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TRADITIONAL AND MODERN APPROACHES TO THE SYNTHESIS OF QUINOLINE SYSTEMS BY THE SKRAUP AND DOEBNER–MILLER METHODS. (REVIEW)

S. A. Yamashkin and E. A. Oreshkina

Recent data on classical and modified methods for the synthesis of quinoline systems by the Skraup and Doebner–Miller reactions, not included in reviews on heterocycles, are discussed.

Keywords: quinoline, Doebner–Miller reaction, Skraup reaction.

The need for compounds containing a quinoline fragment in various regions of human activity has increased in recent times. The great attention paid by researchers to the study of quinoline derivatives is explained by the fact that these compounds exhibit a broad range of antimicrobial activity [1-4] and, particularly, antitubercular activity [5] and antimalarial activity [6, 7] and are also present in antiallergic and antiasthmatic agents [8]. Classical methods are widely used for their synthesis, and two of these are discussed in the present review.

The most important way of constructing the quinoline system involves the cyclization of a substituent in the side chain of a benzene ring. This applies to the synthesis of quinolines by the Skraup and Doebner–Miller reactions. In the classical form, however, these syntheses take place under fairly harsh conditions, and this reduces their preparative value. In recent years, however, the efforts of synthetic chemists have been directed toward modification of these methods. Both traditional and modified approaches to the synthesis are discussed in this review.

The first report on the synthesis of quinoline, realized by passing the vapor of ethylaniline and other alkylanilines over heated lead oxide, was published by Koenigs in 1879; in another method (1880) quinoline was obtained by heating the product from the addition of acrolein to aniline. Soon after this Skraup (1880) [9] and Doebner and Miller (1881) put forward their methods [10]; both these syntheses are close to Koenigs' acrolein method and have found widespread application.

THE SKRAUP AND DOEBNER–MILLER REACTIONS (THE TRADITIONAL APPROACH)

The construction of the quinoline system by the Skraup and Doebner–Miller methods is based on the reaction of an aromatic amine containing at least one free *ortho* position with a reagent providing a source of the three-carbon fragment.

In the classical Skraup method the aromatic amine is heated with glycerol (**1**), sulfuric acid (which catalyzes the dehydration of glycerol to acrolein (**2**)), and an oxidizing agent **7**, transforming the initially formed 1,2-dihydroquinoline (**6**) into the fully aromatized heterocycle **8**. In the simplest case, with aniline (**3**) as amine and nitrobenzene (**7**) as oxidizing agent, the reaction is represented by the following scheme [11].

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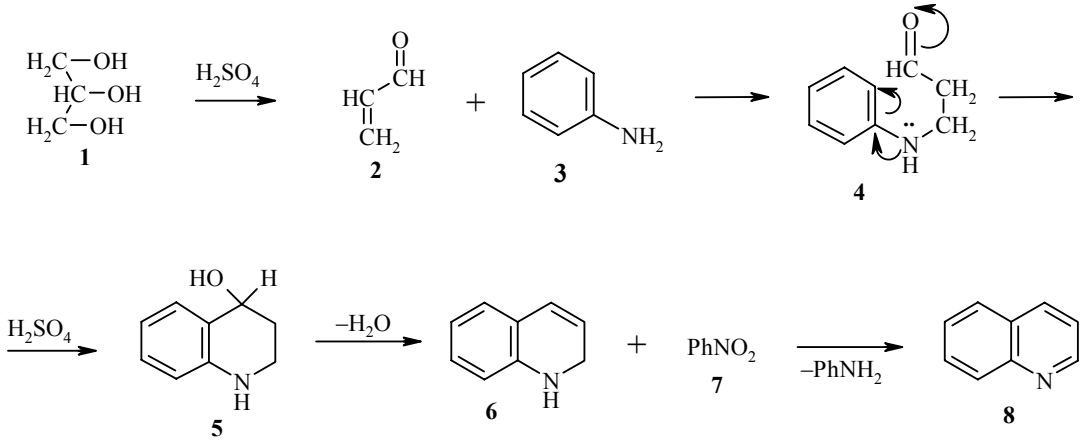
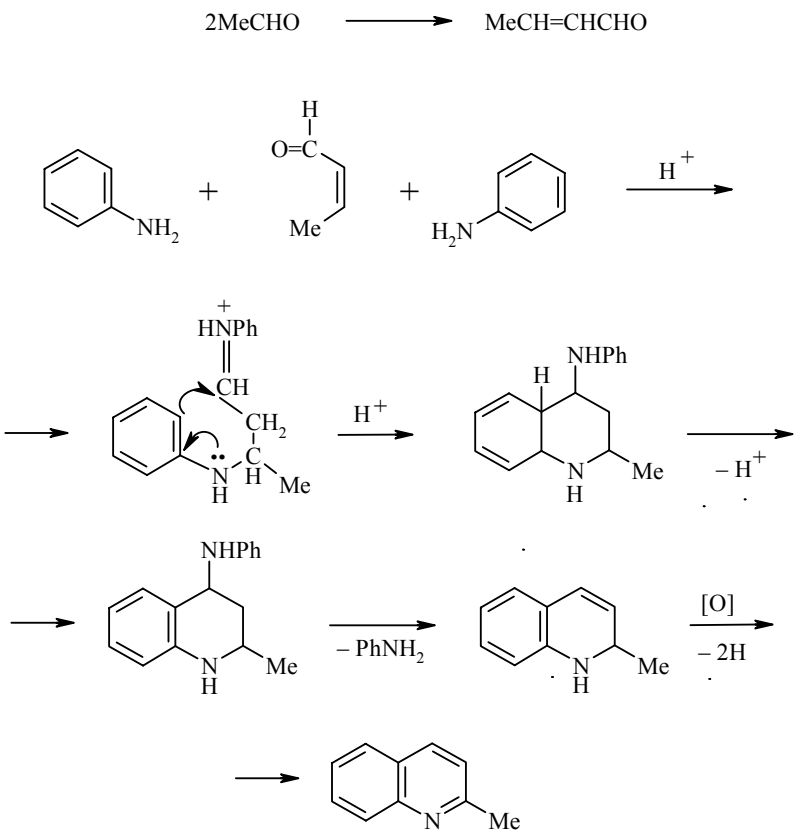


The Doebner–Miller reaction is traditionally described as a process in which the first stage is probably a crotonic condensation of two molecules of an aldehyde or ketone, resulting in the formation of an α,β-unsaturated compound. The latter reacts with the aniline, forming a Schiff base and, intermediately, after cyclocondensation 4-amino-1,2,3,4-tetrahydroquinoline. The dihydroquinoline is then formed, and further oxidation leads to the quinaldine derivative [12-14]. Zinc chloride both with [15, 16] and without hydrochloric acid can be used as condensing agent. It is assumed that the most likely mechanism for this reaction is the following [11].



