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DEVELOPMENT OF THE CATALYTIC SYNTHESIS OF COMPOUNDS OF THE QUINOLINE SERIES (THE N. S. KOZLOV REACTION) (REVIEW)*

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This article is dedicated to the 80th anniversary of the Institute of Physical Organic Chemistry, National Academy of Sciences of Belarus (in 1929-1959 the Institute of Chemistry, Academy of Sciences of the BSSR). It contains a review of the advances in the synthesis and properties of condensed heterocyclic systems containing a quinoline fragment – derivatives of quinaldine, benzo[f]quinoline, indeno- and indoloquinoline, benzo[a]phenanthridine, benzoacridine, tetrahydroquinoline, 1,7- and 4,7-phenanthroline. The reactions forming the basis of the synthesis of the heterocycles are described – catalytic reaction of amines with acetylene, catalytic condensation of azomethines with methyl and α-methylene ketones, triple-component condensation of arylamines, carbonyl compounds, and CH acids.

Keywords: azaphenanthrenes, azomethines, benzoacridones, benzoquinolines, quinaldine, quinolines, phenanthrolines, CH acids, bactericides, luminophores.

Catalytic Synthesis of Quinaldine

The systematic researches conducted at the Institute in the field of the chemistry of heterocyclic compounds date back to the middle of the thirties when N. S. Kozlov (1907-1993) and co-workers developed a new method for the production of quinoline bases by the catalytic condensation of primary amines of the aniline series with acetylene in the presence of the salts of copper, mercury, and silver. To explain the mechanism of this reaction it was suggested that the initial product of the condensation was N-vinylaniline (**1**), which readily isomerizes to N-ethylideneaniline (**2**). The reaction of two molecules of the latter, of which one acts as azomethine and the other as a molecule with a mobile hydrogen atom, leads to the formation of the corresponding dimers **3**, which undergo cyclization to quinaldine (**4**) and its derivatives when heated (Scheme 1).

* Dedicated to the 80th Anniversary of the Institute of Physical Organic Chemistry, National Academy of Sciences of Belarus.

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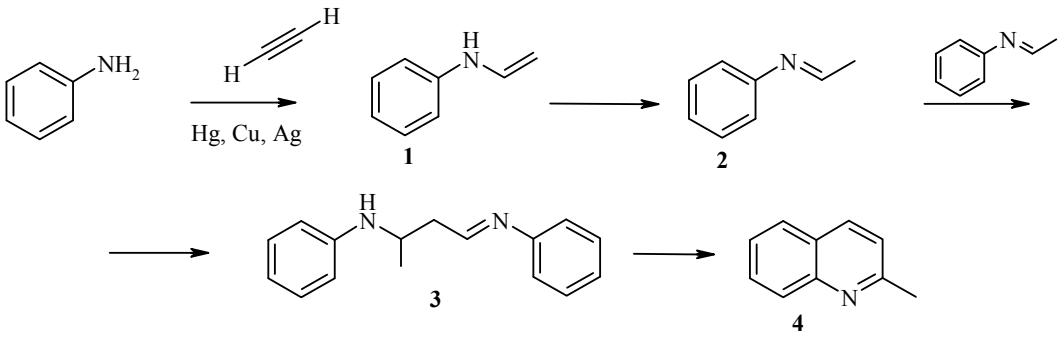
Scheme 1

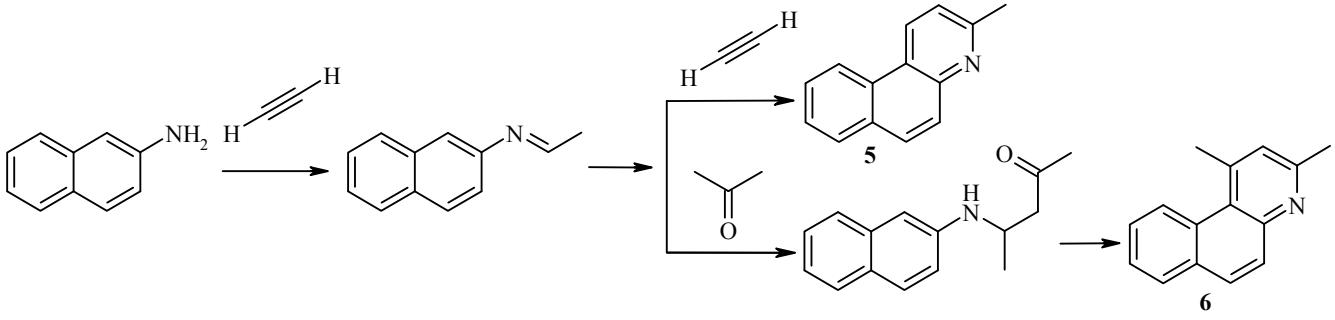


The results of the investigations of those years are reflected in a series of papers and a monograph entitled "Catalytic Synthesis of Quinaldine" [1-4]. About these investigations Academician N. D. Zelinsky wrote: "The new methods for the synthesis of quinoline compounds, which are not inferior to the well-known Skraup and Doebner–Miller methods, received from N. S. Kozlov a completely independent and original theoretical basis". This reaction was given the name of the scientist and is known as the N. S. Kozlov reaction [5].

Synthesis of Methyl and Aryl Derivatives of Benzo[*f*]quinoline

The bicyclic amine 2-naphthylamine was brought into reaction with acetylene. As a result it was possible for the first time to realize the synthesis of 3-methylbenzo[*f*]quinoline (**5**) [6]. During the catalytic reaction of 2-naphthylamine with acetylene in the presence of acetone, 1,3-dimethylbenzo[*f*]quinoline (**6**) was obtained (Scheme 2).

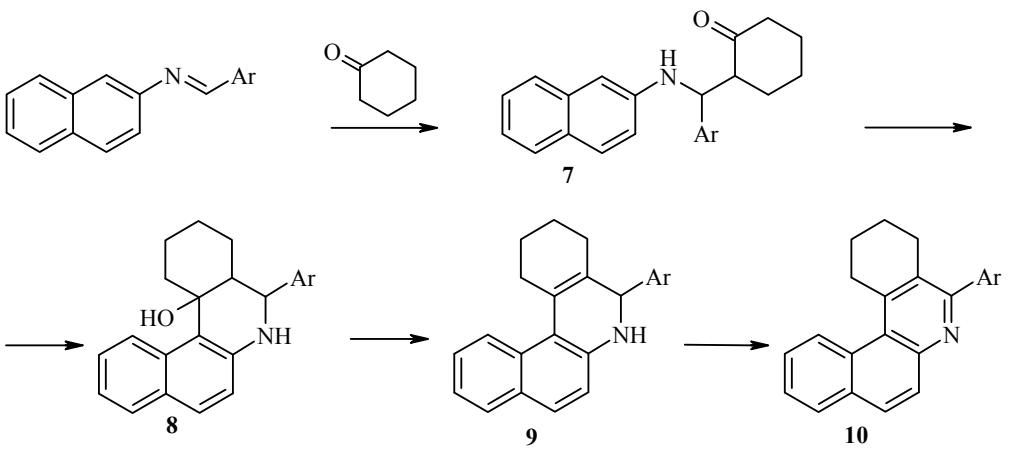
Scheme 2



The proposed reaction mechanism also included a stage with the formation of an azomethine and its subsequent reaction with a compound containing a mobile hydrogen atom. The ideas expressed above about the mechanism of the reaction led to the logical conclusion about the possible development of a quinoline synthesis starting from azomethines and compounds with mobile hydrogen atoms. In the sixties a study was started on the presently well-known catalytic condensation of azomethines with CH acids. Since most of the investigations started from azomethines of the 2-naphthylamine series the final products were numerous derivatives of benzo[*f*]quinoline, which were promising for use in various branches of science, medicine, industry, and agriculture. Structurally diverse CH acids were used in the reaction – methyl ketones of the aliphatic, aromatic, and heterocyclic series, esters of β-oxo acids, cyclic ketones, and β-dicarbonyl compounds. It was found that the reaction of Schiff bases with CH acids, which takes place in solution in an aliphatic alcohol, is catalyzed most effectively by a proton (conc. HCl), activating both the azomethine and the CH-acid compound.

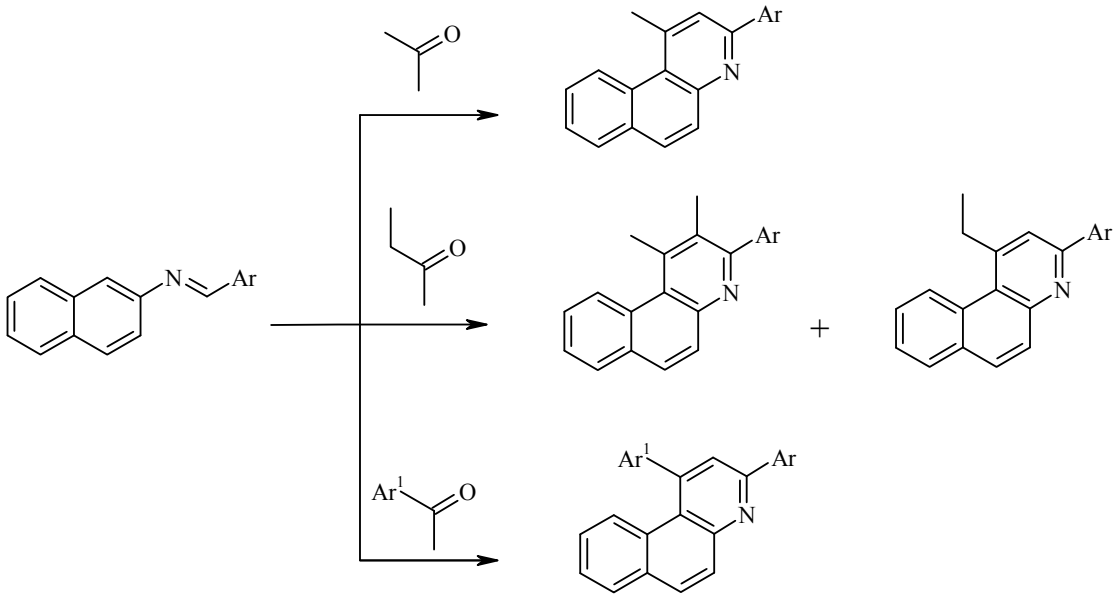
It was established that the benzo[*f*]quinoline ring is formed through a series of stages. The reaction mechanism was proved for the case of the reaction of benzylidene-2-naphthylamine with cyclohexenone by isolation of all the theoretically possible reaction products – the adduct of the azomethine and the CH acid **7**, the cyclic amino alcohol **8**, the dihydro derivative **9**, and the fully aromatic annelated by carbocycle benzo[*f*]quinoline **10** [7] (Scheme 3).

