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PYRROLOQUINOLINES*. (REVIEW)

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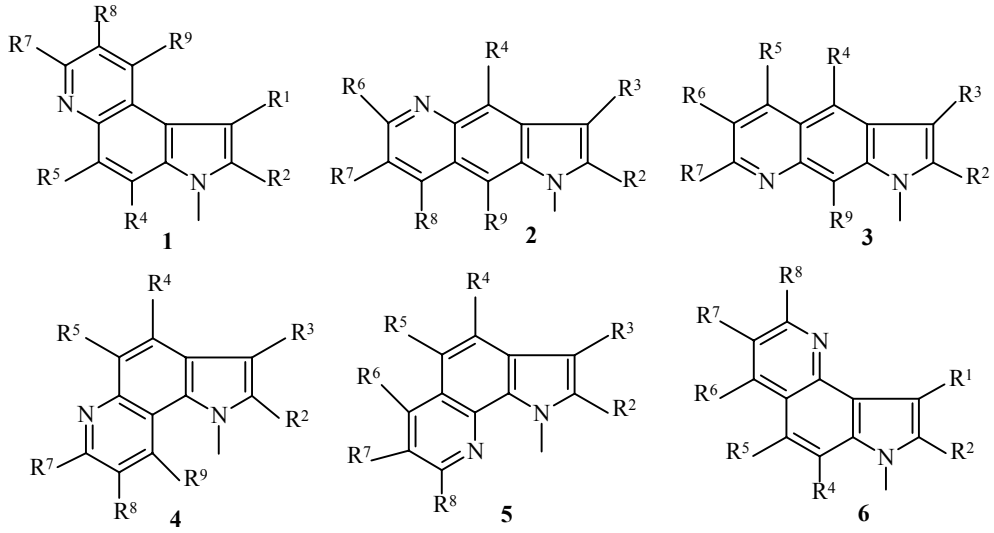
Methods for the synthesis of six types of pyrroloquinolines with various types of ring fusion and their chemical properties are reviewed.

Keywords: aminoindoles, pyrroloquinolines, quinolylhydrazines, synthesis, chemical characteristics.

Contemporary organic chemistry is paying more and more attention to the development of methods for the synthesis of condensed heterocyclic structures containing indole and pyridine fragments (pyrrole and quinoline). The interest in such compounds is due to the prospect of seeking new biologically active substances, since their molecules contain two widely known pharmacophoric fragments. In this connection a new direction has been initiated in the synthesis and study of pyrroloquinolines and the structural analogs of such well known natural compounds as the alkaloid vomipyrine and the coenzyme of certain bacterial and animal dehydrogenases – methoxanthine (PQQ). Many of the recently obtained pyrroloquinolines exhibit clearly defined physiological activity [1-8].

The present review covers papers concerning pyrrolo[3,2-*f*]- (**1**), pyrrolo[2,3-*g*]- (**2**), pyrrolo[3,2-*g*]- (**3**), pyrrolo[2,3-*f*]- (**4**), pyrrolo[3,2-*h*]- (**5**), and pyrrolo[2,3-*h*]quinolines (**6**), in the molecules of which the pyrrole ring is annellated with the benzene fragment of the quinoline.



* Dedicated to E. Lukevics, outstanding scientist and human being, without whom the existence of our favorite journal would have been impossible, on the occasion of his 65th birthday.

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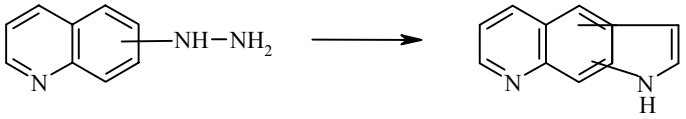
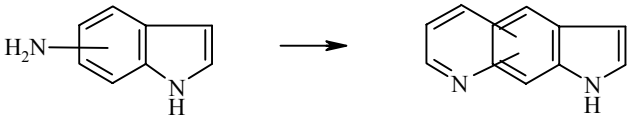
Here and subsequently the superscripts of the radicals in the molecules of the pyrroloquinolines correspond to the numbering of the atoms according to the IUPAC nomenclature.

1. METHODS OF FORMATION OF THE PYRROLOQUINOLINE SYSTEM

There are two main paths for the formation of the tricyclic system of pyrroloquinolines, based on annellation of the pyrrole ring to the benzene part of the quinoline molecule or annellation of the pyridine ring to the benzene fragment of the indole bicycle. In the first approach hydrazines of the quinoline series are used as starting compounds for attaching the pyrrole ring.

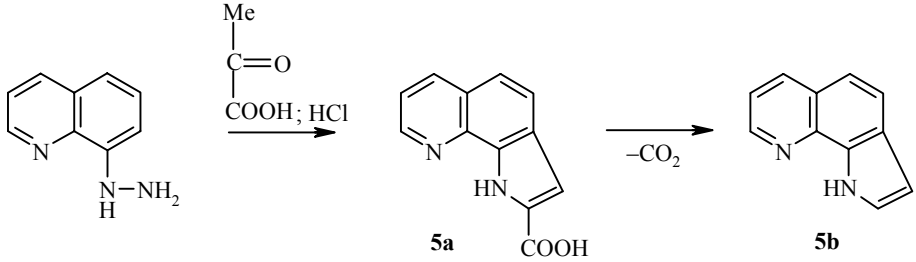


The second method for the synthesis of pyrroloquinolines uses aminoindoles as starting compounds for annellation of the pyridine ring to the benzene ring of the indole molecule.

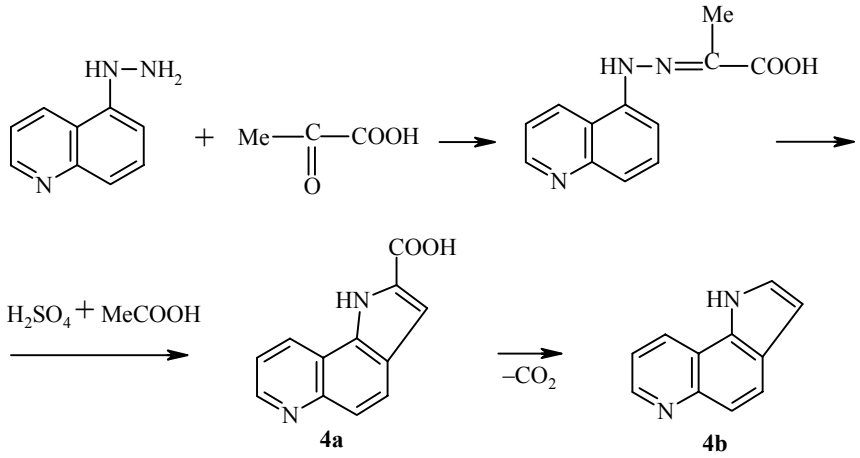


1.1. Synthesis of Pyrroloquinolines from Quinolylhydrazines

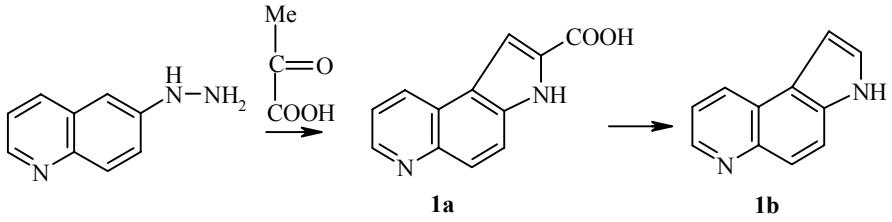
This method for the production of pyrroloquinolines is based on the Fischer cyclization of various quinolylhydrazones. The first investigations in this region were carried out as far back as the end of the nineteenth century [9, 10]. Thus, pyrroloquinoline **5a** was first obtained in 1891 from 8-quinolylhydrazine and pyruvic acid with, it is true, a small yield [9]. Later, different authors were able to increase the yields of compounds **5a**,**b** significantly [7, 11, 12].



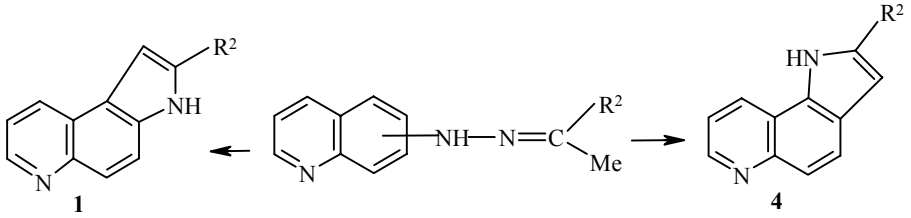
The hydrazone of pyruvic acid, obtained from 5-quinolylhydrazine, was converted similarly with a quantitative yield into 1H-pyrrolo[2,3-*f*]quinoline-2-carboxylic acid (**4a**) by the action of a 3:1 mixture of glacial acetic acid and sulfuric acid and, after decarboxylation, into unsubstituted 1H-pyrrolo[2,3-*f*]quinoline (**4b**) [10, 11, 13].



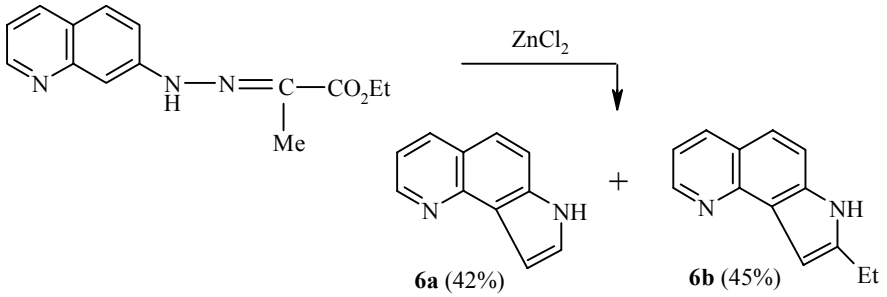
Under these condition it is also possible to obtain quantitative yields of the above-mentioned 1H-pyrrolo[3,2-*h*]quinoline-2-carboxylic (**5a**) and also 3H-pyrrolo[3,2-*f*]carboxylic (**1a**) acids from the corresponding hydrazones of pyruvic acid [13, 14].