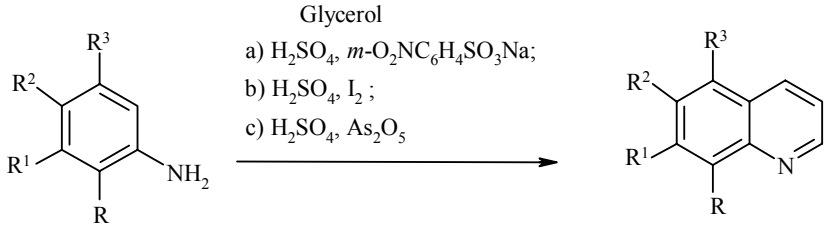
However, analysis of reviews and published data on the syntheses makes it possible to identify two points of view regarding their assignment to one or the other method. Supporters of the first method [R. Elderfield, 1952 (1955 [11]), R. H. F. Manske and M. Kulka, 1953 (1956 [17]), A. Surrey, 1961 (1962 [18]),

P. A. Klare, 1979 (1985 [19])] regard the Skraup synthesis as reaction of the substituted aromatic amine not only with glycerol but also with the α,β-unsaturated compounds, where the only difference between this and the Doebner–Miller reaction is the use of different reagents to achieve dehydrogenation of the intermediate product (dihydroquinoline) to the quinoline. Thus, the reagent in the Doebner–Miller method is the Schiff base formed from the initially employed substances, which is capable of adding hydrogen and thereby completing the dehydrogenation. In the Skraup reaction, however, dehydrogenation is realized by means of a specially added oxidizing reagent. In the end these authors in their papers pointed out the similarity between the mechanisms for the production of the quinoline systems by the Skraup and Doebner–Miller methods. Elderfield, however, suggests that the production of quinoline derivatives, substituted both in the carbocyclic and in the heterocyclic ring, in the Skraup method can be regarded as a special case of the Doebner–Miller synthesis, in spite of the fact that Skraup described his method approximately a year before the discovery of the Doebner–Miller reaction.

The second point of view (B. I. Ardashev, 1954 [20]) differs from the first in that it is not possible to obtain quinolines substituted in the pyridine ring during the Skraup reaction, whereas their synthesis is standard in the Doebner–Miller reaction.

Most investigators probably adhere to the first point of view. Even replacement of the nitrobenzene by another more effective oxidizing agent makes it possible to associate the described reactions with the Skraup synthesis. In recent modifications of the syntheses, in contrast to the classical version, the aromatic nitro compound previously used as oxidizing agent has been replaced by arsenic pentoxide [21-24], iodine [25, 26], iron(III) salts [27], and *m*-nitrobenzenesulfonic acid or its salts [28, 29]. The use of inorganic oxidizing agents usually reduces the degree of resin formation, leading to the production of purer compounds. The addition of iron(II) sulfate [30] or boric acid [21] has been recommended in order to reduce the exothermic nature of the reaction, which can take place very vigorously.

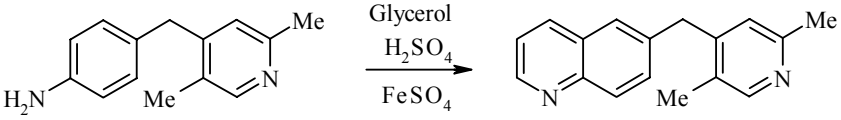
If unsymmetrical substituted anilines are used in the Skraup reaction, it is necessary to consider the possibility of the formation of isomers. *ortho*-Monosubstituted anilines only give 8-substituted quinolines in the Skraup reaction [31]. Controlled synthesis is also possible if di-, tri-, and tetrasubstituted anilines are used [2, 6, 25, 29, 32, 33].



9a–c **10a–c**

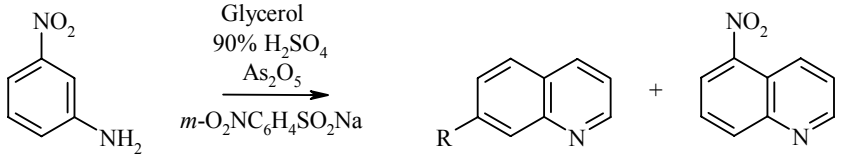
9, 10 a R = OH, $R^1 = R^3 = H$, $R^2 = F$ (57%); **b** R = OMe, $R^1 = R^2 = H$, $R^3 = CO_2H$;
c R = Cl, $R^1 = NH_2$, $R^2 = NO_2$, $R^3 = H$ (98%)

It is clear that the *para*-substituted aminobenzenes can close at any symmetrical *ortho* position, forming 6-substituted quinolines [30, 34]. 6-[(2,5-Dimethyl-4-pyridyl)methyl]quinoline (**12**) was obtained from 4-(*p*-aminobenzyl)-2,5-dimethylpyridine (**11**) with 2,5-dimethyl-4-(*p*-nitrobenzyl)pyridine, from which the amino derivative **11** was produced, as oxidizing agent [30].



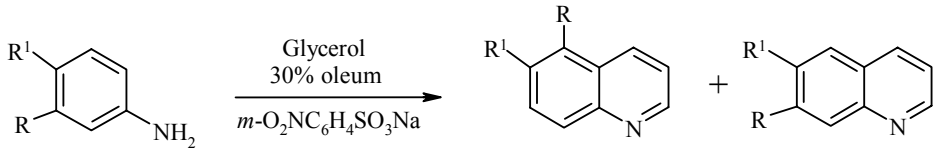
11 **12**

meta-Substituted anilines are converted into a mixture of quinolines with substituents at both position 5 and position 7 [23].



Strong electron-donating substituents (OMe, OEt, NMe_2) at position 3 of the initial aniline promote ring closure at position 6 with the preferential formation of 7-substituted quinolines (75-81%). The presence of weaker electron-donating substituents (Hal, Alk) at this position leads to a mixture of quinolines with a slight preference for the 7-substituted isomers (51-60%). Strong electron-withdrawing groups (such as NO_2) promote cyclization at position 2 with the formation of 5-substituted quinolines as the main products (yield 78%) [35, 36].

Under these conditions 3,4-disubstituted anilines **13** give a mixture of 5,6- and 6,7-disubstituted quinolines **14** and **15** [35, 37]. Oleum was used as catalyst for 3,4-dihaloanilines in the Skraup reaction [34].

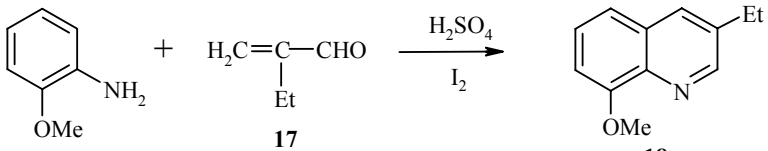


13a–f **14a–f** **15a–f**

13–15 a R = R^1 = F; **b** R = R^1 = Cl; **c** R = F; **d** R = Cl; **e** R = Br; **f** R = I; **c–f** R^1 = Br

It is possible to see a clear relationship in the obtained results; the higher the electronegativity of the halogen substituents in the amines **13**, the greater the possibility of the formation of compounds **15**. (If 3,4-difluoroaniline is used in this reaction it is possible to obtain the isomer **15** with a yield of 99%.) If the size of the substituent at position 3 of the arylamine **13** is increased, the probability of the formation of the quinoline **14** is increased probably on account of steric factors. This is seen most clearly in the ratio of the isomers **14** and **15**, formed from substituted anilines **13c-f** containing the same substituent at position 4 (in this case bromine). Here the highest yield of the quinolines **14** is obtained with iodine at position 3 (64%) and the lowest with fluorine (less than 1%).

If the Skraup reaction is used in its classical form (the reaction of substituted anilines with glycerol), only quinolines unsubstituted in the pyridine ring can be obtained. If previously prepared acrolein is used, strong resin formation is observed. The use of other unsaturated carbonyl compounds leads to the formation of quinolines substituted in the pyridine ring with wholly satisfactory yields [11]. Such syntheses have currently found widespread use. Thus, the quinolines **18** containing substituents in both rings are easily formed from the aniline derivative **16** and α,β-unsaturated carbonyl compounds **17** [26].

