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METHODS FOR THE SYNTHESIS OF CINNOLINES (REVIEW)*

O. V. Vinogradova and I. A. Balova

This review analyses the principal approaches to the synthesis of the cinnoline nucleus, used as synthetic precursors of arenediazonium salts, arylhydrazones, and arylhydrazines, and also reductive methods for the synthesis of polycondensed derivatives of cinnoline. The mechanisms of the transformations and the possibilities and limitations of the various methods are discussed. Special attention is paid to methods based on the cyclization of derivatives of arenediazonium salts, which have been developed substantially in recent years.

Keywords: cinnolines, benzo[*c*]cinnolines, synthesis, cyclization, arylhydrazones, arenediazonium salts, *ortho*-ethynylarenediazonium salts.

The chemistry of compounds of the cinnoline series is a vigorously developing branch of organic chemistry in so far as the compounds exhibit a broad range of biological activity. In recent years a large number of papers have appeared on research into the biological activity of compounds of the cinnoline series [1-6]. They bear witness to the possibility of using them as anticancer [7-10], fungicidal, and bactericidal [11-15] preparations. Compounds of the cinnoline series have antithrombocytic [16] and antituberculosis [17] characteristics and also exhibit anesthetizing [18] and sedative [19] activity. Derivatives of cinnolines are also used as agrochemicals [20].

Apart from their biological activity compounds containing a cinnoline fragment exhibit a series of interesting physical characteristics. Thus, luminescence was detected in pyrrolo[1,2-*b*]cinnolines, where the relative quantum yield amounted to 90% [21]. The possibility of using aryl-substituted cinnolines as materials for nonlinear optics was demonstrated [22, 23].

The cinnoline ring was first synthesized by Richter during the diazotization of *ortho*-amino-phenylpropionic acid and cyclization of the obtained arenediazonium salt [24]. Several reviews and monographs on the synthesis and characteristics of cinnolines have now been published [25-30].

Among methods for the synthesis of cinnolines it is possible to identify three main approaches using derivatives of arenediazonium salts, arylhydrazones, and arylhydrazines as precursors and also reductive methods for the synthesis of polycondensed derivatives of cinnoline, among which a special position is occupied by benzo[*c*]cinnolines in view of their biological activity [10, 31, 32].

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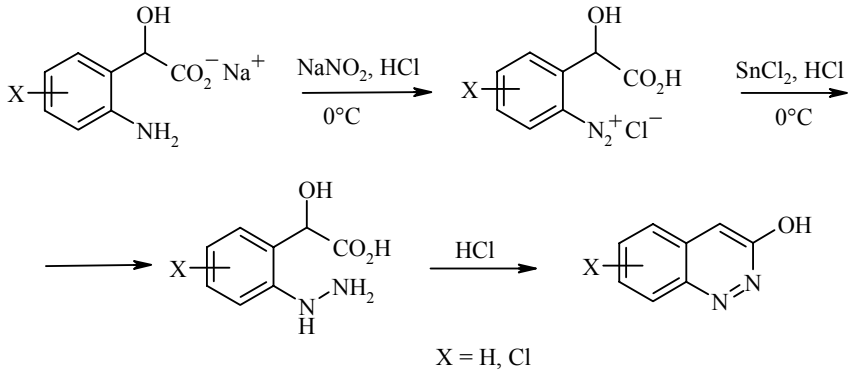
1. ARYLHYDRAZONES AND ARYLHYDRAZINES AS PRECURSORS OF CINNOLINES

This approach is the most universal since it makes it possible to obtain derivatives of cinnoline with various types of substituents at various positions and includes methods in which the cinnoline system is formed at various positions of the pyridazine ring. As a rule ring closure occurs during attack of the amino group at a CC, CO, or CN multiple bond.

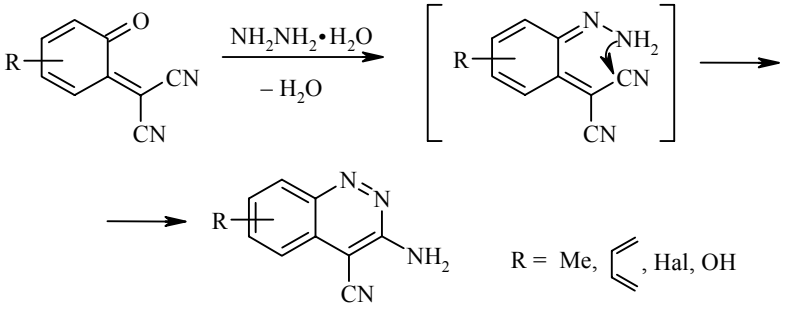
An example of the production of cinnoline through the formation of the N(2)–C(3) bond is the classical method for the synthesis of 3-hydroxycinnolines–the Neber–Bossel method [33, 34]. During the diazotization of (2-aminophenyl)hydroxyacetates and reduction of the diazonium salt the obtained hydrazine undergoes cyclization to 3-hydroxycinnoline when boiled in HCl (Scheme 1). Substituents in the aromatic ring have an appreciable effect on the course of cyclization, and in the case of the unsubstituted and 4-chloro-substituted ring the yields of the desired compounds are 60 and 7% respectively.

Scheme 1



A similar approach was afterwards used by Gomaa's group (Scheme 2) [35]. In this case the final products were obtained with good yields (65-80%), irrespective of the electronic nature of the substituent in the aromatic ring.

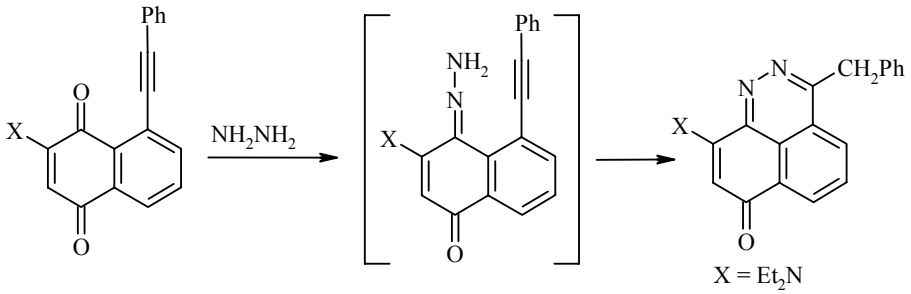
Scheme 2



Another example of the formation of the bond in this position of the cinnoline system is the cyclization of 3-diethylamino-5-phenylethynyl-1,4-naphthoquinone [36]. 3-Benzyl-9-diethylaminobenzo[*d*,*e*]cinnolin-7-one was obtained with a yield of 60% in the reaction of diethylamino-5-phenylethynyl-1,4-naphthoquinone with hydrazine (Scheme 3). The reaction is sensitive to the nature of the substituent in the naphthoquinone ring. Thus in the absence of the diethylamino group (X = H) the reaction of 5-ethynyl-substituted quinones with

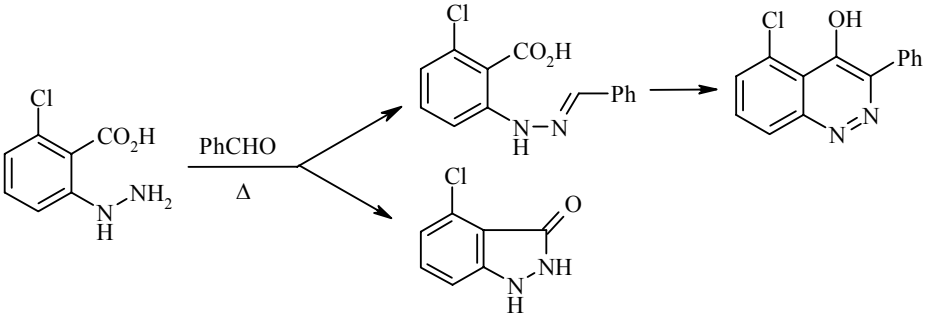
N-nucleophiles leads to the formation of a seven-membered diazepine ring. In the case of 2,3-dimethyl-substituted 5-phenylethynyl-1,4-naphthoquinone condensation with a molecule of hydrazine did not occur, and the derivative underwent reductive cyclization with the formation of naphtho[1,8-*bc*]pyran. The authors found no explanation for such dependence of the direction of the reaction on the nature of substitution.