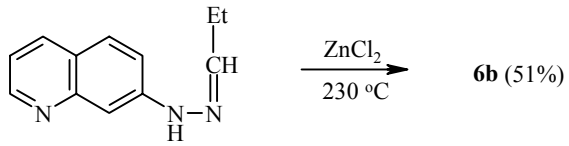
The isomeric quinolylhydrazones of ethyl pyruvate undergo cyclization just as readily with the formation of pyrroloquinolines of types **1** and **4** ($R^2 = CO_2Et$) [13].



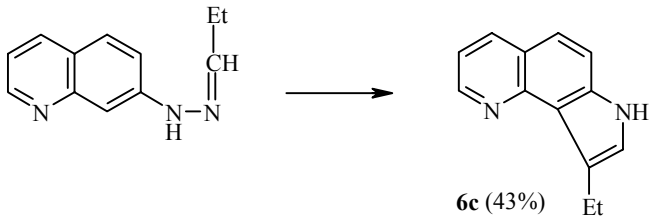
Unlike the 5- and 6-quinolylhydrazones, the 7-quinolylhydrazone of pyruvic acid readily undergoes cyclization in the presence of zinc dichloride to form pyrrolo[2,3-*h*]quinoline (**6a**) and 2-ethylpyrrolo[2,3-*h*]-quinoline (**6b**) [8].



As seen, in this case cyclization is accompanied by decarboxylation and partial alkylation at the α-position of the pyrrole ring with the formation of the pyrroloquinoline **6b**. The latter was also obtained from the corresponding hydrazone of butyraldehyde.

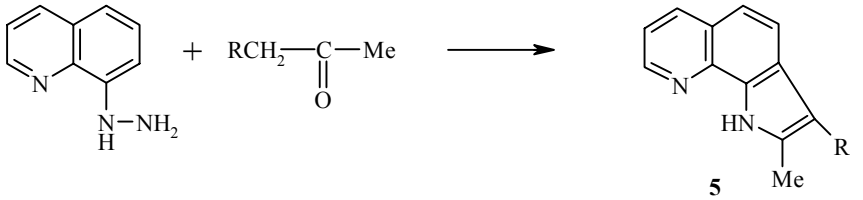


The authors explain the formation of compound **6b** by migration of the ethyl group at high temperature from position 1 to position 2 in the initially formed 1-ethylpyrrolo[2,3-*h*]quinoline (**6c**). In fact, if ethyl polyphosphate is used as cyclization agent in this condensation and the reaction is carried out under milder conditions (at 140°C), 1-ethyl-3H-pyrrolo[2,3-*h*]quinoline (**6c**) is formed exclusively.



The suggestion about the formation of the pyrroloquinoline **6b** is supported by the quantitative transformation of one to the other during heating at 230°C with zinc chloride.

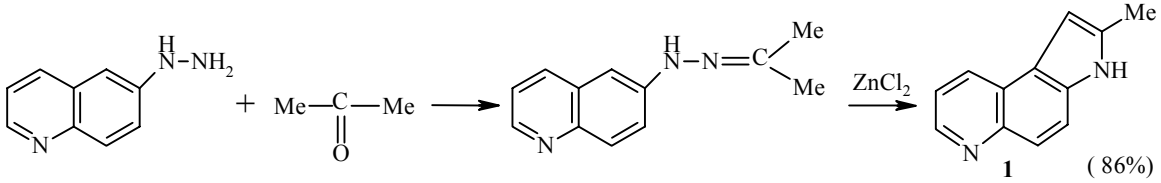
The corresponding methyl-, dimethyl-, and methylethyl-substituted pyrrolo[3,2-*h*]quinolines (**5**) were obtained by cyclization of the 8-quinolylhydrazones of acetone butanone, and methyl propyl ketone [15].



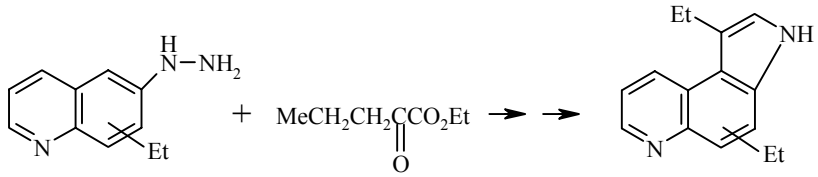
R = Me (90%); Et (70%), H (87%)

It should be noted that the yields of the pyrroloquinolines during the cyclization of hydrazones depend largely on the employed catalyst. Thus, acetone 8-quinolylhydrazone undergoes cyclization best in PPA (yield 87%), and butanone and methyl propyl ketone 8-quinolylhydrazones react best in a mixture of glacial acetic and hydrochloric acids. 2,3-Dimethyl-1H-pyrrolo[3,2-*h*]quinoline (**5**) (R = Me) is obtained readily by boiling methyl ethyl ketone briefly with the hydrate of 8-quinolylhydrazine hydrochloride in a mixture of alcohol and hydrochloric acid (yield 90%).

2-Methylpyrrolo[3,2-*f*]quinoline (**1**) (R^2 = Me) is obtained during the cyclization of 6-quinolylhydrazine hydrazone and acetone [5, 16].



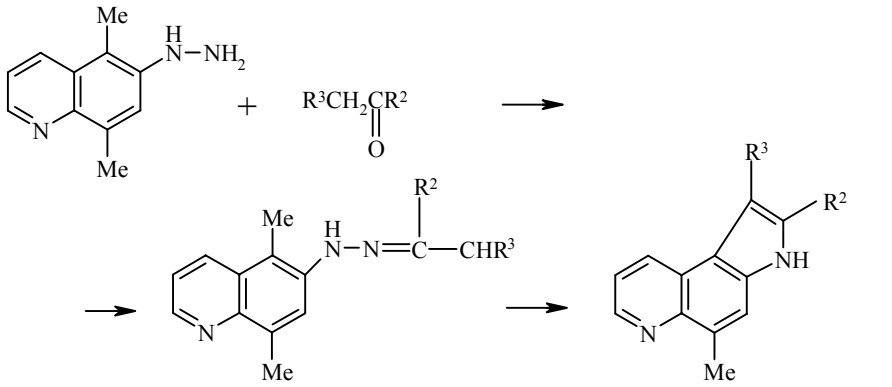
Alkyl-substituted [3,2-*f*]pyrroloquinoline **1** (4-Et and 5-Et) were also obtained in research devoted to determination of the structure of one of the alkaloids of the strychnine series – vomipyrine [17].



1 4-Et и 5-Et

The presented experimental data indicate that the cyclization of 6- and 7-quinolylhydrazones with two free *ortho* positions takes place stereoselectively with the formation of only the angular pyrroloquinolines **1**, **4**-**6**.

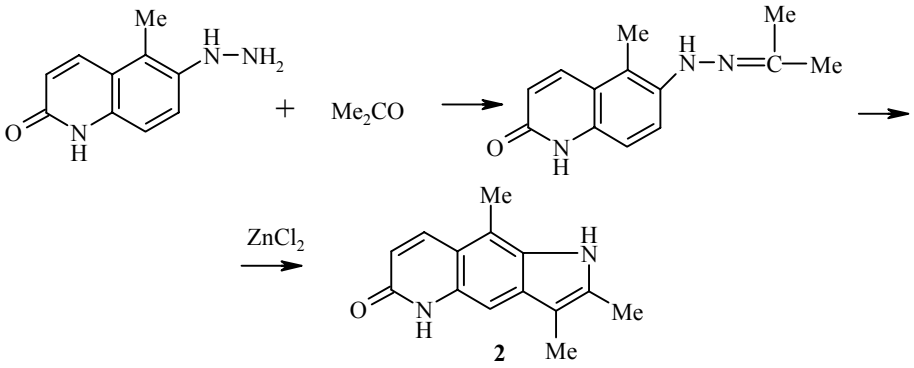
Attempts to convert 6- and 7-quinolylhydrazones into pyrrolo[3,2-*g*]- and pyrrolo[2,3-*f*]quinolines of types **3** and **4** unsubstituted in the pyridine ring were unsuccessful [18, 19]. Moreover, it was established that even in the case where position 5 in the 6-quinolylhydrazone is blocked by an alkyl substituent in order to direct the cyclization toward the formation of the linear pyrrolo[*g*]quinoline the methyl group is removed and angular structures of type **1** are formed exclusively.



1 $R^2 = R^3 = Me$; $R^2 + R^3 = (CH_2)_4$

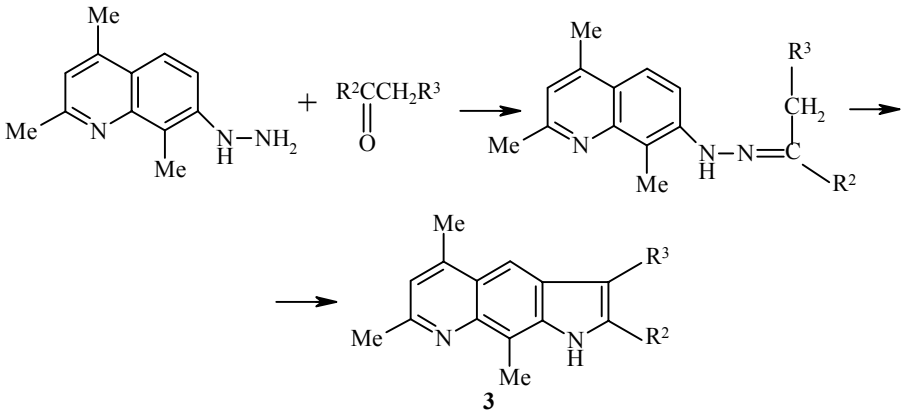
Here successful reaction requires a strong mineral acid and high temperature.

Cases of the synthesis of linear pyrrolo[*g*]quinolines hydroxy- and alkyl-substituted in the pyridine ring are known. Thus, indolization of the hydrazone obtained from acetone and 6-hydrazino-5-methyl-1,2-dihydro-2-quinolone leads to the corresponding pyrrolo[2,3-*g*]quinolone of type **2** [20].