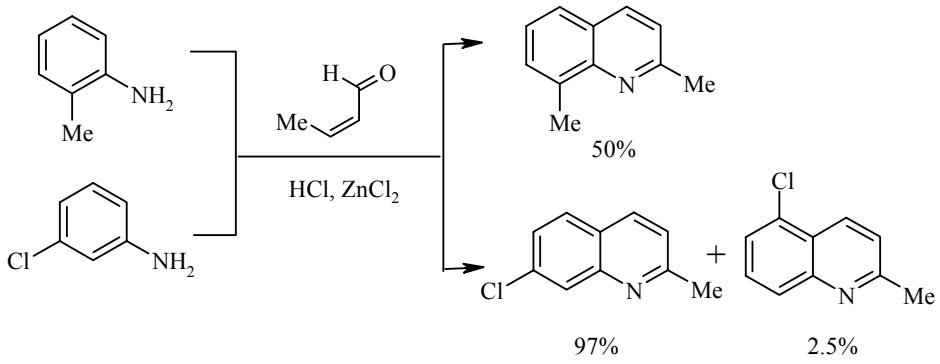


16 **17** **18**

In view of the fact that the experimental conditions are relatively severe it is natural that substituents in the aromatic amine that are sensitive to the hot solution of the strong acid undergo substantial changes or are completely eliminated during the Skraup synthesis.

As demonstrated by the authors in [38], hydrochloric acid gives better results than sulfuric acid, and the addition of zinc chloride to the reaction mixture increases the yield. Therefore, according to data in [11], any α,β-unsaturated carbonyl compound and practically any aromatic amine can be used in the Doebner–Miller reaction.

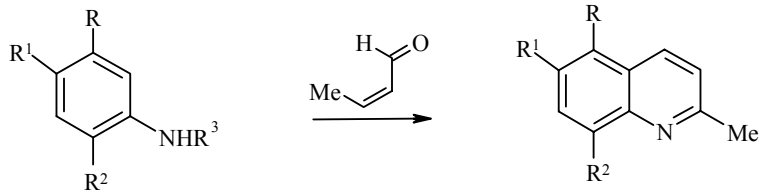
The Doebner–Miller synthesis can be applied to substituted amines with a wide range of substituents that withstand the acidic reaction medium. Here alkyl-, aryl-, hydroxy-, carboxy-, hydrosulfide-, sulfo-, halo-, alkoxy-, and sulfoxide-substituted quinolines are obtained [39, 40]. As in the Skraup reaction, the problem of the regioorientation of closure of the pyridine ring and the formation of the isomeric quinolines arises when substituted aromatic amines are used. Aromatic amines with *ortho* substituents give the 8-substituted isomers [15], while 3-(*meta*)-substituted anilines give 7- and 5-substituted derivatives of quinoline. As a rule the 7-substituted isomers predominate, while in some cases the 5-substituted quinoline is not observed at all [41]. The same tendency is observed if other carbonyl compounds, such as the products from crotonic condensation of cyclohexanone, methyl isobutyl ketone, and methyl ethyl ketone, are used instead of crotonaldehyde [15, 16]. On account of the pharmacological significance of 7-substituted quinolines some procedures for their isolation from the reaction mixture in the Doebner–Miller reaction have been patented [16, 42].



CONTEMPORARY MODIFICATIONS OF THE DOEBNER–MILLER AND SKRAUP REACTIONS

One serious shortcoming of both Doebner–Miller and Skraup reactions is the laborious procedure for the isolation of the quinoline from the reaction mixture. This is due to parallel polymerization of the α,β-unsaturated aldehydes catalyzed by the acid and results in low yields. Investigations of recent decades have therefore been devoted to the search for better conditions for the reactions.

It is possible to avoid polymerization of the unsaturated carbonyl compounds if the Doebner–Miller reaction is conducted in a two-phase system consisting of an organic and an aqueous acidic part (e.g., ethanol–sulfuric acid, toluene–6 M HCl, heptane–6 M HCl, xylene–6 M HCl, 1,2-dichloroethane–6 M HCl, toluene–toluenesulfonic acid) [43, 44]. The reactions take place smoothly and with good yields even in the absence of oxidizing agents (47-80%). In the case of the formation of the quinolines **20a-c** from the anilines **19a-c** it was established [43] that the most favorable system was a mixture of toluene and 6 M hydrochloric acid. (The yield amounted to 80%.)



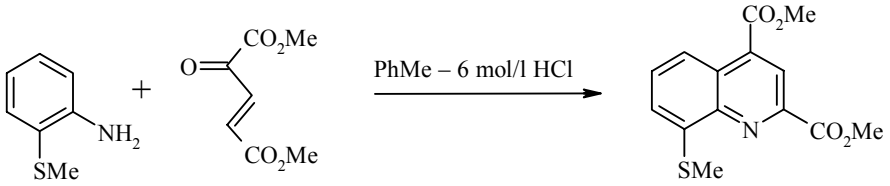
19a–c **20a–c**

19, **20 a** R = R^1 = R^2 = F, R^3 = Ac; **b** R = Me, R^1 = R^2 = R^3 = H; **c** R = H, R^1 = OMe, R^2 = R^3 = H

The system consisting of 12 N hydrochloric acid, toluene, and tetrabutylammonium chloride was most successful for the synthesis of 2-alkyl-8-quinolinecarboxylic acid (yield 57%) [44].

The method has the following advantages: 1) Relatively high yields (50-80%) compared with the single-phase reaction; 2) no need for strict control during the addition of the aldehyde; 3) possible isolation of the almost colorless pure substances by neutralizing the aqueous phase.

A similar approach was used in [7] for the reaction of the aniline derivative **21** with α,β-unsaturated compounds of the 2-ketoglutaconate type **22**.

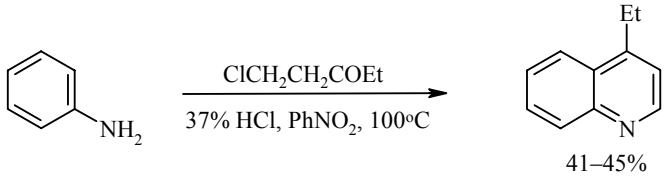


21 **22** 56%

As already mentioned, the harsh conditions (the high temperature and the large excess of concentrated sulfuric acid) of the Skraup synthesis lead to a sharp reduction in the yields of the quinolines when initial anilines with functional substituents unstable in strongly acidic media are used [45-49]. Referring to this, some investigators [45-49] have therefore developed new methods for the synthesis of quinoline derivatives. Others have worked on increasing the effectiveness of the Skraup synthesis [50, 51] and modified it by reducing the aggressiveness of the reaction medium.

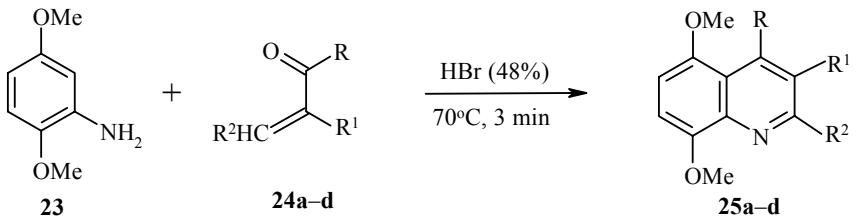
Quite often the concentrated sulfuric acid in Skraup reactions has been replaced by the less concentrated acid or by hydrochloric acid [52, 53], by a solution of HCl in an alcohol (2-butanol, methanol) [54-56], or by the weaker orthophosphoric acid [6, 57], thereby reducing the temperature from 130-150 to 60-100°c. Catalytic amounts of polyphosphoric acid have also been used for this purpose [58]. The less rigorous conditions created in this way have made it possible to achieve higher yields (69-85%).

In the scheme presented below the precursor of the α,β-unsaturated ketone is 1-chloro-3-pentanone.



41–45%

Two-phase systems (HCl/dioxane, HCl/CH_2Cl_2, HBr/MeOH, $AlCl_3/CH_2Cl_2$) were also used in the synthesis of quinolines from 2,5-dimethoxyaniline (**23**) and crotonaldehyde (**24b**), which the authors represented as a Skraup synthesis [59], but very low yields were obtained (0-28%). The use of somewhat weaker concentrated acids as catalysts for 3-15 min at 70-100°C proved more effective.

