CLOSURE OF THE PYRIDINE RING IN THE COMBES QUINOLINE SYNTHESIS (Review)

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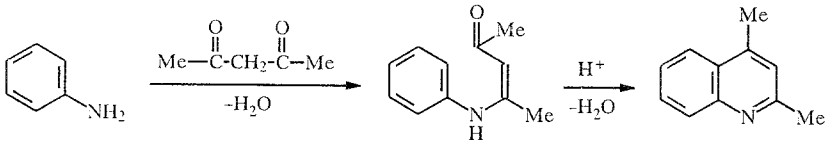
Closure of the pyridine ring in the Combes quinoline synthesis occurs by a type of intramolecular electrophilic substitution. With two free ortho positions the direction of ring formation depends both on the initial electrophilic attack, i.e., the nucleophilicity of the ortho carbon atom, and on the possibility of stabilizing the intermediate complex. The steric requirements of substituents both in the enaminoketone chain and in the position ortho to the point of attack exert a significant effect on the direction of ring closure. The steric factor is decisive when forming condensed angular quinoline structures.

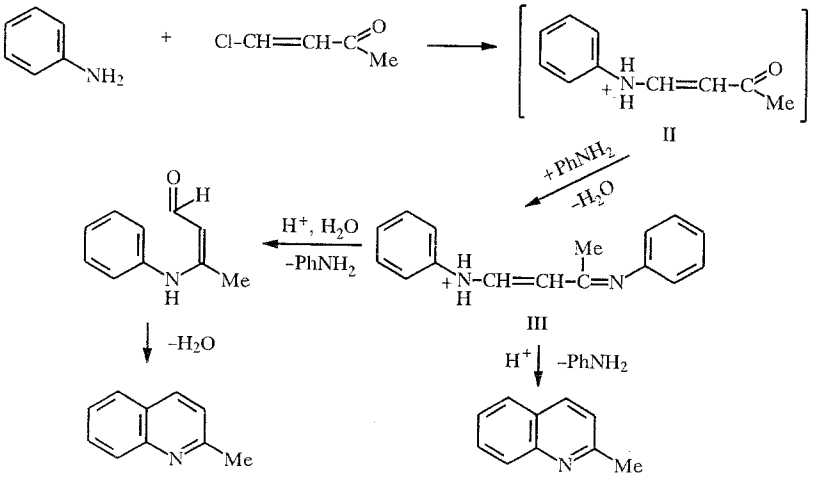
Many syntheses leading to the formation of the quinoline system are known at present, but the majority of them lead to closure of the pyridine ring from benzene derivatives [1]. The most interesting syntheses are those in which aromatic amines serve as starting materials. The widely known reactions of Skraup [2], Döbner—Miller [3-5], Combes [6, 7], Conrad—Limpach [8-10], etc., belong to this group. Closure of the pyridine ring onto the carbon atom in the ortho position to the amino group is general for forming quinolines of this type. The problem of the direction of cyclization arises for unsymmetrical structures. The direction of cyclization in the Combes reaction will be considered in the present review, mainly for condensed amines (amino group on a benzene ring), since this problem is scarcely touched upon in the known monographs [11].

The Combes reaction consists of the condensation of aromatic amines with 1,3-diketo compounds. It proceeds initially with the formation of enamines like (I), the cyclization of which with acidic reagents leads to a quinoline.



I

The condensation of arylamines with β-chlorovinyl ketones or chlorovinyl aldehydes seemed as though it must lead to enamines like (I) and so is considered as a variant of the Combes synthesis. However, it has been proposed [12-14] that the



II

III

*Deceased.

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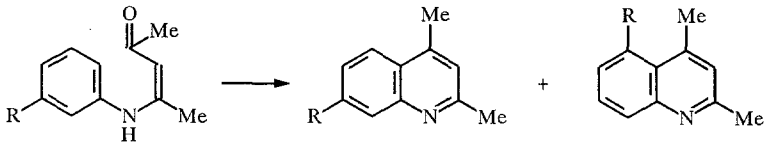
enamine salt (II) formed initially reacts directly with a further molecule of amine giving the enaminoimine (III) which is converted into a quinoline derivative [there is no reliable proof in the literature of the formation of salts like (II)].

Since this cyclization is more reminiscent of the Skraup and Döbner—Miller reactions [15], it will not be considered here.

