXI) with dimethyl fumarate [85]:

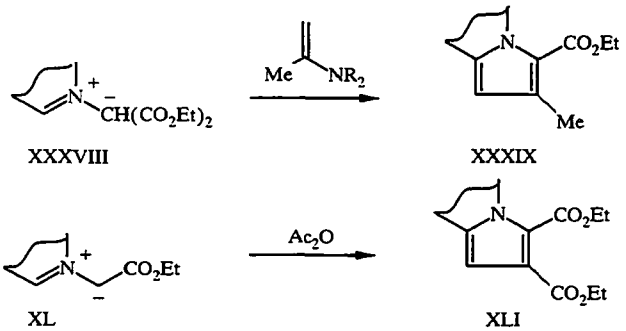


The reactivity of 1,3-dipoles and dipolarophiles depends on the electronic and steric nature of the substituents; substitution at positions 1, 2, and 3 of the indolizidine system that forms is restricted as a rule to electron-withdrawing and small groups. Acetylenes are often used as dipolarophiles. For example, the reaction of the ylide (XXXIII) with dimethyl acetylenedicarboxylate leads to compound (XXXIV) [86, 87]. The dicyanomethylide (XXXV), which is easily formed in the reaction of isoquinoline with tetracyanooxirane, readily enters into cycloaddition with the formation of compounds of the (XXXVI) type [88]. In [89] the frontier orbital interaction was calculated, and it was shown that an experiment with isoquinoline dicyanomethylide agreed well with the theoretical predictions. Reactions with acetylenes were also examined in [90, 91].

N-Furylmethylisoquinolinium bromides were also used as dipole component [92, 93]. The reaction of the methylide (XXXV) with diethyl [(*p*-tolylsulfonyl)ethynyl]phosphonate and related acetylenes [94], leading to compound (XXXVII), is well known:

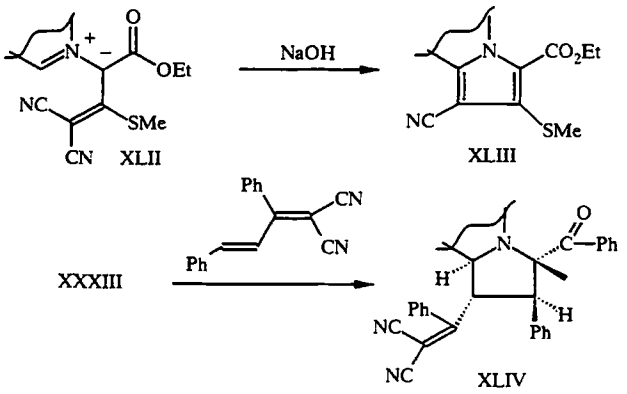


A large number of investigations have been carried out with various alkenes as dipolarophiles, and in the simplest case the alkene can be acrylonitrile [95, 96]. In the case of stabilizing ylides such as (XXXVIII) it is possible to use alkenes containing methoxy groups [97]. In [98] enamines were used, and in this case compounds (XXXIX) were obtained:



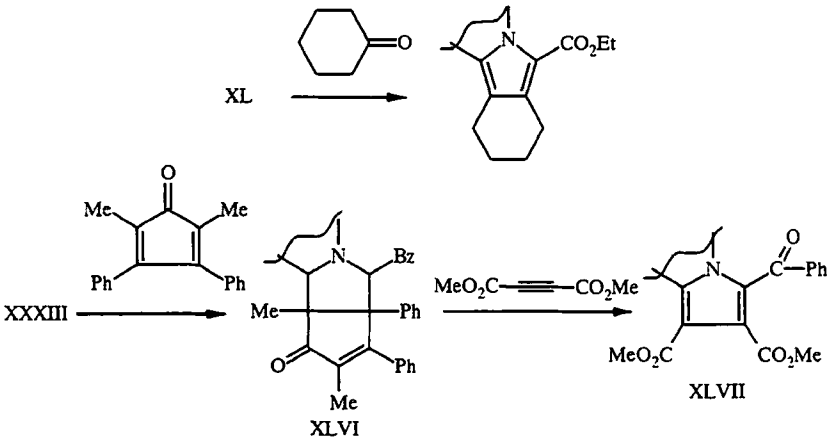
The possibility of using inactivated and electron-rich olefins (stilbene, indene, allyl alcohol, butoxy- and thiophenoxyethylenes, etc.) in reaction with dipoles of the (XXXV) and (XXXVIII) type was demonstrated in [99]. Various

alkenes and 1,3-dipoles were presented in [100-109]. Isoquinolinium ylides of the (XL) type react with acid anhydrides with the formation of compounds (XLI) [110]. The novelty of the method in [111], which represents the intramolecular cyclization of compound (XLII), is undoubted:

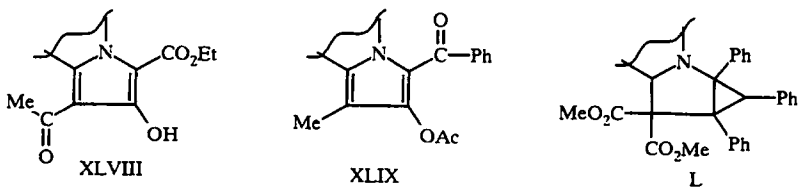


The regio- and stereoselectivity of the 1,3-dipolar cycloaddition of nitriles of the *trans*-1,3-butadiene series were studied for the ylide (XXXIII) [112, 113]. The authors explain the selectivity of the process by the fact that the reaction takes place as *endo*-addition of the dipolarophile molecule to the *anti*-form of the ylide through a five-center transition state [112] with the conservation of orbital symmetry. It should be noted that all the examples examined above with the exception of [85] involved the aromatic system of isoquinoline. Investigations showed the successful application of the 3,4-dihydroisoquinoline system for the same purposes [114-118]. The regioselectivity of such reactions was established by means of the CNDO/2 and CNDO/S approximations [117].

Ketones, which probably react in the enolic form can be used as dipolarophile [119, 120]. Compound (XLV) is formed in this way:

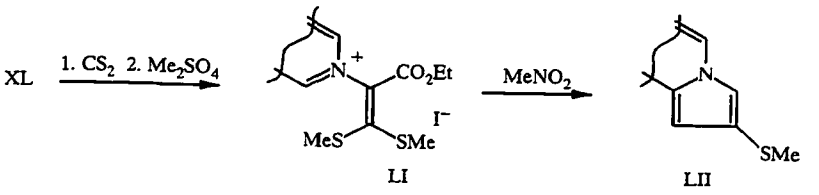


The example in [121] is interesting. In this process, compound (XXXIII) reacts with a cyclopentadienone derivative to form the adduct (XLVI), which forms the final reaction product (XLVII) in reaction with dimethyl acetylenedicarboxylate. The reactions of 1,3-dipoles with acylketenes leads to substances of the (XLVIII, XLIX) type [122, 123].

