MOLECULAR DESIGN OF HETEROCYCLES.*

2.† "STRUCTURE—SYNTHESIS" MAGIC RULE IN THE SYNTHESIS OF SIX-MEMBERED HETEROAROMATIC RINGS (REVIEW)

E. V. Babaev

This review deals with the frequency of occurrence of literature references to various types of reagents used in syntheses of the pyridine ring and a number of its heterocyclic analogs (classed as heteroalternant systems). It is shown that the nature of the terminal groups in the reagents, the parity of the chain of atoms between the terminal groups, and the position of the heteroatom are interrelated and are subject to "magic" rules (principles of alternation and heteroalternation). These rules can be interpreted within the frame of a new concept, "structure—synthesis," based on preservation of the electrophilic—nucleophilic nature of the reagents in the heterolytic formation of even-membered rings. A complete classification of pyridine-ring syntheses that are allowed by the rules provides a means for predicting the polar type of reagents for the last unknown synthesis of pyridines of the type CNCCC + C.

The available textbooks [2-8] and a series of monographs [9-13] on the chemistry of heterocycles all contain a certain flaw of logic: There is no interlinking of sections dealing with the synthesis of heterocycles and sections dealing with their structure and reactivity. Indeed, the description of the method of synthesis generally precedes or concludes sections on the structure and reactions of heterocyclic nuclei, without any interlinking of the two areas. Over the course of many years, as a result, it has become traditional to regard synthesis of heterocycles as merely a special case — or extension — of the chemistry of acyclic or aromatic systems.

In this review, an attempt will be made to eliminate this defect of logic. As we will attempt to show, the methods of synthesis of a large class of six-membered heteroaromatic systems — pyridine and a number of its analogs — fit into a simple scheme of "magic rules" that are organically related to the electronic structure and reactivity of the heterocycles themselves. Thus, for a significant class of heterocycles, an avenue has been opened for the introduction of direct correlations of the "structure—synthesis" type — correlations that are useful not only in classifying methods of synthesis that are already known, but also in predicting basically new methods. The idea for the present work came to the author while teaching a course in heterocyclic chemistry at the Chemistry Department of Moscow University in 1989-1993, as a direct result of attempting to compress the course to the greatest possible degree by establishing logical connections between the different parts of the course.

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*This article is dedicated to Prof. A. R. Katritsky on the occasion of his 65th birthday.
†See [1] for Communication 1.

Scheme 1. Various methods for pyridine ring assembly, corresponding to one- and two-component syntheses. The numbers denote the numbers of examples found in the literature (see text).

6 + 0	5 + 1	3 + 3	4 + 2
110	129	286	40
5	1	3	31
15	7	0	10

1. CLASSICAL SCHEMES FOR ASSEMBLY OF HETEROCYCLES: ADVANTAGES AND DISADVANTAGES

The assembly of the skeleton of one heterocyclic nucleus or another from noncyclic structures can be accomplished by various methods; and one of the most graphic methods of demonstrating the diversity of the methods that may be used for such assembly is the dismemberment of the skeleton of the heterocycle into fragments; on paper, this is done by simply removing (or marking by a dotted line) the skeletal bonds that arise during the course of the reaction. As an example of such dismemberment of the original structure into fragments, consider Scheme 1, which contains possible one- and two-component syntheses of the pyridine ring. By now it is difficult to establish the authorship of this construction, which is intuitively obvious; as far back as the 1950s, the use of such "diagrams" or "schemes of synthesis"* was extremely popular [11, 12]. Today it is simply impossible to review the methods of synthesis of a specific heterocycle without such schemes (see for example [9, 10]); and in the classic handbook [14], these diagrams are numbered methodically and used for a comprehensive classification of the synthesis of diverse benzannelated systems.

All of the advantages of describing heterocyclic syntheses by such schemes are obvious at first glance: Knowing the reaction mechanism and the substances that are used, it is not at all difficult to draw the corresponding diagram for the cyclization of any alicyclic fragment or fragments, and hence to establish the structural kinship between different syntheses of a given heterocycle, or even the syntheses of different heterocycles. (We had shown previously how to enrich such diagrams in order to account for still other heterocyclic predecessors [15-17]). It is also relatively easy to see the natural relation of such schemes to the component requirements of the synthesis, i.e., the number of individual fragments that are required to construct the cyclic skeleton. Finally, the combinatorial character of such schemes is obvious: It is not at all difficult to sort out, either manually or by a programmable microcalculator, all conceivable schemes for the synthesis of simple heterocycles.

What can such schemes still offer the chemist? Theoretical schemes can be compared with real syntheses; and for each assembly scheme, the number of examples reported in the literature can be compared (as was done in Scheme 1). Thereby we can find which of the assembly methods are still unknown (see for example the assembly method denoted by bold lines in Scheme 1), and an attempt can be made to "devise" likely reagents that might be suitable for use in an unknown type of synthesis. A discussion of such attempts is given in the review [17].