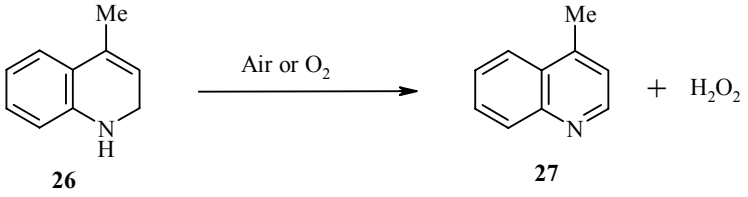


24, **25 a** R = R^1 = R^2 = H, **b** R = R^1 = H, R^2 = Me; **c** R = R^2 = H, R^1 = Me;
d R = Me, R^1 = R^2 = H

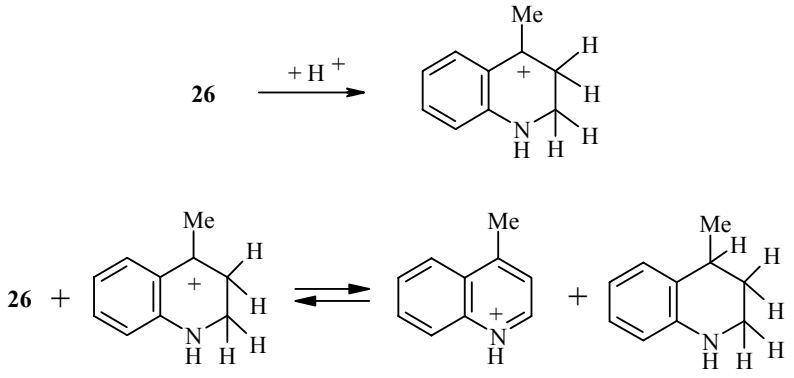
The highest yield (52%) was obtained with 48% HBr for 15 min at 70°C even without oxidizing agents.

In a search for more effective oxidizing agents in the Doebner–Miller reaction the authors of [60] investigated the mechanisms of dehydrogenation of 1,2-dihydrolepidine (**26**) by various oxidizing agents in detail.

1. Oxidation with Air. In an alcohol solution 1,2-dihydrolepidine is readily oxidized at 65°C. In addition, hydrogen peroxide, which is clearly formed during the autooxidation of compound (**26**), was also detected.

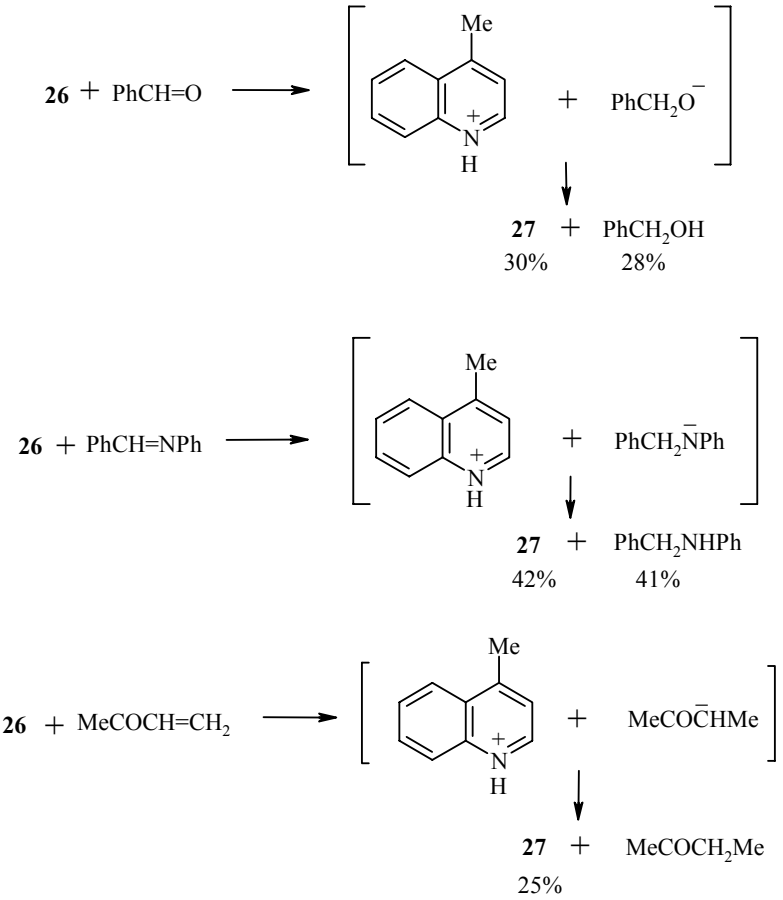


2. Disproportionation. In an alcohol solution of HCl compound **26** gives a mixture of the quinoline **27** and 1,2,3,4-tetrahydrolepidine. Gaseous hydrogen is not formed. According to GLC, 46% of 1,2,3,4-tetrahydrolepidine and 54% of lepidine are formed in the transformation. These facts indicate that one molecule of the 1,2-lepidine is oxidized while another is reduced. The disproportionation is due to the action of the acidic catalyst, which is capable of intramolecular hydrogen transfer [60].



Protonation of the β-carbon atom of 1,2-dihydrolepidine gives a tertiary carbocation, stabilized by conjugation with the electrons of the benzene ring and *o*-amino group. The carbocation readily removes a hydride ion from another molecule of 1,2-dihydrolepidine, since this gives the stable protonated lepidine and 1,2,3,4-tetrahydrolepidine. Thus, the 1,2-dihydrolepidine acts as an effective hydride ion donor or reducing agent.

3. Oxidation by Organic Compounds. 1,2-Dihydrolepidine in ethanol is also oxidized to the quinoline **27** by an aldehyde, imine, or α,β-unsaturated ketone. The oxidizing agents are in turn reduced and transformed into ethanol, amine, and saturated ketone respectively [60].



However, 4-amino-2-butanone, 2-ethoxymethyl ethyl ketone, methyl ethyl ketone, and nitrobenzene cannot oxidize 1,2-dihydrolepidine in ethanol at 65°C.

4. Oxidation with Fe^{3+}. The rate of oxidation of 1,2-dihydrolepidine by $FeCl_3$ to lepidine is very high. Even in very dilute solutions, such as a mixture of $5 \cdot 10^{-5}$ M of $FeCl_3$ and $5 \cdot 10^{-5}$ M of 1,2-dihydrolepidine in ethanol at room temperature, lepidine is formed instantly, whereas 1,2,3,4-tetrahydrolepidine is not oxidized under these conditions.

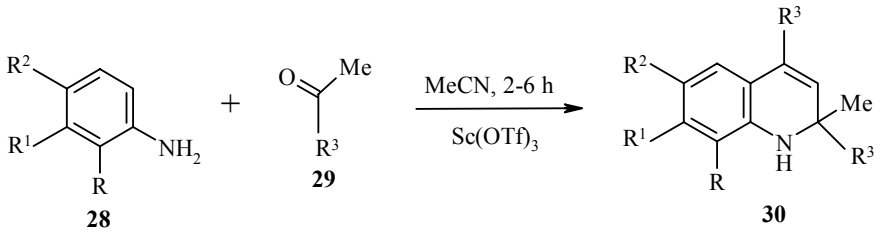
In conclusion the oxidizing agents can be arranged in order of decreasing reactivity as follows: $Fe^{3+} >>$ 1,2-dihydrolepidine–HCl (disproportionation) $>> O_2 >$ PhCHO ≈ PhCH=NPh > $MeCOCH=CH_2$.