Scheme 3



In order to produce methyl- and aryl-substituted benzo[*f*]quinolines acetone, methyl ethyl ketone and derivatives of acetophenone were brought into reaction with arylmethylidene-2-naphthylamines [8-10] (Scheme 4).

Scheme 4

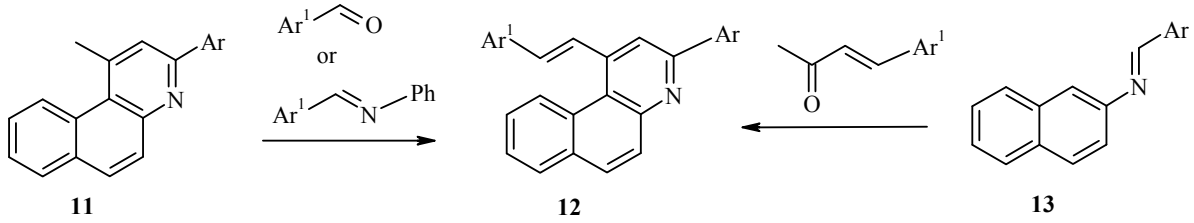


On account of the presence of the methyl group in the molecule and the functional substituents in the phenyl rings the obtained benzophenones are valuable starting substances for the synthesis of other more complex compounds, such as aldehydes, amines, and azomethines of the benzo[*f*]quinoline series [11-14].

Synthesis and Reactions of Styryl Derivatives of Benzo[*f*]quinoline

Practically important examples of reactions at the methyl group in the series of benzo[*f*]quinolines of type **11** leading to polyconjugated heteroaromatic systems **12** – styril dyes, luminophores, and light-sensitive materials – are Knoevenagel condensation with aldehydes and reaction with azomethines of the aniline series ("anil synthesis") [15-17]. A wide range of the arylvinyl (styryl) derivatives of benzo[*f*]quinoline formed as a result of these reactions was also obtained by the catalytic condensation of arylmethylidne-2-naphthylamines **13** with substituted benzylideneacetones [18-20] (Scheme 5).

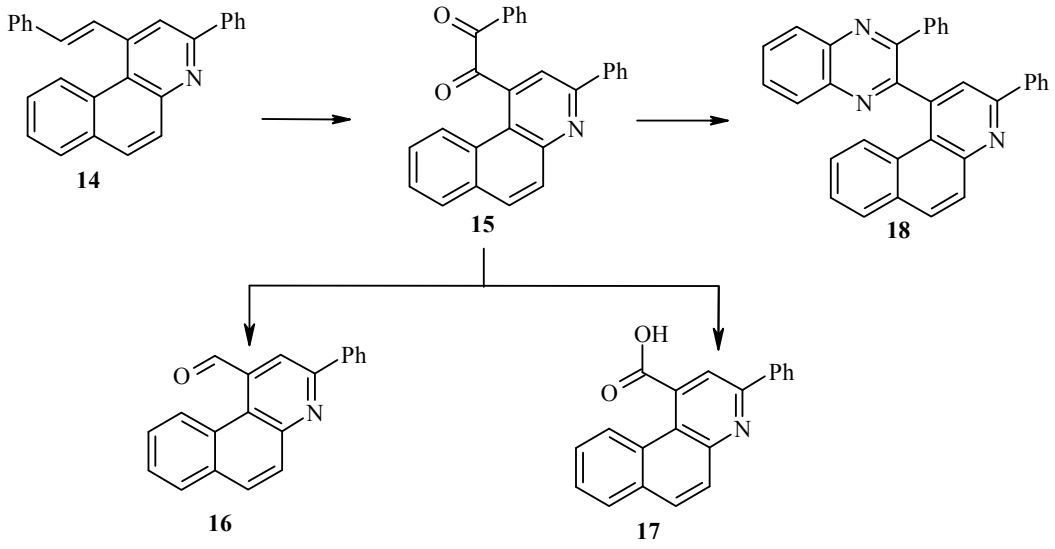
Scheme 5



11 **12** **13**

The oxidation of 3-phenyl-1-styryl-benzo[*f*]quinoline (**14**) with potassium permanganate under the conditions of the Wagner reaction led to the synthesis of difficultly obtainable carbonyl derivatives of benzo[*f*]quinoline: 1-phenyl-2-(3-phenylbenzo[*f*]quinolin-1-yl)ethanedione (**15**), 3-phenylbenzo[*f*]quinoline-1-carbaldehyde (**16**), and 3-phenylbenzo[*f*]cinchoninic acid (**17**) [21]. An effective method was developed for the production of phenyl(3-phenylbenzo[*f*]quinolin-1-yl)ethanedione, making it possible to achieve a product yield of 80%. 3-Phenyl-1-(3-phenylquinoxalin-2-yl)benzo[*f*]quinoline (**18**) was synthesized by the condensation of the diketone **15** with *o*-phenylenediamine (Scheme 6).

Scheme 6

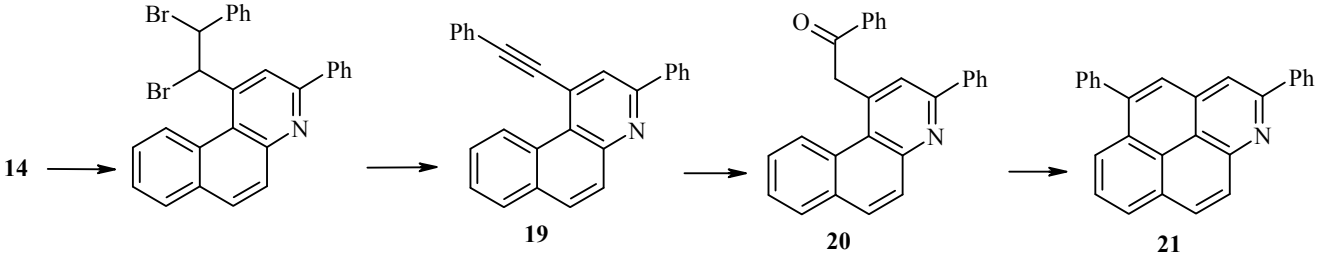


14 **15** **18**

16 **17**

The dibromo and acetylene derivatives of benzo[*f*]quinoline were synthesized on the basis of compound **14**. 1-Phenacyl-3-phenylbenzo[*f*]quinoline (**20**), which readily undergoes cyclization to the new heterocyclic system of azapyrene **21**, was obtained by the hydration of 3-phenyl-1-phenylacetylenylbenzo[*f*]quinoline (**19**) [22, 23] (Scheme 7).

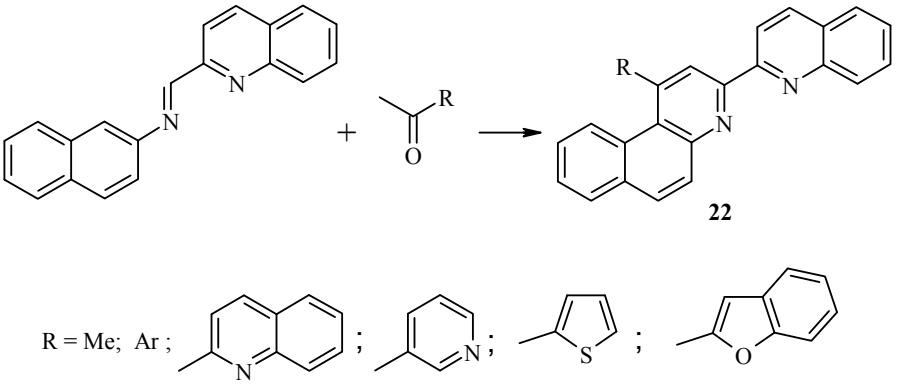
Scheme 7



Synthesis of Multinuclear Heterocyclic Compounds

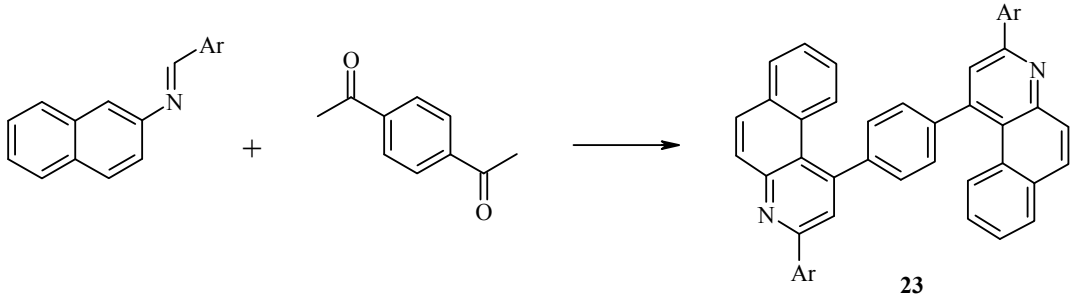
The catalytic condensation of azomethines with CH acids forms the basis for the production of polyheterocyclic compounds containing the residues of other heterocycles in the molecule together with the benzoquinoline ring [24-30]. There are two variants of the insertion of the heteryl substituents in the benzo[*f*]quinoline molecule: a) Reaction of arylmethylidene-2-naphthylamines with methyl ketones of the heterocyclic series (2-acetylthiophene, 3-acetylpyridine, 2-acetylquinoline, 2-acetylbenzofuran); b) reaction of the azomethine obtained from 2-naphthylamine and a heterocyclic aldehyde with a methyl ketone of the aliphatic or aromatic series. The combination of one and the other method leads to 1,3-diheterylbenzo-[*f*]quinolines **22** (Scheme 8).

Scheme 8

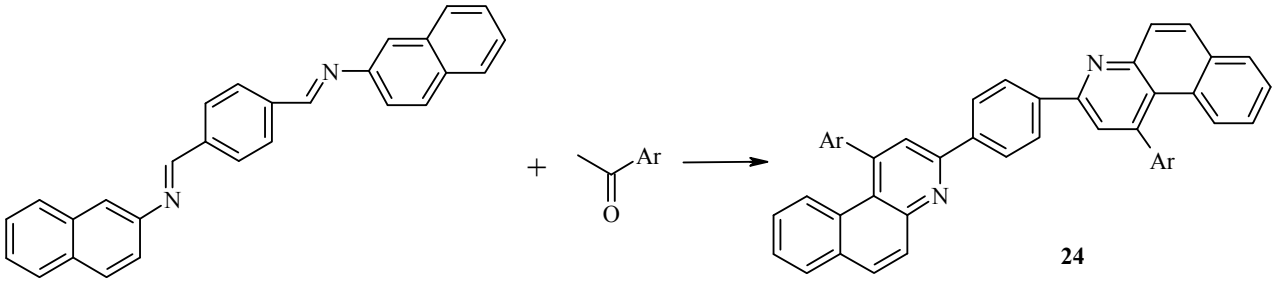


The isomeric polycyclic compounds **23** and **24**, containing two benzoquinoline substituents in the molecule, were synthesized (Scheme 9) by the reaction of arylmethylene-2-naphthylamines with *p*-acetyl-acetophenone or by the condensation of diazomethine, produced from terephthalic anhydride and 2-naphthyl-amine, with methyl aryl ketones [31].