Scheme 3



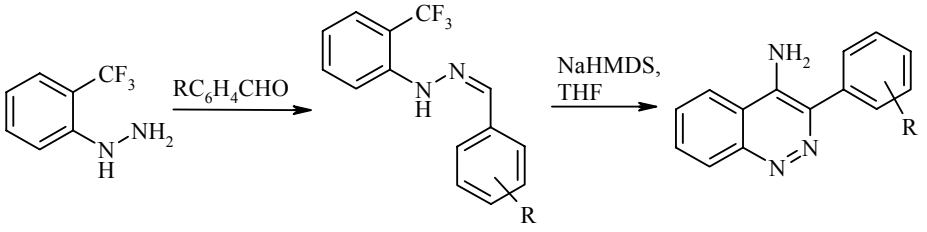
For a long time the only example of the formation of a cinnoline ring through the construction of the $C_{(3)}$–$C_{(4)}$ was the reaction realized by Pfannstiel and Janecke [37, 38], as a result of which the hydrazone formed by boiling 6-chloro-2-hydrazinobenzoic acid in benzaldehyde underwent cyclization to 5-chloro-4-hydroxy-3-phenylcinnoline. However, the yield of cinnoline was low since the main direction of reaction was cyclization of the initial hydrazine to 4-chloroindazolone (Scheme 4) [38].

Scheme 4



This approach found development as a result of work by Kiselev's group [39, 40]. While studying the chemistry of the anion-activated CF_3 group they showed that the hydrazones obtained from *ortho*-trifluoromethylarylhydrazines and benzaldehydes undergo cyclization by the action of a base, forming a pyridazine ring (Scheme 5).

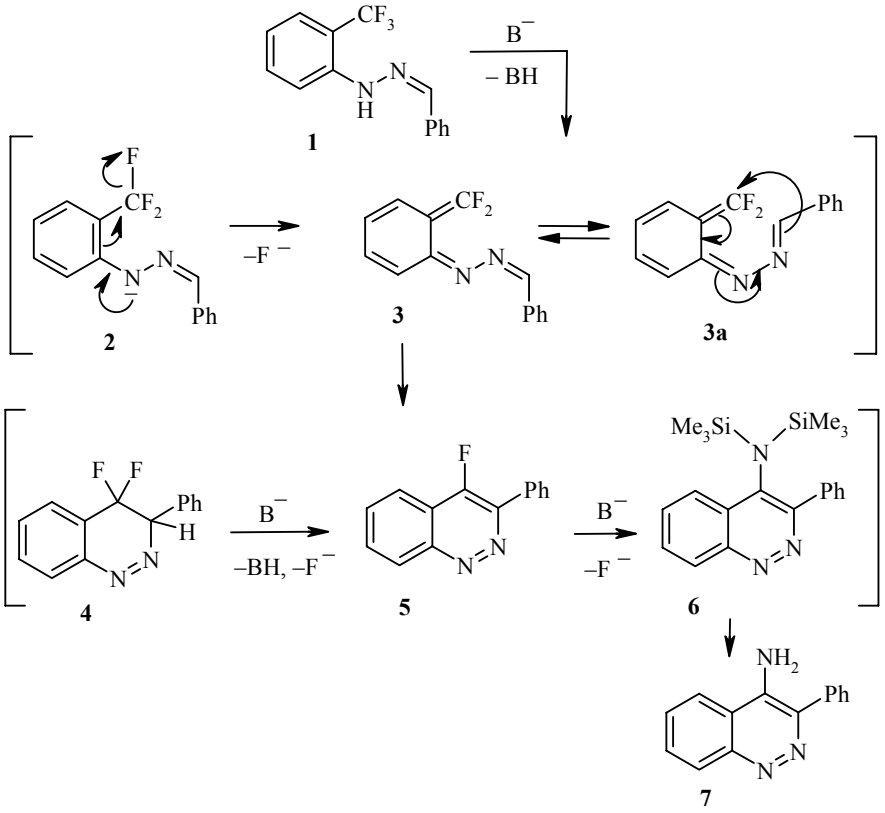
Scheme 5



R = H, F, Cl, Me, OMe, Pyr

The products in this case are 4-amino-3-arylcinnolines, and their yields amount to 60-90%. The authors suggest that the deciding factor for cyclization is the presence of the CF_3 group, which promotes ionization of the N–H bond in the hydrazone; at the same time the fluoride ions can act as leaving groups at the fourth carbon atom, which is necessary to complete the cyclization. The cyclization mechanism proposed by the authors [40] is presented in Scheme 6.

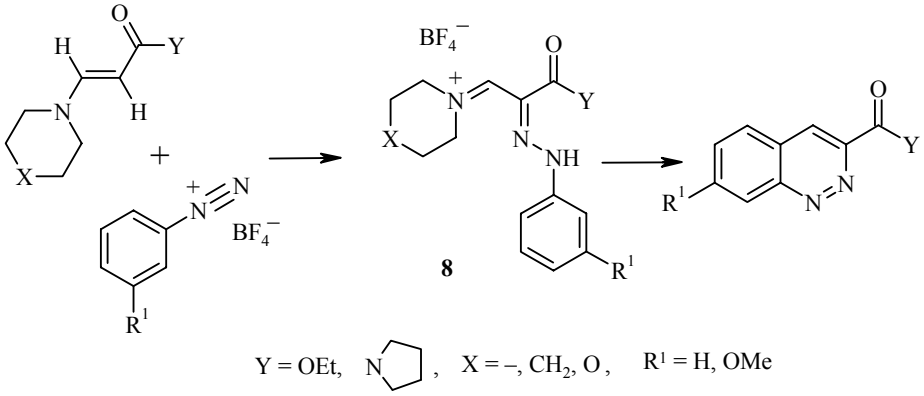
Scheme 6



The formation of the quinonemethylidene intermediate **3**/**3a** had been postulated earlier in work by Strekowski's group [41] in a study of the mechanisms of similar transformations. Important for the progress of the cyclization is the structure of hydrazone fragment; cyclization does not occur for the hydrazones obtained from the *ortho*-substituted benzaldehydes, but the hydrazones containing a *meta*- and *para*-substituted phenyl fragment readily undergo cyclization irrespective of the electronic and steric characteristics of the substituent. The optimum conditions involve reaction in THF at -35 to -15°C in the presence of a four-fold excess of sodium hexamethyldisilylamide (NaHMDS) as base. The formation of cinnoline is not observed if lithium diisopropylamide (LDA) and also lithium morpholide and piperidide are used. However, cyclization is not sensitive to the nature of the metal used as cation and takes place successfully with the lithium and also the potassium derivative.

An example of the formation of the C(4)–C(4a) bond is the cyclization of the monoarylhydrazones formed in the reaction of the esters and amides of 3-aminopropenoic acid with arenediazonium tetrafluoroborates, studied by Kanner's group (Scheme 7) [42].

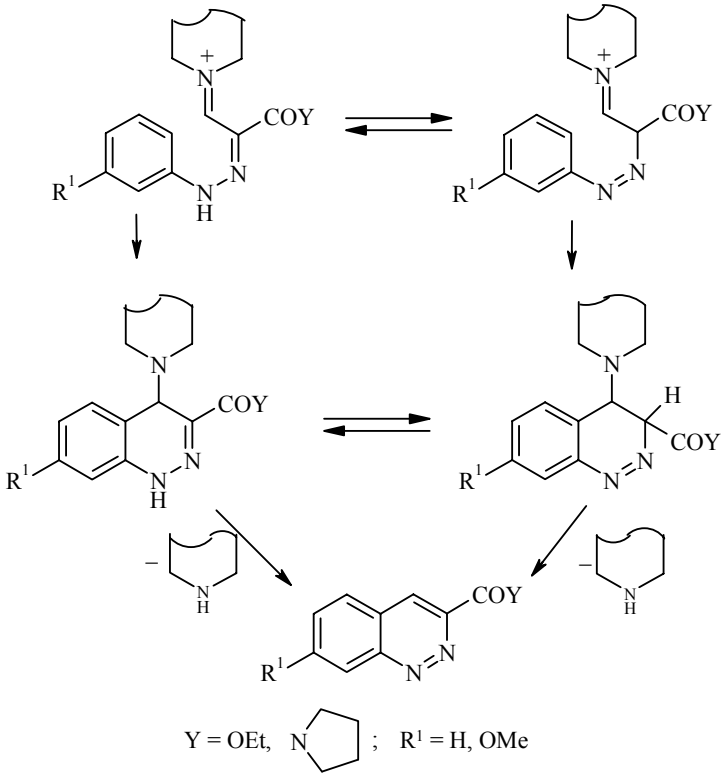
Scheme 7



The substituent in the benzene ring has a strong effect on the course of the cyclization. In the case of R^1 = H the cyclization of compound **8** takes place on boiling in acetonitrile for several days. If a methoxyl substituent is introduced the hydrazone **8** undergoes spontaneous cyclization in the course of the reaction. There is a general tendency for higher reactivity in the derivatives of the amides compared with the esters and also for the derivatives of morpholine compared with those of pyrrolidine and piperidine. The authors proposed the mechanism in Scheme 8 in order to explain this effect of the substituents.