A mixture of nitrobenzene with hydrochloric acid [61] or trifluoroacetic acid [62] has also been used as oxidizing agent.

Thus, the differences between these methods of synthesis are wiped out by using oxidizing agents in the Doebner–Miller reactions and not using them in the Skraup synthesis and also by conducting the syntheses in inorganic acids (HCl, HBr) at lower concentrations. At the present time, therefore, it is convenient to call the reactions Skraup–Doebner–Miller reactions or Skraup-like reactions, as used by some contemporary authors [52].

The reactions presented below can be considered in these terms.

During the development of methods for the synthesis of various 2,2,4-trisubstituted 1,2-dihydroquinolines [63], which are widely used in pharmacology [64], from substituted anilines or aminoheterocycles it was found that good yields and reduced reaction times can be achieved if lanthanoid catalysts and microwave techniques are employed [65]. Previously the best method for the production of such compounds was reaction of the respective aniline and acetone (or other ketone) in the presence of iodine at 145°C, which takes 2-3 days [66].

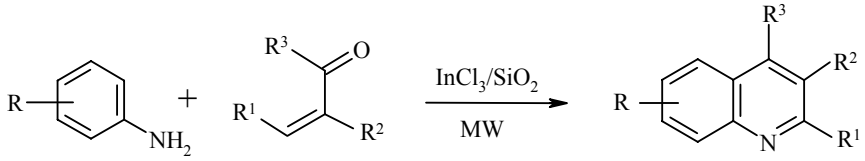


R = H, Me, OMe; R^1 = H, F, Cl; R^2 = H, Me, *i*-Pr, *c*-C_6H_{11}, Ph, OMe, OPh, Cl, CO_2H, NO_2;
R^3 = Me, Et, Ph

The cyclization of the anilines **28** with acetone, which gives an unsaturated ketone as a result of a crotonic condensation, takes place smoothly in the presence of $Sc(OTf)_3$ even at room temperature and gives high yields of compounds **30** (59-98%). In individual cases two isomeric cyclization products are obtained, as often happens in the Skraup and Doebner–Miller reactions. By using a series of aminoheterocycles (5-aminoindole, 5-aminoquinoline,6-aminoindazole, 5-amino-1,3-benzodioxole) it was possible to obtain moderate yields of the corresponding condensed quinolines. Not only acetone but also a series of other ketones (2-butanone, 3-methyl-2-butanone, acetophenone, *m*-acetofluoro- and *m*-acetochlorophenone, *p*-methoxyacetophenone) also react successfully under analogous conditions. Thus, compounds that were previously almost impossible to obtain by standard procedures have become accessible using the present approach.

This reaction is presented by the authors as a new modification of the Skraup reaction. However, this statement is debatable, since such a reaction was presented by Rim [19] as a variant of the Doebner–Miller reaction. In his interpretation a 2,2,4-substituted 1,2-dihydroquinoline is formed as intermediate as a result of heating the substituted aniline with 2 mole of acetone in HCl and is aromatized to quinoline as a result of elimination of the alkane.

A simple and effective modification was developed for the synthesis of quinolines substituted in the benzene and pyridine rings [65] from derivatives of aniline **31** with alkyl vinyl ketones **32**.

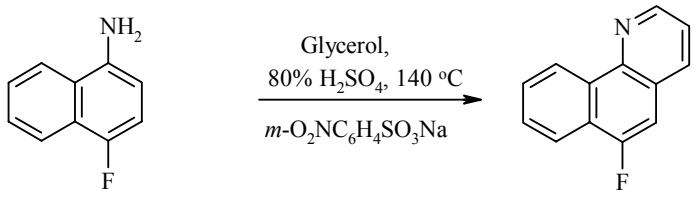


31 a, h, i R = H, **b** R = 2-Me, **c** R = 4-Me, **d** R = 3-Me, **e** R = 2-OMe, **f** R = 4-OMe, **g** R = 3-OMe; **32 a** $R^1 = R^2$ = H, R^3 = Me; **b** R^1 = Me, R^2 = H, R^3 = *p*-$MeOC_6H_4$; **c** R^1 = Pr, R^2 = Et, R^3 = Me; **33 a** R = H, **b** R = 8-Me, **c** R = 6-Me, **d** R = 7-Me, **e** R = 8-OMe, **f** R = 6-OMe, **g** R = 7-OMe, **a**–**g** $R^1 = R^2$ = H, R^3 = Me; **h** R = R^2 = H, R^1 = Me, R^3 = *p*-$MeOC_6H_4$; **i** R = H, R^1 = Pr, R^2 = Et, R^3 = Me

The procedure is conducted at the surface of silica gel, enriched with indium(III) chloride, by the action of microwave (MW) radiation without a solvent, where the $InCl_3/SiO_2$ acts as an agent that transforms the dihydroquinoline into quinoline. The advantages of the method are: 1) Experimental simplicity; 2) fast reaction; 3) high yields (60-87%); 4) availability of the reagents.

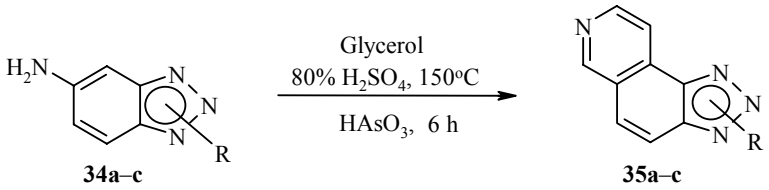
SYNTHESIS OF POLYCYCLIC DERIVATIVES OF QUINOLINE USING THE SKRAUP AND DOEBNER–MILLER REACTIONS

Many planar tri- and tetracyclic and, particularly, nitrogen-containing heterocycles are well known as potential anticancer agents. Benzo[*h*]quinoline, benzo[*c*]phenanthridine, and other isomers are the main components of antitumor products [67, 68]. The synthesis of such structures is based on annelation of the pyridine ring to aminoheterocycles or condensed aromatic amino derivatives by the Skraup and Doebner–Miller methods. The amino derivatives of naphthalene, anthracene, phenanthrene, indole, and other condensed aromatic compounds form so-called aroquinolines under the conditions of the Skraup reaction. For example, 1-naphthylamine forms benzo[*h*]quinoline, while benzo[*f*]quinoline is obtained from 2-naphthylamine. With these procedures it is also possible to synthesize substituted analogs of these compounds of interest from the pharmacological standpoint [69].



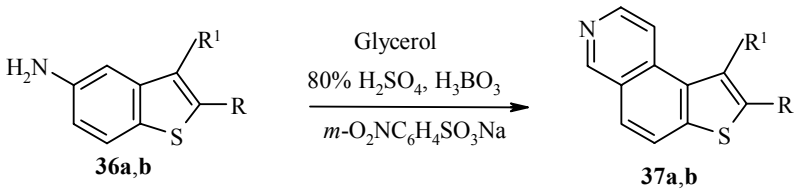
By using the Skraup and Doebner–Miller methods it is possible to synthesize compounds with two or more heteroatoms (identical or different), and this significantly extends the range of synthetically produced biologically active substances.

Thus, the triazoloquinolines **35a-c** were obtained with good yields from the 5-aminotriazoles **34a-c** by the Skraup reaction [70], while the thieno[2,3-*f*]quinolines **37** were obtained from the aminobenzo[*b*]thiophene derivatives **36** [71, 72].