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*In the following material we will adhere to the term "assembly scheme" or "assembly method" to denote diagrams of the type depicted in Scheme 1. In the English-language literature, the term "disconnection scheme" is used.

Meanwhile, an obvious disadvantage of these diagrams is that they do not offer any information whatever on the chemistry involved in the formation of the skeletal bond. In fact, a single scheme may describe processes that are basically different. For example, in the synthesis of quinolines by the Camps reaction (1) or by the Madelung reaction (2) [18], it would appear that exactly the same skeletal bond $C_{(3)}$—$C_{(4)}$ is formed, i.e., it would appear that the schemes of the syntheses should be expressed by a common diagram I:

R = Alk, X = H   R = H, X = OH   I
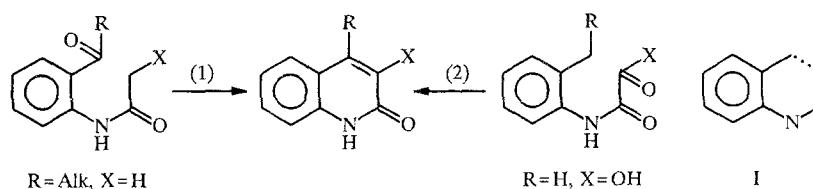
However, it is obvious to any organic chemist that in these intramolecular condensations, the carbonyl and methylene components (i.e., the electrophilic and nucleophilic centers) have simply changed places relative to the heteroatom (or the benzene ring).

As a result, the heuristic and classifying function of assembly schemes comes down to a description of the number and mutual positions of the skeletal bonds of the final ring that are formed; or, equivalently, these schemes may function to account for the size of the chain of the original reactants and the position of the heteroatom in the chain. Clearly, it is advisable to modify the conventional assembly schemes in some manner, after supplementing them with information on the nature of the reaction centers.

2. HOW TO ACCOUNT FOR THE NATURE OF REACTION CENTERS

In the above example, the indistinguishability of the electrophilic and nucleophilic nature of the centers and their relative positions in the original reactant was responsible for the paradoxial identification of two different reactions by a single assembly scheme. Let us note that in summary reviews of the strategy of synthesis of five- and six-membered heterocycles [9], it has been specifically the nature of the reaction centers in the reagents for heterocyclization that attracted the most attention. Thus, Potts' classification [19] included the concept of bielectrophiles (in particular, 1,1-, 1,2-, and all the way up to a 1,5-bielectrophile) and also the concept of binucleophiles (in particular, 1,2-, 1,3-, and 1,4-binucleophiles). Also, Potts mentioned in passing the importance of a third category of reagents that are simultaneously electrophiles and nucleophiles, but focused primary attention on the "design" of bielectrophiles and binucleophiles by varying the degree of unsaturation (hybridization) of the reaction center.

Analogously, after examining the rich and extremely diverse material on the syntheses of six-membered heterocycles, McKillop and Boulton [20] came to the conclusion that in this field of synthesis, the concept of electrophilicity and nucleophilicity of the centers (readily identifiable in the original reagents) plays an important role: In many cases, electrophilic and nucleophilic centers "alternate along the ring."* Unfortunately, these authors never formulated clearly the exact content of the "alternation rule," rather limiting themselves to citing examples of syntheses proceeding through one assembly scheme or another, in particular those with the participation of an electrophilic heteroatom.

The views that we have considered thus far in regard to the importance of the electronic nature of the reagents' reaction centers in describing heterocyclization were developed further, for example, in the work of Katritsky [21] and Jorgensen [22]. Nonetheless, during the past decade, we have never been successful in finding any examples of the heuristic utilization of this concept in the design of heterocyclic structures or reactions. In the following sections we will advance our own generalized, graphic, and readily formalized interpretation of approaches that had been proposed previously.

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*In the original [20], the electrophilic and nucleophilic centers are said to "tend to alternate around the ring."

Scheme 2. Classification of reagents used in synthesis of heterocycles according to EN type (examples)

1,K:	1,1	1,2	1,3	1,4	1,5

EN type

(NN) $\dot{N}H_3$ $\dot{N}H_2\dot{O}H$ $\dot{N}H_2CH=\dot{C}HCOR$ $\dot{N}H_2CON\dot{H}NH_2$ $\dot{N}H_2COCH_2CO\dot{C}H_2CO_2R$

(EE) $\ddot{C}H(OR)_3$ $R\dot{C}OCOR$ $\dot{C}H_2=CHCOR$ $R\dot{C}O(CH_2)_2\dot{C}OR$ $HO\dot{C}H=CHCH=CH\dot{C}HO$

(EN) $Cl\dot{C}H_2CN$ $R\dot{C}H_2\dot{C}OAr$ $R\dot{C}OCH_2\dot{N}H_2$ $R\dot{N}HCH=CH\dot{C}OR$ $\dot{N}H_2COCH_2NH\dot{C}HO$

Note. A dot above the chemical formulas denotes the nominally localized position of a reaction center.