ORIENTATION DURING RING CLOSURE OF SUBSTITUTED ANILINES

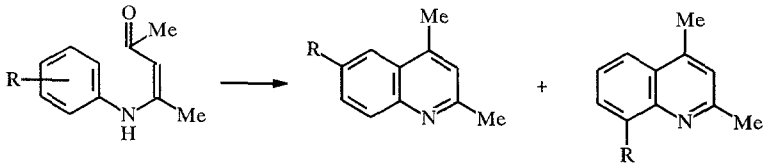
The direction of cyclization for substituted anilines with two free ortho positions depends on the character and position of the substituent in the nucleus. There are data indicating that cyclization occurs more readily as the nucleophilicity of the ortho positions becomes greater [16-18]. The presence of a strong donating group or a halogen in the meta position to nitrogen (i.e., ortho or para to the point of cyclization) facilitates the process to a significant extent [9].



R=Me, OMe, NH_2, OH, Hal

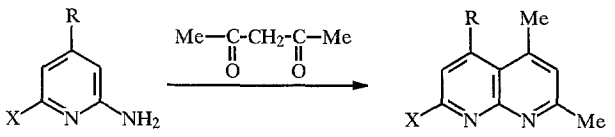
The predominant formation of one particular isomer depends on the steric requirements of the substituent R and on the structure of the initial 1,3-diketo compound [16, 17, 20].

Alkyl substituents activate ring formation far less if they are located in the meta position to the point of attack [19]. Such donor groups as OH, OMe, or NH_2 in the same position practically block cyclization although they must increase the overall electron density at any point of the aromatic nucleus [16, 17, 21]. Halogen at the same position has a similar effect (see below for the reaction mechanism).



R=2-, 4-OMe, Hal; 4-NH_2, OH

No examples of the Combes reaction for aromatic amines having electron-accepting substituents are known. β-Aminopyridine also does not give a cyclization product [22], although the corresponding naphthyridines are obtained from 2,6-diamino- and 2-amino-6-methylpyridines [23, 24].

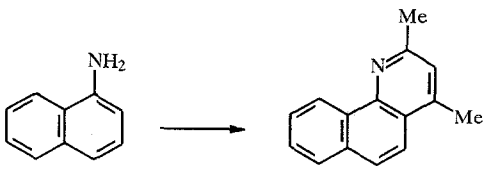


X=NH_2, R=H; X=H, R=Me

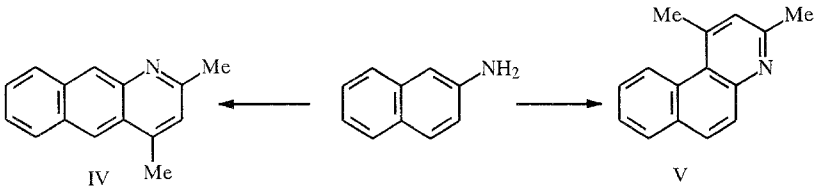
The reaction also proceeds successfully for anilines with two donating groups although in the case of two methoxyl groups it is necessary that one of them is in the position meta to the nitrogen atom [17, 25].

DIRECTION OF RING FORMATION IN CONDENSED STRUCTURES

Cyclization occurs unambiguously at the β position for 1-naphthylamines [20, 26].



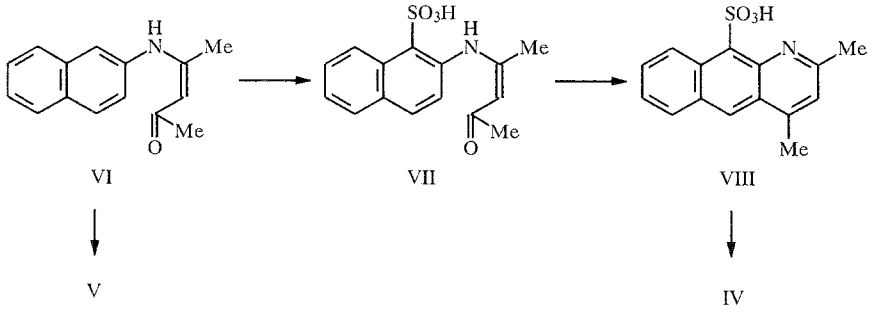
2-Naphthylamine may give both angular and linear benzoquinolines but the formation of the angular structure (V) is preferred.



Even at the end of the last century Markwald [27] correlated many experimental data and deduced the empirical rule that the Skraup reaction occurs at the ends of one double bond [in naphthalene the (α—β) double bonds are assumed to be fixed] and in the Combes reaction at the ends of two different double bonds. Although this rule is observed in the majority of cases, it is not an explanation. Fris [28, 29] attempted to explain the predominant formation of angular structures in a series of carbocycles from the point of view of "napthoid" and "benzoid" systems and the energy advantage of the latter. In the opinion of the author the "benzoid" structure of phenanthrene is more advantageous than the "naphthoid" of anthracene. In fact, the resonance energy of phenanthrene is greater than that of anthracene (99 against 86 kcal/mole). Consequently, the formation of a third ring from naphthalene occurs preferably to generate the "benzoid" system of phenanthrene. The energy advantage of angular structures may be judged from the heat of combustion. The heat of combustion of a naphthotriazole of angular structure is 3.4 kcal/mole less than that of the linear isomer [28].