2

The 2,4,8-trimethyl-7-quinolylhydrazones of various aliphatic ketones undergo similar cyclization with the formation of linear pyrrolo[3,2-*g*]quinolines of type **3** [21].



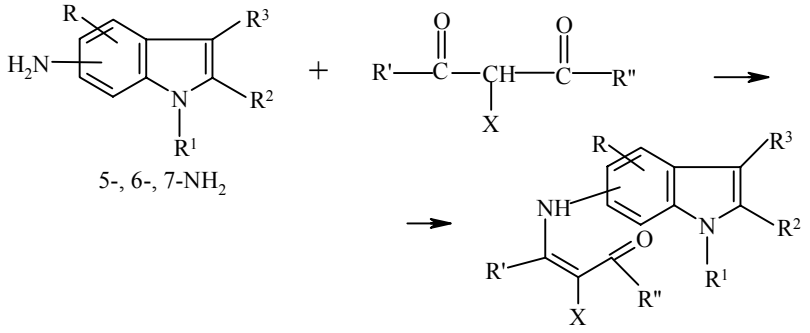
3

R^2, R^3 = alkyl, cycloalkyl

1.2. Synthesis of Pyrroloquinolines from Aminoindoles

The method involves annellation of the pyridine ring to the benzene part of the indole bicycle using 2- or 2,3-alkyl-substituted aminoindoles with the amino groups at various positions in the benzene ring.

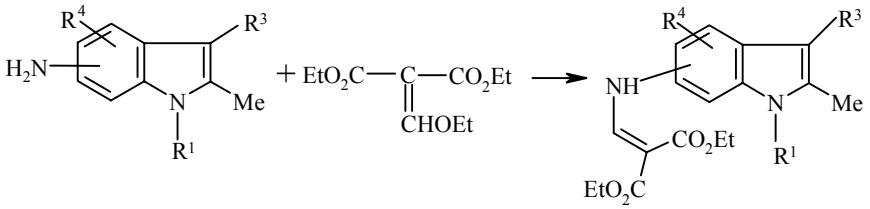
However, not all the reactions used during the formation of the quinoline system itself from aniline and derivatives were suitable for the aminoindole models. For example, the Skraup and Doebner–Miller syntheses were unsuitable in this case. This is explained by the rigorous reaction conditions, leading to destruction of the indole system itself. The reactions of aminoindoles with β-dicarbonyl compounds were successful. Here the initial stage of the synthesis in the case of diketones is the formation of β-indolyleneamino ketones (R' = R" = Me, Ph; X = H) [22, 23]. For all the intermediates in this case and subsequently the radicals in the side chain are indicated by primes.



5-, 6-, 7-NH_2

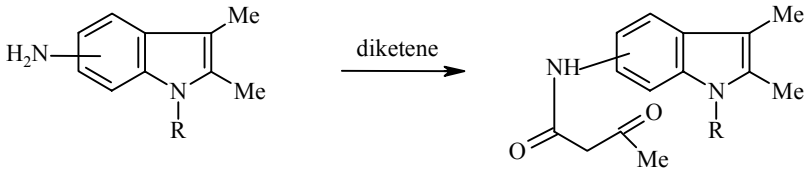
R^1 = H, Me, Ph; R^3 = H, Me; R = H, Me, OMe

In the same scheme with aldehydes the intermediate stage of the process is the formation of β-indolyleneamino aldehydes (R' = R" = H, X = NO_2) [24], while in the case of acetoacetic ester it is the formation of β-indolylamino crotonates (R' = Me, R" = OEt, X = H) [23, 25]. Condensation with ethoxymethylenemalonic ester takes place through the formation of indolylaminomethylenemalonic esters [6, 23, 26].



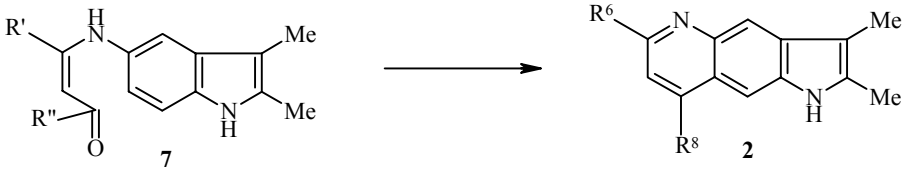
R^1 = H, Me; R^3 = H, Me; R^4 = H, Me, OMe

If diketene is used the indolylamides of acetoacetic acid are formed initially [27].



During further cyclization of the above-mentioned intermediates the pyrroloquinoline system is formed, i.e., the cyclization of enamino ketones and aldehydes, amides, aminocrotonates, and aminomethylenemalonic esters takes place with annellation of the pyridine ring to the benzene ring of the indole.

1.2.1 Cyclization of Enamino Ketones. Under the influence of acidic agents (trifluoroacetic acid, polyphosphoric acid) the enamino ketones **7** give only linear pyrroloquinolines of type **2**, i.e., cyclization takes place at position 6 [28-35].

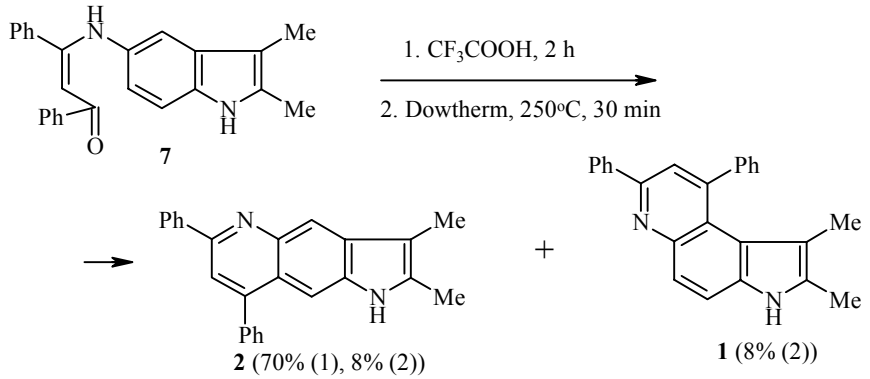


$R^6 = R^8$ = Me (CF_3CO_2H, 30 min, 80%)

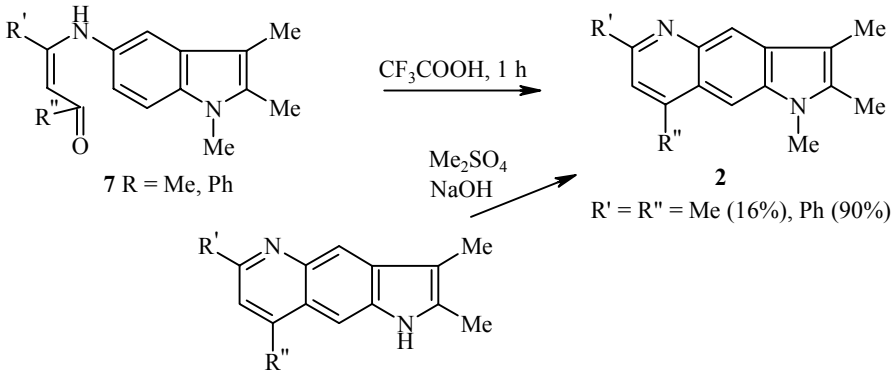
R^6 = Me, R^8 = Ph (CF_3CO_2H, 1 h, 86%)

R^6 = H, R^8 = Me (PPK, 2 h, 32%)

The enamino ketone **7** (R' = R" = Ph) also forms a linear pyrroloquinoline of type **2** ($R^6 = R^8$ = Ph) under the conditions of acid cyclization, but if the reaction is carried out in Dowtherm at 250°C (a thermal process) it is possible to obtain a small yield of an angular pyrroloquinoline of type **1** ($R^7 = R^9$ = Ph) [30].

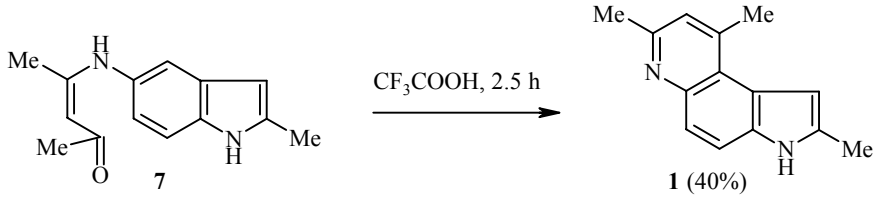


The presence of a methyl group at the pyrrole nitrogen atom of the initial enamino ketone does not lead to changes in the direction of cyclization [36]. Thus, in trifluoroacetic acid the N-methyl-substituted enamines **7** (R' = R" = Me, Ph), like enamines not substituted at the pyrrole nitrogen atom, are converted with high yields into pyrroloquinolines with linear fusion of the rings **2** ($R^6 = R^8$ = Me, Ph).

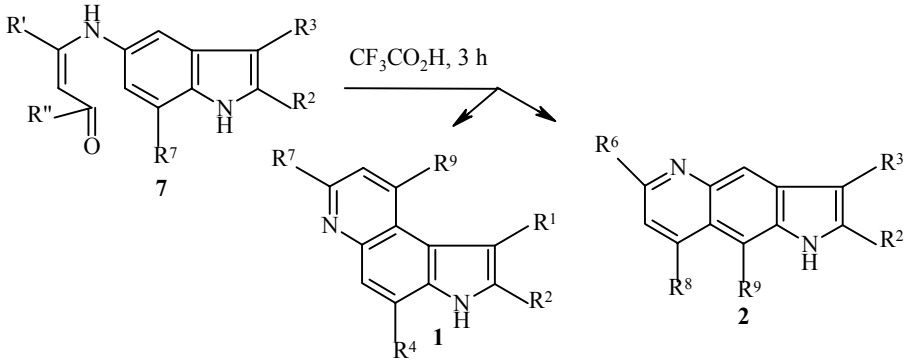


An alternative synthesis of N-methylated pyrroloquinolines was realized by methylation of the corresponding 1H-pyrroloquinolines with dimethyl sulfate in acetone in the presence of potassium hydroxide.