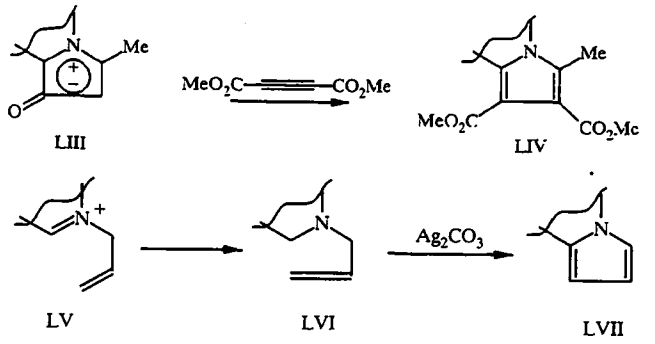


In reaction with 1,2,3-triphenylcyclopropene, the stable ylides (XXXV) and (XXXVIII) give substances similar in structure to compound (L) [124, 125]. Reactions of 1,3-dipoles under the conditions of phase-transfer catalysis are known [126]. The chemistry of isolated ylides was examined in [127].

During successive treatment with carbon disulfide and dimethyl sulfate, the ylide (XL), which is a nucleophile, gives the salt (LI) [128, 129], and this reacts with the C-nucleophilic nitromethane. The further elimination of the ready leaving groups and decarboxylation lead to compound (LII):

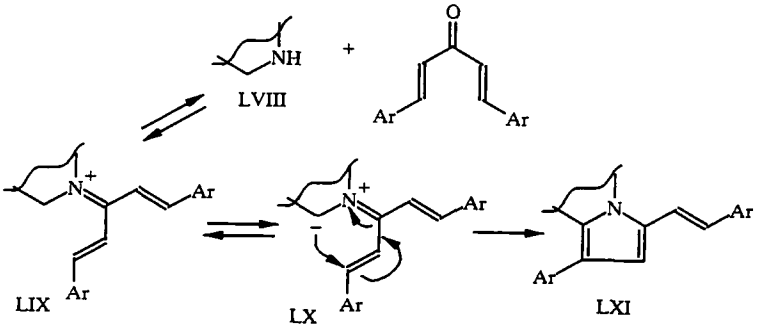


The 1,3-dipolar cycloaddition reactions of compounds (LIII), called "munchnones," are original [130]:

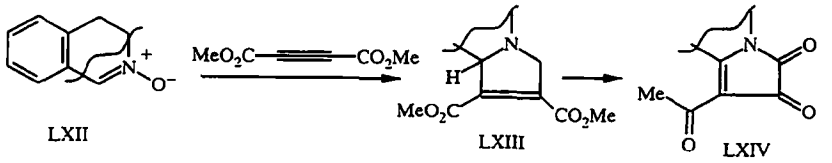


A series of tertiary N-allylamines (LV) were obtained in [131, 132]. They were submitted to oxidative cyclization by the action of silver carbonate with the formation of compounds (LVII) as final reaction products.

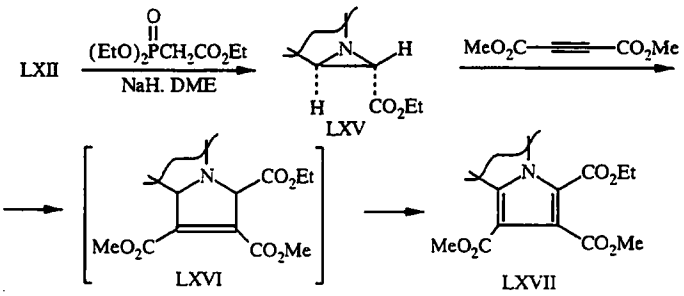
In the opinion of the authors of [133], azomethine ylides of the (LIX) type, generated from 1,2,3,4-tetrahydroisoquinoline and diarylideneacetone, undergo 1,5-electrocyclization followed by prototropic rearrangement with the formation of compounds (LXI):



An appreciable number of the publications concerned with methods for the construction of the pyrrolo[2,1-*a*]isoquinoline system have been devoted to the chemistry of nitrones, which are also 1,3-dipoles. Compound (LXIII), which gives the dihydroxypyrroline (LXIV) during rearrangement, was obtained by the reaction of the nitrone (LXII) with acetylenedicarboxylate [134]:

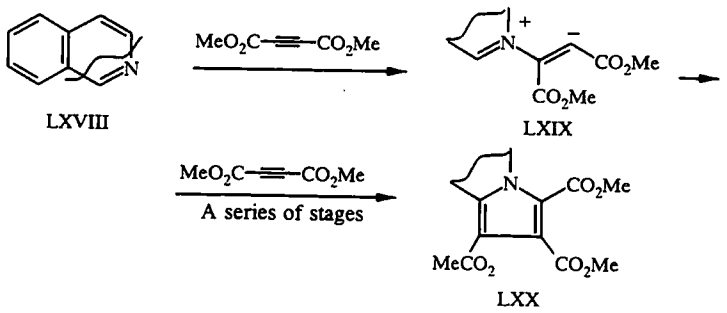


A similar result was obtained with unsaturated carboxylic acids [135], ethyl propiolate [136], 1,2-di(trifluoromethyl)acetylene [137], and phospholipids [138] as dipolarophiles. In the last case, the reaction takes place through the formation of the aziridines (LXV). They react with dimethyl acetylenedicarboxylate with the formation of the intermediate (LXVI), which is aromatized to the pyrrole (LXVII):

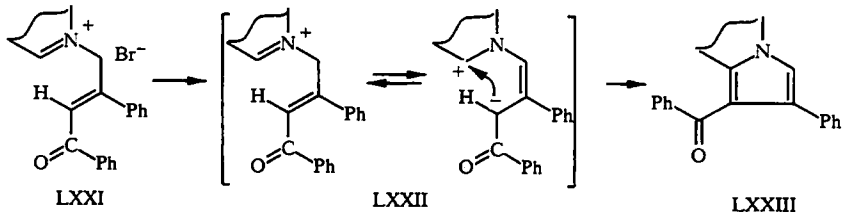


The stereochemistry of the cycloaddition reactions involving the nitrones is complicated by a stage involving cycloinversion of the isoxazoline (LXIII) to the final product (LXIV). The dependence of the stereochemistry of this process on the substituent in the alkene was examined in [139].