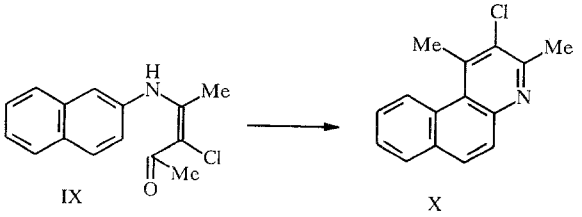
Huisgen [30] has published similar considerations on ring formation which explain the formation of angular systems from the point of view of resonance stabilization of the final structures. He cites and considers many examples of angular ring formation, regardless of the mechanism, as a result of an energy gain. Consideration of the process in this way does not correspond with every combination of known factors.

Even for the classical model of β-naphthylamine the direction of cyclization proved to be ambiguous. Thus the enaminoketone (VI) obtained from β-naphthylamine and acetylacetone is converted in good yield by concentrated sulfuric acid predominantly into the benzoquinoline (IV) of linear structure [31, 32], although the angular isomer (V) is also isolated in small amounts in some cases [20, 31]. Possibly the breaking of the rule here is linked with the competing but reversible sulfonation of the α position of the naphthalene nucleus since the cyclization products were obtained as sulfonic acids which were then converted further into free bases. However, in no case was the structure of the sulfonic acid proved (the position of the sulfonic acid group was not established). It is also not known whether sulfonation precedes cyclization or the reverse.



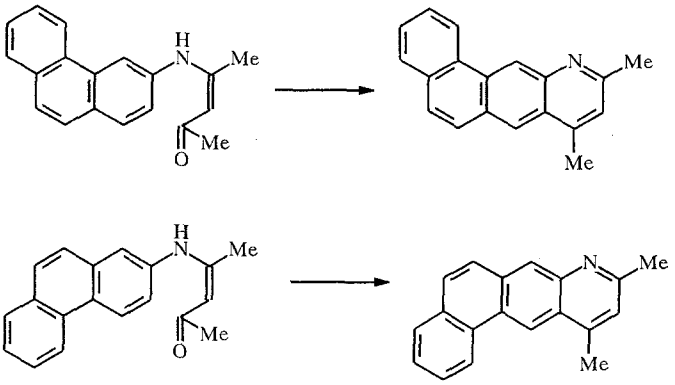
The comparative behavior of structures like the initial and final in electrophilic substitution reactions suggests that the enaminoketone is first sulfonated and the molecule then cyclizes with the formation of a linear derivative.

The formation of small quantities of the angular isomer may be explained by the cyclization of the unsulfonated molecules which competes to some extent with sulfonation. On reducing the concentration of sulfuric acid its sulfonating ability is reduced and correspondingly the cyclization reaction begins to predominate over sulfonation. In fact the product of condensing β-naphthylamine with chloroacetone (IX) in 90% sulfuric acid is cyclized into the benzoquinoline (X) with an angular ring junction [33].



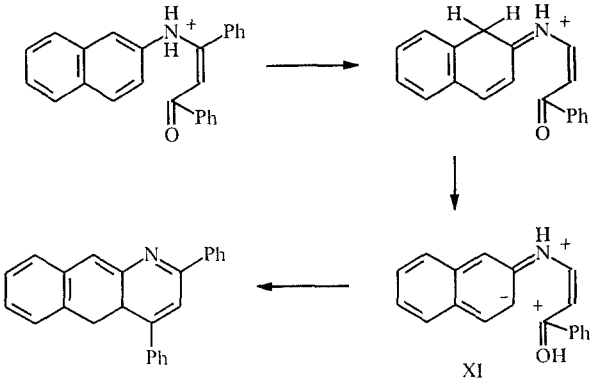
Sulfonation may block cyclization onto the α-carbon atom of a naphthalene ring but the introduction of a sulfonic acid group into a benzene ring must deactivate it toward electrophilic attack at any position. The analogous reaction in hydrogen

fluoride, when such substitution cannot occur, leads exclusively to the linear benzoquinoline (IV). Under the same conditions 2- and 3-aminophenanthrenes similarly give linear cyclization products [34].