Only the angular pyrroloquinoline **1** (R^3 = H) was obtained during cyclization of the enamino ketone **7** without a substituent at the β-position of the indole [30].



At the same time the cyclization of the enamine **7** unsubstituted at position 3 in the pyrrole ring, which has phenyl substituents instead of methyl in the enamino ketone function (R^3 = H, R' = R" = Ph), in trifluoroacetic acid leads to the formation of a mixture of the angular (**1**) (R^1 = H, $R^9 = R^7$ = Ph) and linear (**2**) (R^3 = H, $R^6 = R^8$ = Ph) isomers in a ratio of 5:1 (overall yield 49%), i.e., cyclization takes place preferentially at position 4 [30].



Change in the character of the substituent in the pyrrole ring (replacement of α-Me by Ph) does not have a significant effect on the direction of ring formation. The enamino ketones **7** (R^2 = Ph, R^7 = H, R' = R" = Me, Ph) are also converted by the action of trifluoroacetic acid into a mixture of pyrroloquinolines with angular and

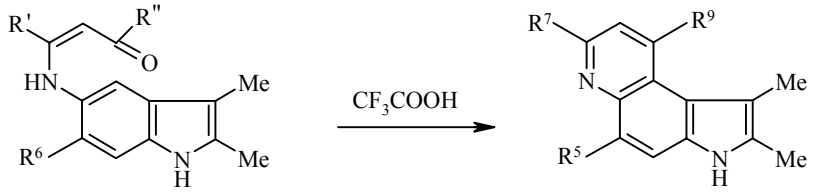
linear fusion of the rings in ratios of 4:1 between **1** ($R^7 = R^9 = Me$, $R^2 = Ph$, $R^1 = H$) and **2** ($R^6 = R^8 = Me$, $R^2 = Ph$, $R^3 = H$) and 7:1 between **1** ($R^7 = R^9 = R^2 = Ph$, $R^1 = H$) and **2** ($R^6 = R^8 = R^2 = Ph$, $R^3 = H$) [36].

A mixture of angular (**1**) ($R^1 = R^2 = R^4 = R^7 = R^9 = Me$, 8%) and linear (**2**) ($R^2 = R^3 = R^6 = R^8 = R^9 = Me$, 30%) pyrroloquinolines in a ratio of 4:1 was also found in the reaction mixture obtained by boiling compound **7** ($R' = R'' = R^2 = R^3 = R^7 = Me$) in trifluoroacetic acid [37].

Similar results were obtained during the cyclization of the enamino ketone **7** ($R' = R'' = Ph$). In this case the overall yield of the pyrroloquinolines amounted to 52%, and the ratio of the linear and angular isomers was also 4:1 (according to the integral intensity of the proton signals in the ^1H NMR spectrum of the reaction mixture).

Thus, it can be concluded on the basis of the data on the ratio of the angular and linear pyrroloquinolines that in all cases under the conditions of the Combes reaction the *peri* effect of the β-methyl group predominates somewhat over the *ortho* effect of the 7-Me group during annellation of the γ-methyl- or γ-phenyl-substituted pyridine fragment.

Angular pyrroloquinolines with two methyl or methyl and phenyl groups in the *peri* position are nevertheless formed if an enamine with a substituted position 6 is used for cyclization. Thus, when heated in trifluoroacetic acid (6 h) the enamino ketone **7** ($R' = R'' = R^6 = Me$) is converted with a good yield into the pyrroloquinoline **1** ($R^1 = R^2 = R^5 = R^7 = R^9 = Me$) [30].



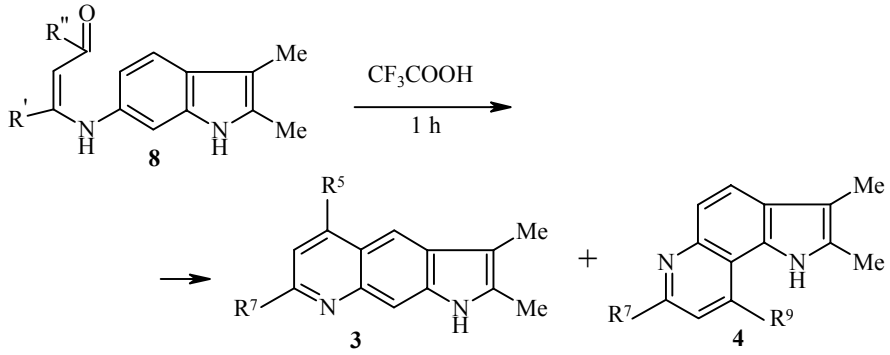
7 **1**

$R^5 = R^7 = R^9 = Me$ (88%); $R^5 = Me$, $R^7 = R^9 = Ph$ (85%); $R^5 = OMe$, $R^7 = R^9 = Me$;
$R^5 = OMe$, $R^7 = R^9 = Ph$ (12%)

More prolonged heating (8 h) is required to complete the analogous reaction in the case of the diphenyl-substituted enamine **7** ($R' = R'' = Ph$, 85%)

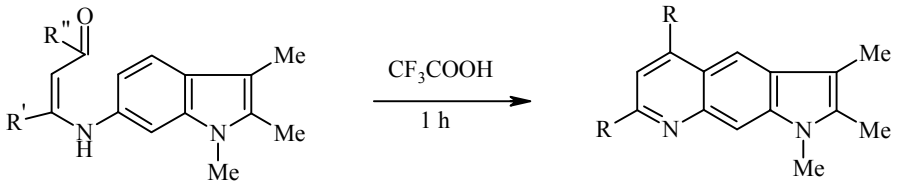
The enamines **7** ($R' = R'' = Me$, Ph, $R^6 = OMe$), which have a methoxy group at the *meta* position to the point of closure of the ring, are transformed into pyrroloquinolines with greater difficulty [38]. Heating for 10 h is required for the complete conversion of the initial enamine **7** (R = Me), while the enamine **7** ($R' = R'' = Ph$) has to be boiled for 15 h.

Analogous results in the Combes reaction were obtained with 6-aminoindoles. Namely, the 3-(6-indolylamino)vinyl ketone **8** ($R' = R'' = R^2 = R^3 = Me$) is converted by the action of trifluoroacetic acid into a mixture of the two corresponding isomeric pyrroloquinolines (linear of type **3** and angular of type **4**), which are isolated in a ratio of 4:1 (overall yield 87%) [30].



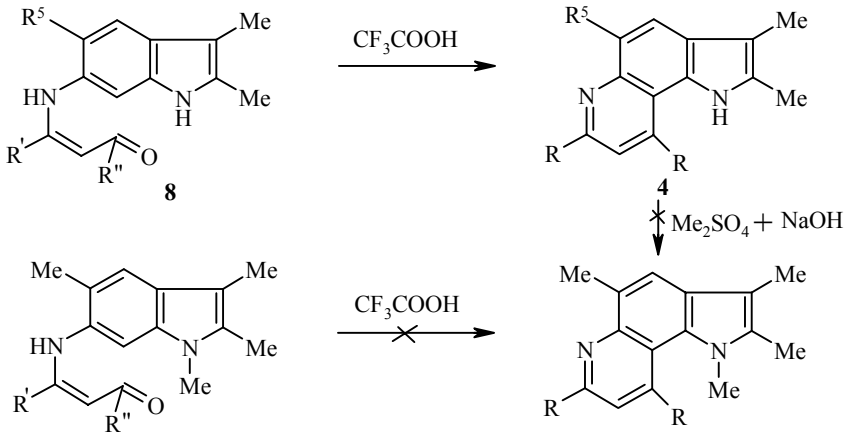
8 **3** **4**

The preferred formation of the linear pyrroloquinoline here too is evidently due to steric hindrances arising on account of the approach of the N–H proton to the methyl group at position 9. If the N–H proton is replaced by a methyl group, position 7 is completely blocked for cyclization, i.e., the enamino ketones **8** (R' = R" = Me, Ph) only form the linear pyrroloquinolines of type **3** [30].



8 **3** R = Me (73%); Ph (63%)

The specific production of angular pyrroloquinolines of type **4** can be achieved by using substituted 5-methyl- or 5-methoxy-6-aminoindoles, which should form only pyrrolo[2,3-*f*]quinolines under the conditions of the Combes reaction, as starting compounds. In fact, the respective angular pyrroloquinolines **4** were isolated when compounds **8** (R^5 = Me, OMe, R' = R" = Me, Ph) were boiled in trifluoroacetic acid [39-41].



8 **4**

R' = R"	R^5	Reaction time	Yield of **4**, %
Me	Me	1	93
Ph	Me	1	88
Me	OMe	14	52
Ph	OMe	20	25

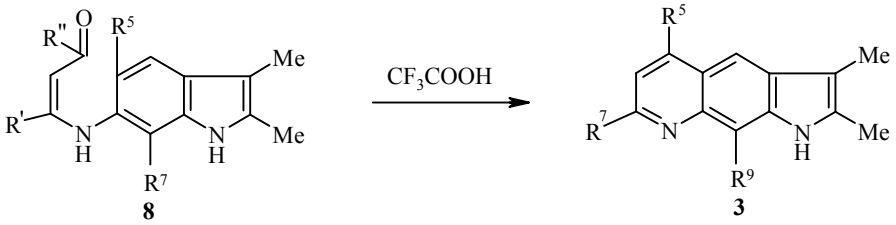
The results of the experiment confirm the suggestion about the steric requirements of the substituent at the pyrrole nitrogen atom during closure of the pyridine ring at position 7 of the indole.

The enamino ketones **8**, containing a methyl substituent at the pyrrole nitrogen atom, do not undergo cyclization even after prolonged heating in trifluoroacetic acid and are recovered unchanged.

The steric blockage of the pyrrole nitrogen atom in the angular pyrroloquinolines **4** is confirmed by the impossibility of methylation at the indole nitrogen atom with dimethyl sulfate.