3. GENERALIZED CLASSIFICATION OF REAGENTS ACCORDING TO EN TYPE

Let us add to the existing classification of 1,K-bielectrophiles and binucleophiles the no less rigorous concept of a 1,K-"ambiphile,"* i.e., a reagent with reaction centers of opposite natures at the ends of the chain from the K-atoms (including these atoms themselves). As a result, the classification of reagents for heterocyclic synthesis acquires the previously lacking harmony and completeness. For simplicity, we will name a reagent with a given chain length and a given nature of the reaction centers as a reagent of a particular EN type. Specific examples of reagents of different EN types are given in Scheme 2.

We should emphasize the naturalness of the concept of a 1,1-ambiphile: Examples of simultaneous combination of electrophilicity and nucleophilicity in one and the same atom are well known — for example, carbenes, electrophilic amines with leaving groups, and, finally, halogen derivatives of CH-acids.

Just as natural is the concept of a 1,1-binucleophile (which for one reason or another was missing in early classification tables [19-22]). Typical 1,1-binucleophiles are water, hydrogen sulfide, and amines or aliphatic nitro compounds, which are often used in heterocyclizations with 1,4- or 1,5-bielectrophiles, forming five- or six-membered hetarenes or a benzene ring [9, 10].

Let us note a few key features of 1,1-binucleophiles:

1) Binucleophilicity is different from "simple" nucleophilicity. Upon incorporation into a ring, a binucleophile must form bonds with two electrophilic neighbors. It is natural that the "mononucleophilic" trimethylamine or the 2-nitropropane anion is incapable of heterocyclization.

2) A binucleophile is capable of forming, with its future neighbors in the ring, either two σ-bonds only, or an additional π-bond. The first case limits the use of many binucleophiles in the synthesis of conjugated rings. Thus, it is difficult to visualize dimethylamine or nitroethane as fragments for the construction of heteroaromatic rings. At the same time, these reagents are used as binucleophiles in the synthesis of saturated rings.

3) The concept of 1,1-binucleophiles can be extended to the case of 1,1-trinucleophiles, in view of the potential capability of a nucleophile to be a bridgehead atom of a polycyclic structure (compare ammonia in the synthesis of Urotropin or the known recyclization of Urotropin under the influence of nitromethane to form nitrotriazaadamantane).

4) Only the simplest hydrides of Group VI (water, hydrogen sulfide, etc.) can act as binucleophiles (compare the syntheses of furans and pyryllium salts). Although examples of heterosystems with three-coordinated oxygen or sulfur are well known (compare S- or O-alkylated cations of thiophene or dibenzofuran [9, 10]), the methods described for their synthesis do not include the participation of 1,1-binucleophilic species.

Let us note, finally, that the EN type of a reagent is a higher level of abstraction than the traditional "synthon." A synthon is often understood to be some class of synthetically equivalent (interchangeable) reagents, for example bromoacetaldehyde and its acetal. In turn, the EN type includes synthons of monotypical functionality — both more highly oxidized and more highly reduced. For example, bromoacetaldehyde, dichloroethane, and glyoxal, which differ in degree of unsaturation, all belong to the single type of 1,2-bielectrophiles.

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*While recognizing that the term is poor (possibly "heterophilicity" or amphotericity [23] would be closer in meaning), we will nonetheless use this term in the following material. The author had cooperated previously in promulgating the term "ambiphilicity" in the specific context of affinity for both types of reaction — electrophilic and nucleophilic [24].

Scheme 3. Criteria for selection of structures and reactions

SYNTHESIS OF PYRIDINES

↓ (Selection of reactions on the basis of types of ring construction)
— Recyclizations
— Cleavage of annelated rings

CYCLIZATIONS

↓ (Selection of reactions according to cyclization mechanism)
— Electrocyclic processes and reactions of cycloaddition
  with unexpressed polarity in reagents
— Radical reactions
— Cyclization with skeletal rearrangements
— Catalytic processes with undetermined mechanism

HETEROLYTIC CYCLIZATIONS

↓ (Selection of reactions according to number of components of synthesis)
— Syntheses with three or more components

ONE- AND TWO-COMPONENT SYNTHESES

↓ (Selection of structures according to type of annelated rings)
— Annelated benzene rings and heterocycles
— Annelated three- and four-membered rings

MONOCYCLES (INCLUDING ANNELATED ALICYCLES)

↓ (Selection of structures according to degree of unsaturation)
— Di, tetra-, and hexahydropyridines

Maximally unsaturated pyridines (including pyridones, etc.)