The rate-determining stage is the formation of the bond between the imine carbon atom and the aromatic ring, which can be regarded formally as an electrophilic substitution reaction. It is clear that this

Scheme 8



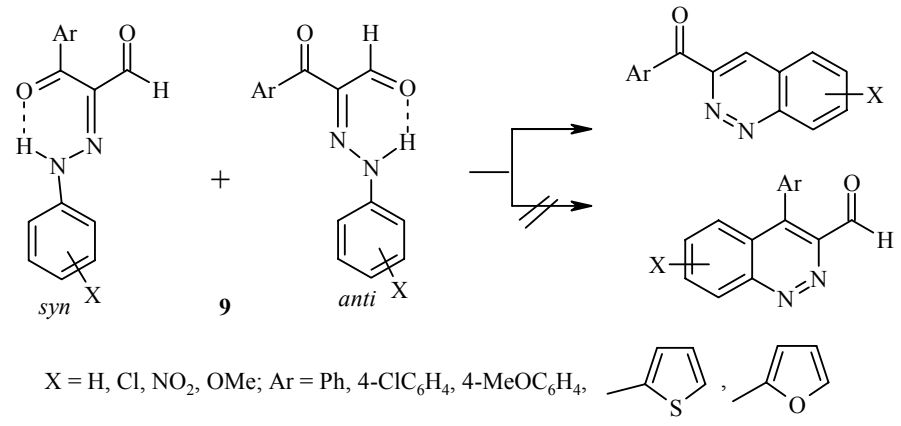
process must be accelerated by electron-donating substituents in the aromatic ring. The decrease of the basicity in the series pyrrolidine (pK_a 11.3) – piperidine (pK_a 11.2) – morpholine (pK_a 8.4) leads to an increase in the electrophilicity of the imine carbon atom, which must increase its reactivity and accelerate the cyclization.

The significantly lower activity of the pyrrolidine derivatives compared with the activity of the piperidine derivatives is explained by the nature of the five-membered ring, for which the configuration with the exocyclic double bond is more stable. The difference in the behavior of the ester and amide derivatives was also explained by the effect of the electronic effects of these groups on the cyclization reaction centers; both groups increase the electrophilicity of the imine carbon atom and reduce the nucleophilicity of the benzene ring that is in conjugation. Nevertheless the ester group, which has a large negative resonance effect, reduces the activity of the corresponding derivatives in comparison with the amide.

Research by the Egyptian authors [43-47] was also directed toward methods for the synthesis of 3-aroyl-substituted cinnolines in view of their supposed biological activity. By analogy with Kanner's work 3-aryl-2-arylhydrazono-3-oxopropanals **9** were used as starting compounds. The yields of the 3-aroylcinnolines amounted to 35-65% (Scheme 9).

Cyclization was realized in the gas phase or by boiling the initial hydrazones in concentrated sulfuric acid. In the case of compounds containing donating groups in the aromatic substituents of the hydrazone fragment polyphosphoric acid was used. In spite of the fact that the initial compounds exist in the form of a mixture of *syn* and *anti* isomers the cyclization takes place selectively with the formation of one of the possible regioisomers.

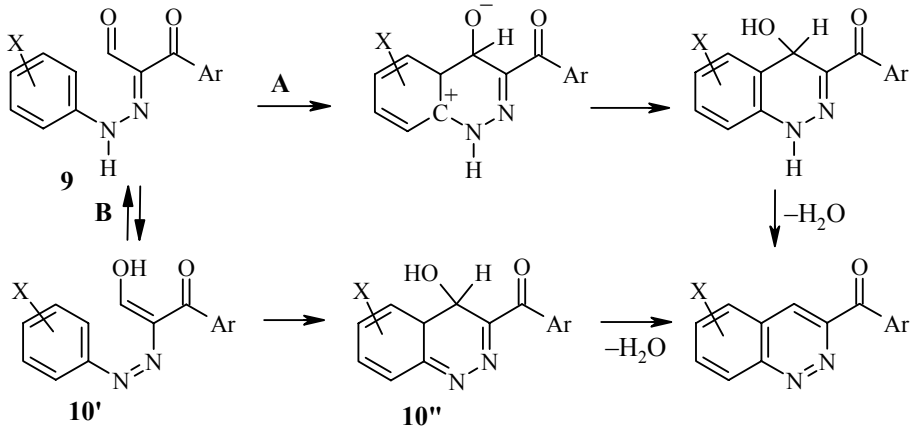
Scheme 9



In order to investigate the mechanism of the transformation an investigation was carried out into the kinetics of the reaction in the gas phase with variation of the nature of the substituents in the aromatic ring of the hydrazone [44, 47]. Initially two possible reaction paths were proposed (Scheme 10). The first includes the mechanism described in Kanner's papers, where the rate-determining stage involves attack by the carbonyl carbon atom in the aromatic ring (mechanism **A**). According to the second mechanism, the cinnoline ring is formed as a result of a 6-π-electrocyclic reaction, which precedes the thermal isomerization of **10** to **10′** (mechanism **B**).

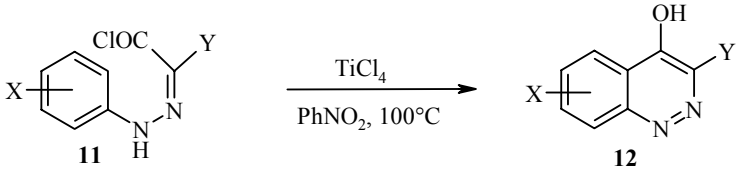
A kinetic investigation of the cyclization at 550 K showed the absence of a significant effect from the nature of the substituent on the rate of the reaction. Since the reaction by mechanism **A** must be accelerated by electron-donating substituents while for the isomerization **9**-**10′** the presence of electron-accepting substituents that increase the acidity of the nitrogen atom must lead to an increase in the rate, it was concluded on the basis of the experimental data that the rate-determining stage of the reaction is the cyclization of compound **10′** to **10″** taking place through a quasiaromatic six-membered transition state.

Scheme 10



The formation of a cinnoline ring with the participation of arylhydrazones through the construction of a bond between the fourth carbon atom and the benzene ring can also be realized under the conditions of the Friedel–Crafts reaction. This approach was first described in 1956 by Barber and co-workers [48, 49]. They realized the cyclization of the phenylhydrazone of mesoxalyl chloride catalyzed by titanium salts, as a result of which after alkaline hydrolysis they obtained 4-hydroxycinnoline-3-carboxylic acid (Scheme 11). In our days this method has been used in the synthesis of polycondensed derivatives of cinnoline [50].

Scheme 11

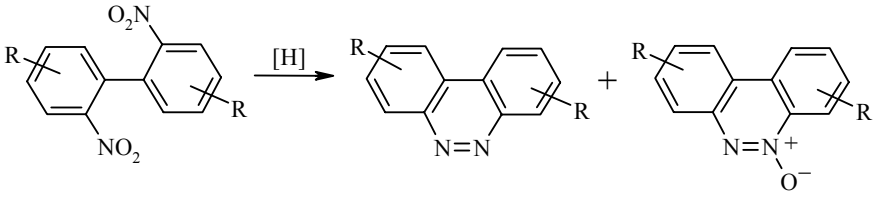


11 Y = COCl, **12** Y = COOH; **11**, **12** X = Me, OMe, NO_2, Cl, Br, F

2. SYNTHESIS OF BENZO[*c*]CINNOLINES

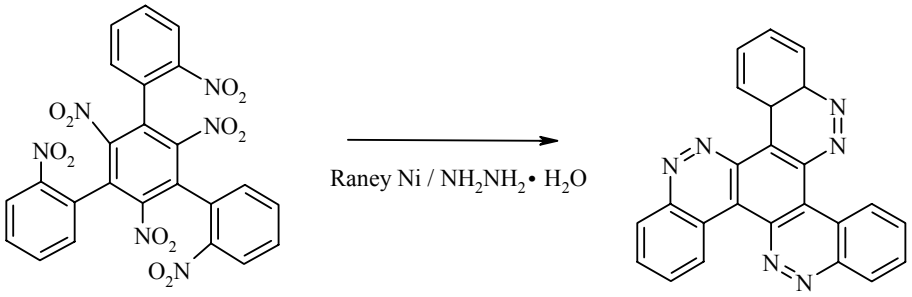
A powerful tool for the production of benzo[*c*]cinnolines is the reductive cyclization of 2,2′-dinitrobiphenyls (Scheme 12) [51, 52].