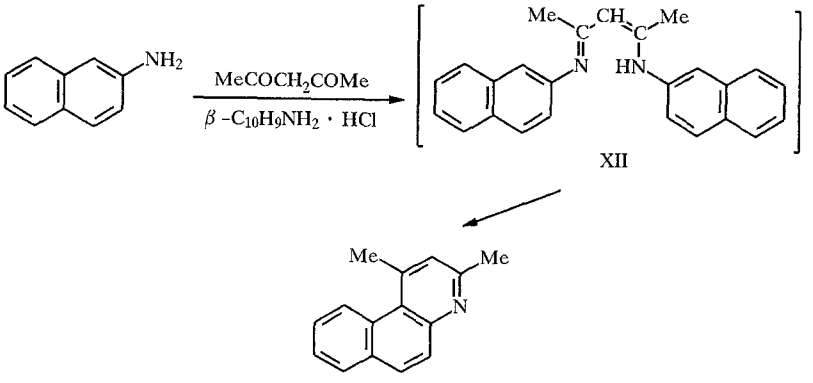
Also unexpected was the observation that only the angular benzoquinoline (V) [34] was obtained from β-naphthylamine when using $ZnCl_2$ as cyclizing agent and carrying out the cyclization in alcohol (method of Petrov [35]).

The data given above indicate that by changing the acidic agent the structure and stabilization of the transition state is changed, i.e., the actual reaction mechanism is changed, which in its turn causes a change in the direction of ring formation. According to Huisgen [36], the Combes reaction with β-naphthylamines in strongly acidic media is not a normal electrophilic substitution but goes through the step of the bis-cation (XI).



XI

The presence of a charge on the nitrogen atom leads to partial dearomatization and a corresponding deactivation of the α position which in its turn hinders angular cyclization. If a Lewis acid ($ZnCl_2$) is taken as cyclizing agent then the usual electrophilic attack at the more reactive α position occurs with the formation of the angular isomer. According to Johnson [34] the reaction in this case proceeds through the intermediate formation of the β-enaminoimines (XII) and therefore complies with other rules.

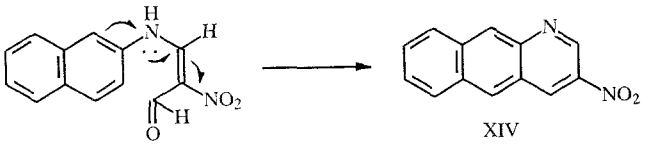


XII

Johnson explains the preference of derivatives of β-naphthylamine to cyclize at either $C_{(1)}$ or $C_{(3)}$ by the difference in the extent of deactivation of these atoms. The more reactive position 1 is correspondingly more readily deactivated toward electrophilic attack than position 3 when an electron-accepting group is located on the amino group or when the nitrogen atom is itself transformed from an sp^2- to an sp^3-hybridized form by protonation and its p-pair of electrons is bound. Although these considerations are only qualitative they correspond to several experimental facts. For example, on condensing β-naphthylamine

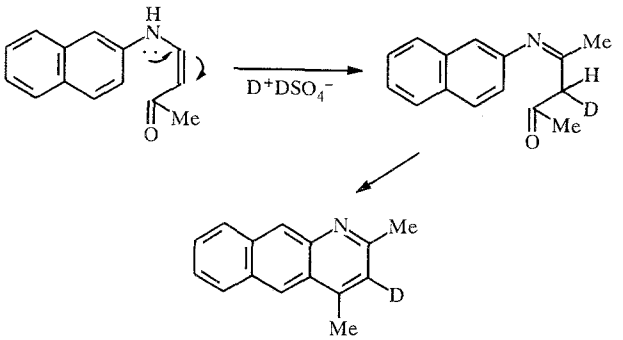
with nitromalonic dialdehyde the resulting enamine (XIII) has the structure of a formamide vinylog, the basicity of which is further enhanced by the nitro group, also located at the vinyl position. If it is accepted that protonation (at the nitro group, naturally) causes an even greater shift of electrons from the $C_{(1)}$ atom of the naphthalene nucleus then the appreciable deactivation of this atom can be understood.

The exclusive formation of the linear isomer (XIV) in the complete absence of steric hindrance may be explained in this way [37].

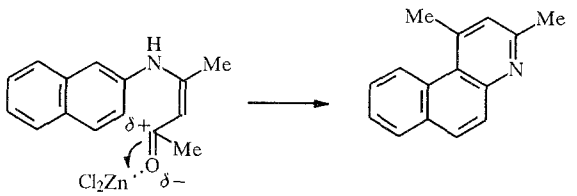


XIII XIV

The ideas of Huisgen regarding the mechanism of linear cyclization proved to be imprecise for another reason too. It was made clear that protonation occurs not at the nitrogen atom but at the carbon atom of the enaminoketone group [38], although following this the nitrogen atom also acquires the ammonium form which does not remove the possibility of blocking the α position.