34a–c **35a–c**

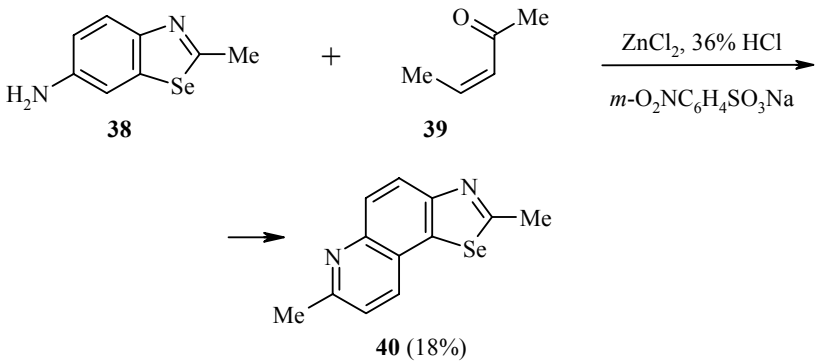
34, 35 a R = 1-H (70%), **b** R = 2-Me (55%), **34 c** R = 1-Me, **35 c** R = 3-Me(51%)



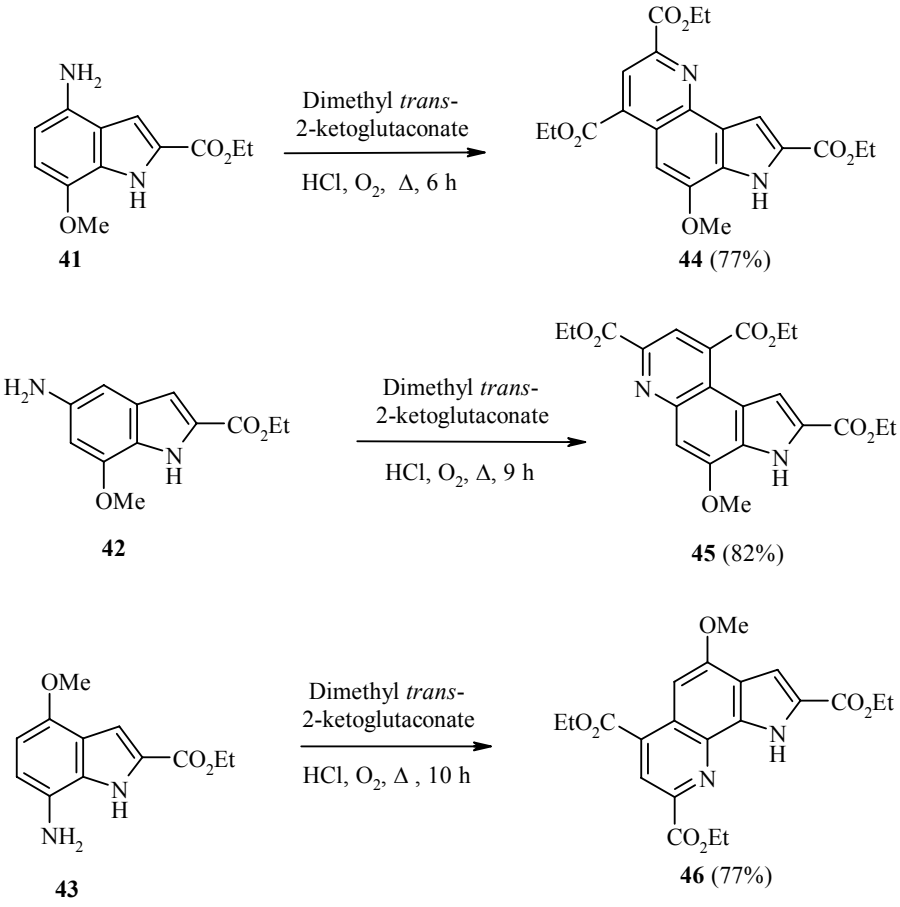
36a,**b** **37a**,**b**

36, **37 a** R = H, R^1 = Me (18%), **b** R = CO_2H, R^1 = H (80%)

The reaction of 6-amino-2-methylbenzoselenazole (**38**) with 3-penten-2-one (**39**) is a reaction of the Doebner–Miller type [73].

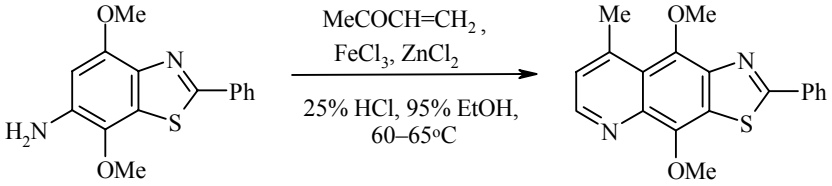


Tricyclic molecules in which the quinoline system is condensed with a five-membered heterocycle are often the starting materials for the synthesis of analogs of compounds found in nature. Thus, an important stage in the production of analogs of the coenzyme 4,5-dioxo-4,5-dihydro-1H-pyrrolo[2,3-*f*]quinoline-2,7,9-tricarboxylic acid [74] is the synthesis of pyrroloquinolines **44**-**46** from aminoindoles **41**-**43** and dimethyl *trans*-2-ketoglutaconate by the Doebner–Miller reaction [75].



This reaction has often been used for the production of other similar structures [76].

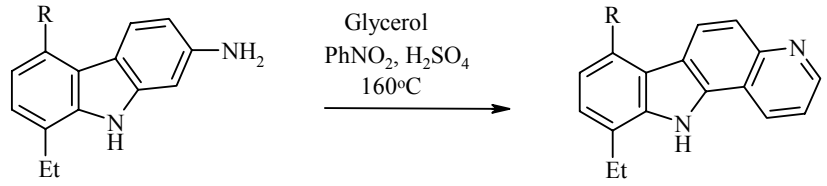
The pyridine ring in the precursor **48** of an analog of *Kuanoniamide A* is formed with the use of methyl vinyl ketone [77, 78].



47 **48** (11%)

In the examples presented above the preferential formation of tricyclic systems with angular fusion of the rings is observed in both the Skraup and the Doebner–Miller reactions even if there is an alternative cyclization path. However, the formation of compound **48** with linear structure is possible if there is one substituted *ortho* position in relation to the amino group (e.g., with the presence of a methoxy group).

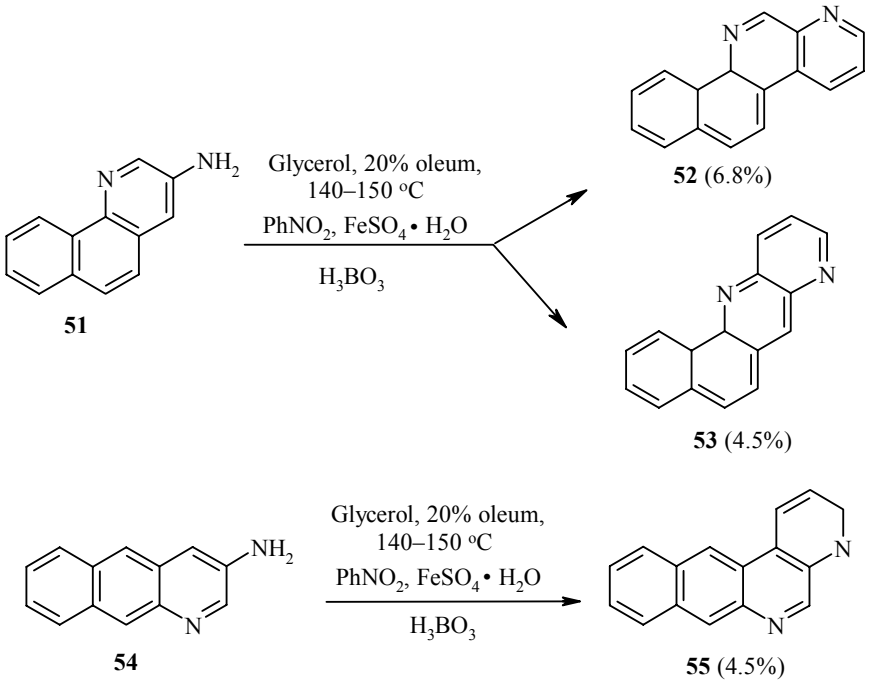
A tendency to form angular polynuclear compounds is observed under the conditions of the Skraup reaction with 3-amino-9-ethylcarbazole (**49a**) and 3-amino-9-ethyl-6-methylcarbazole (**49b**), which are transformed according to the Markwald rule into the 7H-pyrido[2,3-*c*]carbazoles **50a**,**b** [79].