Scheme 12



In spite of the fact that this method has quite a large number of limitations associated with the construction of the initial compounds it is practically the only method used for the synthesis of such structures in contemporary chemistry. A wide range of reagents can be used as reducing agent [52], and the most frequently employed are lithium aluminum hydride, sodium sulfide, and sodium amalgam; Zn (in the presence of $CaCl_2$) and Ni (in an alkaline medium); acetophenone can also be used as reducing agent. Often a mixture of cinnoline and its oxide at one or two nitrogen atoms is formed in the reaction; reduction of the oxide can be achieved by the addition of the reagent previously used for the reduction of the nitro groups. The method can be used to obtain polycondensed compounds containing a cinnoline fragment in the presence of several structural fragments capable of cyclization (Scheme 13) [53, 54].

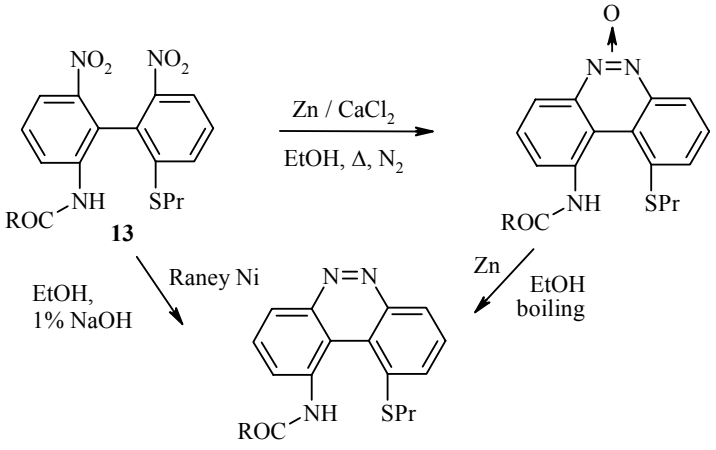
Scheme 13



The presence of substituents at positions 6 and 6′ hinders cyclization on account of steric factors; in this situation the reaction only takes place by the path with reduction of the nitro groups and the formation of nitroamino or diamino derivatives of biphenyl. In this case intermolecular azo coupling leading to azo compounds can also occur.

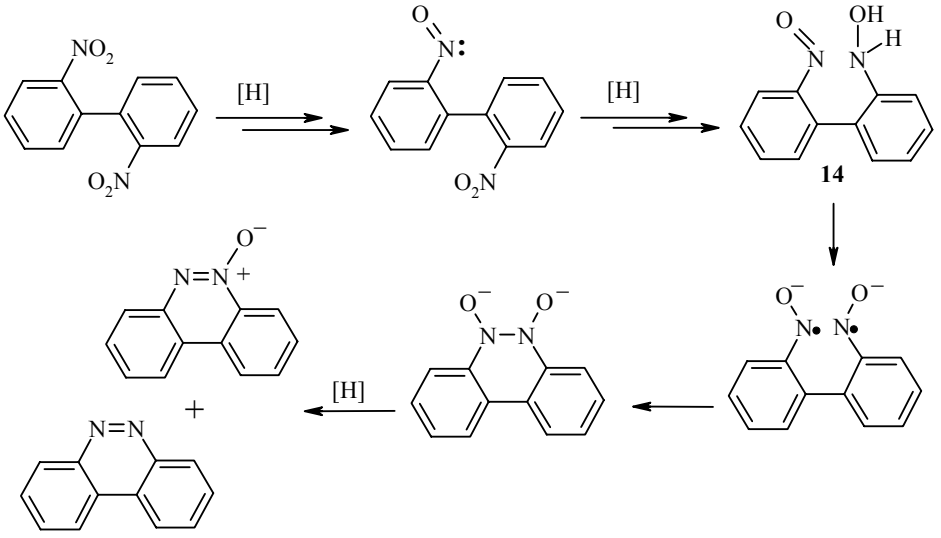
A successful example of the synthesis of 1,10-substituted benzo[*c*]cinnolines is found in the papers by Benin [55] (Scheme 14). By using metallic Zn or Ni in boiling ethanol as reducing system it was possible to realize the cyclization of tetrasubstituted biphenyls **13**. The corresponding benzocinnoline was obtained with an 80% yield.

Scheme 14



In the literature the mechanism proposed by Russell [56] is generally accepted as an explanation for the formation of the N=N bond. It is assumed that, initially, reduction of the dinitrobiphenyls takes place with the formation of 2-(2′-nitrosophenyl)phenylhydroxylamine **14** (Scheme 15). Intramolecular one-electron transfer between the nitrogen functions of this intermediate leads to the generation of a bis(radical-anion), the recombination of which and subsequent reduction of the obtained particle lead to the production of benzo[*c*]cinnoline N-oxide as initial product.

Scheme 15



The radical-ion character of the intermediate explains certain limitations that the reaction has with respect to the structure of the initial compounds. Thus, the presence of $–NH_2$, –CN, and –OH groups is undesirable since they readily form radicals under the conditions of the oxidation–reduction process, leading to resinification of the reaction mixture. In addition, the presence of aldehyde and primary alcohol groups can often complicate the reaction as a result of the possibility of their oxidation to the corresponding carboxyl compounds. Halogens in the aromatic ring are also unstable against the action of reducing agents, and they are substituted by a hydrogen atom. However, the great variety of the employed reducing systems and the possibility of varying the reaction conditions make it possible to find solutions to these problems in each specific case.

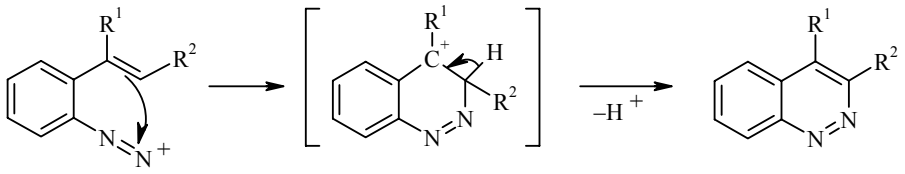
3. CYCLIZATION OF ARENEDIAZONIUM SALTS

This group of methods includes the first examples of the synthesis of the cinnoline system: Richter, Widman–Stoermer, and Borsche–Herbert cyclizations. In spite of its long history the Richter reaction has only attracted the attention of investigators in the last decade as a method for the synthesis of 4-halocinnolines. At the same time the Widman–Stoermer and Borsche–Herbert reactions are already well-studied reactions and are discussed in detail in the reviews [25-30].

The Widman–Stoermer reaction is a method for the production of cinnolines containing alkyl, aryl, of heteroaryl substituents at position 4 (Scheme 16). The pyridazine ring is formed during diazotization of *ortho*-vinylanilines followed by cyclization involving the diazonium cation and the double bond of the substituent.

The reaction takes place at room temperature and gives yields close to quantitative. An important restriction of the method is the compulsory presence of a substituent at the α-carbon atom of the vinyl substituent, and the reaction gives highest yields in the case of alkyl or aryl groups. The cinnolines are not formed in the presence of strong accepting substituents (R^1 = COOH). In some cases the presence of a phenyl substituent at the β-carbon atom of the double bond leads to the formation of phenanthrene, taking place by the Pschorr reaction, in competition with the cyclization [25-30].

Scheme 16



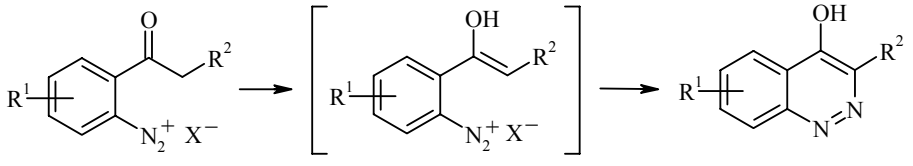
R^1 = Alk, XC_6H_4, 2-Py; R^2 = H, Alk, XC_6H_4, 2-Py

The Widman–Stoermer reaction is rarely used these days since the obtained 4-alkyl- and aryl(hetaryl)-substituted cinnolines only find limited use in contemporary synthesis. In view of the substantial demands on the nature of the substituents in the initial compound it is often more convenient to introduce the aryl fragment into the already formed cinnoline ring. For this purpose it is possible to use the cross-coupling of halogenocinnolines with acylboric acids (the Suzuki–Miyaura reaction) [22].

In the middle of the last century the Borsche and Herbert reaction was widely used as a method for the production of 4-hydroxycinnolines. The method involves diazotization of *ortho*-aminoacetophenones followed by cyclization of the obtained arenediazonium salt (Scheme 17) [25-30].