Final: One- and two-component heterolytic cyclizations of maximally unsaturated pyridines, including those containing annelated alicycles.

We should emphasize the main feature of reagent classification on the basis of EN type: *This classification pertains to the behavior of the particular reagent in a given reaction only.* For example, hydroxylamine is a 1,2-binucleophile in syntheses of isoxazoles, but it will naturally be a 1,1-binucleophile in syntheses of N-oxides of pyridines. Acetone, depending on the reaction, may act as a 1,1-bielectrophile, 1,2-ambiphile, or 1,3-binucleophile. The flexibility of this sort of classification consists specifically of this: The potential *ambiguity* (multiplicity) of modes of reaction of a given molecule is compensated by the *absolutism* of definition of its EN type if the reaction mechanism is known.

4. EN TYPES OF REAGENTS USED IN PYRIDINE RING SYNTHESIS

We will use the classification of reagents on the basis of EN type in analyzing the following problem: Exactly how are reagents distributed by type in the reported syntheses of (let us say) the pyridine ring, which is the most typical representative of six-membered hetarenes. Such a statement of the problem requires extremely precise criteria for the selection of (1) the literature sources that are used, (2) the actual structures that are classed as "pyridines," and (3) the methods of pyridine ring construction.

Selection of Literature Data. Methods of pyridine ring synthesis are covered in extensive chapters in a series of reviews of heterocyclic chemistry [20, 25-28], a number of monographs [29-31], and a series of specialized reviews of pyridine chemistry [32-34]; in recent years, serious attention has also been given to syntheses of nitropyridines [35, 36]. In selecting the data for our review, we have used primarily the most informative sources [32-34], which contain tabulated data on syntheses of specific pyridines all the way up to the 1980s; and we have supplemented this information wherever possible with earlier references and also later references. Our experience in setting up a computer database on syntheses of pyridines is discussed in a separate communication [37].

Selection of Structures and Reactions. At the start, we used rather severe criteria in selecting syntheses of pyridines (see Scheme 3), limiting ourselves to an examination of one- and two-component syntheses of maximally unsaturated pyridines. In this first stage, actually, we selected the most traditional methods of C—C and C—N bond formation in heterocycles, i.e., reactions of intramolecular or intermolecular nucleophilic substitution, addition to an activated multiple bond, and condensation (addition—detachment). In Scheme 3, the initial selection corresponds to motion downward in the direction of the arrows (the horizontal lines correspond to rejected items); in the future, step by step, we propose to eliminate the restrictions that had been introduced, i.e., to move in Scheme 3 in the direction opposite to the arrows.

Typical examples of two-component syntheses of pyridines (taken at random from the database [37]) are shown in Scheme 4. Thereby we illustrate in the first place all of the types corresponding to assemblies from Scheme 1 (there is an example for each case), in the second place the method by which the EN type of the reagent should be determined for a specific synthesis,* and in the third place how to express the EN type graphically. Following the selection principles of Scheme 3, we classed as heterolytic cyclizations only those examples of cycloaddition and electrocyclization in which the influence of the substituents clearly indicated the EN type of the reagent.

For each reaction and structure satisfying the criteria of Scheme 3, we examined the assignment of the reagent to a specific EN type, in much the same manner as for Scheme 4. The total quantity of methods of synthesis that were analyzed is shown in Scheme 1 in the form of numbers corresponding to one method or another of assembling the pyridine skeleton. The frequencies of encountering reagents of the various EN types are listed in Scheme 5.†