The introduction of the OMe group at position 5 of the enamino ketones **8** (R^5 = OMe), by analogy with the enamines based on the 5-aminoindoles **7** (R^6 = OMe), has an additional deactivating effect. More prolonged boiling in trifluoroacetic acid is required in order to convert such methoxy-substituted enamines **8** into the corresponding angular pyrroloquinolines **4**.

The enamino ketones of 7-substituted 6-aminoindoles were used during the production of pyrroloquinolines of type **3** with specific linear fusion of the rings [37, 42]. After 1-2 h (heat, trifluoroacetic acid) the enamines **8** (R' = R" = R^7 = Me, R' = R" = Ph, R^7 = Me) give good yields of compounds **3** (R^9 = Me, R' = R" = Me, Ph)

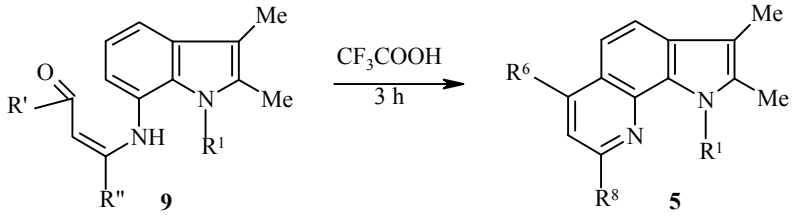


8 **3**

R' = R" = R^5 = R^7	R^9	Reaction time, h	Yield of **3**
Me	Me	1	55
Ph	Me	2	50
Me	OMe	0.5	60
Ph	OMe	2	40

Quite unexpectedly, the 7-methoxy-substituted 6-(acylvinyl)indoles **8** (R' = R" = Me, Ph, R^7 = OMe) undergo cyclization just as smoothly under the same conditions with the formation of the corresponding pyrroloquinolines **3**. Such a mixed effect of the methoxy group at the *meta* position to the point of cyclization in 5-, 6-, and 7-methoxyindoles on the course of the Combes reaction once again points to a unique distribution of electron density in the indole structure.

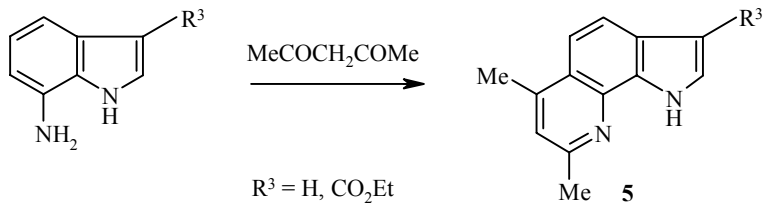
During cyclization of the enamines **9** (R^1 = Me, R', R" = Me, Ph), obtained from 7-aminoindoles, the formation of only the corresponding pyrrolo[3,2-*h*]quinolines **5** could be expected, whereas the alternative possibility of ring closure at the pyrrole fragment with the formation of tricyclic structures having a bridgehead nitrogen atom, i.e., 1,7-diazepinoindoles, could not be ruled out for the enamines **9** (R^1 = H) without a substituent at the nitrogen atom [43]. However, in no case was such a path detected. All the enamino ketones **9** employed in the reactions were converted by the action of trifluoroacetic acid into the substituted pyrrolo-[3,2-*h*]quinolines **5**, i.e., heterocyclization only takes place at position 6 of the benzene ring of the indole.



9 **5**

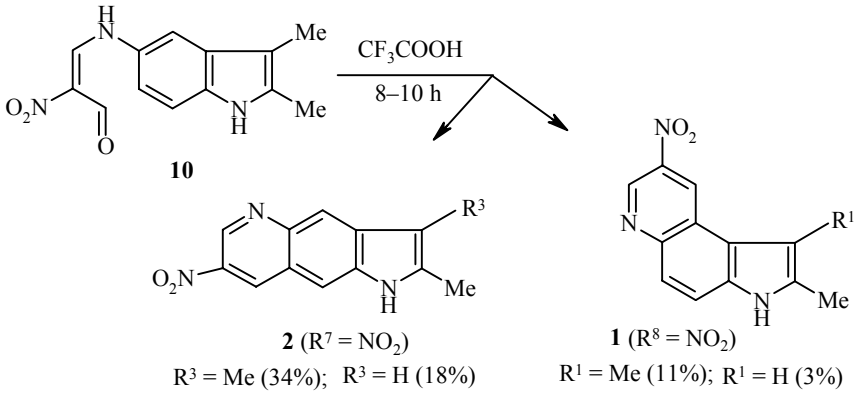
R^1	R^6	R^8	Yield of **5**, %	R^1	R^6	R^8	Yield of **5**, %
H	Me	Me	69	Me	Me	Me	65
H	Me	Ph	70	Me	Me	Ph	67
H	Ph	Ph	60	Me	Ph	Ph	54

No traces of 1,7-diazepinoindole were found during the cyclization of the enamines of 7-aminoindole with a free position 2 [44].



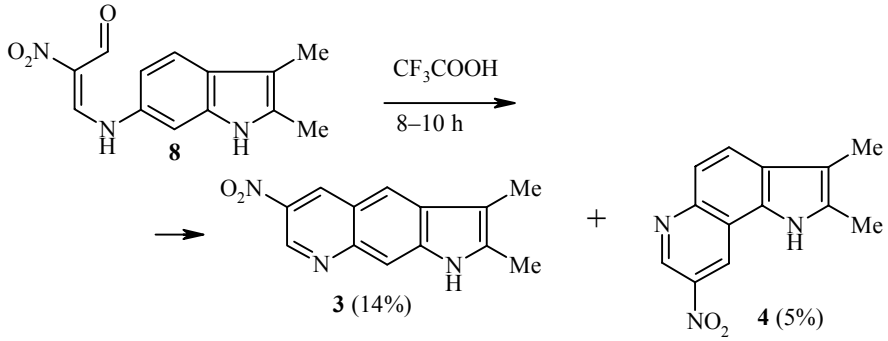
1.2.2. Cyclization of Enamino Aldehydes. A decrease in the steric hindrances during cyclization with the formation of angular pyrroloquinolines is also possible on the part of the enamino chain.

In fact, the product **10** from the condensation of 2,3-dimethyl-5-aminoindole with nitromalonaldehyde together with the linear isomer **2** ($R^7 = NO_2$) also forms the angular isomer **1** ($R^8 = NO_2$) in a ratio of 3:1 [24].



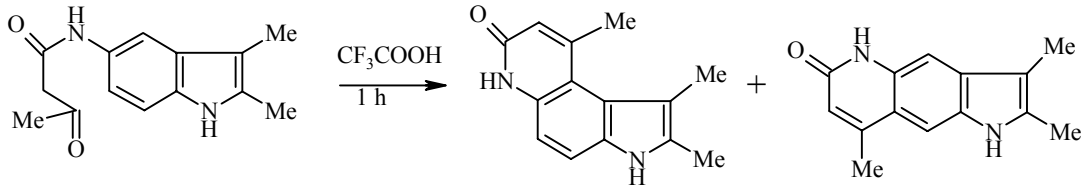
Nitropyrroloquinolines are formed from the enaminoaldehyde with a free β-position in the indole ring with smaller yields.

This reaction also takes place for the enamino aldehyde **8**, obtained from 2,3-dimethyl-6-aminoindole, and leads to the formation of both the linear (**3**) and the angular (**4**) pyrroloquinoline, isolated in a ratio of 3:1. (Approximately the same result was obtained with acetylacetone.)



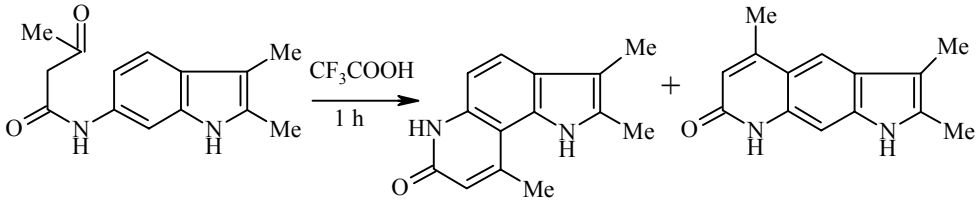
Thus, the presented data confirm the effect of steric factors in the enamine residue on the regioorientation of cyclization.

1.2.3. Acid Cyclization of Indolylamides of Acetoacetic Acid. The indolylamides of acetoacetic acid were investigated in this reaction. As in the case of the enamino ketones, trifluoroacetic acid with boiling was used as cyclizing agent. It was established that under these conditions the 5-indolylamide of acetoacetic acid forms two isomeric pyrroloquinolones with an overall yield of 62% and with the linear and angular isomers in a ratio of 2.5:1 [27].



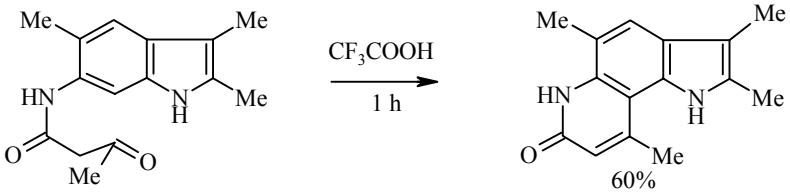
Thus, the formation of a system with two methyl groups in the *peri* positions is hindered in this case too, although to a lesser degree than during the formation of a pyrroloquinoline with similar structure from an enamino ketone whose cyclization under the same conditions does not lead to any formation of a pyrroloquinoline with angular fusion of the rings.

The acid cyclization of the 6-indolylamide of acetoacetic acid also leads to the formation of a mixture of two isomeric pyrroloquinolones with a small preference for the angular isomer (1.2:1, overall yield 56%).