The reaction is fairly universal and makes it possible to obtain a wide range of cinnoline derivatives containing substituents at various positions of the ring; the yields here amount to 70-90%. Diazotization is carried out with $NaNO_2$ in hydrochloric, sulfuric, or formic acids.

Scheme 17



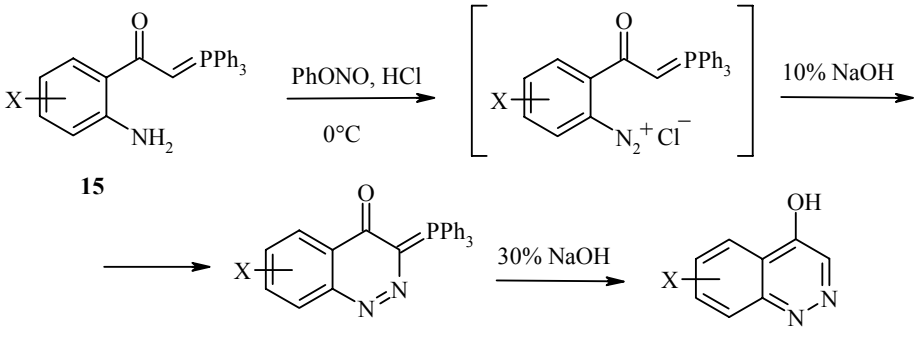
R^2 = H, Hal, Alk, Aryl

It is assumed that the cyclization takes place through the formation of the enolic form of the ketone and is facilitated by the presence in the aminoacetophenones of accepting substituents, which increase the electrophilic characteristics of the diazo group depending on the nature and position. In the absence of such substituents the rate-determining stage is the acid-catalyzed enolization, and the reaction becomes sensitive to the concentration of the acid. In this case it is expedient to conduct the diazotization in concentrated hydrochloric acid [57-59]. The presence of donating substituents in the aromatic ring initiates the concurrent process of hydrolysis of the arenediazonium salt and the formation of the corresponding *ortho*-acetyl derivatives of phenol. In contrast to the Widman–Stoermer reaction, in the presence of a phenyl substituent in the acetyl

fragment of the initial compound the formation of 9-phenanthrol by the Pschorr reaction can be avoided, and in this case 4-hydroxycinnoline is the only product [60]. The limited application of this method is due to the difficulties involved in the synthesis of the initial substituted *ortho*-aminoacetophenones and to the side reactions involving substitution in the benzene ring [25-30].

A modification of the Borsche–Herbert method was proposed in [61], where the phosphorus ylides of *ortho*-aminoacetophenones **15** were used for cyclization (Scheme 18). As an advantage of the method the authors mention the availability of the initial compounds, which can be obtained with good yields from the corresponding ester derivatives. Also the yields of the 4-hydroxycinnolines obtained by the method are high.

Scheme 18



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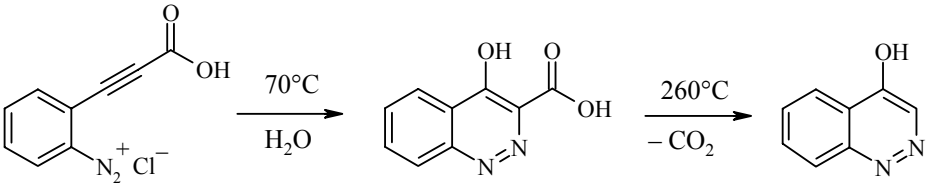
From the synthetic standpoint the cyclization of *ortho*-ethynylarenediazonium salts (the Richter reaction) is becoming ever more important as a method for the synthesis of 4-halogenocinnolines. On account of the reactivity of the halogen atom in electrophilic substitution reactions these compounds are convenient building blocks for the production of biologically active compounds [25, 62, 63], including the 4-amino derivatives of cinnoline and their salts [64]. On the other hand the development in recent decades of methods for Pd-catalyzed cross coupling has made the initial *ortho*-ethynyl-substituted arenediazonium salts containing various types of substituents in the aromatic ring accessible.

The reaction was discovered during the diazotization of *ortho*-aminophenylpropionic acid and cyclization of the diazonium salt in aqueous solution at 70°C (Scheme 19). After decarboxylation of the obtained 4-hydroxycinnoline-3-carboxylic acid 4-hydroxycinnoline was isolated with a quantitative yield [24]. However, attempts to repeat this synthesis by other investigators led to substantially lower yields [65, 66].

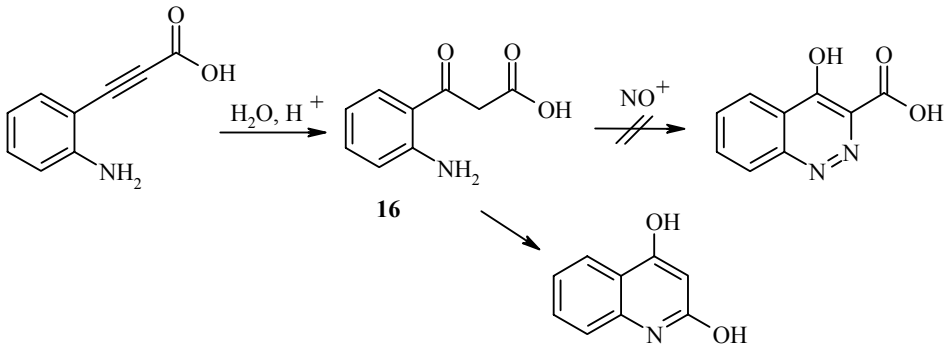
Scheme 19



The formation of the same product as in the Borsche–Herbert method as a result of the Richter cyclization prompted the search for analogies in the mechanisms of these two reactions. In papers by Schofield and Simpson it was suggested that hydration of the triple bond with the formation of the corresponding *ortho*-aminobenzoylacetic acid occurs initially during the diazotization of *ortho*-aminophenylpropionic acids and

cyclization then takes place according to the mechanism of the Borsche–Herbert reaction through an enolic intermediate [66-68]. In order to check this suggestion the diazotization and cyclization of (2-amino-benzoyl)acetic acid (**16**), which according to the hypothesis must act as intermediate in the synthesis performed by Richter, were carried out (Scheme 20).

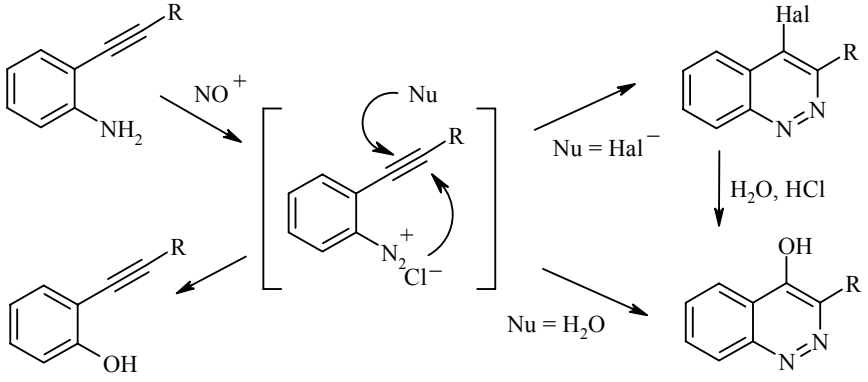
Scheme 20



However, all attempts to isolate the required acid or its diethyl ester in the individual state were unsuccessful since during preparation it underwent spontaneous cyclization to 2,4-dihydroxyquinoline. A similar problem was observed during the diazotization of 2-amino-3-methoxyacetophenone, which must act as intermediate in the Richter reaction for 2-amino-3-methoxyphenylacetylene. In the presence of a donating substituent the Borsche–Herbert reaction is realized when the concentrated acids are used, while diazotization of 2-amino-3-methoxyacetophenone under the conditions of the Richter reaction does not lead to the formation of cinnoline [66-68]. At the same time 2-amino-3-methoxyphenylacetylene itself readily forms the corresponding cinnoline. While refuting the hypothesis about the initial hydration of the triple bond in the course of the Richter reaction, the authors put forward the alternative suggestion that the reaction begins with coordination of the diazonium cation to the triple bond followed by the addition of a water molecule [67]. Later on during study of the acidity constants and UV spectra of various hydroxycinnolines it was shown that 4-hydroxycinnolines exist in the form of the other tautomeric form – 4-(1H)-cinnolinones [69, 70].

The investigations in this region continued in the work of Vasilevsky's group [71-74]. There it was shown that during the diazotization of 2-aminotolane in HCl medium 4-chlorocinnoline, isolated with a yield of 5%, is formed as a second product in addition to 4-cinnolinone. By realizing this reaction at room temperature it was possible to increase the yield of the 4-chloro derivative to 41% [71]. This fact also indicated that the halide anion acts as nucleophile participating in the cyclization. It was also suggested that the 4-cinnolinones are formed at least partly as a result of hydrolysis of the corresponding 4-halocinnoline (Scheme 21).