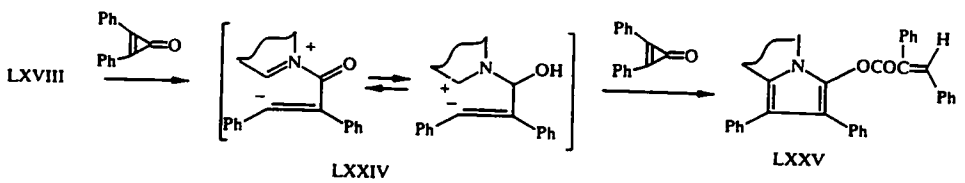
The reaction of the isoquinoline (LXVIII) with acetylenedicarboxylate, in which one of the paths leads to pyrrolo[2,1-*a*]isoquinoline (LXX), is known in the literature. The proposed mechanism of this condensation [140] is complex. At the same time, it was suggested that 1,3-dipoles were formed as intermediates [141-143]:



Another type of cycloaddition leading to the pyrrolo[2,1-*a*]isoquinoline system is cyclization with the participation of 1,5-dipoles. The simplest example of this type of reaction can be considered to be 1,5-dipolar cycloaddition with N-allylisoquinolinium ylides [2]. In the simplest case, N-allylisoquinolinium bromide (LXXI) smoothly forms the corresponding indolizine (LXXIII) when treated with potassium carbonate in alcohol or chloroform. The reaction takes place through the formation of the dipolar ion (LXXII):



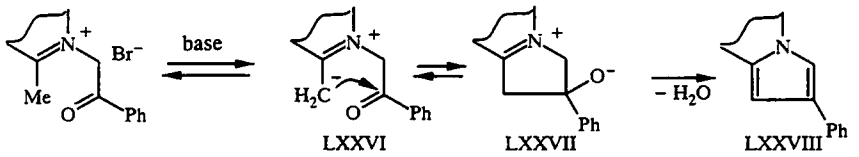
1,5-Dipolar cycloaddition involves the use of cyclopropenones. Thus, for example, the reaction of the isoquinoline (LXVIII) with diphenylcyclopropenone gives compound (LXXV) [144]:



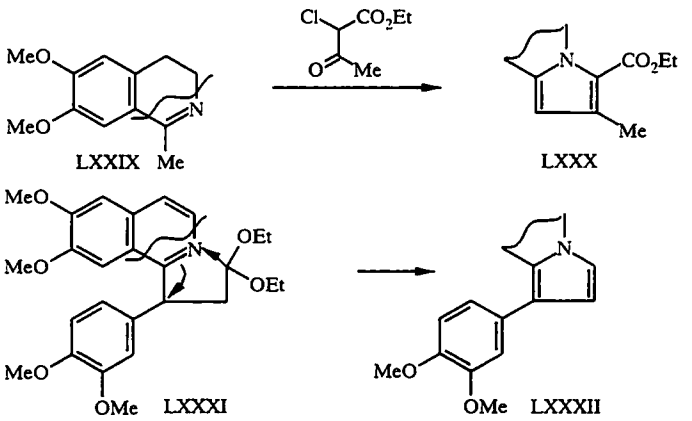
The analogous reaction of the isoquinoline (LXVIII) with diphenylcyclopropenethione [145] and also the reaction of diphenylcyclopropenone and the corresponding thione with 3,4-dihydroisoquinoline [146] are known. The reactions of 3,4-dihydroisoquinoline with diphenylcyclopropenone and thiafulvene have also been investigated [147].

3. Cyclization by the Chichibabin Method and with the Use of Enamines of the Isoquinoline Series

The classical method for the construction of the pyrrolo[2,1-*a*]isoquinoline system is cyclization of the quaternary ammonium salts obtained from α-alkylpyridines and α-halogeno ketones. The reaction was discovered in 1927 by Chichibabin [148]. It is assumed that the reaction takes place through the intermediate (LXXVI) and is reminiscent of 1,5-dipolar cyclization [2]:

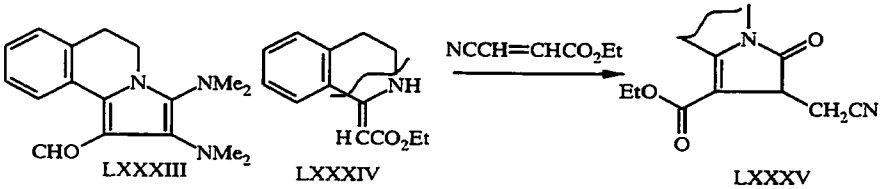


Aromatic or 3,4-dihydroisoquinoline, having a methyl group at position 1, can be used as the initial base. Photographic filters were obtained as a result of the Chichibabin cyclization of the aromatic isoquinoline [149]. Similar results were obtained during the reaction of α-halogenocarbonyl compounds with papaverine [37]. The reaction of 1-methyl-3,4-dihydroisoquinoline with bromoacetophenone [150, 151] and also the cyclization of compound (LXXIX) with α-chloro ketones, e.g., with chloroacetoacetic ester, are known [152, 153]:

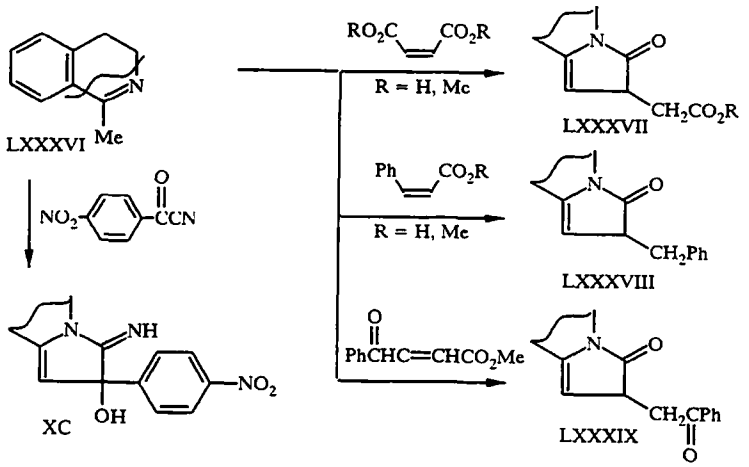


In addition to the Chichibabin reaction, there are a whole group of methods for the condensation of 1-methylisoquinoline with various electrophilic reagents, leading to the pyrrolo[2,1-*a*]isoquinoline system. The isoquinoline ring may be aromatic [37, 149], but in the overwhelming majority of cases it is hydrogenated. The possibility of these reactions is due to the fact that 1-methyl-3,4-dihydroisoquinoline (and, probably, the corresponding heteroaromatic ring) exists in the form of an enamine. Thus, for example, the papaverine derivative (LXXXI) gives compound (LXXXII) when treated with formic acid in DMFA [154, 155]. A new pyrroloisoquinoline (LXXXIII) was obtained from 1-methyl-3,4-dihydroisoquinoline by the action of phosphorus oxychloride and DMFA in the Vilsmeier–Haack reaction [156]. The same tricyclic system is formed during the reaction of enamines of the 1,2,3,4-tetrahydroisoquinoline series with nitroalkenes [157].