5. ALLOWED AND PROHIBITED TYPES OF REAGENTS IN SYNTHESIS
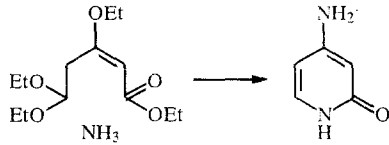# OF PYRIDINE RING. ALTERNATION RULE
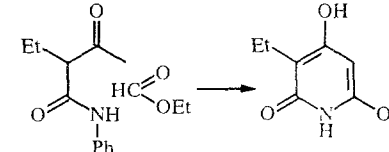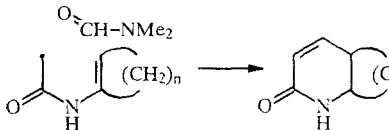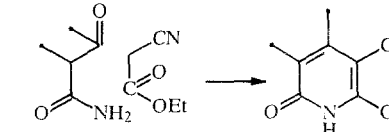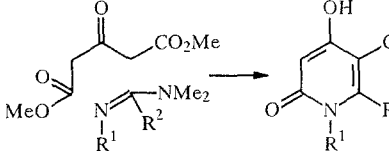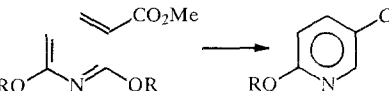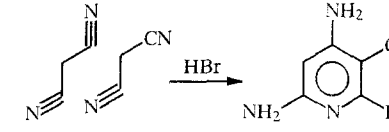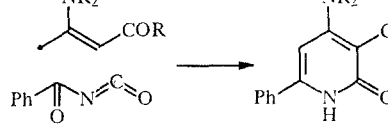
No *a priori* knowledge was assumed with regard to whether one EN type or another dominated in the synthesis of pyridines. Meanwhile, an analysis of the data of Scheme 5 reveals a distinct clustering of reagents of different EN types on the principle of "encountered" or "not encountered at all." Moreover, we can be confident in relating the frequency of encounter of a particular EN type of reagent with the parity of chain length of the reagent and the electronic nature of the terminal groups. For example, reagents with an odd-membered chain usually proved to be either bielectrophiles (EE) or binucleophiles (NN), but never ambiphiles (EN). And indeed, on the one hand, certain bielectrophiles are well known in the synthesis of pyridines: monocarboxylic acid derivatives (1,1-EE), three-carbon fragments of the type of 1,3-dicarbonyl compounds (1,3-EE), and five-membered reagents of the type of glutaconic dialdehyde (1,5-EE). On the other hand, we find typical odd-membered binucleophiles: amines (1,1-NN), enamines (1,3-NN), and certain 1,5-binucleophiles with the nitrogen atom in the middle or at the end of the chain.

In turn, among reagents with an even-membered chain length, we do not encounter any EE or NN types; these even-membered reagents are always ambiphilic species. Characteristic examples of even-membered ambiphiles are methyl ketones, nitriles, and isocyanates containing neighboring centers that are opposite in nature (1,2-EN); the 1,4-ambiphiles that are encountered are usually enamides or enamines of β-dicarbonyl compounds. In order to complete the picture, let us note that even-membered 1,6-reagents, in which the chain is closed heterolytically into a ring, are obviously ambiphilic.

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*In Scheme 4, the nucleophilic and electrophilic centers in the reagent are indicated by solid circles and open circles, respectively.

†If one EN type or another was encountered in more than 20 references, we limited ourselves to counting the references in the reviews [32-34]. If an EN type was encountered only as isolated examples or was not encountered at all, the numbers listed in Schemes 1 and 5 correspond to the total number of references known to the author (a dash indicates that the particular type was not encountered).

Scheme 4. Examples of known two-component syntheses of pyridines, and assignments of reagents to different EN types.

Assembly scheme	Example of reaction	EN type of reagents
		1,5-EE + 1,1-NN
		1,5-NN + 1,1-EE
		1,5-NN + 1,1-EE
		1,4-EN + 1,2-EN
		1,4-EN + 1,2-EN
		1,4-EN + 1,2-EN
		1,3-NN + 1,3-EE
		1,3-NN + 1,3-EE

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Size/type	Bielectrophiles (EE)	Ambiphiles (EN)	Binucleophiles (NN)
1,1	8	—	129
1,2	—	81	—
1,3	289	—	289
1,4	—	81	—
1,5	129	—	8
1,6	—	130	—

For convenience, we will divide reagents for pyridine syntheses into two classes, which we will arbitrarily term "allowed" (encountered) and "prohibited" (not encountered):

— allowed	EE	1,1-	1,3-	1,5-
	EN	1,2-	1,4-	1,6-
	NN	1,1-	1,3-	1,5-
— prohibited	EE	1,2-	1,4-	1,6-
	EN	1,1-	1,3-	1,5-
	NN	1,2-	1,4-	1,6-

Then, the empirical rule that has been obtained can be formulated thus: **In reagents that are "allowed" for the synthesis of pyridines, the parity of the chain is opposite to the equality of the terminal functions.**

Actually, each of the categories (parity and equality) has only two logically permitted values (even—odd and equal—unequal). In the proposed rule, *equality* of the functions at the ends of the chain is related to *parity* in a sort of "inverse proportionality." Specifically: If the chain is *even-membered*, the reaction centers at its ends are *unequal* in their nature (they have opposite "philicities," i.e., the reagent is ambiphilic). On the other hand, an *odd-membered chain* corresponds to *equality* of the terminal functions (uniformity of the reagent, i.e., either bielectrophilicity or binucleophilicity).

We will now give this rule a more graphic interpretation. Let us examine a reagent with a molecule (template) that is linear and rather long, with alternating electrophilic and nucleophilic centers. It is obvious that reagents that are "allowed" for the synthesis of pyridines can be superposed on this template in such a manner that their ends coincide in electrophilicity or nucleophilicity with the corresponding groups in the template. In turn, "prohibited" reagents cannot be superposed on the template while preserving the nature of the reaction centers. In other words, *the nature of the reaction centers at the ends of the molecular chain of reactants that are used for the synthesis of pyridines can be established by truncating the chain with alternating charges.*

We will subsequently call this rule, in two equivalent formulations, the *rule of alternation in reagents* (see [20]).