49a,**b** **50a**,**b**

49, **50 a** R = H (16%), **b** R = Me (60%)

In a modified Skraup reaction with glycerol 3-aminobenzo[*h*]- or 3-aminobenzo[*g*]quinolines form naphthonaphthyridines [80, 81], and 3-aminobenzo[*h*]quinoline (**51**) gives a mixture of isomers **52** and **53**, whereas 3-aminobenzo[*g*]quinoline (**54**) only gives compound **55** [82].

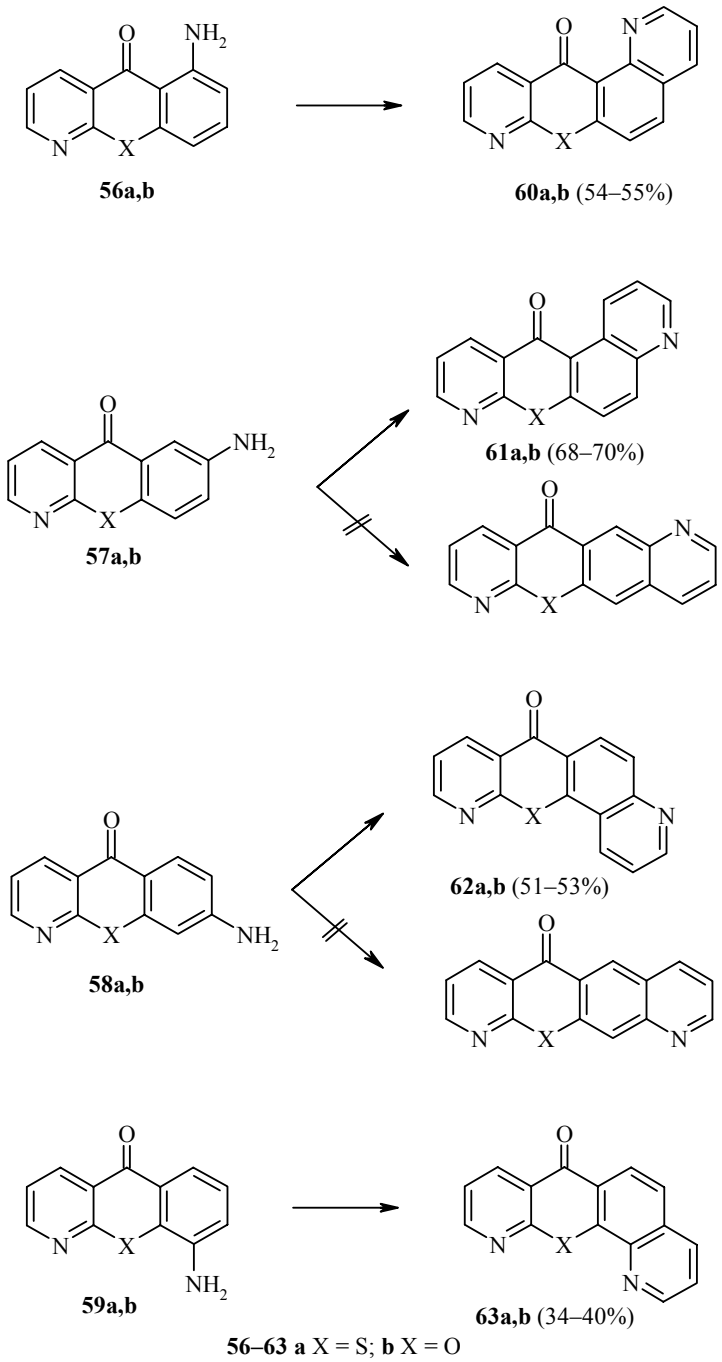


51 **52** (6.8%)

53 (4.5%)

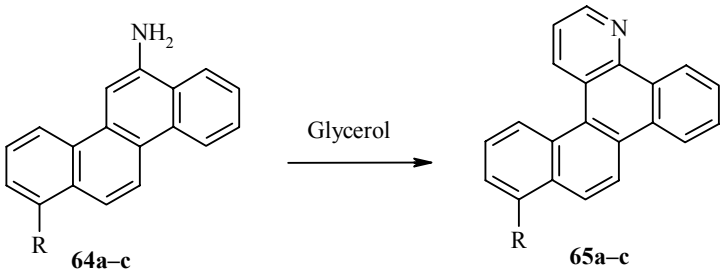
54 **55** (4.5%)

Only quinoline derivatives of the "benzenoid" type **60a**,**b**–**63a**,**b** are obtained from 6-amino-, 7-amino-, 8-amino-, and 9-amino-5H-[1]-benzothiopyrano[2,3-*b*]pyridin-5-one (**56a**), (**57a**), (**58a**), and (**59a**) and 6-amino-, 7-amino-, 8-amino, and 9-amino-5H-[1]benzopyrano[2,3-*b*]pyridin-5-one (**56b**), (**57b**), (**58b**), and (**59b**) with glycerol [83, 84] in the presence of H_3BO_3, oleum, nitrobenzene, and $FeSO_4 \cdot 7H_2O$. While obeying the Markwald rule, compounds **57a**,**b** and **58a**,**b** probably do not give linear isomers.



56–63 a X = S; **b** X = O

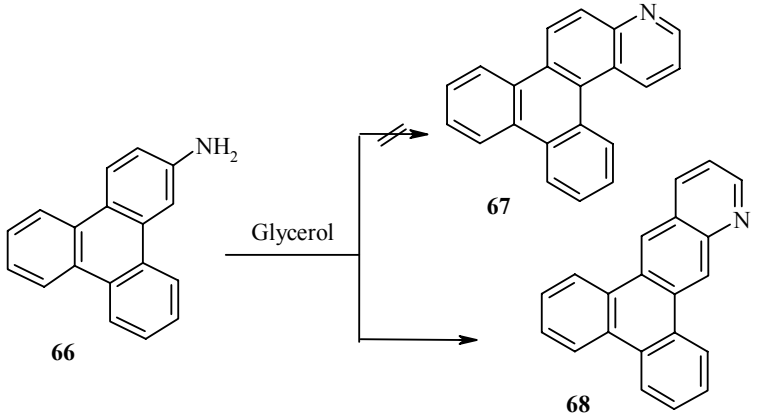
The use of aminochrysenes **64a-c** as starting compounds in the Skraup synthesis led to the pentacyclic structures **65a-c** [85].



64a–c **65a–c**

64, 65 a R = F, **b** R = Cl, **c** R = Br

However, contrary to the Markwald rule, cyclization of the amine by the Skraup reaction does not take place angularly with the formation of phenanthro[9,10-*f*]quinoline **67** but linearly with the formation of the antaraquinoline **68** [85].