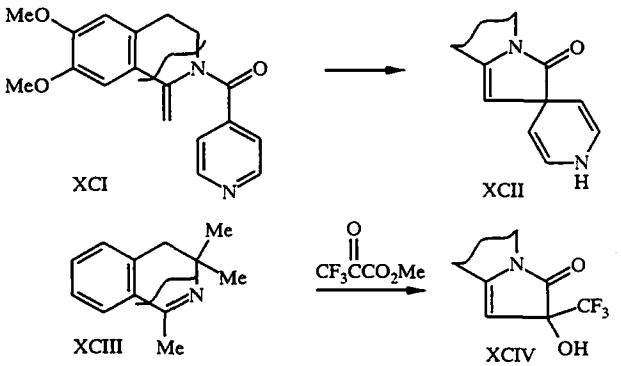
Investigations into the reactions of enamines of the 3,4-dihydroisoquinoline series with conjugated nitriles deserve attention. The reaction of the enamino ester (LXXXIV) with 3-ethoxycarbonylacrylonitrile leads to compound (LXXXV) [158]:



Syntheses based on the analogous conjugate addition of enamines of the 3,4-dihydroisoquinoline series are known. Thus, the reaction of the enamine (LXXXVI) with fumaric and maleic acids or their esters gives compounds (LXXXVII), and the reaction with cinnamic acid or its methyl ester gives the lactams (LXXXVIII) [159]. Analogous results were obtained with the anhydrides and imides of unsaturated carboxylic acids [160-162]. For example, the reaction with methyl β-benzoylacrylate leads to compound (LXXXIX) [161]. The formation of the condensed compound (XC) was observed during the reaction of the enamine (LXXXVI) with *p*-nitrobenzoyl cyanide [163].

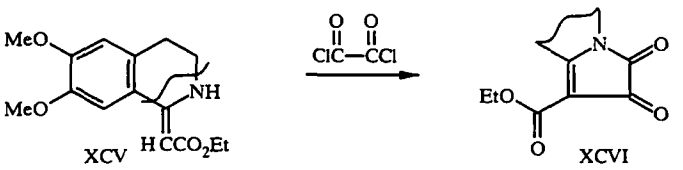


During a novel reaction [164] in an excess of isonicotinoyl chloride, the acylated enamine (XCI) forms the spirodihydropyridine (XCII):

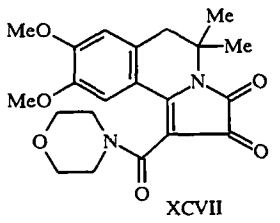


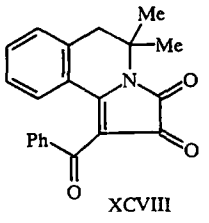
A series of papers were concerned with the search for methods for the synthesis of various enamines of the 3,4-dihydroisoquinoline series, which can be used as starting materials for the construction of the pyrrolo[2,1-*a*]isoquinoline system. Thus, the Ritter reaction was studied, and methods were developed for the synthesis of 1-methyl- and 1-benzyl-3,3-dialkylisoquinolines [165, 166], enamino esters [167], and enaminoamides [168] of the isoquinoline series and also the respective benzo[*f*] derivatives [169]. Using the obtained enamides, e.g., compound (XCIII), the authors investigated their reactions with fluorocarbonyl reagents. The products of the reaction of the enamine (XCIII) with methyl trifluoropyruvate is the condensed isoquinoline (XCIV) [170]. The Noshpa molecule [1-(3,4-diethoxybenzylidene)-6,7-diethoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride] was modified in a similar way [171].

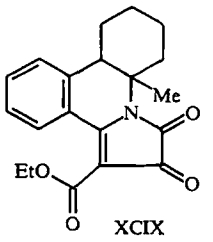
The reaction of enamines with oxalyl chloride is of particular significance. If enamines of the 3,4-dihydroisoquinoline series are used as starting reagents, the corresponding dioxopyrrolines are formed, while the enamino ester (XCV) forms compound (XCVI) [172, 173]:

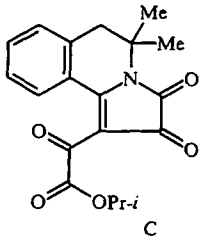


Analogous results were obtained with 1-methyl-3,4-dihydroisoquinolines [174, 175], the corresponding benzyl derivatives [175, 176], and benzo[*f*]isoquinolines [177, 178] as starting compounds. The authors of [179] obtained amides of the (XCVII) type and ketones such as (XCVIII) [180]. The method that we developed for the synthesis of enamines of the phenanthridine series makes it possible to obtain tetracyclic substances of the (XCIX) type [180]. By further investigations it was possible to develop methods for the synthesis of tetracarbonyl compounds such as (C) [182].


XCVII


XCVIII

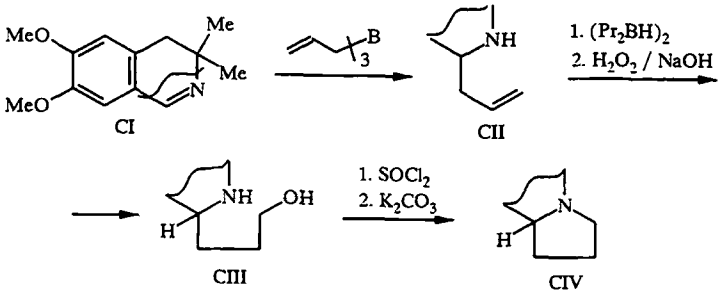

XCIX


C

A distinctive feature of the dioxopyrrolines (XCVI-C) and the corresponding compounds having aryl, alkyl, or a hydrogen atom at position 1 is their bright red color. We studied the electronic spectra of these compounds and their derivatives [183]. Their color is due to structural features of the dioxopyrroline fragment, which has a series of chromophores (C=O, C=C, Ph) in the ring. A condition that favors the creation of a general π-conjugated system is the planar structure of the pyrrole ring.