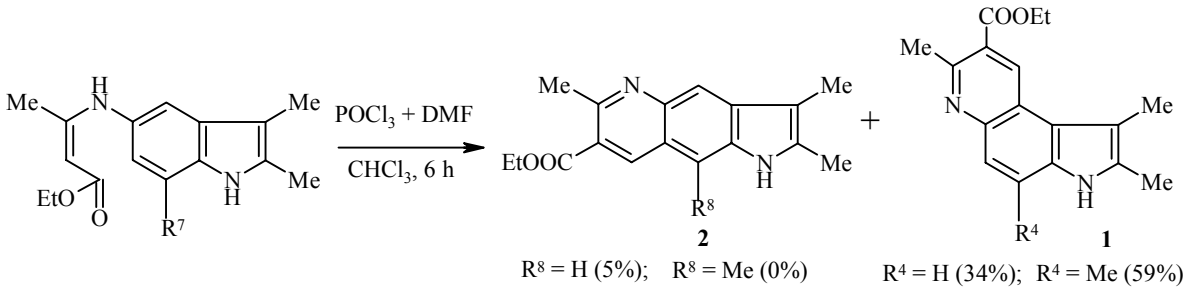


On account of their low solubility and low mobility on sorbents these isomers were not isolated in the individual form, and their ratio was estimated from the ^{1}H NMR spectrum of the reaction mixture.

An angular pyrroloquinolone of type **4** is easily formed during cyclization of the (6-amino-5-methylindolyl)amide of acetoacetic acid, in which the position for alternative attack is blocked by a methyl substituent.

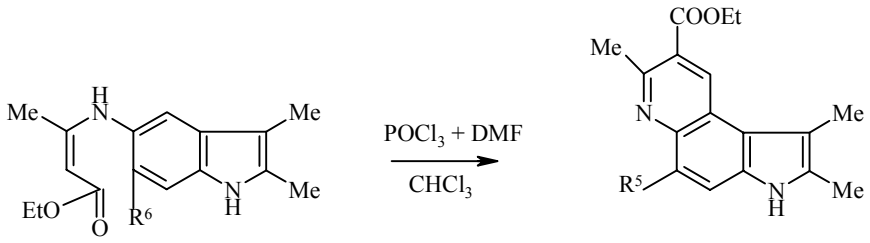


1.2.4. Cyclization of Amino Crotonates and Enamino Ketones under the Conditions of the Vilsmeier Reaction. When equimolar amounts of β-(2,3-dimethyl-5-indolylamino)crotonate and Vilsmeier reagent are boiled in chloroform for 6 h, two easily separable isomeric pyrroloquinolines are formed with a preference for the angular isomer (ratio 1:7) [45].



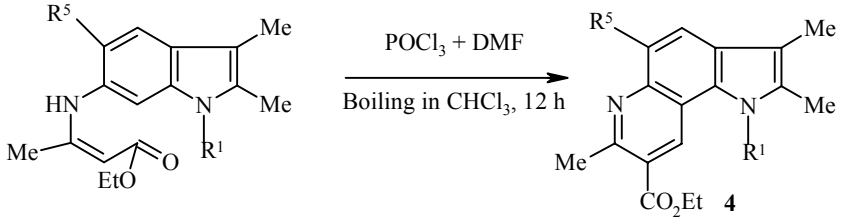
R^8 = H (5%); R^8 = Me (0%) R^4 = H (34%); R^4 = Me (59%)

The formation of the angular-fused pyrroloquinoline from the aminocrotonate having a methyl group at position 7 was preferred even more [37]. Here the formation of the linear isomer was not detected by chromatography in spite of the free position 6 for alternative opening of the pyridine ring. Annellation of the pyridine ring during the cyclization of β-(trimethyl-5-indolylamino)crotonates with hydrogen or methyl substituents at position 6 under the same conditions takes place in a similar way with the formation of only the angular pyrroloquinolines [38, 46].



R^5 = H, 6 h (51%); R^5 = Me, 6 h (80%); R^5 = OMe, 10 h (8%)

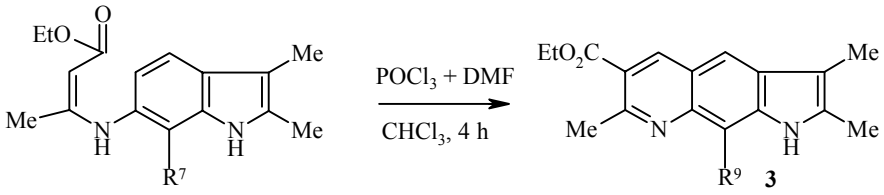
The deactivating effect of the methoxyl group at the *meta* position to the point of ring opening is also observed in this reaction. Thus, the formation of the angular pyrroloquinoline from β-(2,3-dimethyl-6-methoxy-5-indolylamino)crotonate under Vilsmeier conditions requires more prolonged heating and give a significantly lower yield than in the case of the corresponding 6-methyl analog. A similar effect from the methoxy group is observed during the cyclization of β-2,3-dimethyl-5-methoxy-6-indolylamino)crotonate (R^1 = H, R^5 = OMe, 36%) An increase in the reaction time is also required in this case, and due to this the yield of the desired pyrroloquinoline is reduced.



R^1 = H, R^5 = OMe (36%); R^1 = H, R^5 = Me (60%); R^1 = R^5 = Me (51%)

As already mentioned, it is possible to synthesize a pyrroloquinoline of type **4** with *peri* substituents N–H and γ-Me. Similarly it was possible to synthesize an angular pyrroloquinoline from β-(1,2,3,5-tetramethyl-6-indolylamino)crotonate (R^1 = R^5 = Me, 51%) A pyrroloquinoline of type **4** is formed even more readily from an aminocrotonate with a free position 1 (R = H), where the *peri* effect of the substituents is reduced to a minimum (N–H, γ-H).

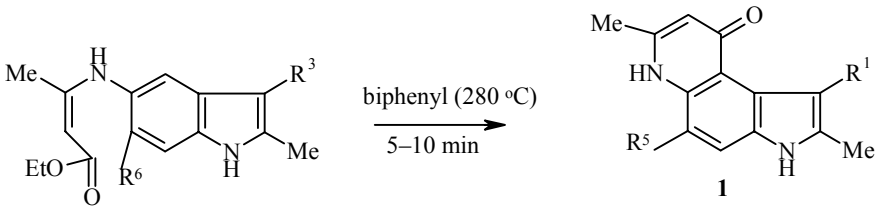
Linear pyrroloquinolines of type **3** with the same substituents in the pyridine ring (R^9 = Me, OMe) are readily formed from 7-substituted aminocrotonates [37, 42].



R^9 = OMe (39%)

It should be noted that the pyrroloquinoline **3** (R^9 = OMe) is formed just as readily as compound (**3**) (R^9 = Me) and with a good yield. Thus, the effect of the methoxy group in the *ortho* position to the enamine chain but at different positions of the benzene ring (5, 6, 7) on the course of the cyclization of aminocrotonates under Vilsmeier conditions agrees with the transformation of analogous enamino ketones into pyrroloquinoline in the Combes reaction.

1.2.5. Thermal Cyclization of Amino Crotonates. In the case of the crotonates of 5-aminoindoles the formation of a pyridine ring is possible both at position 4 and at position 6. However, irrespective of the presence or absence of a substituent at position 3 of the indole ring (R^3 = H, Me) boiling in biphenyl leads with good yields to the formation of pyrroloquinolines of type **1** with angular fusion of the rings, i.e., ring formation takes place at position 4 of the indole [26]

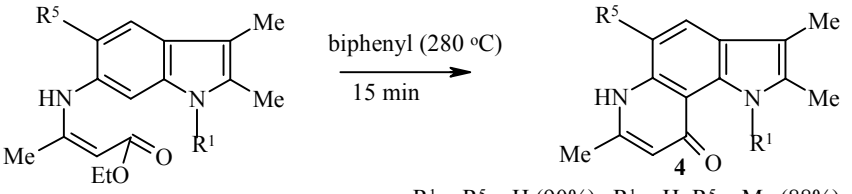


1

$R^1 = R^5$ = H (95%); R^1 = Me, R^5 = H (89%);
$R^1 = R^5$ = Me (59%); R^1 = Me, R^5 = OMe, traces

The methyl group at position 6 of β-(5-indolylamino)crotonate does not have a significant effect on the cyclization process. The corresponding angular pyrroloquinoline ($R^1 = R^5$ = Me) is formed with a fairly high yield (59%) [38]. However, the introduction of the methoxy group deactivates position 4 to electrophilic attack so much that 6-methoxy-5-indolylaminocrotonate cannot be converted thermally into the corresponding pyrroloquinolone. After boiling for 30 min in biphenyl resinification occurs, only trace quantities of the pyrroloquinoline are detected by chromatography, and the initial enamine remains.

When boiled in biphenyl, the aminocrotonates obtained from the various substituted 6-amino-2,3-dimethylindoles give good yields of only the angular pyrroloquinolones of type **4**, irrespective of the presence or absence of substituents at the pyrrole nitrogen atom and at position 5 [26, 27].



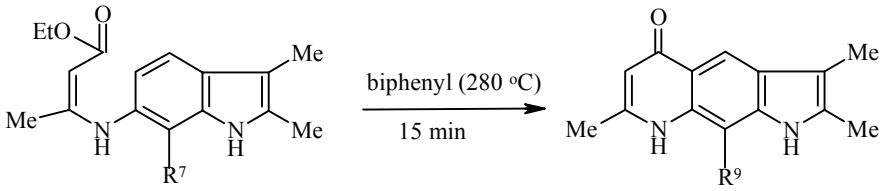
4

$R^1 = R^5$ = H (90%); R^1 = H, R^5 = Me (88%);
$R^1 = R^5$ = Me (52%); R^1 = H, R^5 = OMe, TLC

Thus, as in the case of the 5-analogs, the formation of the angular pyrroloquinolines from 6-aminoindoles is preferred even in the presence of a free position for the alternation formation of the linear systems.

Even in the absence of steric hindrances for closure of the pyridine ring the high-temperature cyclization of the aminocrotonate obtained from 6-amino-2,3-dimethyl-5-methoxyindole (R^5 = OMe) requires an increase in reaction time (by virtue of the deactivating effect of the methoxyl substituent at the *meta* position to the point of attack), and this leads to strong resinification. This hinders isolation of the pyrroloquinolone in the pure form, and its formation can only be established qualitatively by TLC.