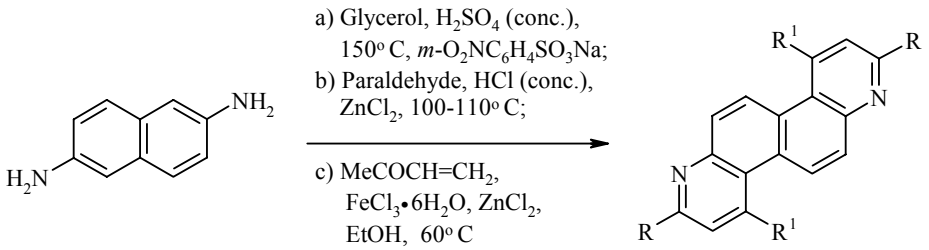


66 **67** **68**

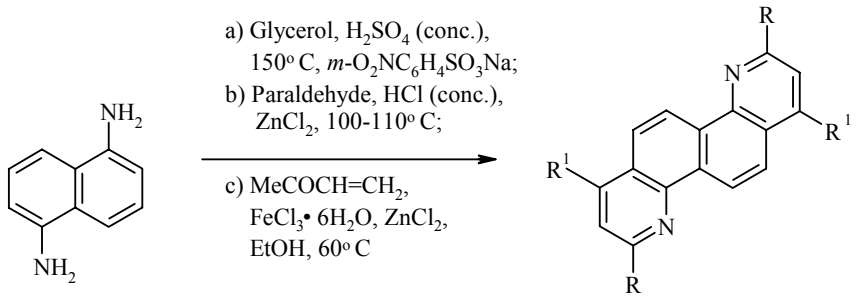
The anomalous reaction path is probably due to strong steric hindrances at the *peri* position of the initial compound **66**.

Another method for the production of polynuclear heterocyclic systems uses diamines as starting compounds in the Skraup and Doebner–Miller reactions.

The isomeric 1,7- and 4,10-diazachrysenes **69** and **72** were obtained by the Skraup reaction from the corresponding naphthylenediamines. 2,8-Dimethyl-1,7-diazachrysene (**70**) and 3,9-dimethyl-4,10-diazachrysene (**73**) were obtained by the Doebner–Miller reaction by condensation with paraldehyde. 4,10-Dimethyl-1,7-diazachrysene (**71**) and 1,7-dimethyl-4,10-diazachrysene (**74**) were obtained by condensation of the respective diamines with methyl vinyl ketone in the presence of $FeCl_3$ as effective oxidizing agent [86].



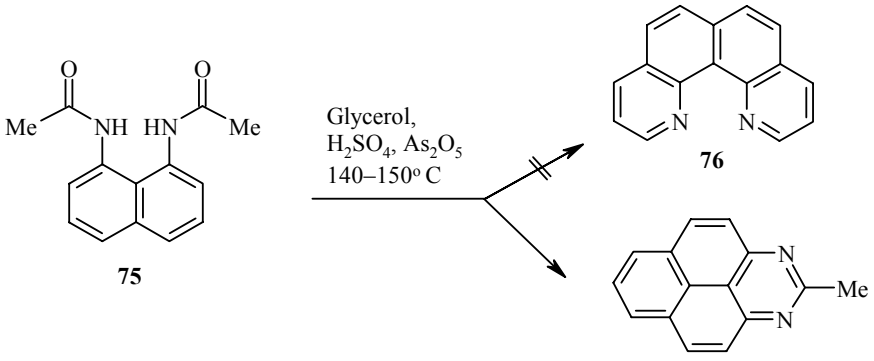
69–71



72–74

a) **69**, **72** R = R^1 = H (29–30%); b) **70**, **73** R = Me, R^1 = H (12–15%);
c) **71**, **74** R = H, R^1 = Me (15–16%)

In reaction with glycerol N,N'-diacetyl-1,8-naphthylenediamine (**75**) should give quino[7,8-*h*]quinoline (**76**) [87]. However, it was found that 2-methyl-1,3-diazaprene (**77**) was in fact formed [88].

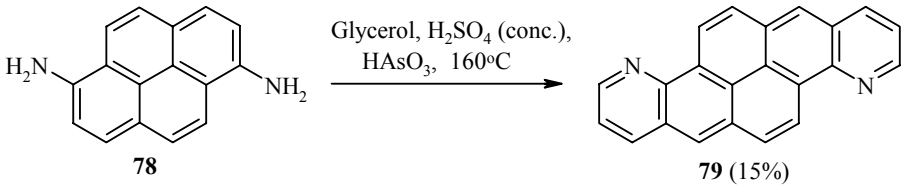


75

76

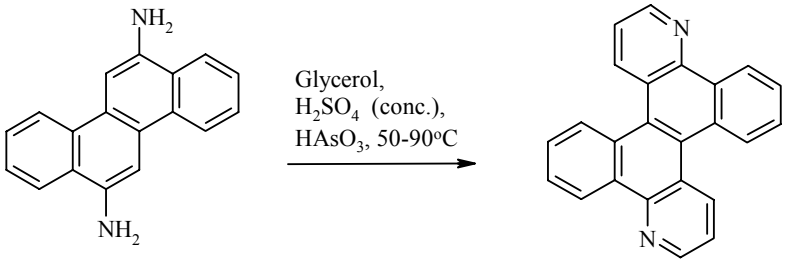
77 (37%)

In [87] the transformation of a series of aromatic diamines in a double Skraup cyclization was investigated: 3,8-diaminopyrene (**78**) gave 4,11-diazadibenzo[*a*,*h*]pyrene (**79**), 6,12-diaminochrysene (**80**) gave 4,11-diazadibenzo[*g*,*p*]chrysene (**81**) [87], and the diamines **82**, **84**, and **86** gave compounds **83**, **85**, and **87** [89].



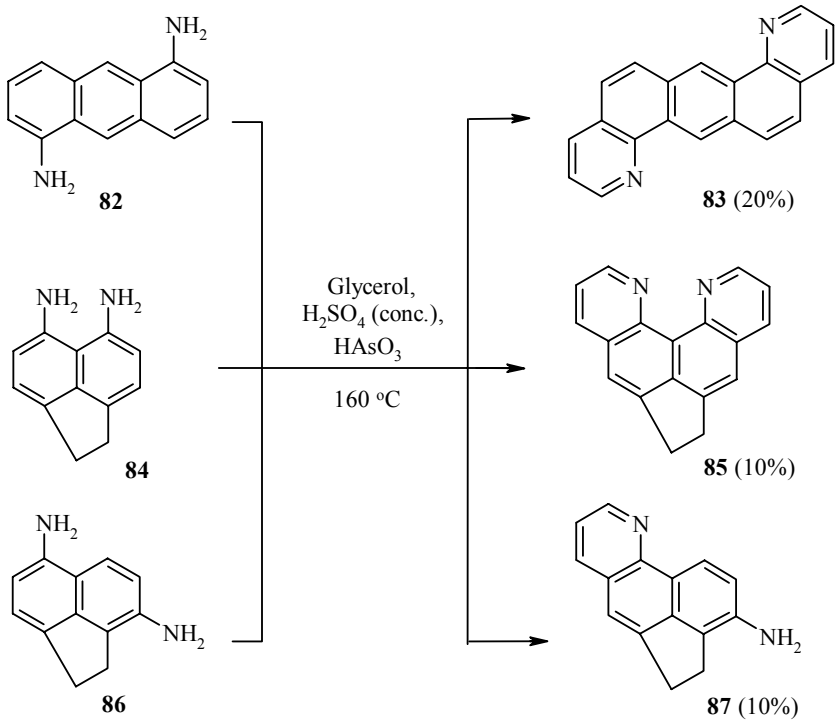
78

79 (15%)



80

81 (30%)



The fact that the amino group in compound **86** does not participate in cyclization but remains in the structure **87** is explained by the specific direction of the Skraup reaction and by the adherence to the Markwald rule. According to the latter the angular structures are mostly produced when the additional pyridine ring is formed from the polycyclic aromatic amines in the Skraup and Doebner–Miller reactions.

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