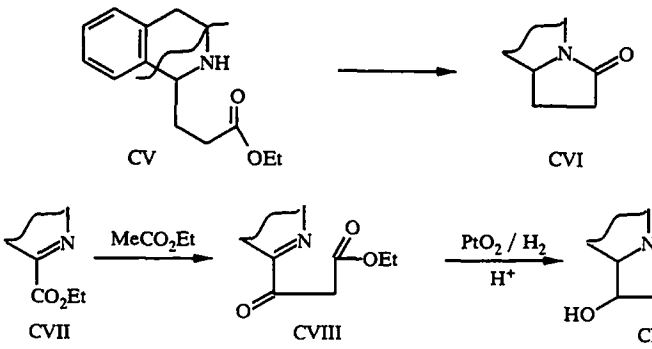
4. Annelation of Pyrrole with the Use of 1-Propyl-Substituted Isoquinolines

The classical method for the construction of the system under discussion is closure of the pyrrole ring in 1-(γ-bromopropyl)isoquinoline [45]. In spite of the age and the obvious nature of the method, there are hardly any examples of its use in the literature. A new approach to the construction of the tricyclic system proposed in the patent [184] involved allylboration. The reaction of the azomethine (CI) with triallylborane leads to compound (CII), which during hydroboronation–oxidation at the double bond forms the alcohol (CIII). During subsequent treatment with thionyl chloride and potassium carbonate, compound (CIII) gives the condensed compound (CIV):

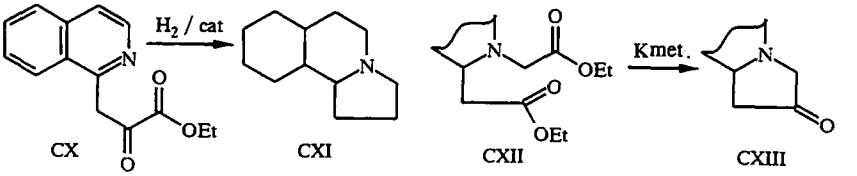


CI CII CIII CIV

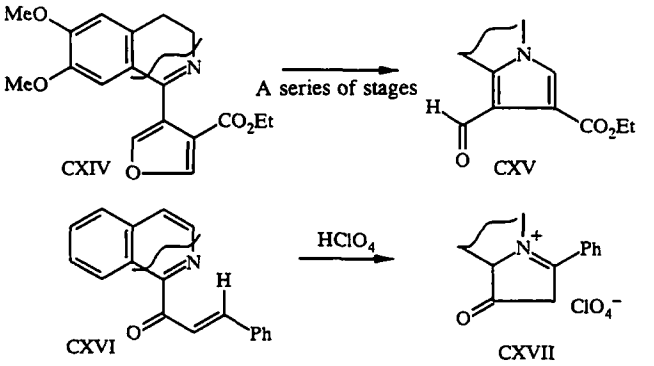
Another classical method for the construction of the pyrrolo[2,1-*a*]isoquinoline system involves the use of β-isoquinolylpropionic esters. There is an example of the use of the acid [185]. Using the Ritter reaction, the authors in [186] synthesized the propionic ester (CV), which underwent cyclization to the corresponding lactam (CVI):



Another example is [187], in which compound (CVII) was condensed with ethyl acetate with the formation of the keto ester (CVIII). During cyclization and catalytic hydrogenation the latter gives the lactam (CIX). The hydrogenation of ethyl 1-isoquinolylpyruvate over copper chromite led to reductive cyclization with the formation of compound (CXI) [188]:



The cyclization of an ester similar in structure to compound (CV) but containing hydroxy groups at the α and β positions of the acid residue is interesting. It was shown [189] that compounds of this type undergo cyclization under the influence of ammonia and that the process is stereospecific. In another paper [190] a compound similar to (CV) was alkylated with ethyl bromoacetate with the formation of the ester (CXII), the intramolecular cyclization of which with metallic potassium led to the ketone (CXIII). An original transformation of 1-furyl-3,4-dihydroisoquinoline derivatives took place under the influence of bases [191-193]:

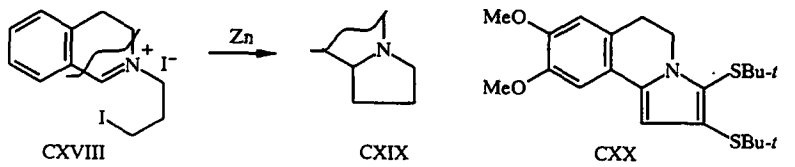


Other examples of annelation of the pyrrole ring on the basis of the 1-*n*-propylisoquinoline skeleton are known in the literature. For example, the treatment of 1-cinnamoylisoquinoline (CXVI) with perchloric acid in alcohol gave compound (CXVII) [194].

5. Other Methods

Some methods for the synthesis of the pyrrolo[2,1-*a*]isoquinoline system are known only from individual papers. It is difficult to classify these methods according to their chemical characteristics.

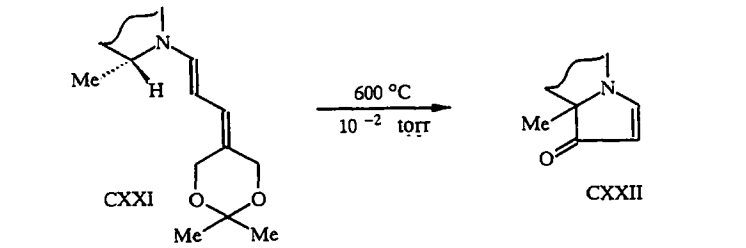
The simplicity and originality of the method in [195] are undoubted. Here, the cyclization of the isoquinolinium iodide (CXVIII) to (CXIX) takes place under the influence of zinc:



CXVIII CXIX CXX

In [196] it was shown that 1,2,3-tri(*tert*-butylthio)cyclopropenium perchlorate and the analogous cyclopropenes in reaction with 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline give compounds of the (CXX) type.