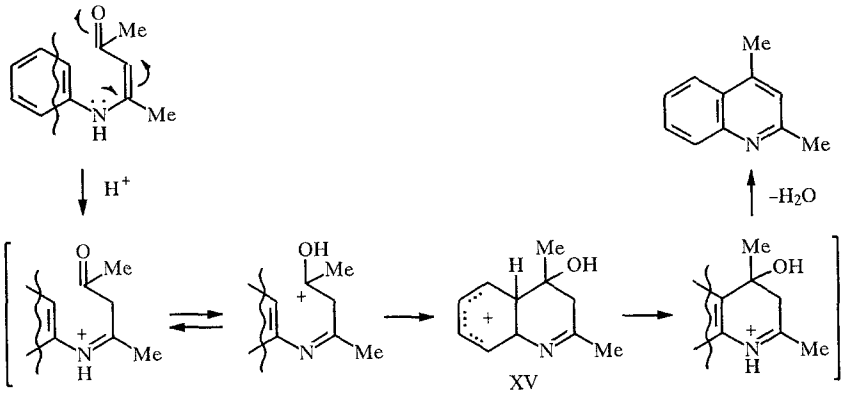
The usual electrophilic attack probably occurs on using zinc chloride as cyclizing agent. An anil in the form of an enaminoketone forms a complex with the catalyst at the oxygen of the carbonyl group. The activated carbonyl carbon atom attacks the most reactive α position electrophilically.



MECHANISM OF THE COMBES REACTION

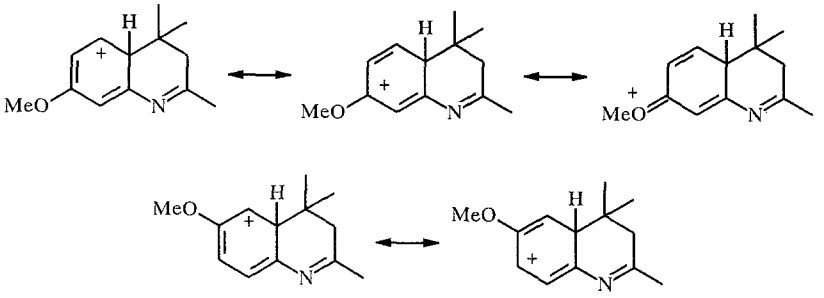
It is agreed that the hypotheses regarding linear and angular cyclization are qualitative. All considerations are based on the different nucleophilicities of the ortho positions. However, it is impossible to disregard the transition state, the stabilization of which is decisive in the formation of quinolines for several aniline models.

By varying the position of electron-donating substituents and halogens investigators have established that the contributions of the substituents toward ring formation are comparable with those in a usual electrophilic attack [39, 40].

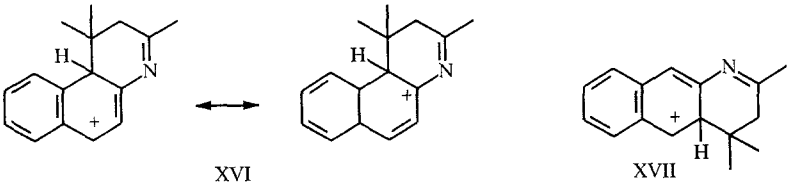


XV

The inability of anilines with methoxy, hydroxy, and amino groups in the position meta to the point of attack to give quinolines under the conditions of the Combes reaction is probably determined by two factors. One of these is the possibility of forming oxonium and ammonium salts which hinder electrophilic attack. In addition, the possibility of cyclodehydration is determined not only by the primary attack but also by the energy advantage of the transition cation (XV). Substituents in the positions para and ortho to the point of attack assist the stabilization of the ion (XV) most of all. Substituents in other positions possessing a positive inductive effect are weaker in this respect. Groups with a +M and +I effect in the position meta to the point of attack are not able to stabilize this ion. Naturally halogens in this position will destabilize the intermediate ion.

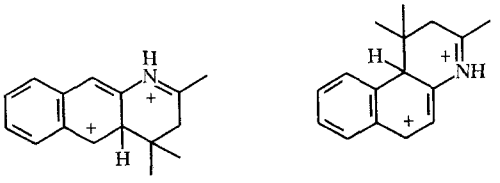


In the case of naphthylamines in weakly acidic medium or in the presence of $ZnCl_2$, the activated carbonyl attacks the most nucleophilic α position with the formation of an angular isomer. These conditions, which assume the nitrogen to be unprotonated, also correspond to higher stabilization of the transition state for attack leading to the formation of the angular isomer (XVI) than for attack with the formation of the linear isomer (XVII).