Scheme 9



Scheme 9 (continued)



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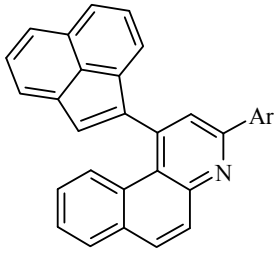
The results from study of the condensation of Schiff bases with CH acids of the aliphatic, alicyclic, aromatic, and heterocyclic series were summarized in the monograph [32]. In later papers data on the synthesis of polycyclic derivatives of benzo[*f*]quinoline **25** and **26** using 1-acetylacenaphthene and anthracene-carbaldehyde were presented [33, 34].



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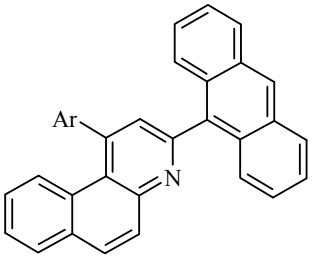

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On account of the large size of the molecules and the highly developed system of conjugated π-bonds the obtained compounds can exhibit specific physiological properties and electric conductivity.

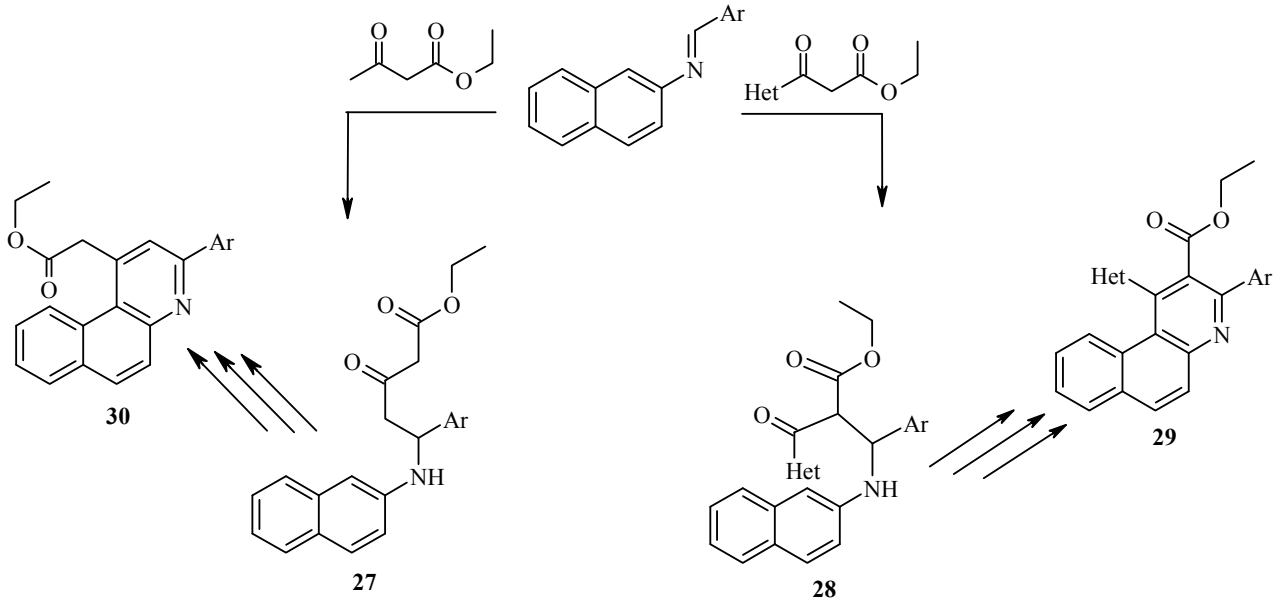
Condensation of Arylmethylidene-2-naphthylamines with the Esters of β-Oxo Acids

The papers [35-38] dealt with study of the catalytic condensation of azomethines of the 2-naphthylamine series with β-keto esters, opening up the way to the production of substituted carboxyl derivatives of benzo[*f*]quinoline with a high potential for biological activity. Acetoacetic ester and the ethyl esters of 2-furyl-, 2-quinolyl-, and 3-pyridyl-β-oxo carboxylic acids were brought into reaction with arylmethylidene-2-naphthylamines. In reaction with azomethines under mild conditions all the above-mentioned esters form the corresponding amino keto esters **27** and **28** – products from addition of the CH acid to the C=N bond of the azomethine. In the case of the heteryl-substituted β-keto esters **28** the final reaction products are ethyl 3-aryl-1-heterylbenzo[*f*]quinoline-2-carboxylates **29**. In the case of acetoacetic ester, in spite of the higher mobility of the protons of the methylene group compared with those of the methyl group, the reaction takes place with the participation of the less sterically hindered methyl group with the formation of ethyl (3-arylbenzo[*f*]quinolin-1-yl)acetates **30** as a result of cyclization (Scheme 10). Such a reaction path is confirmed by the isolation of the intermediates – ethyl 5-(2-naphthylamino)-3-oxo-5-phenylpentanoate and ethyl {3-(*p*-methoxyphenyl)-3,4-dihydrobenzo[*f*]quinolin-1-yl}acetate.

In the reaction of the azomethines with quinaldylacetic ester the aminohydroxy ester and the dihydro derivative of benzo[*f*]quinoline were isolated in addition to the intermediate amino keto esters, and it was

thereby demonstrated that the presence of the bulky quinoline substituent in the molecule of the oxo ester leads to retardation of the cyclization, dehydration, and dehydrogenation processes of the intermediate compounds. This makes it possible to stop the process at any of the stages and to obtain all the theoretically possible reaction products.

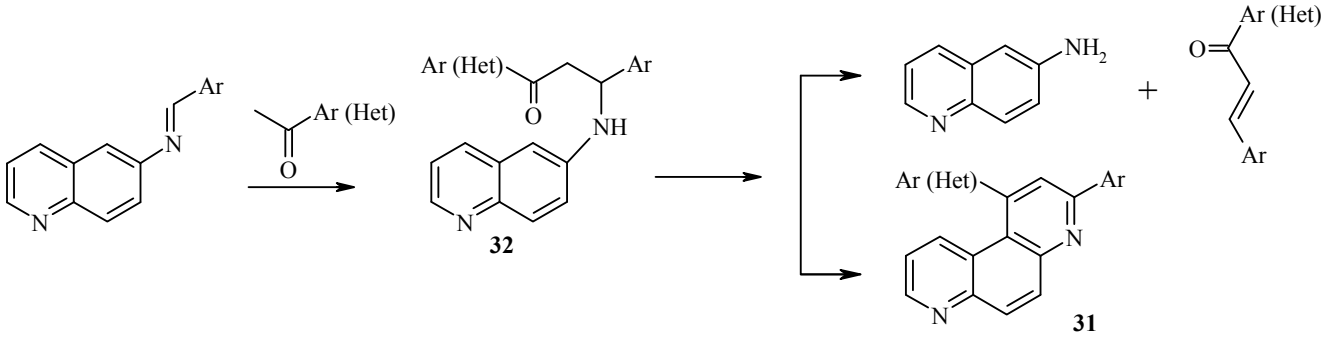
Scheme 10



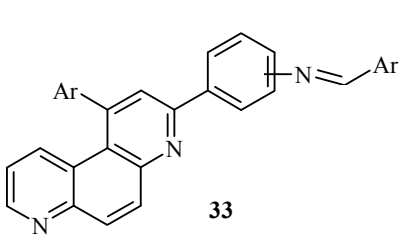
Synthesis of Derivatives of 4,7-Phenanthroline

On the basis of the catalytic condensation of azomethines of the 6-aminoquinoline series with CH acids effective methods were developed for the production of 4,7-phenanthrolines **31** – the diaza analogs of benzo[*f*]quinoline systems [39-42]. It was shown that the reaction of arylmethylidene-6-quinolylamines with acetophenone and its *para*-substituted derivatives, 3-acetylpyridine, and 2-acetylquinoline in an aliphatic alcohol in the presence of HCl takes place through the stage of the formation of intermediate β-amino ketones of the quinoline series **32**. It was established that the amino ketones undergo transformations in two directions depending on the structural factors and on the condensation conditions: a) Dehydrocyclization to derivatives of 4,7-phenanthroline **31**; b) hydramine cleavage to 6-aminoquinoline and α,β-unsaturated ketones (Scheme 11).

Scheme 11



Separate investigations were devoted to the synthesis of hydroxy, nitro, and amino derivatives of 4,7-phenanthroline [43, 44] since it is known that the insertion of these groups into the molecule of the heterocyclic compound leads to enlargement of the range of its physiological activity. The synthetic approach to the production of phenanthrolines simultaneously containing hydroxy and nitro groups in the molecule was based on the possibility of varying the substituents in the aldehyde part of the azomethine molecule and in the phenyl ring of the acetophenone. The synthesis of the aminophenanthrolines is realized by reduction of the nitro compounds with tin dichloride in a mixture of acetic and hydrochloric acids. On the basis of the obtained amino derivatives new mono- and bisazomethines of the 4,7-phenanthroline series **33-35** were synthesized.