Let us note that "prohibited" reagents, i.e., odd-membered ambiphiles such as O-hydroxylaminesulfonic acid (1,1-EN) and α-aminoketones (1,3-EN), or even-membered bielectrophiles such as α-haloketones (1,2-EE) and γ-oxocarbonyl compounds (1,4-EE), which are widely used in obtaining five-membered heterocycles, have not yet found any applications as synthons in one- or two-component syntheses of pyridines.

Perhaps one of the clearest examples of the potential use of "prohibited" reagents in synthesis (with implicit observation of the alternation principle) goes back to the work of Krohnke [38] on the methodology of repolarization of the prohibited function in a reagent by masking this function, reaction (3) [39]:
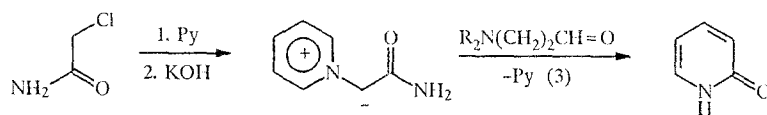
As can be seen, the prohibited 1,2-bielectrophilicity of the original α-haloamide is completely suppressed by transforming it into a pyridinium salt, the stable ylide of which is a typical allowed 1,3-binucleophile. (Prohibited α-haloketones can be involved in the synthesis in a similar manner [38].) However, the masked electrophilicity does not disappear, and it is manifested very specifically: The pyridine that is initially added to the reagent is eliminated in the last stage in the form of a leaving group.

We know of only one two-component reaction (4) [40] that could be interpreted as an exception to the alternation rule. Actually, the anionoid reagent in reaction (4) appears at first glance to be a 1,3-ambiphile (owing to the combination of the electrophilic imine grouping and the nucleophilic carbanion grouping in an odd-membered chain):
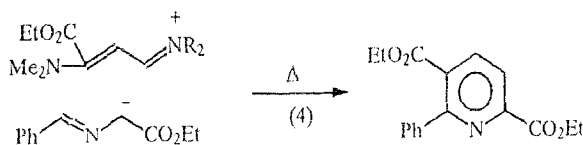
Meanwhile, the explicit conjugation effect in the anion (π-system of the azaallyl type) indicates that this reagent in this particular reaction acts as an ordinary allowed 1,3-binucleophile.

6. HETEROALTERNATION PRINCIPLE

In addition to examining the parity of the chain and the nature of the terminal groups, it is also useful to consider the permissible positions of the nitrogen atom in the skeleton of an undefined "allowed" reagent. (Let us note that Potts, in his classification of bielectrophiles [19], segregated reagents with heteroatoms in the chain in individual subclasses.)

In Scheme 6 we show "allowed" reagents, further divided into different classes depending on the location of the heteroatom; also shown is the frequency with which each class is encountered. As an aid to understanding this diagram (the same as was done in Scheme 4), terminal nucleophilic atoms are denoted by solid circles, terminal electrophilic atoms by open circles. One can easily be convinced of the validity of the following **rule of heteroalternation**:

Reagents that are "allowed" in the synthesis of pyridines contain a heteroatom that either (1) is a nuclear center, (2) is located at an even number of bonds away from a nucleophilic center, or (3) is located at an odd number of bonds away from an electrophilic center.

Now making use of our model of a hypothetical chain with alternating centers and comparing this model to Scheme 6, it is easy to see that the nitrogen atom will most frequently be superposed on those specific sites of the chain where a nucleophilic center would be found:
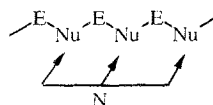
Among two-component syntheses, we know of two examples that are clearly exceptions to the heteroalternation rule (but not to the alternation rule). The first of these is reaction (5), which was used by Stevens [41] in developing a new synthesis of pyridoxine:
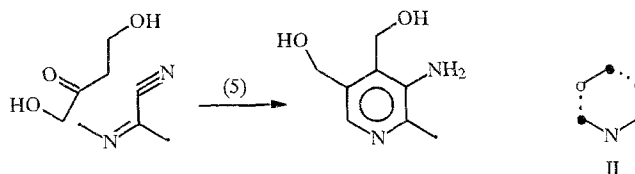
In the corresponding assembly Scheme II, the nitrogen atom is located next to a nucleophilic center, which violates the heteroalternation rule. In this case, the unexpected manifestation of CH acidity of the methyl group is due to a "nonstandard" combination of substituents in the reagent, apparently as a result of transmission of the electron-acceptor influence of the cyano group through the C—N multiple bond.