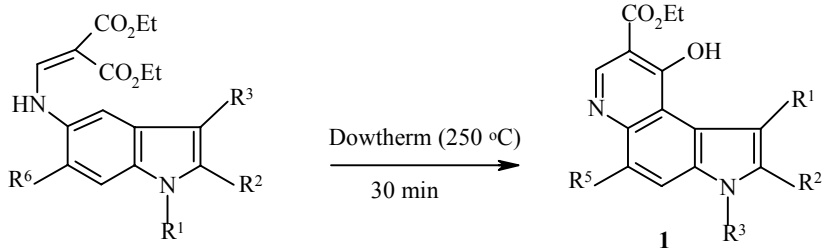
It was shown that linear pyrroloquinolones of type **3** are formed easily and with good yields when 7-substituted 6-aminoindolylcrotonates, for which angular cyclization is impossible on account of the presence of the substituent at position 7, are boiled in biphenyl [37, 42]. Here, as in the previous cases, no deactivating effect from the methoxyl group at position 7 was observed, in contrast to the effect of the 5-methoxy substituent.



R^9 = Me (52%), OMe (47%)

1.2.6. Thermal Cyclization of N-Indolylaminomethylenemalonates. Pyrroloquinolines with specific angular fusion of the rings are formed by heating 5-indolylaminomethylenemalonates with a substituted position 6, having only one position free for closure of the pyridine ring, in Dowtherm [38]. In this case the deactivating effect of the methoxy group at position 6 also requires an increased reaction time.

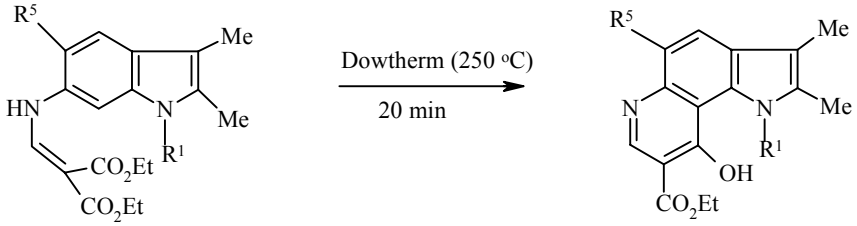
When heated in Dowtherm N-(5-indolyl)aminomethylenemalonates with a free position 6 also form angular pyrrolo[3,2-*f*]quinolines of type **1**, containing two functional groups (hydroxyl and ethoxycarbonyl) in the pyridine ring, for all initial compounds having different substituents at positions 1, 2, and 3 of the pyrrole fragment [6, 36, 46].



1 R^3 = H, R^1 = R^2 = R^5 = Me (76%); R^3 = H, R^1 = R^2 = Me, R^5 = OMe (58%);
R^1 = R^3 = R^5 = H, R^2 = Me (56%); R^1 = R^3 = R^5 = H, R^2 = Ph (57%);
R^3 = R^5 = H, R^2 = R^1 = Me (68%); R^1 = R^2 = R^3 = Me, R^5 = H (46%)

Thus, the thermal cyclization of N-(5-indolyl)aminomethylenemalonates, as for the corresponding crotonates, is regiospecific.

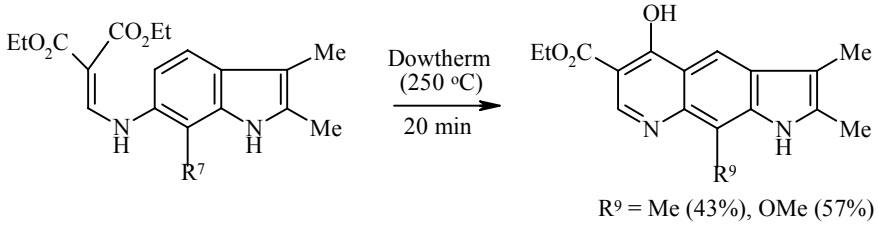
The main products from the high-temperature cyclization of various substituted derivatives of N-(2,3-dimethyl-6-indolyl)aminomethylenemalonic ester are pyrroloquinolines with angular structure formed on account of intramolecular acylation with attack at the $C_{(7)}$ atom [6].



R^1 = R^5 = H (70%); R^1 = H, R^5 = Me (92%), R^1 = R^5 = Me (23%); R^5 = OMe, R^1 = H (30%)

It should be noted that the methyl group at the pyrrole nitrogen atom does not prevent cyclization [27], and it is possible to isolate pyrroloquinolines with a methoxy group at position 5 [39]. Thus, the products from the condensation of aminoindoles and ethoxymethylenemalonic ester with the OCH_3 group at positions 5 and 6 are converted, unlike the analogous aminocrotonates, into the corresponding pyrroloquinolines. This is probably explained by their greater reactivity, and a less high temperature is required for the reaction.

Linearly fused pyrroloquinolines with the same functional groups in the pyridine ring are easily formed from 7-substituted N-(6-indolyl)aminomethylenemalonates [37, 42].

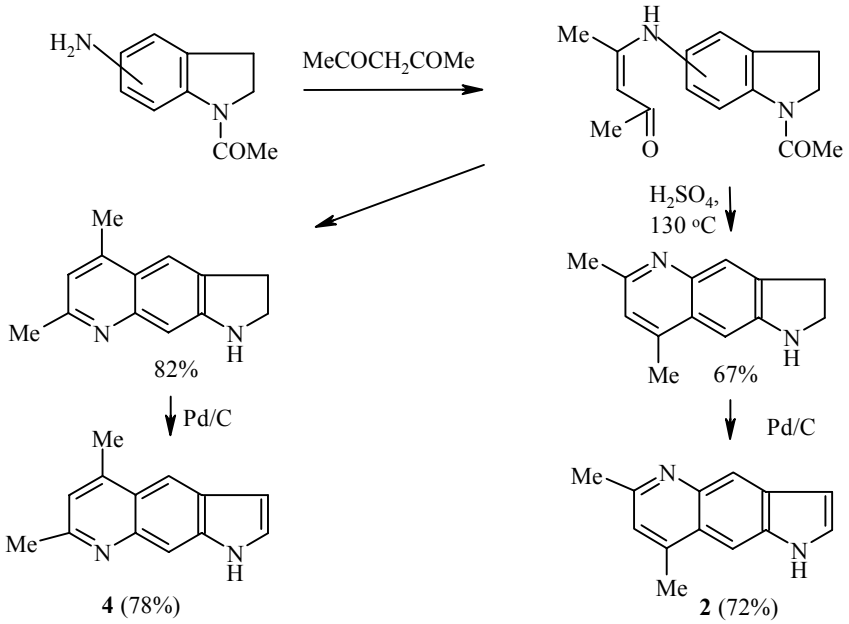


R^9 = Me (43%), OMe (57%)

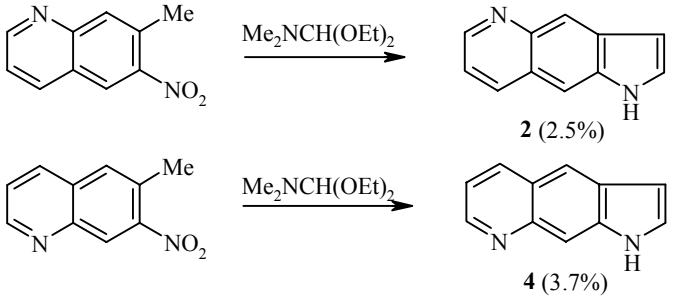
Thus, irrespective of the steric requirements of the *peri* substituents in the forming structures, the thermal cyclization of N-(indolyl)aminomethylenemalonates, like that of the β-(indolylamino)crotonates, takes place strictly specifically with the formation of pyrroloquinolines with angular fusion of the rings. The linear analogs can also be obtained if the possibility of alternative ring closure is excluded by the introduction of a substituent at one of the *ortho* positions in the initial amine.

1.3. Other Methods of Production of Pyrroloquinolines

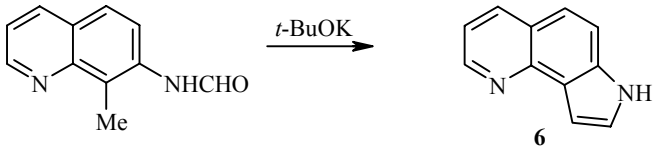
Linear 5,7-dimethyl-1H-pyrrolo[2,3-*g*]quinoline (**4**) (R^5 = R^7 = Me) and 6,8-dimethyl-1H-pyrrolo-[3,2-*g*]quinoline (**2**) (R^6 = R^8 = Me) were obtained from the corresponding aminoindolines and acetylacetone with aromatization of the pyrroline ring at the last stage of the process [8, 47].



As in the case of aminoindoles, the use of aminoindolines for the production of pyrroloquinolines in the Doebner–Miller and Skraup reactions proved unacceptable. The yield of the 2,3-hydrogenated pyrroloquinolines amounted to 2-4%, and in a number of cases the desired compound was not detected at all in the reaction mixture [8, 47]. The unsubstituted pyrrolo[2,3-*g*]quinoline (**2**) and pyrrolo[3,2-*g*]quinoline (**4**) were obtained from the corresponding nitromethyl-substituted quinolines also, it is true, with small yields (2-4%) [8]. In this case the Lehmgruber–Bacho method, widely known in indole chemistry, was used for the annellation of the pyrrole ring to the benzene ring of the quinoline.



Attempts were also made to use the Madelung method. Thus, 8-methyl-7-formylaminoquinoline was subjected to cyclization in order to obtain 3H-pyrrolo[2,3-*h*]quinoline (**6**), but the yield in this case was insignificant [1].