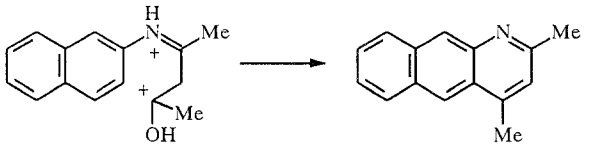


XVI XVII

On protonating the nitrogen atom (sulfuric acid medium) the advantages of stabilizing the transition state for the angular isomer disappear and the primary ring closure process becomes decisive.



In this case it is proposed that the enaminoketone is cyclized in the doubly protonated form (XVIII) [19], i.e., the nitrogen atom is positively charged; consequently deactivation of the α position is assisted and the electrophilic attack occurs at the β position, which is less subject to deactivation.



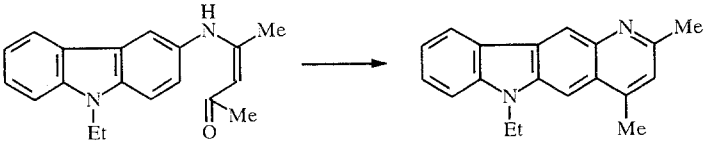
XVIII

It must be emphasized that β-naphthylamine does not usually give α-substituted compounds in various electrophilic substitution reactions [41]. In addition, several other factors may influence the direction of cyclization. Steric hindrance during ring closure is one of them.

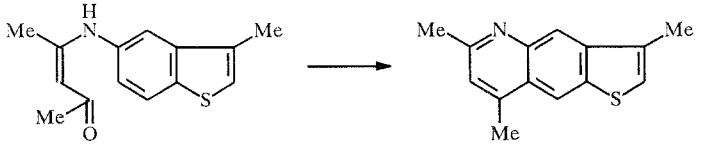
STERIC EFFECTS ON CYCLIZATION

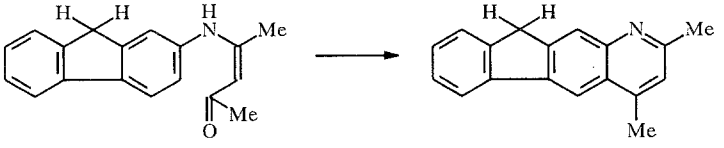
As already indicated, the preferential formation of isomeric quinolines from aniline compounds depends on the spatial requirements of the substituent in the benzene ring and on the structure of the initial 1,3-dicarbonyl compound.

A similar phenomenon is also observed for condensed amines. For example, it is difficult to explain why on using HF as cyclizing agent the cyclization of β-naphthylamine with acetylacetone is exclusively the formation of the linear isomer. It is also completely possible that under mild conditions (room temperature) steric effects emerge which hinder the formation of the angular structure. In several cases this hindrance is not overcome by heating. It has been reported that the enamine of aminocarbazole is converted on heating in polyphosphoric acid only into the linear pyridocarbazole [42].

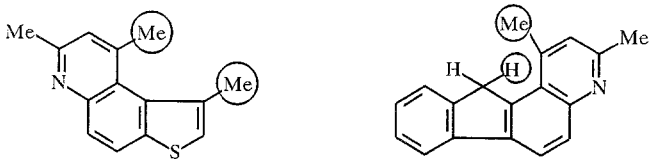


Under the same conditions aminothiophen and aminofluorene similarly give a thiophenoquinoline and a pyridofluorene of linear structure, respectively [21].



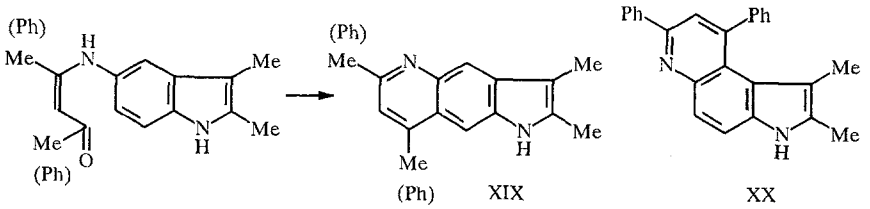


In angular systems a partial overlap of peri substituents most probably occurs if they are present.



In reality the formation of these systems is linked with certain difficulties.

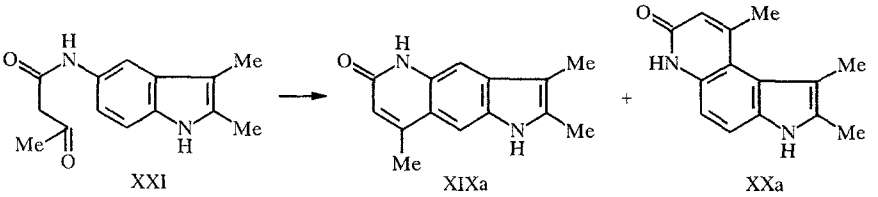
The Combes heterocyclization of 5- and 6-aminoindoles has been studied most from this aspect. The enaminoketones obtained from 2,3-dimethyl-5-aminoindole are converted in acidic medium into pyrroloquinolines with linear ring junctions only [43, 44].