Scheme 21



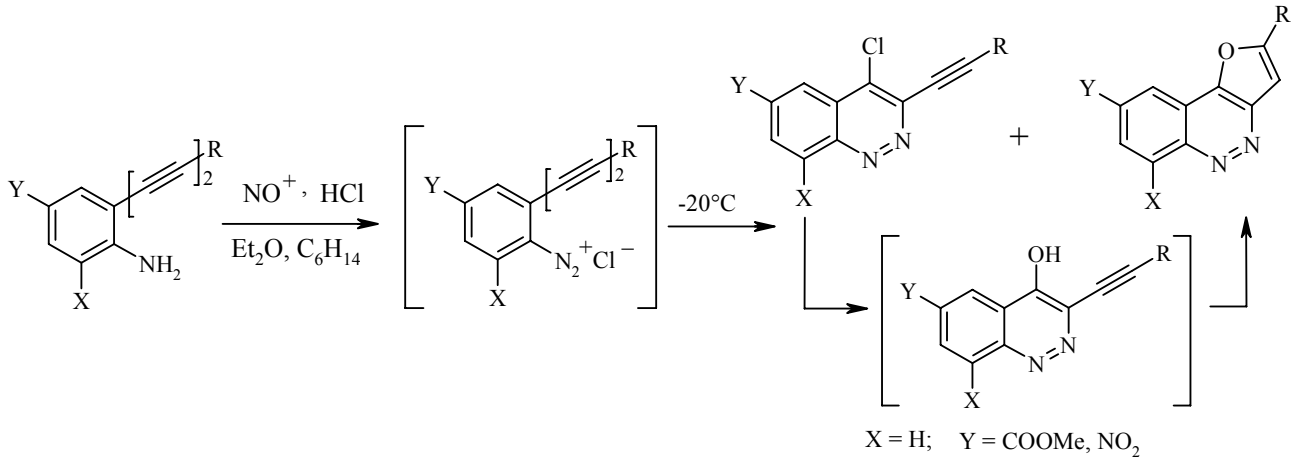
This possibility was refuted in Schofield's papers on account of unsuccessful attempts to detect the formation of the 4-halocinnoline even in the presence of donating substituents (–OMe) in the benzene ring, which should increase the stability of the chlorine atom against hydrolysis reactions [67]. When 4-chlorocinnoline was boiled in dilute hydrochloric acid it changed completely into 4-cinnolinone; the reverse transition from 4-cinnolinone to the halogen derivative was not observed [71]. The formation of the 4-halocinnoline is promoted by decrease of the reaction temperature, increase in the nucleophilicity of the halogen atom, and the presence of donating substituents. In the reaction at room temperature and with HBr instead of HCl it was possible to increase the yields of 4-bromocinnolines from 11-54% to 56-93%. It was shown that the 4-cinnolines are not formed during the cyclization of 5-amino-4-ethynylpyrazoles. On account of the π-electron excess of the pyrazole ring the halogen atom in the formed pyrazolo[3,4-*c*]pyridazine is resistant to hydrolysis [74].

An important limitation of the Richter reaction is the presence of the acetylene fragment of the electron-accepting substituent at the β-carbon atom. The 2-pyridyl- or diethylamino groups are protonated under the reaction conditions, as a result of which cyclization does not occur; the only products are the corresponding phenols. This fact is explained on the basis of the proposed Ad_E mechanism of the reaction; electron-accepting substituents reduce the electron density of the triple bond, preventing electrophilic addition of the diazonium cation [71].

The effect of the nature of substituents in the aromatic ring and the reaction conditions on the composition and yield of the products of the Richter reaction was studied in detail in the series of *ortho*-alka-1,3-diynylarenediazonium salts produced during the diazotization of the respective arylamines. In the absence of substituents in the aromatic ring and also in the presence of donating or weakly accepting substituents (Me, Br) the only reaction products were 4-chloro-3-ethynylcinnolines, the yields of which amounted to 30-55%. In the case of the *ortho*-alka-1,3-diynylarenediazonium salts containing electron-accepting substituents such as $–NO_2$ or –COOMe groups furo[3,2-*c*]cinnolines were isolated as the main products together with the 4-chloro-3-ethynylcinnolines [75].

By spectrophotometric investigations it was possible to establish that the only products from the Richter cyclization in the presence of electron-accepting substituents are 3-alk-1-ynyl-4-chlorocinnolines, which undergo hydrolysis in the course of the reaction. The 3-alk-1-ynyl-4-hydroxycinnolines formed as a result of hydrolysis undergo spontaneous cyclization, giving 2-alkylfuro[3,2-*c*]cinnolines (Scheme 22) [76].

Scheme 22

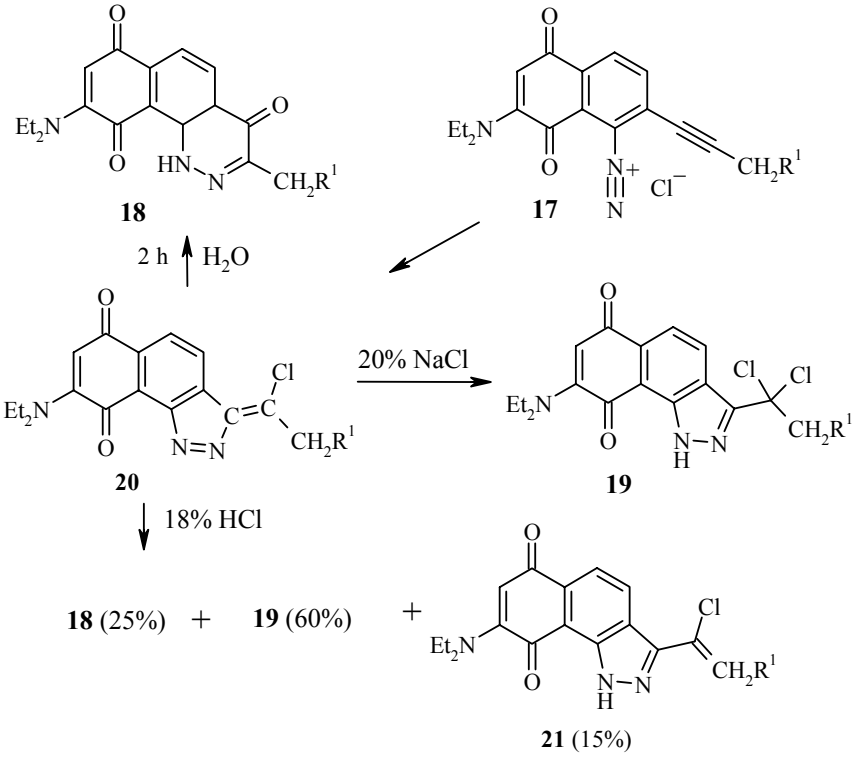


When the reaction was carried out in methanol saturated with HCl furo[3,2-*c*]cinnolines were obtained with yields of 39-54% even during the diazotization of anilines not containing accepting substituents. On the

basis of the investigations it was established that a series of transformations take place in the MeOH medium. The cyclization of *ortho*-alka-1,3-diynylarenediazonium salts also leads initially to the formation of 3-alk-1-ynyl-4-chlorocinnolines, which soon undergo solvolysis in the course of the reaction, giving 4-methoxycinnolines. It was possible to isolate 4-methoxycinnoline by treating the reaction mixture with anhydrous triethylamine. The presence of water, released as a result of diazotization, in the reaction mixture leads to subsequent hydrolysis of the 4-methoxycinnoline. On account of the further cyclization of 4-hydroxycinnoline to furo[3,2-*c*]cinnoline the hydrolysis reaction is irreversible. The solvolysis and hydrolysis reactions are promoted by protonation of the cyclization products in the anhydrous methanol saturated with HCl [76].

In papers by Fedenok's group, concerning investigations of the cyclization of derivatives of 6-alkynyl-1,4-naphthoquinone-5-diazonium salts [77-79], it was found that the reaction in this case leads to the formation not only of the pyridazine but also the pyrazole ring depending on the conditions of cyclization. Cyclization of the diazonium salt **17** with dilution of the reaction mixture with water leads to closure of the pyridazine ring and the formation of compound **18**. If the initial solution of the diazonium slat **17** is diluted with 20% NaCl, after 2 min compound **19**, containing a pyrazole ring, is formed as the only reaction product (Scheme 23).