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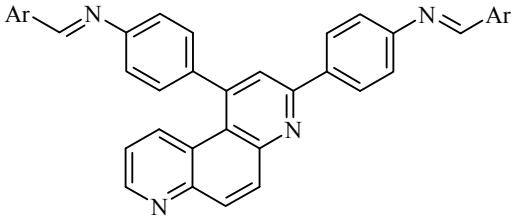

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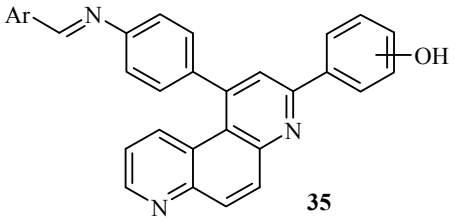
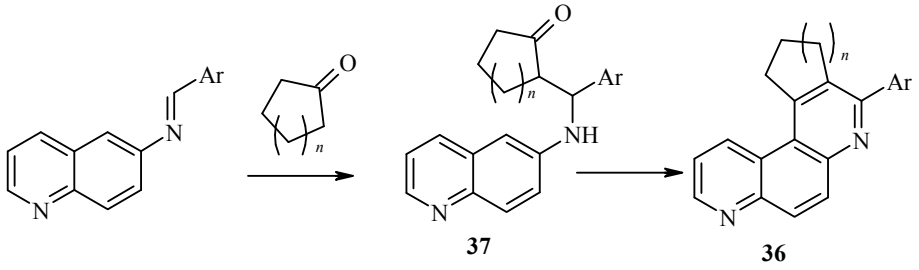


35

The condensation of azomethines with cyclic ketones [45-52] deserves special attention since it makes it possible to insert cyclopentane and cyclohexane rings, which are fragments of a series of natural compounds (steroids, alkaloids, prostaglandins) exhibiting cytotoxic, antitumor, pesticidal, and other types of activity, into the azaphenanthrene molecule. 3-Aryl-substituted 4,7-phenanthrolines **36** annelated with a cyclopentane or cyclohexane ring were synthesized by boiling arylmethylidene-6-quinolylamines with cyclopentanone and cyclohexanone in *n*-butyl alcohol in the presence of concentrated HCl [53, 54]. When the reaction was carried out at room temperature the precursors of phenanthrolines – 2-[(aryl)(6-quinolylamino)methyl]cyclohexanones **37** – were isolated (Scheme 12).

Scheme 12



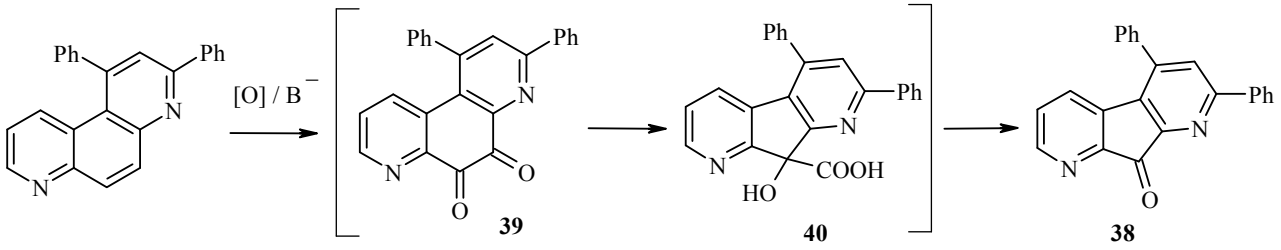
37 **36**

Oxidation of 1,3-Diphenyl-4,7-phenanthroline

Interest in the oxidation of 4,7-phenanthroline, originally undertaken to obtain evidence for the angular structure of the compound obtained by the Skraup method from *p*-phenylenediamine or 6-aminoquinoline, in recent decades is due to the search for effective methods for the synthesis of 4,7-phenanthrolinequinones

(medicinal formulations Entobex, Mexaform) and their analogs, which exhibit high antibacterial activity and are used for the treatment of gastrointestinal diseases. With the aim of bringing new derivatives of 4,7-phenanthroline into the oxidation reaction we first studied the chemical behavior of 1,3-diphenyl-4,7-phenanthroline during the action of potassium permanganate when heated in an alkaline solution of KOH [55]. 2,4-Diphenyl-1,8-diazafluoren-9-one (**38**) was obtained with a yield of 36% as the only product instead of the expected 1,3-diphenyl-4,7-phenanthroline-5,6-dione (**39**), diphenyl-substituted 3,3'-bipyridyl-2,2'-dicarboxylic acid, or 3,3'-bipyridyl.

Scheme 13

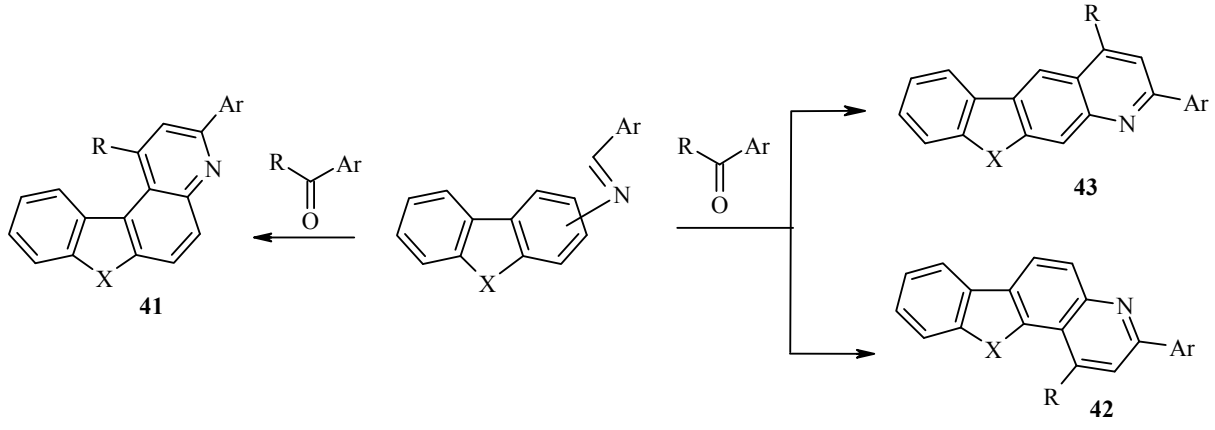


Apparently, the 1,3-diphenyl-4,7-phenanthroline-5,6-dione (**39**) formed at the first stage of the reaction undergoes a rearrangement similar to the benzil rearrangement to the unstable α-hydroxy acid **40**, which is decarboxylated with the formation of 2,4-diphenyl-1,8-diazafluoren-9-one (Scheme 13). With regard to the results of investigations into the transformations of phenanthrene- and diazaphenanthrenequinones in an alkaline medium the discovered oxidative transformation can be used for the development of a new approach to the production of difficultly obtainable compounds of the diazafluorenone series.

Synthesis of Indolo- and Indenoquinolines

The 1-methyl-, 1-arylvinyl-, and 1-aryl-3-arylindolo[2,3-*f*]quinolines **41** were synthesized by the catalytic condensation of carbazole-containing azomethines with acetone, substituted benzylideneacetones, and acetophenones. It was shown that of the two alternative cyclization paths resulting in the formation of linear and angular condensed products the second is realized as the thermodynamically most favorable [56] (Scheme 14).

Scheme 14



R = Me, Ar^1, CH = CHAr; **41** X = NH **42** X = CH_2; **43** X= CH_2, CO

The condensation of azomethines of the 2-aminofluorene series with CH acids leads to the formation of angular products (derivatives of indeno[*f*]quinoline **42**) in a mixture with the linear products with a predominance of the latter (3-aryl-10H-indeno[1,2-*g*]quinolines **43**, X = CH_2) only in the case of acetone. If ketones of large size are used in the reaction the main products (indenoquinolines) have linear structures [57, 58]. During the reaction of acetophenone with arylmethylidene-2-aminofluoren-9-ones the carbonyl group in the azomethine molecule makes position 1 of the fluorene ring even less available for closure of the newly formed ring, and the only reaction products in this case are compounds with linear structure – 2-aryl-4-phenyl-10H-indeno[1,2-*g*]quinolin-10-ones **43** (X = CO) [59].

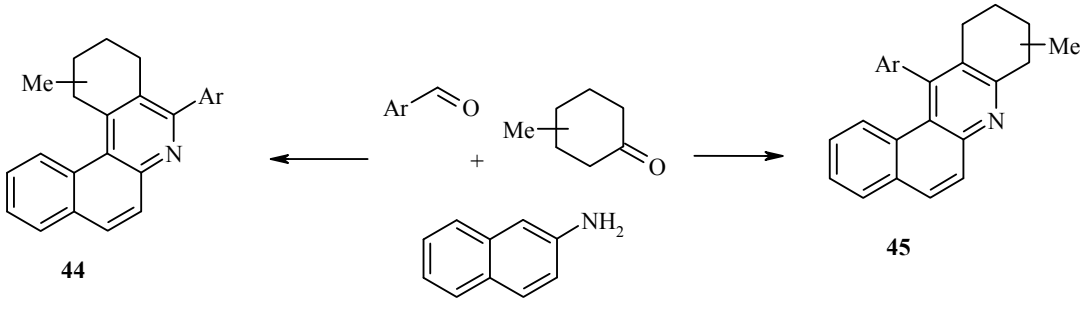
In 1979 a method for the production of complex polycyclic aza aromatic compounds based on the catalytic condensation of azomethines with CH acids obtained recognition in the chemical literature as the "N. Kozlov synthesis" [60].

Triple-Component Condensation in the Design of Condensed Nitrogen-Containing Heterocycles

Investigations of new approaches to the synthesis of polynuclear heterocyclic structures based on multicomponent reactions developed vigorously in the middle of the nineties. The triple-component condensation of structurally varied aryl(heteryl)amines, aldehydes, and CH acids was studied as a method for the combination (assembly) of several structural fragments containing the component substrates into the single molecule of a functionalized polycyclic aza heterocycle for the purpose of producing derivatives of benzo[*f*]quinoline, benzo[*a*]phenanthridine, benzo[*a*]acridine, and 1,7- and 4,7-phenanthroline.

The advantages of the single-stage method were demonstrated for the case of the synthesis of 1-aryl(or methyl)-3-aryl(or heteryl)benzo[*f*]quinolines, benzo[*a*]phenanthridines, cyclopenta[*c*]benzo[*f*]quinolines, and 4,7-phenanthrolines, starting from 2-naphthyl- or 6-quinolylamine, aromatic or heteroaromatic aldehydes, acetone, acetophenones substituted in the phenyl ring, and cyclic ketones [61-66]. Triple-component condensation is particularly effective in cases where it is difficult to isolate the azomethines in the crystalline state [61] or aminals are formed instead of azomethines [67, 68]. At the same time the formation of azomethines as intermediates and their subsequent acid-catalyzed reaction with the methyl ketones is the most likely path for the synthesis of the above-mentioned azaphenanthrene derivatives. Another variant of triple-component condensation is also possible when the enamine formed at the first stage from the amine and the CH acid adds a molecule of benzaldehyde and the obtained arylamino ketone undergoes dehydrocyclization to the azaphenanthrene system. Both versions of the reaction were detected during study of the reaction of 2-naphthylamine with aromatic aldehydes and 2-, 3-, and 4-methylcyclohexanones [69, 70]; in the case of 3- and 4-methylcyclohexanones the isomeric cyclization products 5-aryl-2(3)-methyl-1,2,3,4-tetrahydrobenzo[*a*]phenanthridines **44** and 12-aryl-9(10)-methyl-8,9,10,11-tetrahydrobenzo[*a*]acridines **45** were obtained (Scheme 15).