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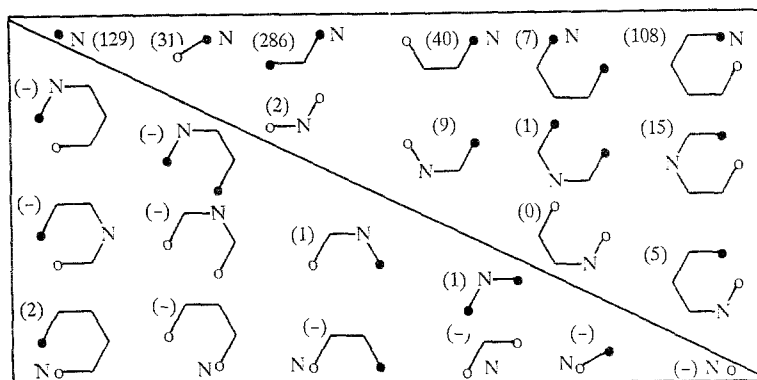
This diagram shows the length of the chain of the allowed reagent, the electrophilic or nucleophilic nature of the terminal atom (open and solid circles, respectively), and the position of the nitrogen atom entering into the skeleton of the pyridine. The numbers correspond to the number of references in which the reagent was used for the synthesis of a pyridine ring. Structures of reagents in the upper right part of the diagram are encountered most frequently, those in the lower left hardly ever.

The second example of violation of the heteroalternation rule is the unusual cyclization (6) [42]:

$$R^1, R^2, R^3 = CN, CO_2Me, SO_2Me$$
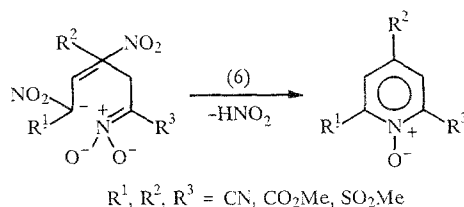
The reaction apparently proceeds as a result of carbanion attack at the *electrophilic* nitrogen atom of the *aci* form of the nitro compound. In this case, the heteroalternation rule is, in effect, inverted, as a consequence of the atypical electrophilic nature of the heteroatom. (Let us note that the use of reagents with an electrophilic heteroatom in the syntheses of other heterocycles is well known; but in terms of obtaining pyridines, this example is more likely "exotypical"; compare [19-21].)

It should be noted that the only type of reagent that satisfies the heteroalternation rule but is not encountered in Schemes 4 and 6 (i.e.,no syntheses of pyridines reported in the literature) is the 1,5-bielectrophile with a C—C—C—N—C skeleton.

7. APPROACHES TO INTERPRETATION OF THE RULES

We should assume that an interrelation between the parity of the chain and the polar nature of the functions is somehow included in the features of electronic structure of "allowed" reagents. Let us note that the stringent criterion of maximum unsaturation of the pyridines (Scheme 3) necessitates the no less stringent requirements of maximum unsaturation of the acyclic structures. As a consequence, in the first approximation, acyclic reagents are reasonably well described within the framework of conjugated π-systems (the existence of a σ-system of an annelated alicycle can be neglected). Perhaps the only exception may be found in the σ-system of the class comprised of ortho-esters, acetals, and their heteroanalogs; in all other cases, nonconjugated reagents are at least representable in the form of conjugated systems. (For example, methyl ketones or β-dicarbonyl compounds are represented by π-systems of tautomeric enols or deprotonated forms.) Thus, we need to determine what specific features of π-systems of "allowed" reagents are different from those of "prohibited" reagents.

It is known that in describing π-systems (for example, within the framework of the simple Hückel method [43]), two different types of heteroatoms can be distinguished: an X-type atom, which brings two electrons into the π-system (in an enamine, for example), and a Y-type atom, which brings in one electron (the heteroatom of a cyano or carbonyl group, for

example). Let us note that nucleophilicity can be associated specifically with an X-type atom (and also with an isoelectronic carbanion center), whereas electrophilicity is characteristic for those atoms (usually carbon atoms) that are adjacent to a Y-type heteroatom. Thus, the design of π-conjugated reagents of different EN types comes down to combining X atoms (including carbanions), C—Y groupings, and an arbitrary number of carbon atoms that bring one electron into the π-system. Now let us examine the possible cases.

1) In the π-System There is Only One X Atom or One C—Y Group. It is not difficult to see that the addition of an all-carbon chain to an X-type atom can be accomplished only with an even number of carbon atoms (compare enamines, dienamines, divinylamine). It is obvious that the π-systems of the resulting reagents (in view of the commonplace conjugation) must be *odd-membered binucleophiles*. (The addition of an even-membered carbon chain requires a radical-type π-system.) For the same reasons, only an even-membered chain of carbon atoms can be added to a C—Y fragment (for example, the transformation of formaldehyde to acrolein and divinyl ketone or the passage from hydrocyanic acid to acrylonitrile). In this case, the conjugation effect naturally leads to an *odd-membered bielectrophile* (an even-membered chain plus the carbon atom from C—Y).