Scheme 23



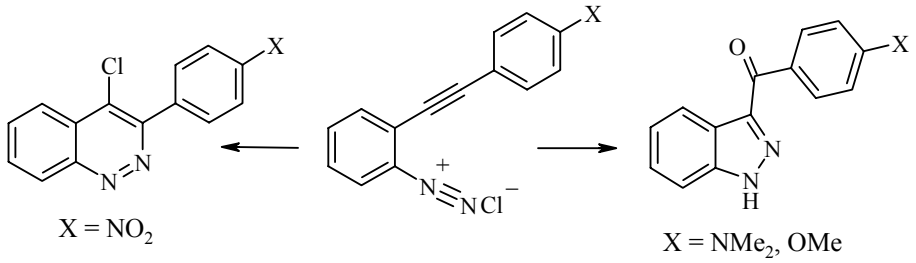
On the basis of quantum-chemical calculations of the energy profile of the reaction [80] it was concluded that the cyclization of the arenediazonium salt with the formation of both a six-membered ring and a five-membered ring is an energetically unfavorable process with a high activation energy. Moreover, attack by the terminal nitrogen atom at the β-carbon atom of the triple bond is unlikely on account of the large distance between them. In the opinion of the authors the reaction must begin with the addition of the halogen at the second position of the triple bond, which according to the calculations has a small positive charge (+0.05). As a result of change in the initial geometry of the system cyclization leads to the formation of a five-membered ring containing an exocyclic double bond.

During the cyclization of the diazonium salt **17** 3 min after dilution of the reaction mixture with water it was possible to detect a compound to which structure **20** was assigned on the basis of the ^{1}H NMR spectrum and also the data from mass-spectrometric analysis (Scheme 23). On treatment of a solution of compound **20** in chloroform with a 20% solution of NaCl it was fully converted, and the product **19** was formed; on dilution with 18% HCl a mixture of products **18**, **19**, and **21** was formed. On the basis of the obtained data the authors concluded that both the six- and the five-membered ring in the series of naphthoquinones is formed through the single intermediate **20** in a multistage process. Ring enlargement takes place under conditions with thermodynamic control, whereas the reactions with retention of the pyrazole ring are kinetically controlled processes.

This is supported by the calculated data, according to which compound **19** is less stable than compound **18** [79]. The formation of naphthocinnolinone **18** was observed when there was a diethylamino group at position 3, which in the authors' opinion reduces the electrophilicity of the exocyclic carbon atom at the double bond in the intermediate **20** and prevents repeated attack of the chloride ions leading to the five-membered products. Thus the formation of a six-membered ring was not observed in the reaction with ethynylnaphthoquinones unsubstituted at position 3.

The same authors carried out investigations into the effect of the reaction conditions and the nature of the substituent at the triple bond for the Richter reaction in the series of *ortho*-phenylethynylanilines [80, 81]. As in the case of naphthoquinones the cyclization was carried out in three versions: with dilution of the reaction mixture containing the diazonium salt with water and with concentrated solutions of NaCl and HCl. The cyclizations conducted in water and NaCl solution were comparable in rate and finished in a few minutes, whereas the reaction in HCl solution required 2 h. It was found that in this case the reaction conditions did not affect the composition of the products, but the electronic nature of the substituents played an appreciable role. The presence of donating groups in the phenyl substituent at the triple bond promoted the formation of the five-membered products whereas the presence of accepting groups promoted the production of the six-membered products (Scheme 24), which may favor the formation of a cationic intermediate in the course of the cyclization.

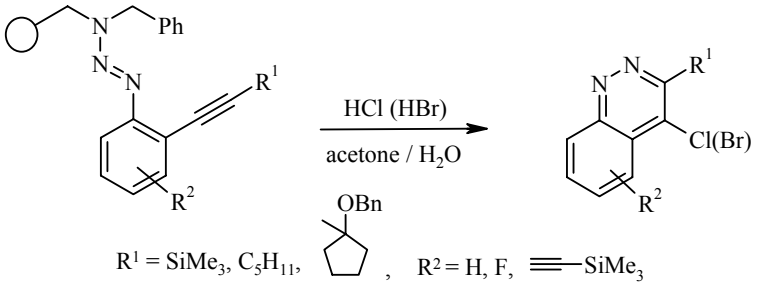
Scheme 24



An interesting modification of the Richter reaction is the use of *ortho*-ethynyl-substituted phenyltriazenes, in which the triazine fragment acts as a masked diazonium cation, for cyclization [82, 83]. This method of synthesis was used for the creation of combinatorial libraries [84]. An obvious advantage of this approach for the Richter reaction is the possibility of separating the diazotization and cyclization stages, which makes it possible to avoid side reactions.

Thus, Brase realized the synthesis of 4-halocinnolines during the treatment of alkynyl-substituted triazines with solutions of hydrohalic acids (Scheme 25) [82, 83]. The reaction was conducted in a solid-phase version on a polystyrene support, which significantly simplified the isolation and purification of the final products. Good yields of 4-halocinnolines were obtained with HCl and HBr, where cyclization took place in acetone under mild conditions.

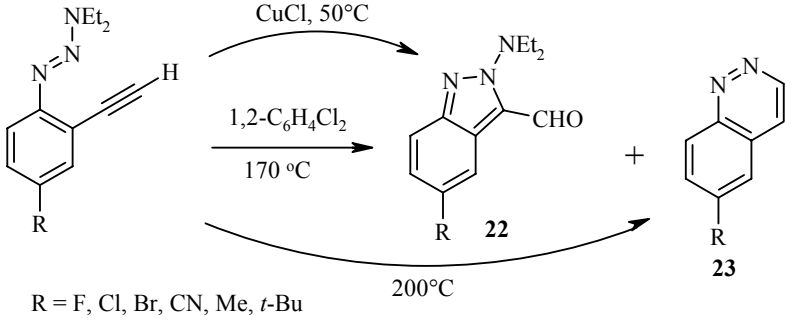
Scheme 25



The corresponding 4-cinnolinones were formed as side products, and their yields increased with increase in the reaction time. When a more dilute hydrohalic acid was used the 4-cinnolinones were the main products. Decomposition of the ethynyl-substituted triazines in HF and HI did not lead to the formation of the desired 4-iodo- and 4-fluorocinnolines.

Another example of the cyclization of *ortho*-ethynyl-substituted triazines by heating the compounds in *ortho*-dichlorobenzene was described in Kimball's papers [85-89]. Initially, on heating to 170°C a mixture of products was obtained – the isoindazole **22** and cinnoline **23** in a ratio of 1:1 (Scheme 26). The authors chose reaction conditions that made it possible to obtain each of the cyclization products selectively. Thus, increase of the reaction temperature to 200°C led to the formation of the cinnoline with yields of 80-90%, while reaction in the presence of CuCl at 50°C made it possible to obtain the isoindazole as the main product (yields 60-80%).

Scheme 26

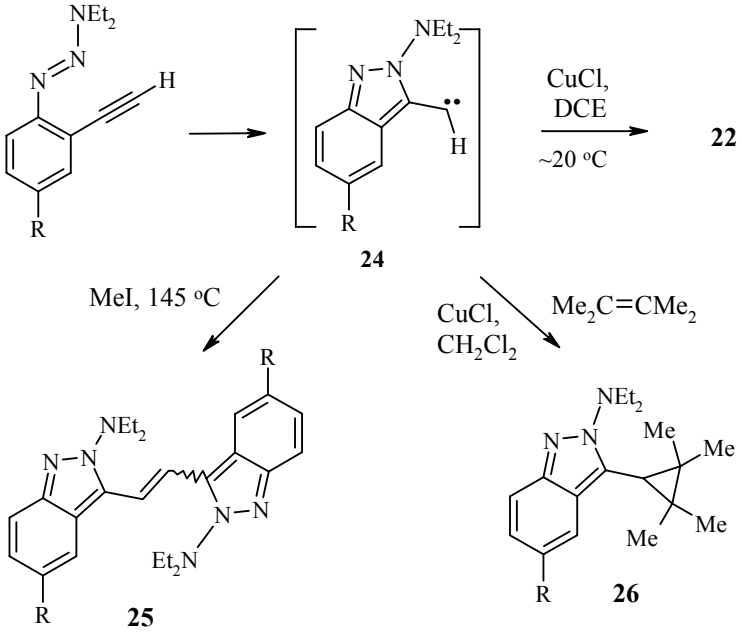


Substituents in the aromatic ring do not have a significant effect on the course of the reaction. According to calculations, isoindazole is less stable, and its formation is characterized by a smaller activation energy compared with cinnoline. It is clear that the formation of cinnoline is a thermodynamically controlled process whereas under kinetic control the reaction is directed toward the isoindazole [87, 88].