Scheme 15



44 **45**

The triple-component condensation developed most strongly as applied to the synthesis of annelated aza- and diazaphenanthrenes with the use of cyclic β-dicarbonyl compounds – derivatives of 1,3-cyclohexanedione, 1,3-indanedione, tetrahydrofuran- and tetrahydropyran-2,4-dione, and 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid) – as CH acids [7-15].

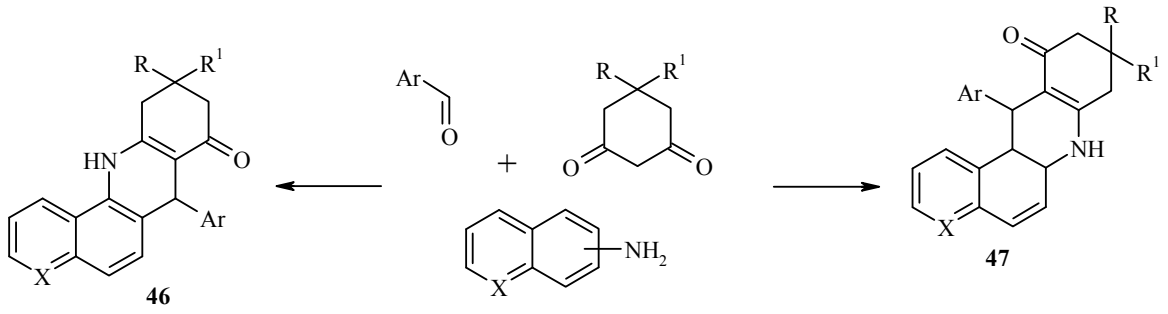
Condensation of Naphthyl- and Quinolylamines with Aromatic Aldehydes and 1,3-Cyclohexanedione Derivatives

On account of the presence of the two enolized carbonyl groups and the methylene group situated between them cyclic β-diketones are widely used in the synthesis of condensed heterocycles. The condensation of amines of the 1- and 2-naphthylamine and 5- and 6-quinolylamine series with aromatic and heteroaromatic aldehydes, and 1,3-cyclohexanedione or its derivatives (dimedone, phendione, 5-methyl-, 5-(*p*-methoxyphenyl)-, 5-(*p*-butoxyphenyl)-, and 5-(2-furyl)-1,3-cyclohexanedione) takes place in a solution of aliphatic alcohol in the absence of a catalyst, the role of which is played by the proton of the enolized form of the β-diketone. As a result of the reaction oxo compounds of tetracyclic structure with an azaphenanthrene (benzo[*f*]quinoline or phenanthroline) fragment are formed [71-76].

Concerning the structure of the obtained condensation products right up to the end of the nineties there were disagreements essentially about the determination of the point of annelation of the carbocycle to the azaphenanthrene system and, accordingly, the assignment of the structure to the partially hydrogenated benzo[*a*]phenanthridone or the isomeric benzo[*a*]acridone system and also the benzo[*a*]- or benzo[*b*][4,7]phenthrolinone and benzo[*b*]- or benzo[*c*][1,7]phenanthrolinone system. Published results from X-ray crystallographic analysis of the products from the condensation of 1- and 2-naphthylamine with aryl aldehydes and dimedone and the data from the ^{1}H and ^{13}C NMR spectra, obtained by two-dimensional NMR procedures (COSY, NOESY, HSQC, and HMBC), demonstrated unambiguously that the oxo derivatives of benzo[*a*]acridine and benzo[*b*][1,7]- and benzo[*b*][4,7]phenanthroline are formed as a result of reaction [75, 76]. A mechanism was proposed for the formation of these compounds, involving rearrangement of the intermediate products from addition of the CH acid at the C=N bond of the azomethine (deamination and addition of the formed 2-arylmethylene-1,3-cyclohexanedione to the amine at the carbon atom with highest electron density, i.e., C-2 or C-1 of the naphthalene ring and C-5 or C-6 of the quinoline ring) and cyclization of the obtained amino diketone.

The effect of the structural factors and the electronic nature of the substituents in the aldehyde molecule on the yield of the desired reaction products was established. Preparative methods were proposed, and new derivatives of benzo[*f*]quinoline, benzo[*a*]acridine, and 1,7- and 4,7-phenanthroline (**46** and **47** respectively) were synthesized (Scheme 16) as prospective luminophores, light-sensitive materials, and bioactive substances with a broad range of activity.

Scheme 16

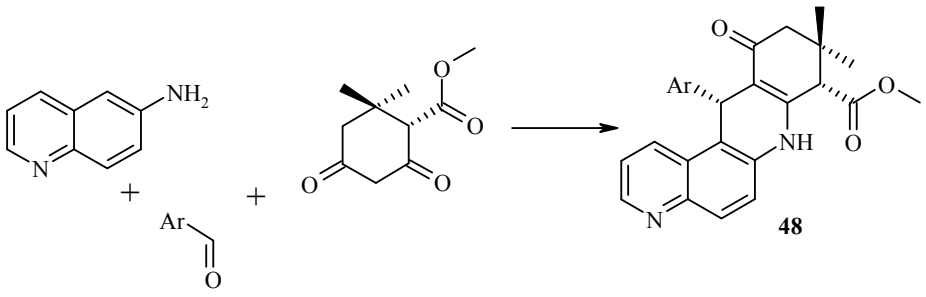


X = CH, N; R = H, R^1 = Ph, Me, *p*-$MeOC_6H_4$, *p*-$BuOC_6H_4$, 2-furyl; R = R^1 = H, Me

It was found that if 5-monosubstituted 1,3-cyclohexanediones [5-Ph-, 5-Me-, 5-(4-$MeOC_6H_4$)-, 5-(4-$BuOC_6H_4$)-, 5-(2-furyl)] containing an asymmetric center were used, the condensation products were formed as mixtures of two diastereomers [77-80].

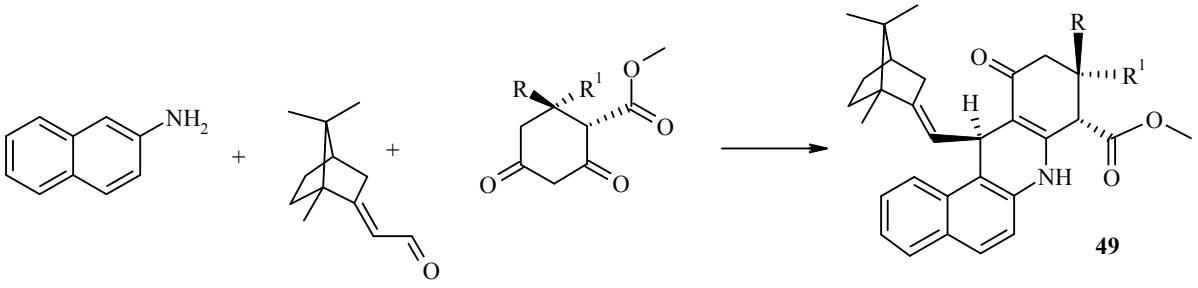
The condensation of 4-methoxycarbonyl-5,5-dimethyl--1,3-cyclohexanedione with 6-quinolylamine and aldehydes of the aromatic, heteroaromatic, and aliphatic series in ethanol leads to the formation of a mixture of *cis*- and *trans*-12-aryl(hetaryl, cyclohexenyl)-8-methoxycarbonyl-9,9-dimethyl-8,9,10,12-tetrahydro-7H-benzo-[*b*]-4,7-phenanthrolin-11-ones **48** (Scheme 17). In this case on account of the CH component of the reaction mixture an additional functional group (an ester group) is inserted into the molecule of the heterocycle together with the asymmetric carbon atoms [81].

Scheme 17



By the triple-component condensation of (2-bornylidene)acetaldehyde and 2-naphthylamine with various, including dissymmetric, cyclic β-diketones derivatives of 12-(2-bornylidene)methyl-8,9,10,12-tetrahydro-7H-benzo[*a*]acridin-11-one **49** containing tree or more asymmetric carbon atoms and the structural fragment of a natural compound were synthesized (Scheme 18). It was established that steric factors determine the preferential formation of the (12*R*)-isomers of benzoacridones (*R/S* = 7:5) and the orientation of the substituents of the cyclohexenone fragment. These same factors give rise to the regiospecificity of the reaction, leading to the exclusive formation of 8,9-disubstituted benzoacridones when 4,5-disubstituted cyclohexane-1,3-diones are used [82].

Scheme 18



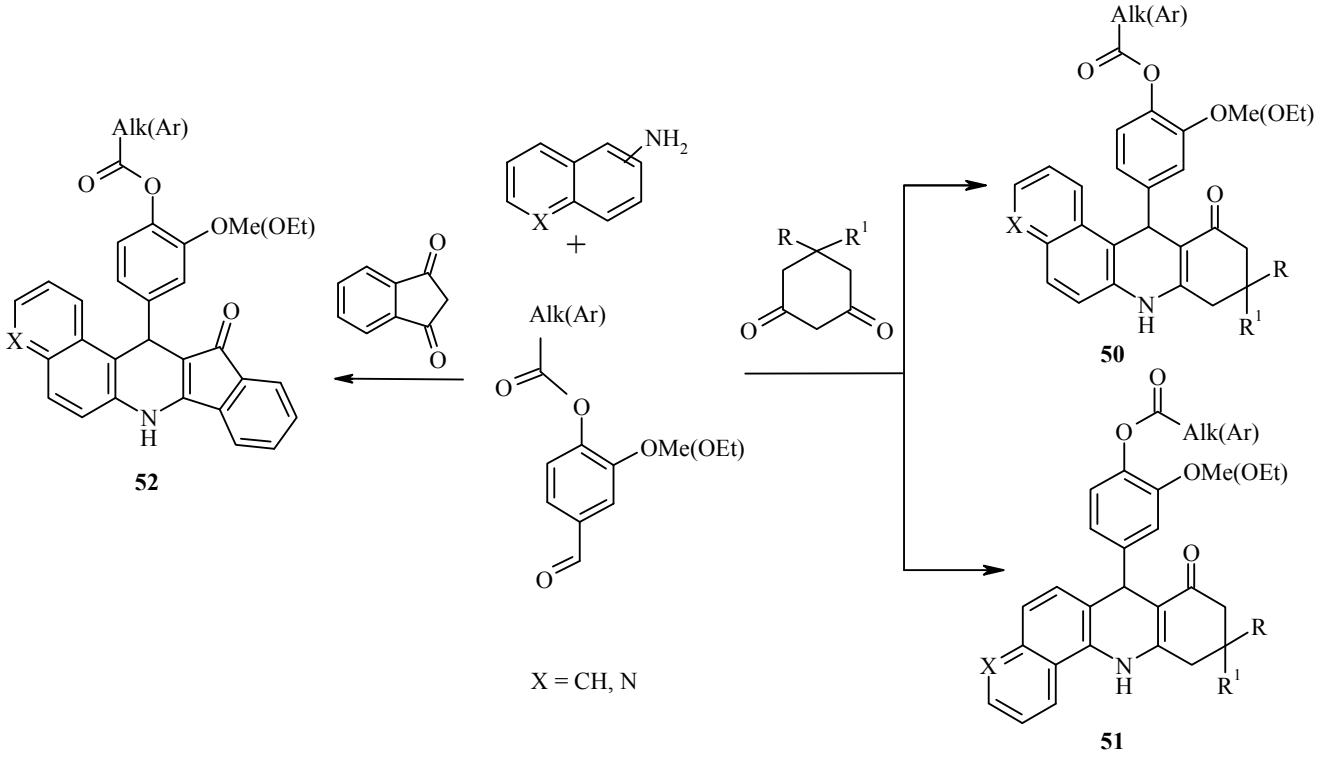
Esters of Vanillin and Vanillal in Condensation with Amines of the Naphthalene and Quinoline Series and Cyclic β-Ketones