Vacuum flash photolysis of (CXXI), which is accompanied by the loss of optical activity, gives the ketone (CXXII) as a mixture of enantiomers [197]:

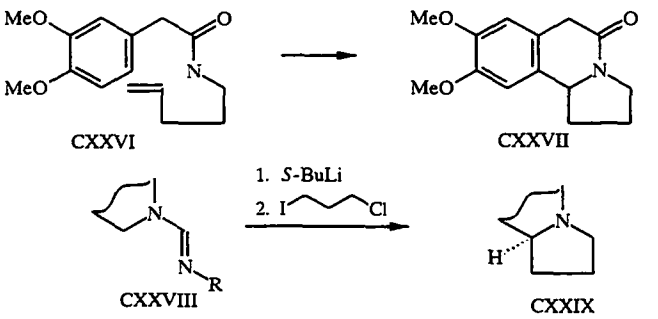


CXXI CXXII

XXXIII CXXIII CXXIV CXXV

In reaction with nitromethane N-phenacylcycloimmonium salts like (CXXIII) form compound (CXXIV). This compound undergoes cyclization, forming the condensed compound (CXXV) through a series of stages [198].

The cyclization of the N-acyliminium ion obtained from compound (CXXVI) leads to compound (CXXVII) [199]:

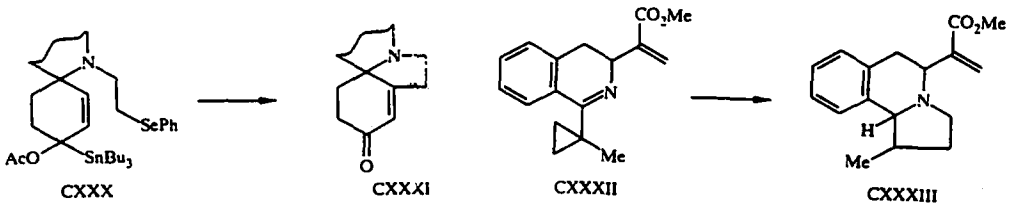


CXXVI CXXVII

CXXVIII CXXIX

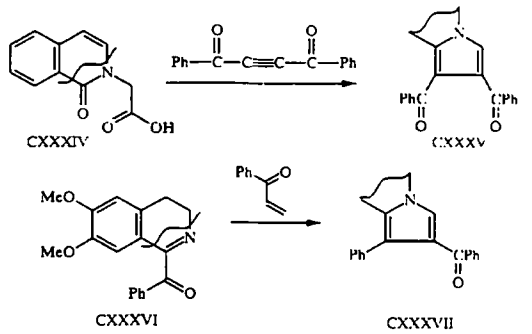
Attention is drawn to a series of transformations of formamidines (CXXVIII), including the reaction with *sec*-butyllithium and 1,3-iodochloropropane. Here the final reaction product is compound (CXXIX) [200, 201].

The use of *gem*-acyloxyallylstannane (CXXX) in free-radical cyclization with the formation of the erythrinane derivative (CXXXI) was demonstrated for the first time in [202]. Using the cyclopropyl group, the authors in [203] obtained the annellated compound (CXXXIII).



CXXX CXXXI CXXXII CXXXIII

Derivatives of pyrrolo[2,1-*a*]isoquinoline were also obtained by lactamization of unsaturated amides and nitriles [204] and by reductive cyclization of amides [205]. In [206] an effective new method, involving the addition of Michael acceptors by means of tin reagents followed by reduction and resulting in the formation of pyrrolo[2,1-*a*]isoquinolines, was proposed. A compound of the (CXXVII) type was obtained during the treatment of a derivative of the alkaloid securinine with sulfuric acid in alcohol [207].



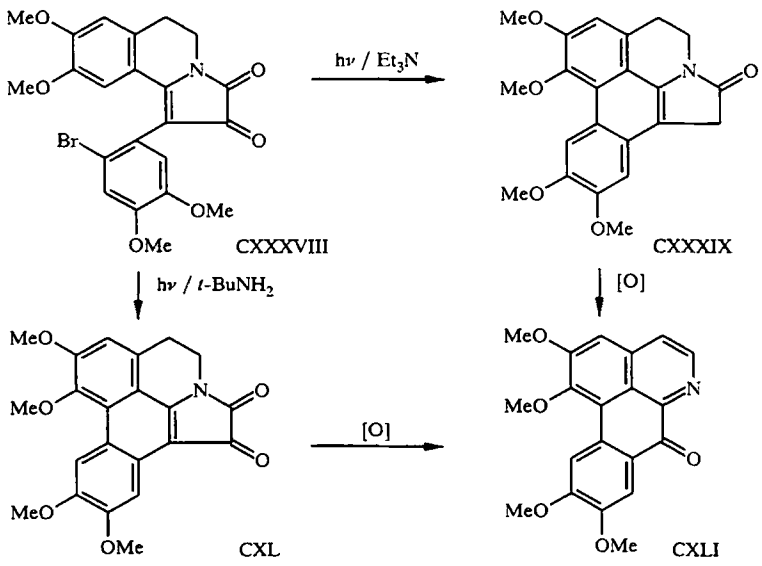
Compounds (CXXXV) are formed when the acid (CXXXIV) is boiled with N,N-dicyclohexylcarbodiimide and dibenzoylacetylene [208].

An example of a simple synthesis of the tricyclic system is the addition of α,β-unsaturated ketones to ketones of the 3,4-dihydroisoquinoline series. This leads to the formation of the ketones (CXXXVII) [209].

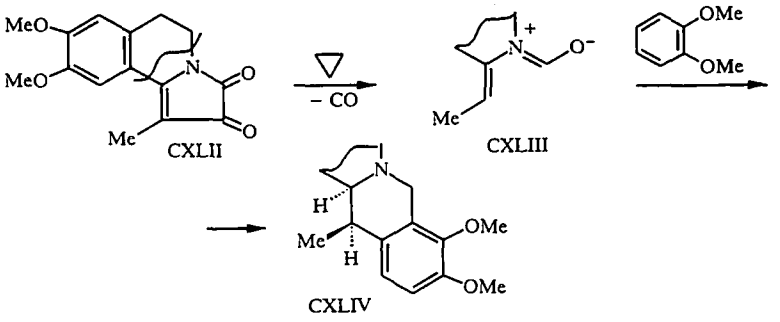
II. REACTIVITY

1. Reactions of 2,3-Dioxopyrrolo[2,1-*a*]isoquinolines

Analysis of the published data shows that the most interesting synthons in the pyrrolo[2,1-*a*]isoquinoline series are 2,3-dioxopyrrolines [172-182]. The properties of these compounds are determined by the structural characteristics of the side chain, by the dicarbonyl fragment, and by the electron-deficient double bond. The possibility of using the side chain of these compounds in the synthesis of the aporphin system was demonstrated in [176]. The authors studied the photochemical transformation of compound (CXXXVIII) in the presence of various amines. It was found that reduction of the ketone carbonyl to a methylene group is observed in the case of triethylamine, and compound (CXXXIX) is formed. In the case of an amine, such as *tert*-butylamine, not containing an α-hydrogen atom the ketone (CXL) is formed. The oxidation of compounds (CXXXIX) or (CXL) by Fremy's salt leads to the oxoglaucine (CXLI). The alkaloids lysicamine and dicentrinone were obtained with good yields by this method:

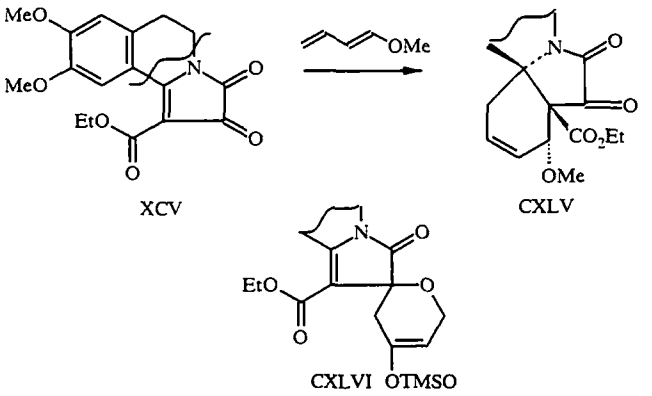


An important property of 2,3-dioxopyrrolo[2,1-*a*]isoquinolines is their ability to undergo decarbonylation followed by polar cycloaddition. The authors of [174, 210] used the cycloaddition of benzyne. It is considered that isoquinolinepyrroledione (CXLII) during decarbonylation generates the 2-azadiene (CXLIII), which in reaction with the respective benzyne gives protoberberines such as (±)-coridaline (CXLIV):



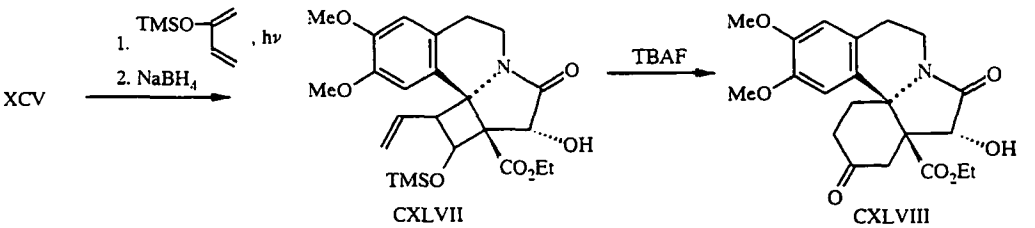
After further investigations it was possible to use this method in the synthesis of other alkaloids. A modification in which 1-halogen-substituted isoquinolines were used was employed. Here the halogen played the role of protecting group, which prevented a second molecule of the aryne from entering into the reaction [211].

The most fruitful application was the use of dioxopyrrolines of the isoquinoline series in the synthesis of erythrinine alkaloids. It was shown that the cycloaddition of these compounds leads to the construction of the erythrinine skeleton, while the reaction of compound (XCV) with activated butadienes takes place regio- and stereoselectively with the formation of compound (CXLV):



In the same paper, 2-trimethylsilyloxy-, 1-methoxy-3-trimethylsilyloxy-, and 1,3-bistrimethylsilyloxybutadienes were also used. Further investigations showed that the reaction can take place not only by the indicated "ene-addition" path but also by "*one*-addition" at the ketone fragment with the formation of spiro compounds of the (CXLVI) type [212]. The fraction of the *one*-addition product increases with increase in the length of the methylene chain in the ring (derivatives of homoerythrinine) and also under the influence of Lewis acids [213, 214]. The alkaloids coccinivine, coccolinine, erysothrine, etc. were synthesized by this method [215, 216].

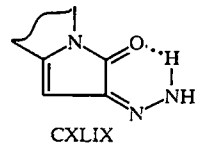
The photocycloaddition of the same dienes leads to the formation of [2+2]-adducts of the (CXLVII) type, which are transformed as a result of a [1,3]-shift into derivatives of erythrinane, such as (CXLVIII) [217, 218]:

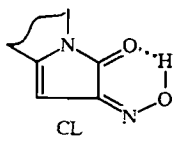


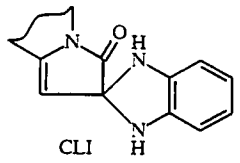
Treatment of compounds of the (CXLVII) type with various acids leads to new framework compounds [219, 220].

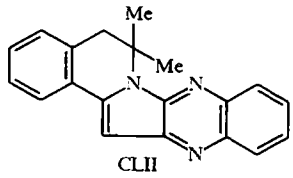
A review of researches into the cycloaddition of dioxopyrrolines is given in [173], where the reactions of cyclobutanes of the (CXLVII) type in particular are examined. As a result of the strain in the cyclobutane ring, these compounds undergo structural rearrangement with the formation of such compounds as hydroindoles, azatropolones, azanorbornenes, azanonanes, etc. This strategy was used successfully in the synthesis of specific erythrine alkaloids [221].

Another reaction center in the molecules of dioxopyrrolines is the dicarbonyl fragment. The simplest reactions of the carbonyl groups in these compounds are the reactions with hydrazines and hydroxylamine [222]. It was shown that compounds of the (CXLIX) and (CL) types are formed.


CXLIX


CL

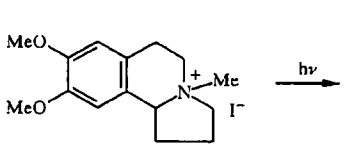

CLI

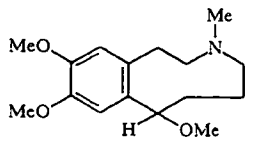

CLII

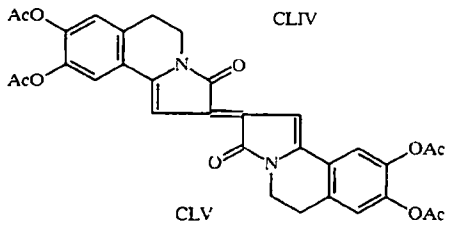
The structure of the products from the reaction with *o*-phenylenediamine depends on the conditions; with boiling in an alcohol medium with the addition of traces of HCl, the spiro compound (CLI) is formed; in glacial acetic acid, condensation occurs with the formation of quinoxalines of the (CLII) type [179, 180], which exhibit good luminescent characteristics [183]. The reduction of the dicarbonyl fragment in the investigated compounds with sodium borohydride is accompanied by hydrogenation of the double bond [182]. The pyrrole ring in these lactams is easily opened by alcoholates with the formation of enaminoketo esters [223].