It was shown that the isoindazole **22** is formed through the carbene intermediate **24** as a result of its reaction with atmospheric oxygen. As evidence for the generation of the carbene the authors prepared its dimerization product **25** and the adduct from the reaction of the carbene **24** with 2,4-dimethylbut-2-ene **26** (Scheme 27).

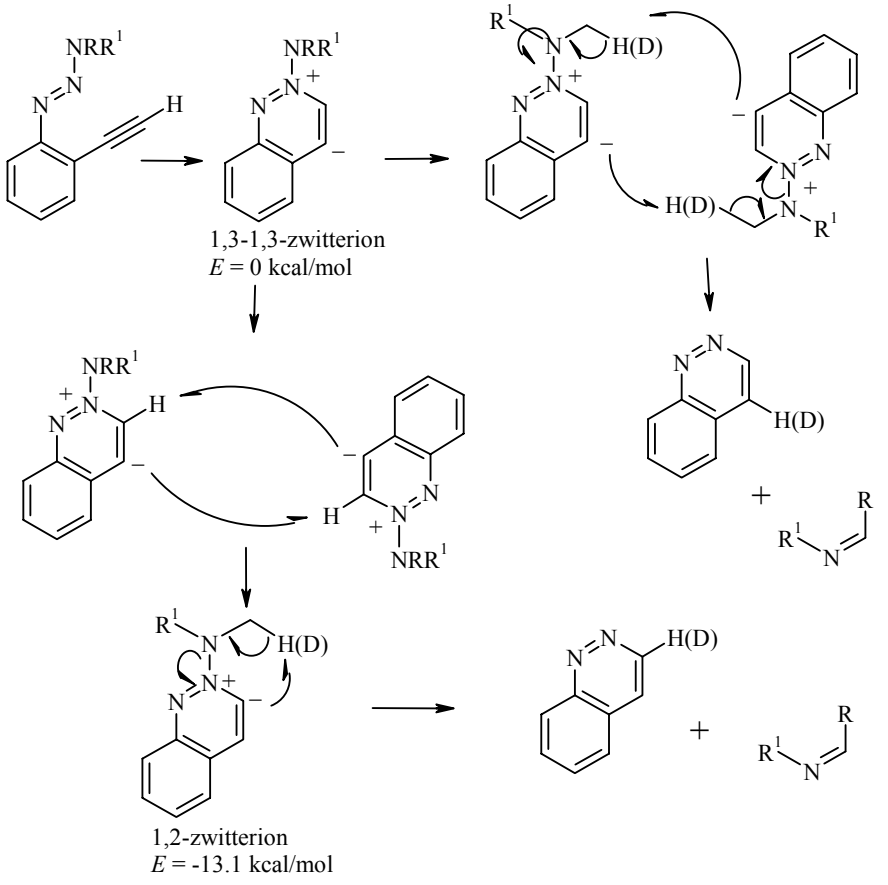
On the basis of quantum-chemical calculations and experimental data it was assumed that the cinnolines are formed from the triazines through a zwitterionic intermediate, which has a small share of biradical character. The proposed mechanism of transformation of the triazines into cinnolines is presented in scheme **28** [86].

Scheme 28



R = CN, *t*-Bu

Scheme 28

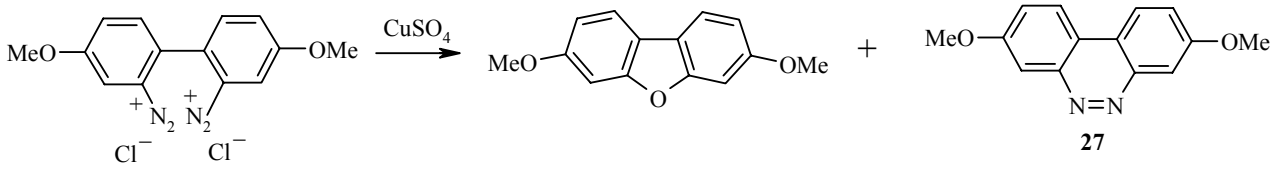


During cyclization in benzhydrol deuterated at the O-H bond cinnolines containing the deuterium atom at both at position 3 and at position 4 were obtained. In terms of the proposed mechanism this is explained by rearrangement of the 1,3-zwitterionic intermediate into the 1,2-zwitterion. Such a rearrangement had already been described in the literature for the case of pyridine systems; the 1,2-zwitterion is regarded as more stable [90]. The diethylamino group leaves in the form of the imine, giving up a proton to the negatively charged carbon atom.

Another approach to the synthesis of complex heterocyclic systems containing the cinnoline system involves electrophilic reactions in the aromatic ring, which take place with the participation of the diazonium cation. This method is not general, and there have not therefore been any systematic investigations in this direction.

The possibility of such a reaction was first demonstrated by Hata's group [91], where the condensed cinnoline **27** was isolated as side product as a result of the diazotization of 2,2′-diamino-4,4′-dimethoxybiphenyl during an attempt to prepare 2,7-dimethoxyphenylene oxide (Scheme 29). Later Sandin and Cairns realized the synthesis of benzo[*c*]cinnoline with a yield of 45% according to the same reaction scheme by using arsenic oxide instead of copper sulfate [92]. This method was not developed further; at present the most convenient method for the production of benzo[*c*]cinnolines is the reduction of 2,2′-dinitrobiphenyls mentioned earlier.

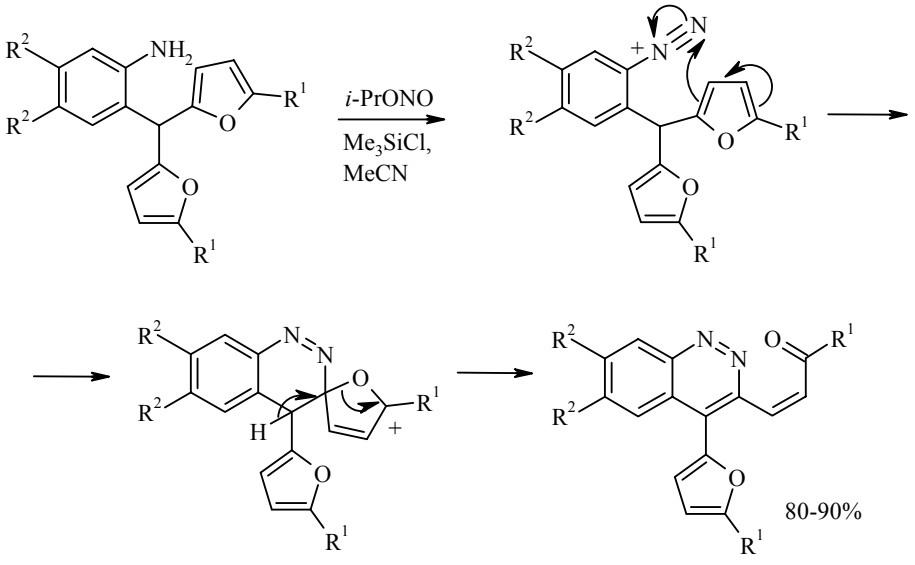
Scheme 29



27

Electrophilic attack by the diazonium ion on the furan ring leads to opening of the ring. The electrophilic mechanism for the process is confirmed by the *cis* configuration of the substituent at position 3 of the cinnoline ring (Scheme 30) [93].

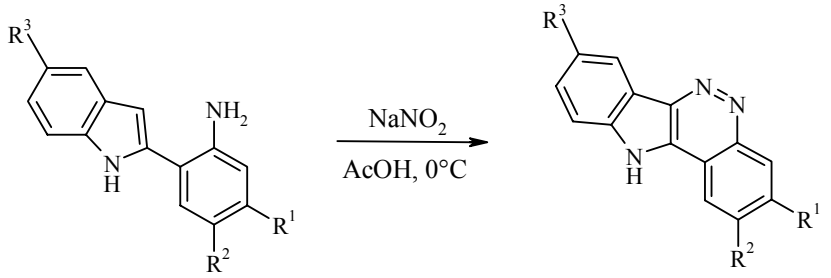
Scheme 30



R^1 = Alk, R^2 = H, OAlk

An example of the use of such cyclization in the pyrrole series is the synthesis of derivatives of indolo[3,2-*c*]cinnolines exhibiting biological activity against leukemia (Scheme 31) [94].

Scheme 31



R^1 = H, Cl; R^2 = H, Cl, Me; R^3 = H, Cl, Br, OMe, NO_2

The chief advantages of the method are the mild conditions, the high yields of the desired products, and the tolerance of the reaction toward the nature of substitution. The last factor makes it possible to insert the functional substituents required for selective bonding with DNA both into the indole fragment and into the cinnoline fragment.

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