Natural compounds [vanillin (4-hydroxy-3-methoxybenzaldehyde) and vanillal (4-hydroxy-3-ethoxy-benzaldehyde)], which belong to the group of vegetable phenols and are used in the confectionery, perfumery, and cosmetic industries, were studied as aldehyde components of the triple-component condensation. Being a

supplier of the methoxy- or ethoxyphenol substituent and methine fragment in the structure of azaheterocycles, vanillin plays a singular role in the synthesis of biologically active compounds of the aza- and diazaphenanthrene series – the analogs of bactericides, cardioprotectors, inhibitors of enzymes, analgesics, alkaloids of the melicopine, evoxanthine, and other series.

In order to increase the number and variety of the functional groups in the molecule of the azaheterocycle, to change its hydrophilic–lipophilic characteristics, and to extend the biological possibilities the initial vanillin molecule was esterified with acid chlorides of the aliphatic (C_1–C_{12}) and aromatic series, and the obtained vanillin esters were brought into reaction with naphthyl- and quinolylamines and derivatives of 1,3-cyclohexanedione and 1,3-indanedione. Triple-component condensation occurs when equimolar amounts of the reagents are boiled in 1-butanol in the absence of a catalyst; in spite of the relatively high temperature this makes it possible to prevent hydrolysis of the vanillin alkanoates and benzoates entering into condensation at the aldehyde group. As a result the derivatives of benzoacridones **50** and **51** (X = CH), benzoindeno-quinolinones **52**, and benzophenanthrolinones **50** and **51** (X = N) containing ether and ester functions together with the ketone carbonyl in the molecule are formed with yields of up to 90% [83-91] (Scheme 19).

Scheme 19



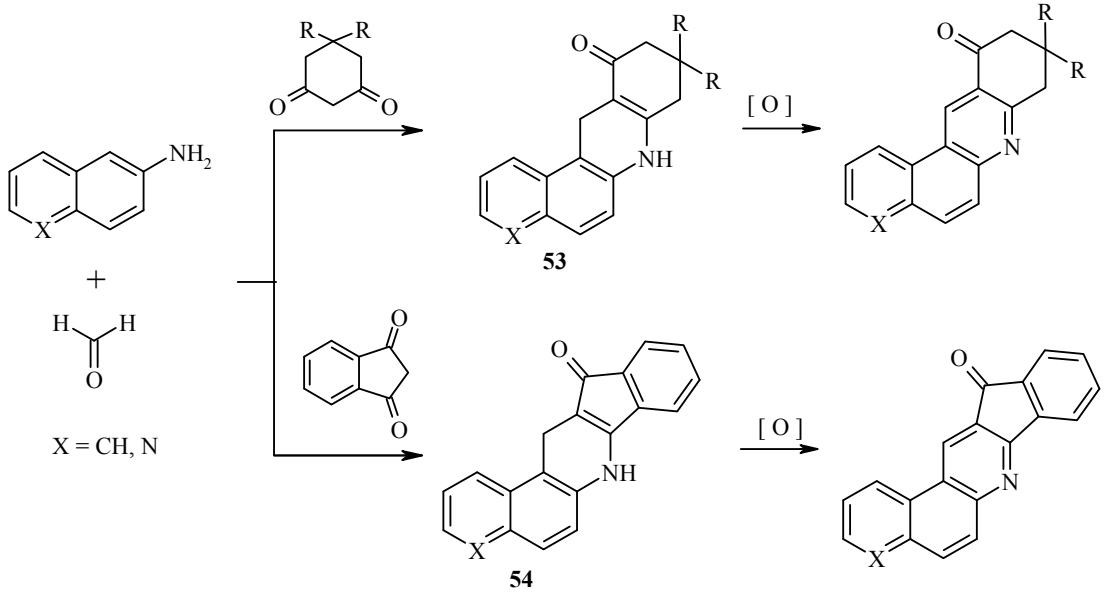
Synthesis of Heterocyclic Systems by Triple-Component Condensation of Aromatic Amines with Formaldehyde and Cyclic β-Dicarbonyl Compounds

The condensation of 2-naphthyl- and 6-quinolylamine with formaldehyde and derivatives of 1,3-cyclohexanedione and indanedione, realized by briefly boiling an equimolar mixture of the reagents in ethanol in the absence of a catalyst, leads to the formation of partially hydrogenated polynuclear heterocyclic compounds **53** and **54** (benzoacridones, benzoindenoquinolinones, 4,7-phenanthrolinones) not containing substituents at the

para position to the nitrogen atom (Scheme 20). As a rule the reaction takes place with high yields (65-90%). The products are precipitated from the hot reaction mixture, which substantially simplifies their isolation and purification. Filtration of the precipitate and washing with ethanol followed by recrystallization from dimethylformamide give pure samples (more than 97%, according to NMR) [92].

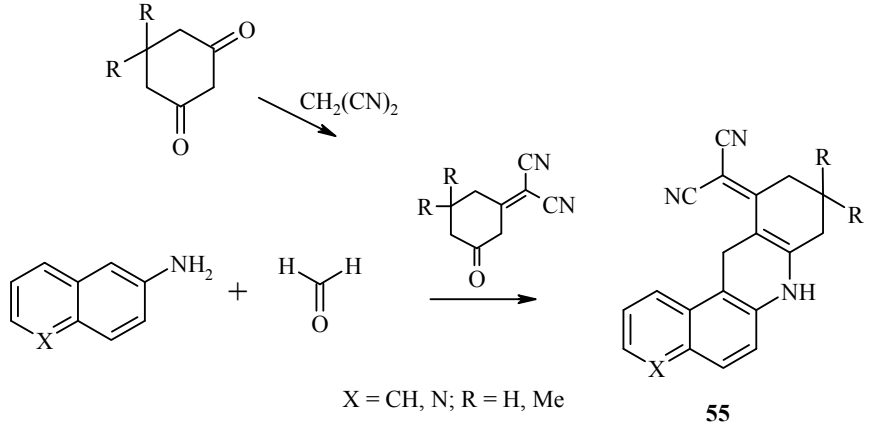
Aromatization of the dihydropyridine ring in the condensation products is realized by oxidation with sodium nitrite in acetic acid solution.

Scheme 20



It was shown that derivatives of benzoacridine **55** containing two nitrile groups in the molecule can be obtained by preliminary modification of the initial diketone by a Knoevenagel reaction with malononitrile followed by condensation of the obtained hydroxycyclohexylidenepropanedinitriles with 2-naphthylamine and formaldehyde [93] (Scheme 21).

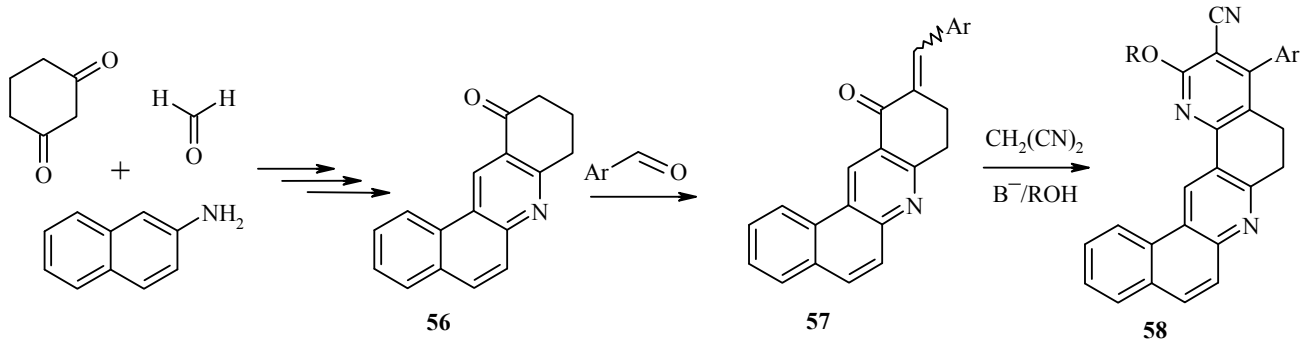
Scheme 21



The reaction of 9,10-dihydro-8H-benzo[*a*]acridin-11-one (**56**) with various aromatic aldehydes was realized in order to produce new polyfunctional compounds containing a partially hydrogenated benzo[*a*]acridine fragment. As a result good yields of the classical products of a crotonic condensation – 10-arylidene-9,10-di-

hydro-8H-benzo[*a*]acridin-11-ones **57** – were obtained. The reaction of the synthesized arylidene derivatives with malononitrile by boiling the mixture of reagents in methanol or ethanol in the presence of 50% aqueous KOH leads to the formation of derivatives of 1,7-diazadibenzo[*a,j*]anthracene **58**, containing nitrile and alkoxyl substituents (Scheme 22); the ether residue here corresponds to the alcohol in which the condensation was conducted [94].