XIX XX

The angular isomer (XX) is formed in small yield from the appropriate enaminoketone if the reaction is conducted in Dowtherm at 250°C.

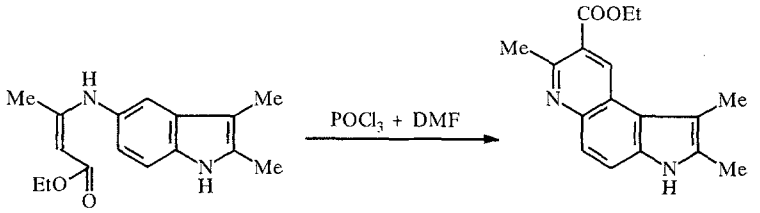
The amide (XXI) behaves in a different way in acidic medium and on boiling in trifluoroacetic acid forms the two isomeric pyrroloquinolines (XIXa) and (XXa) [45].



XXI XIXa XXa

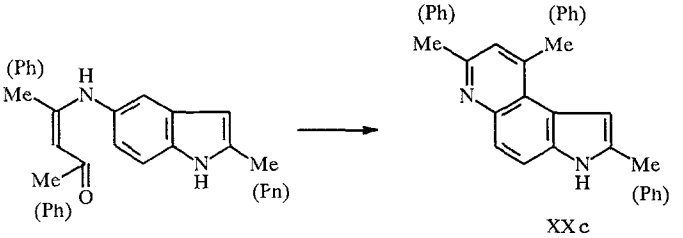
The ratio of linear and angular isomers was 2.5:1. The formation of the (XXa) system with two methyl groups in peri positions is also difficult although less than for (XX).

Predominant formation of the angular pyrroloquinoline occurs on cyclization of the ethyl ester of β-(2,3-dimethylindol-5-yl)aminocrotonic acid under Vilsmeier reaction conditions [46].



XX b

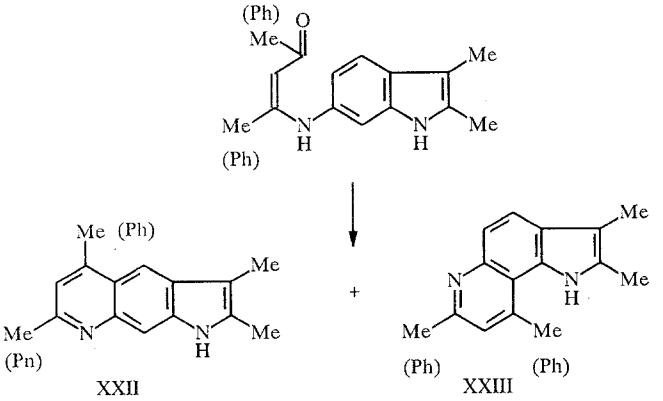
The formation of the pyridine ring similarly goes angular under the action of acids on the enaminoketones of 2-methyl- and 2-phenyl-5-aminoindoles [47].



XX c

The angular structures (XXa, b, c) are more favored than (XX), which in case a is probably linked with the possibility of disturbing coplanarity in the quinolone structures and in the case of b and c with a lessening of the peri interactions.

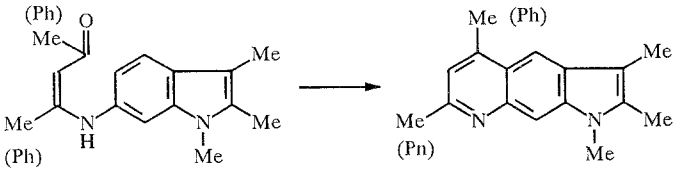
Pyrroloquinolines of angular structure are also formed together with linear structures on cyclization of the enaminoketones of 2,3-dimethyl-6-aminoindole [38].



XXII XXIII

The ratio of isomers (XXII) and (XXIII) varied from 4:1 to 2:1 depending on the substituents.