2. CHEMICAL PROPERTIES OF PYRROLOQUINOLINES

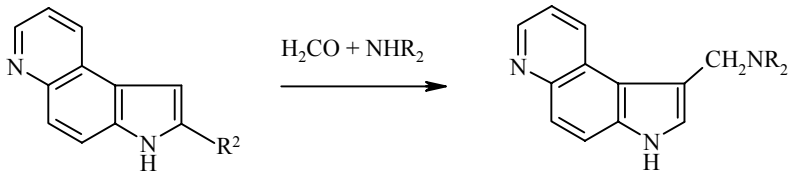
The presence of the indole and quinoline fragments in the molecules of pyrroloquinolines makes it possible to expect for them reactions characteristic of indole and quinoline.

2.1. Electrophilic Substitution Reactions

According to the results from quantum-chemical calculations, the position with greatest electron density in the molecules of pyrroloquinolines is the β-carbon atom of the pyrrole ring [48]. This is confirmed by kinetic investigations into the protonation of the isomeric pyrroloquinolines [49], deuteration of which takes place exclusively at the β-position of the pyrrole fragment.

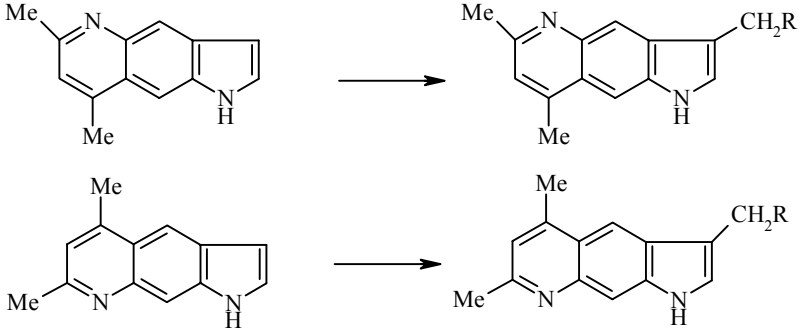
The effect of the pyridine ring leads to some decrease in the electron density at the β-position of the pyrrole fragment and, consequently, to a decrease in its reactivity compared with indole and benzindoles.

2.1.1. The Mannich Reaction. Under the conditions of the Mannich reaction pyrroloquinolines with various types of ring fusion and with a free β position in the pyrrole ring give the corresponding substituted dialkylaminomethyl derivatives. Thus, 3H-pyrrolo[3,2-*f*]quinoline reacts with a mixture of dimethylamine and formaldehyde with the formation of 1-(N,N-dimethylaminomethyl)-3H-pyrrolo[3,2-*f*]quinoline [50, 51].



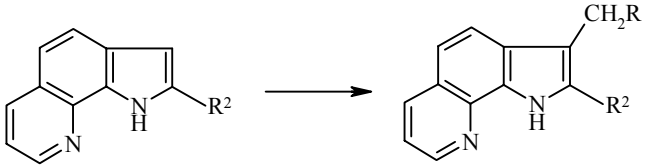
R^2 = H, Me; R = Me, Et, Bu, $(CH_2)_5$, $O(CH_2CH_2)_2$

Linear pyrrolo[2,3-*g*]quinoline and pyrrolo[2,3-*g*]quinoline behave similarly in the Mannich reaction [8].



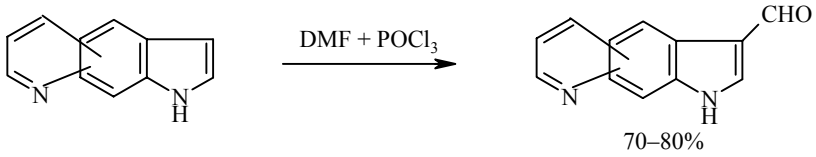
R = NMe_2, piperidino, morpholino

As noted by the authors of [50, 51], pyrrolo[2,3-*h*]quinolines and particularly 2-ethyl-3H-pyrrolo[2,3-*h*]-quinoline exhibit higher reactivity in the Mannich reaction.

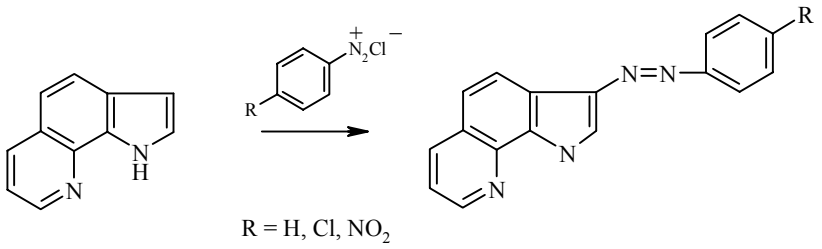


R = NMe_2, NEt_2, NBu_2, piperidino, morpholino; R^2 = H, Me, Et

2.1.2. The Vilsmeier Reaction. The respective formyl-substituted pyrroloquinolines were isolated with good yields by heating 1H-pyrrolo[2,3-*f*]quinoline, 3H-pyrrolo[3,2-*f*]quinoline, and 1H-pyrrolo[3,2-*h*]quinoline with the Vilsmeier reagent [8, 50].

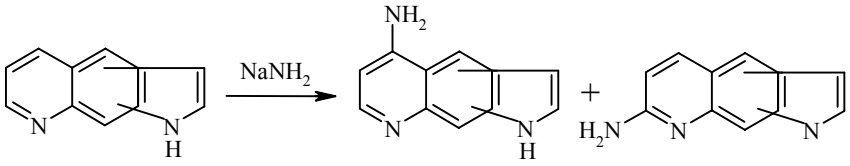


2.1.3. The Azo Coupling Reaction. Azo coupling is a process involving weak electrophiles. Substitution of the β-H of the pyrrole ring with diazonium salts is therefore only realized in the case of a reactive 1H-pyrrolo[3,2-*h*]quinoline [8].



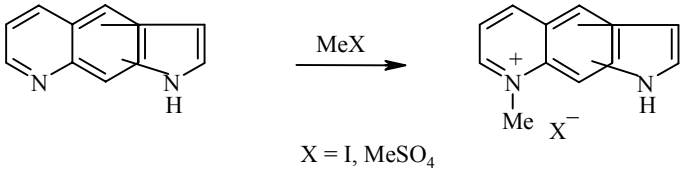
The authors explained the inability of 1H-pyrrolo[2,3-*h*]quinoline to enter into azo coupling by lower nucleophilicity and also by steric factors.

2.2.1. Nucleophilic Substitution Reactions. Amination has been investigated for all the unsubstituted pyrroloquinolines with angular fusion of the rings of types **1**, **4**, **5**, and **6**.

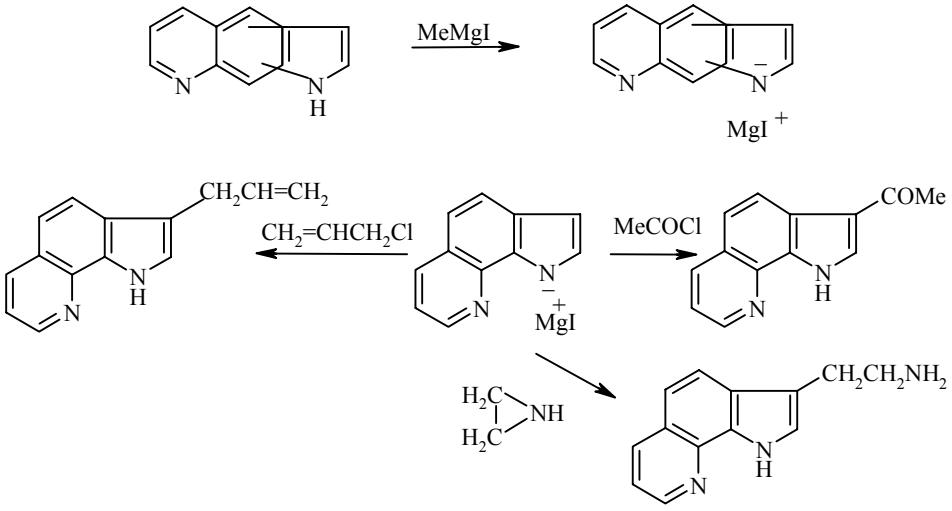


Here it was established that under the conditions of the Chichibabin reaction the amino group enters the pyridine ring with the formation of a mixture of α- and γ-amino-substituted pyrroloquinolines in an approximately equal ratio [8].

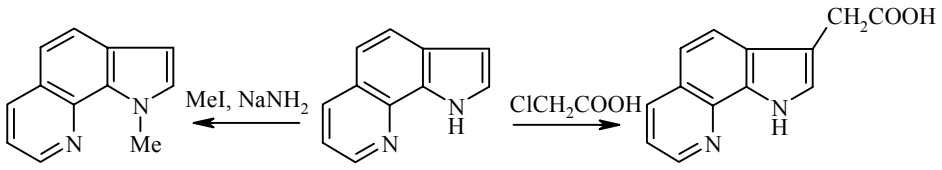
2.3.1. Other Reactions. In reaction with methyl iodide and dimethyl sulfate pyrroloquinolines, like quinolines, are converted into methyl quaternary compounds [5, 8, 51].



Like indoles, with methylmagnesium iodide pyrroloquinolines give the corresponding Grignard reagents, which in the case of pyrrolo[3,2-*h*]quinoline are alkylated at position 3 [51].



In an alkaline medium at increased pressure 1H-pyrrolo[3,2-*h*]quinolines react with monochloroacetic acid to form 1H-pyrrolo[3,2-*h*]quinoline-3-acetic acid, and with methyl iodide in the presence of sodium amide in liquid ammonia they are methylated at the nitrogen of the pyrrole ring [51].



In the case of linear pyrrolo[2,3-*g*]quinolines, as stated above (section 1.2.1), the introduction of a methyl group at the pyrrole nitrogen atom is readily achieved by the action of dimethyl sulfate in the presence of sodium hydroxide in acetone.

From the information presented in this review it is seen that there is a whole series of methods for the express synthesis of pyrroloquinolines with specific fusion of the rings. This not only extends significantly the possibilities of the search for biologically active substances among compounds of this type but also makes it possible to examine the relation between structure and activity. Moreover, the range of synthesized models can be widened significantly by functionalization of the unsubstituted pyrroloquinolines.

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