Scheme 22

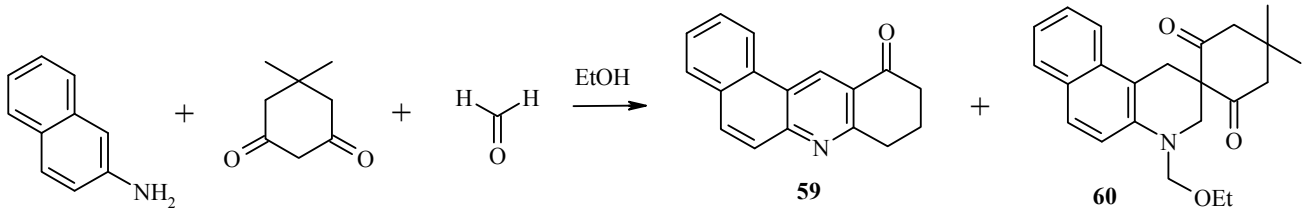


56 **57** **58**

Synthesis of Spirocyclic Derivatives of Benzo[*f*]quinoline

During investigation of the triple-component condensation of aromatic amines with cyclic β-diketones and various aldehydes it was found that the reaction of 2-naphthylamine with dimedone and formaldehyde gave a small amount of the spirocyclic benzo[*f*]quinoline **60**, containing substituents at the second and fourth positions of the ring, in addition to the "classical" product with the benzo[*a*]acridone structure **59** (Scheme 23).

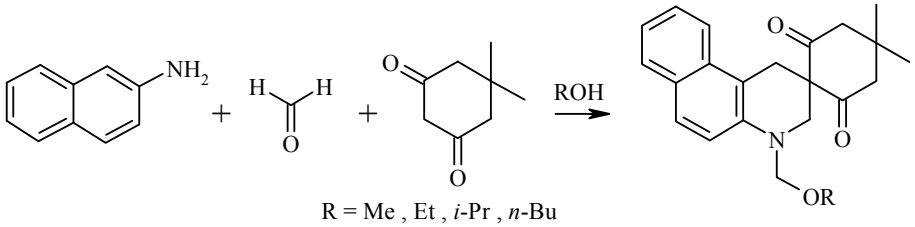
Scheme 23



59 **60**

If the condensation of 2-naphthylamine and dimedone is realized in the presence of a large excess of aliphatic alcohol at room temperature the spirocyclic product becomes the main product; this makes it possible to achieve the planned synthesis of N-alkoxymethylated derivatives of benzo[*f*]quinoline containing a substituted 2-azaspiro[5.5]undecane fragment [95] (Scheme 24).

Scheme 24

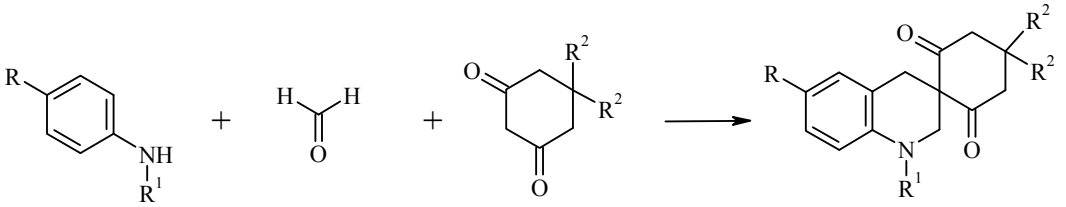


R = Me , Et , *i*-Pr , *n*-Bu

A New Triple-Component Reaction of Anilines, Formaldehyde, and β-Diketones. A Simple Synthesis of 3-Spirosubstituted 1,2,3,4-Tetrahydroquinolines

The reactions of secondary amines of the aniline series with formaldehyde and cyclic β-diketones were studied for the first time [96]. It was shown that the condensation takes place smoothly when a mixture of the initial reagents is boiled briefly in ethanol and gives 3-spirocoupled derivatives of 1,2,3,4-tetrahydroquinoline (Scheme 25).

Scheme 25

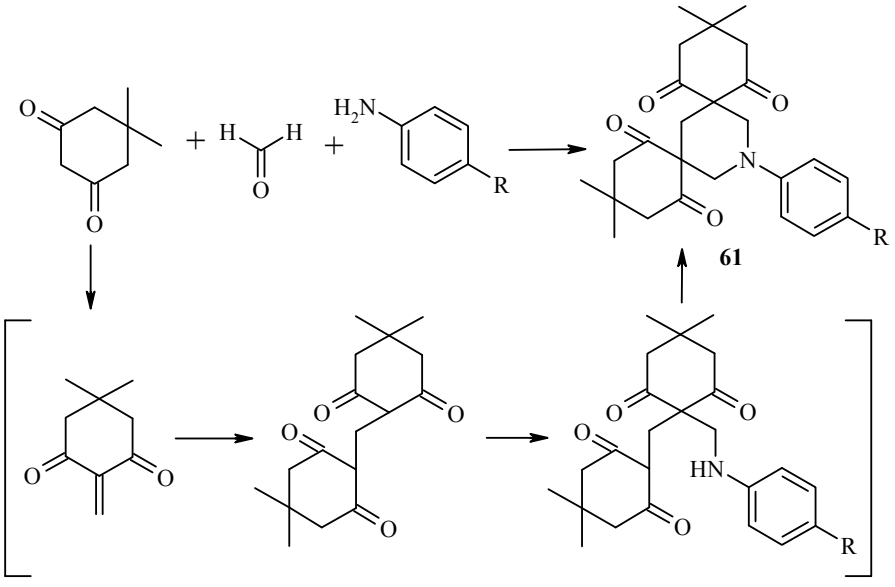


R = Me, OMe; R^1 = Alk, Bz, etc.; R^2 = H, Me

A mechanism of the reaction taking place through the formation of a Mannich base, its rearrangement, and cyclization of the obtained amino diketone to the spirotetrahydroquinoline was proposed. In their structure the obtained compounds contain a 2-azaspiro[5.5]undecane fragment, which forms the structural base of a group of piperidine alkaloids (sibirine, nitramine, nitrabirine, etc.), isolated from *Nitraria sibirica Pall* and having structural similarity to the neurotoxic alkaloids of the histrinicotoxin family. The partially dehydro-genated 2-azaspiro[5.5]undecane system is also a structural fragment of a series of toxins isolated from certain forms of marine oysters.

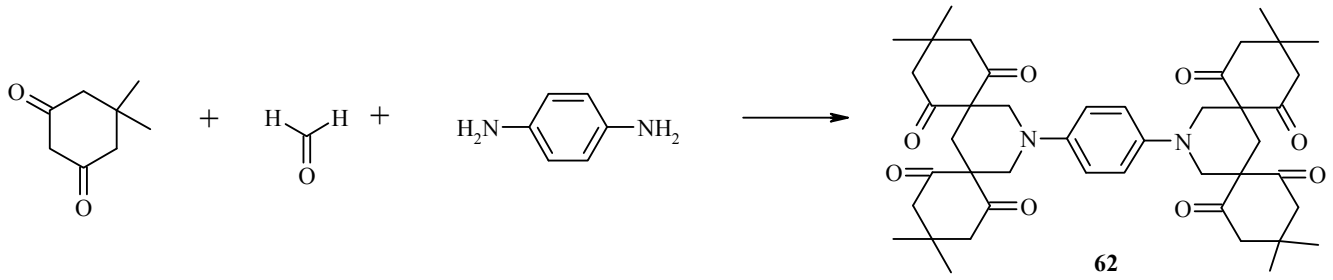
It is interesting to note that the condensation of anilines unsubstituted at the nitrogen atom and containing substituents at the *para* position to the amino group with dimedone and formaldehyde leads to the formation of 3,5-dispirocoupled piperidines **61** [97]. The transformation probably takes place through successive Knoevenagel, Michael, and double Mannich reactions (Scheme 26).

Scheme 26



By bringing *p*-phenylenediamine into such a reaction it was possible to obtain the interesting product **62**, containing two symmetrical bispiropiperidine ring systems [97] (Scheme 27).

Scheme 27



62

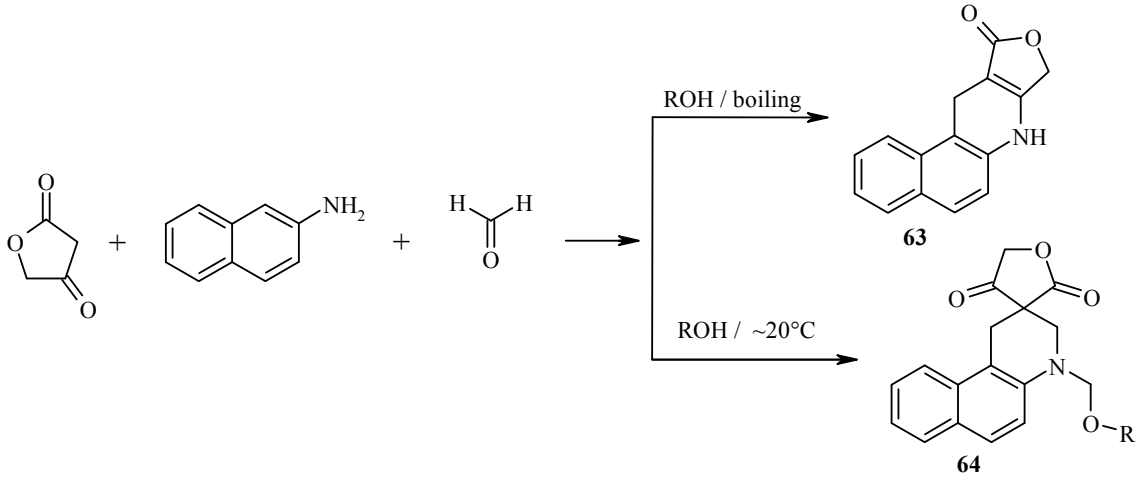
Synthesis of Condensed Heterocycles with Two Different Heteroatoms N and O in the Molecule

The hetero analogs of β-diketones – tetrahydrofuran-2,4-dione (tetronic acid), 2,2-dimethyl-1,3-dioxane-4,6-dione (Meldrum's acid), 6-methyl-, 6,6-dimethyl-, 6-phenyl-, 6-spirocyclooctyltetrahydropyran-2,4-diones – were first used as synthons for triple-component condensation in [98-103].

The reaction of 2-naphthyl- or 6-quinolylamine with formaldehyde or substituted benzaldehydes and tetrahydrofuran- or tetrahydropyran-2,4-diones was used to develop a highly effective method for the synthesis of new condensed heteroaromatic systems with two different heteroatoms N and O in the molecule – derivatives of aza- and diazaphenanthrene annelated with a furan or pyran ring. It was established that the addition and cyclocondensation reactions that occur during the synthesis of the heterocycles are realized with the participation of the carbonyl group of the tetrahydrofuran- or pyrandione with retention of the lactone grouping in the structure of the obtained polycycle.