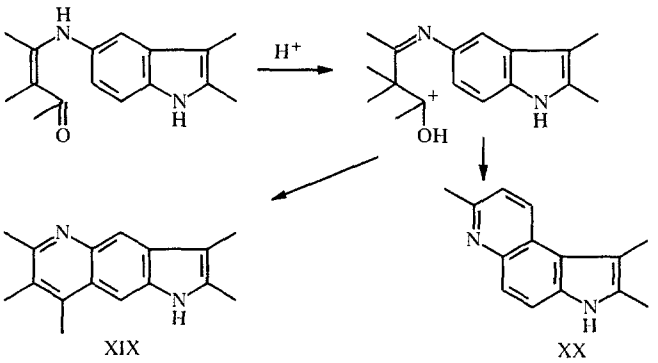
Heterocyclization of 1,2,3-trimethyl-6-aminoindole in the Combes reaction was effected preferentially with the formation of only linear pyrroloquinolines due to the strengthening of the effect of the peri substituents in structures of the type of (XXIII) following the introduction of an N—CH_3 group.



The rules given above were also observed on cyclization of the enaminoaldehydes of 5 and 6-aminoindoles [48].

It must be recorded that enamines of the indole series are cyclized more readily than enamines of anilines and naphthylamines on Combes cyclodehydration. This is probably linked with the effect of the pyrrole fragment which not only enhances the overall nucleophilicity of the benzene ring but also aids delocalization of the cation formed as an intermediate. Substituents in the pyrrole ring also affect the general course of the process. Thus 4-(2,3-dimethylindol-5-yl)aminopent-3-en-2-one is cyclized even at room temperature in trifluoroacetic acid while the same enaminoketone of 2-methyl-5-aminoindole requires heat. This is probably linked with the basicity of the compounds and with processes preceding cyclization. As in the case of anilines, the deactivating influence of a methoxyl group in the meta position to the point of attack (compared to a methyl group in the same position) is generally apparent on cyclization. For example, 4-(2,3-dimethyl-6-methoxyindol-5-yl)aminopent-3-en-2-one is cyclized with far more difficulty than 4-(2,3,6-trimethylindol-5-yl)aminopent-3-en-2-one. All these facts support the hypothesis that Combes ring formation in aminoindoles, as for several amines and naphthylamines, has the character of an intramolecular electrophilic attack.

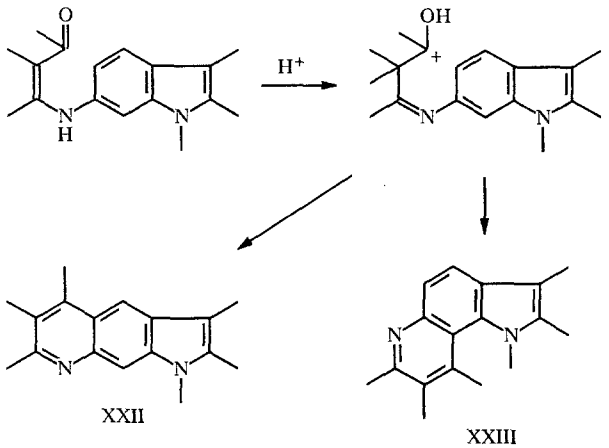
The initial attack must be decisive for the direction of cyclization since the transition state both for angular and for linear isomers seems to be the same. In reality the orientation of ring formation corresponds with the known rules of electrophilic substitution in the benzene ring of indoles. It is known that indoles with electrophilic substituents such as 5-hydroxy(methoxy)indoles are nitrated at position 6 with initial protonation of the pyrrole ring [49]. The aminomethylation of the same models in weakly acidic or neutral media [50] occurs at position 4. For indolylenaminoketones the side chain and not the pyrrole ring is protonated. This is shown by the presence of a sharp singlet for the 3-CH_3 group in the spectra of compounds taken in trifluoroacetic acid and in the case of compounds with a free β position the signal for the β-methylene group is absent. Attack by the carbonyl group is directed preferentially to the $C_{(4)}$ carbon atom with the formation of compounds of the type (XX).



XIX XX

However, the marked ortho effect of a substituent located at $C_{(3)}$ and also of a substituent on the carbonyl carbon atom hinder such a cyclization significantly and contribute to the predominant or exclusive formation of isomer (XIX) by closure at position 6.

Similar rules are observed for derivatives of 6-aminoindole, i.e., preferential cyclization involving $C_{(7)}$ (compare aminomethylation of 6-hydroxyindoles at position 7 [50] and nitration at position 5 for the same models). The strong effect of steric factors when the pyrrole nitrogen is substituted leads to the formation only of the linear isomer [like (XXII)] by cyclization at $C_{(5)}$.



XXII XXIII

The nature of the acidic reagent has no effect on the direction of cyclization.

An increase in the acidity of the medium, i.e., the use of concentrated sulfuric acid, in the expectation of protonating the pyrrole ring and changing the direction of cyclization did not give the anticipated results. Enamines protonated in the pyrrole ring generally do not cyclize.

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