2. Reactions of Other Derivatives of Pyrrolo[2,1-*a*]isoquinoline

The degradation of the pyrrolo[2,1-*a*]isoquinoline skeleton, which opens up the way to the benzazonine system, is worth mentioning. Under UV irradiation in methanol pyrrolo[2,1-*a*]isoquinolinium iodide (CLIII) forms the benzazonine (CLIV) [9, 224].


CLIII

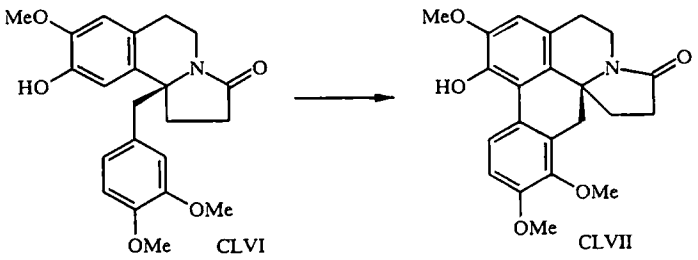

CLIV


CLV

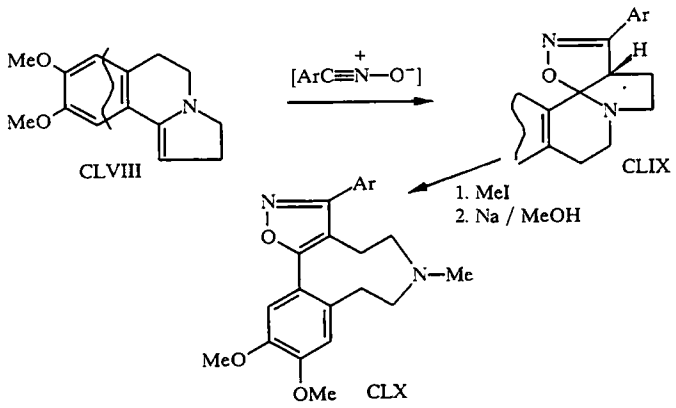
Similar results were obtained when cyanogen bromide [225] and chloroformate [226] were used as cleavage reagents.

Reactions involving the oxidation of various pyrrolo[2,1-*a*]isoquinoline derivatives are known. Thus, during the autooxidation of 8,9-diacetoxy-5,6-dihydropyrrolo[2,1-*a*]isoquinolin-3(2H)-one the pale-blue dimeric pigment (CLV) is formed

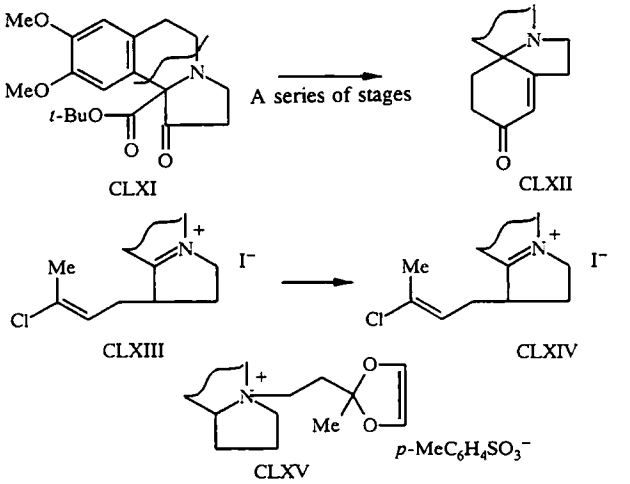
[227]. The authors discuss the relation between this reaction and the biosynthesis of the pigment trichotomine. The oxidation of the conformationally rigid 1-benzyltetrahydroisoquinolines (CLVI) with $VOCl_3$ or $Tl(OCOCF_3)_3$ gives the structure (CLVII), related to aporphin [228]:



The reaction of the enamine (CLVIII) with nitrile oxide gives the adduct (CLIX), which after Hofmann cleavage forms the new nitrogen-containing macrocycle (CLX) [229]:

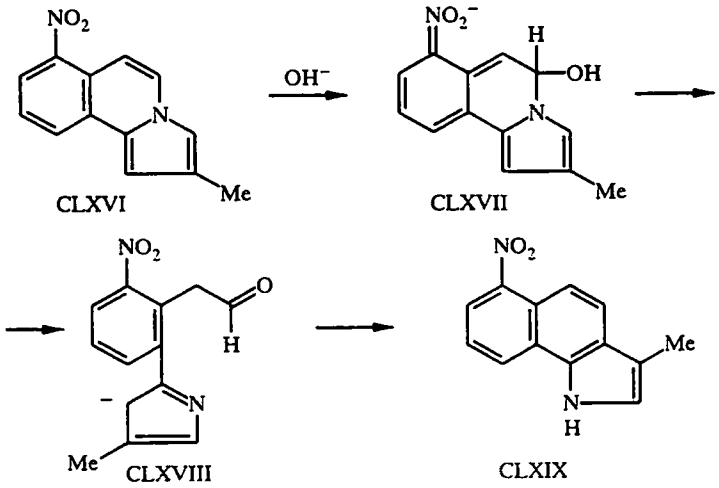


Vicinal tricarbonyl compounds are the subject of the researches in [230]. Having obtained compound (CLXI), the authors arrived at (±)-3-demethoxyerythrotidinone (CLXII):



The ketone (CLXIV) was obtained by the reaction of the indolizine (CLXIII) with potassium hydroxide in chloroform and was isolated in the form of the iodide [231]. Compound (CLXV) is formed by the usual method in the reaction of the respective indolizine base and alkylsulfonate [232].

An original method was discovered in the recyclization of pyrrolo[2,1-*a*]isoquinolinones to benzo[*g*]indoles. Favorable conditions for recyclization are created by the introduction of a nitro group into the molecule of (CLXVI). This increases the sensitivity of the system to the action of nucleophiles and creates more favorable conditions for recyclization [233]:



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