It was found that, depending on the conditions of the synthesis and the ratio of the reagents, the condensation of 2-naphthylamine, formaldehyde, and tetronic acid leads to the selective formation of two types of products differing in the nature of annelation and the mechanism of formation of the benzoquinoline ring: during the reaction of equimolar amounts of the initial substances in boiling aliphatic alcohol the derivative of dihydrobenzo[*f*]furo[3,4-*b*]quinoline **63** is formed with a 65% yield. At room temperature and with the initial substances amine–aldehyde–dicarbonyl compound in ratios of 1:1:≥6 the condensation leads to the selective formation of N-alkoxymethylated spiro derivatives of tetrahydrobenzo[*f*]quinoline **64** with a yield of about 80%.

Scheme 28



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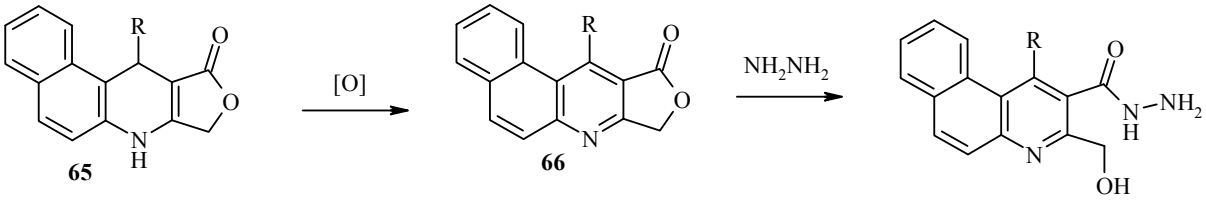
64

The polynuclear N,O-containing heterocycles obtained by triple-component condensation of 2-naphthylamine, aldehydes, and cyclic β-dicarbonyl compounds containing an oxygen atom in the ring are interesting for further use in heterocyclic synthesis. The oxidation of the dihydropyridine ring in the molecule of dihydrobenzo[*f*]furo[3,4-*b*]quinolinone **65** and the subsequent opening of the oxygen-containing ring in the molecule of benzo[*f*][3,4-*b*]quinolinone **66** is an example of a simple and convenient method for the synthesis of difficultly obtainable 2-substituted derivatives of benzo[*f*]quinoline (Scheme 29).

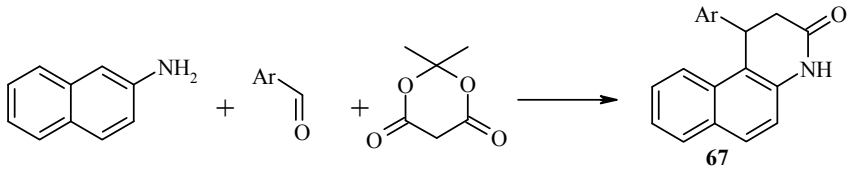
Scheme 29



65 **66**

In the reaction of 2-naphthylamine with aromatic aldehydes and Meldrum's acid with heat in ethanol in the absence of a catalyst the isopropylidenemalonate ring was split with the release of CO_2 and acetone, leading to the formation of prospective for biological investigations oxo derivatives of tetrahydrobenzo[*f*]quinoline **67** [102, 103] (Scheme 30).

Scheme 30

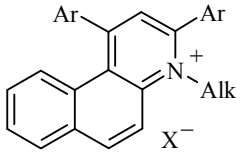


67

The simplicity of the method, the possibility of varying the aldehyde component, the high yield (up to 80%), and the purity (not less than 97%) of the selectively formed reaction products make it possible to use the reaction for the targeted synthesis of the analogs of antitumor preparations – functionalized derivatives of benzo[*f*]quinoline with a hydrogenated pyridine ring.

Synthesis of Biologically Active Derivatives of Benzo[*f*]quinoline and 4,7-Phenanthroline

The main direction in the synthesis of the biologically active compounds is synthesis of the quaternary salts and the adducts with benzo[*f*]quinoline and 4,7-phenanthroline acids, which are cationic substrates (strong electron acceptors) interacting with the molecules of DNA or the molecules of receptors, which are electron donors. The N-alkylation of derivatives of benzo[*f*]quinoline and 4,7-phenanthroline, including multinuclear derivatives, with alkyl, allyl, and benzyl halides and ethyl *p*-toluenesulfonate was studied. As a result mono-, bis-, and trisquaternary salts – analogs of the widely known trypanocidal preparation of the azaphenanthrene series Ethidium bromide (3,8-diamino-5-ethyl-6-phenylphenanthridinium bromide) – were obtained. Substances with high antiviral, bactericidal, fungicidal, antifungal, growth-regulating, and hypotensive activity and powerful inhibitors of the respiratory chain of bacterial membranes were found among the synthesized compounds. Certain compounds exhibiting high antienzyme activity can be used in affinity chromatography for the isolation of the enzyme acetylcholinesterase with a high degree of purity. During investigation of the antibacterial, fungicidal, and antienzyme characteristics of aza- and diazaphenanthrene derivatives it was noticed that the biological activity increases in the transition from the free bases to the quaternary salts **68-70** [104-109].



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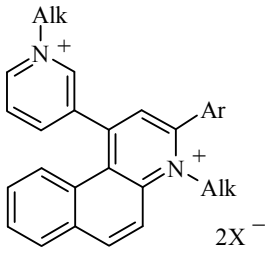

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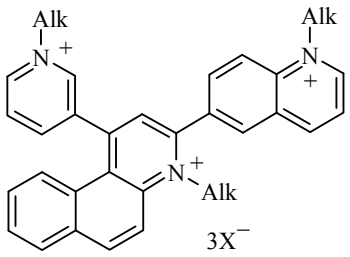
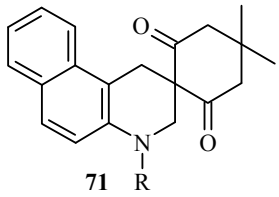


70

A preparative method was developed for the synthesis of new potentially biologically active salts of the spiro derivatives of benzo[*f*]quinoline **71** with a series of natural carboxylic acids (ketopinoic, 10-camphorsulfonic, 3-*exo*-isocamphanonesulfonic, abietic, benzoic, L-alanine, L-valine, L-leucine, L-isoleucine, nicotinic, succinic, 4,4'-biphenyldicarboxylic, and 2-hydroxy-4,4'-biphenyldicarboxylic) by boiling in methanol. The optimum ratios of the reagents in relation to the structure of the acid were selected. The yields of the salts amounted to 91-96% [110].



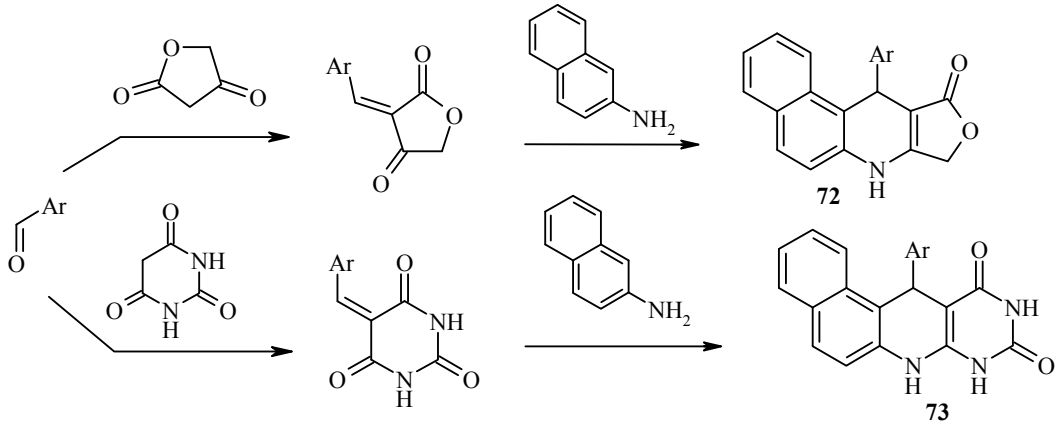
71

Luminophores and Dyes in the Series of Aza- and Diazaphenanthrenes

The system of conjugated bonds that develops in the molecules of the synthesized aromatic aza compounds gives rise to the luminescent characteristics of these heterocycles. The luminescence spectral characteristics of more than 100 compounds of the aza- and diazaphenanthrene series were investigated; among them there were substances (derivatives of benzo[*f*]quinoline, 4,7-phenanthroline) having high fluorescence quantum yields (60-80%) and promising as luminescent additives, e.g., for coloring polymeric fibers [26, 111-119].

The luminescence spectral and nonlinear optical characteristics were studied for carbonyl-containing heterocycles [11-aryl-8,11-dihydrobenzo[*f*]furo[3,4-*b*]quinolin-10(7H)-ones **72**, 12-aryl-8,12-dihydrobenzo-[*f*]pyrimido[4,5-*b*]quinoline-9,11(7H,10H)-diones **73** and the intermediates in their synthesis (the arylidene derivatives of tetrahydrofuran-2,4-dione and 2,4,6(1H, 3H, 5H)-pyrimidinetrione) [93, 120, 121] (Scheme 31).

Scheme 31



72

73

It was established that all the investigated compounds in the crystalline state at room temperature have fluorescence of high and medium intensity, where the fluorescence maxima change over a wide spectral range (400-690 nm). In the series of compounds nonlinear optical effects were detected: two-photon excited fluorescence and second harmonic generation of laser radiation (SHG). These make it possible to regard these compounds as promising materials in the creation of elements for the visualization of invisible IR laser emission, optical data recording, and the creation of nonlinear optical elements for SHG.

Polymethinecyanine dyes of the azaphenanthrene series were synthesized on the basis of the quaternary salts of 1-methyl-, 1,2-dimethyl-, and 1-ethyl-3-arylbenzo[*f*]quinoline [122-125]. The transformation of the β-anilinovinyl derivatives of 3-arylbenzo[*f*]quinolinium salts into the bases of hemicyanines (intraionic dyes, which are intermediate products in the synthesis of unsymmetrical polymethine dyes) was studied. It was established that pentamethinecyanine dyes of the benzoquinoline series are some of the most deeply colored among known polymethine dyes with the same length of chromophore, they have a high generation efficiency (in the range of 20-30%) in the spectral region of 940-1010 nm, and can be used as effective laser media for optical lasers.

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