2) Matched (Conforming) Position of X and Y Groups in Reagent. As soon as the appearance of perturbation in a π-systems of X- and Y-type atoms gives rise to natural polarization of the chain, the additional manifestation of those same atoms may be either matched or mismatched in relation to the induced charges. The only possibility of a matched mutual influence of X and C—Y groups is conjugation between them, either immediate adjacency or vinylogy, i.e., an even-membered chain between them. This obviously leads to π-systems of *even-membered ambiphiles* (1,2-, 1,4-, etc.).

3) Matched Positions of Several X Groups or Several C—Y Groups. We will apply the term *alternant* to π-systems from the two preceding cases. Let us note that we should add to this category certain examples of matched mutual influence between a pair of monotypical groups (X,X or CY,CY). This case, in order to avoid radical centers, requires the appearance of a charged carbon atom between the groups (or the appearance of a corresponding vinylogous odd-membered carbon chain), the charge of which must be opposite to the formal π-charge of the neighbors. One typical example is a carbanion center between two carbonyls (equivalent to a 1,3-dicarbonyl fragment); another example is a carbocation center between two amino groups (equivalent to amidines).

Let us note that in addition to the three cases we have already considered, where the X and CY groups form the skeleton of the reagent that is converted into a ring, we may also have matched addition, to the alternating chain itself, of a substituent of the X- or CY-type (in accordance with the rule of plus to minus, and minus to plus), which will prove to be either substituents in the ring or leaving groups. Of course, the reagents that are obtained also turn out to be alternant reagents.

It is not difficult to see that π-systems with a matched position of the functions, which we have termed alternant, prove to be either odd-membered bielectrophiles or binucleophiles, or even-membered ambiphiles, i.e., "allowed" reagents (compare with Schemes 4-6). In other words, the hypothetical alternating chain, which required truncation in the rule of alternation, proves to be a completely tangible object within the framework of the π-approximation.

π-Systems of the second category — where even one case is observed of a mismatched neighborhood of two groups X and CY (an even-membered chain between monotypical groups, or a charged odd-membered chain between oppositely charged groups) — will be termed *nonalternant*, even though individual units of the chain may prove to be alternant. Clearly, nonalternant π-systems correspond to prohibited reagents.

It is completely obvious that *alternant reagents in heterolytic reactions can form only even-membered rings*. In fact, an alternating chain (or its smaller units), on the basis of a purely combinatorial principle, is capable of closure only into an even-membered ring.* A disruption of the charge alternation may involve the formation of odd-membered rings.

At the same time, it is generally known (see for example Baldwin's rules for cyclization [44]) that six- and five-membered rings are the most readily formed (particularly if they are aromatic rings); therefore, congruent formation of rings of other sizes can be simply neglected. Thus it is not difficult to see that the concept of "allowed" reagents and the validity of the alternation rule are consequences of a more global rule of *control of parity in heterolytic processes*. Any deviation from alternation in the chain may entail either closure of an odd-membered ring or a process that is congruent to the formation of an even-membered ring — polymerization, for example.

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*This can be demonstrated convincingly (for example) by rotating in one's hands a necklace of any size with beads of two alternating colors: in order for the color to alternate throughout the entire ring, there must obviously be an even number of beads in the necklace.

A good example of the loss of unambiguous parity with the formation of a broad group of rings of various sizes (five-, six-, and seven-membered) may be found in reactions of the "prohibited" reagents hydroxylamine or hydrazine with derivatives of glutaconic dialdehyde [9] ("allowed" 1,5-bielectrophiles obtained by closure of even-membered rings of pyrylium or pyridinium salts).

The rule of *heteroalternation* follows naturally from the requirement of alternant nature of reagents only under the condition of replacement of a nucleophilic center in the conjugated chain by an X-type atom. Meanwhile, another possibility that is allowed (which we had not considered previously) is the appearance of a Y-type atom in a new role — not as a terminal atom but as a skeletal atom of the reagent. This is observed specifically for the nitrogen atom in N-alkylimines and N,N-dialkylimmonium salts or 2-azabutadiene, and in the more general case an imine or imminium type of heteroatom (for example, in pyridine or its salts). Such a heteroatom, because of the inductive effect, usually increases the mobility of the proton of the neighboring CH bond (compare the known CH acidity of the α-position of pyridine). This involves "unexpected" nucleophilicity of the neighboring electrophilic carbon atom. In such cases we should specifically expect unique deviations from the heteroalternation rule that we have formulated, as is actually observed in practice; see reactions (4) and (5), where the anomalies are related specifically to the presence of an imino group in the reagent.

There is also a heteroatom of this imminium type in the *aci* form of aliphatic nitrocompounds, where it manifests atypical electrophilic properties; compare the anomalous reaction (6).

8. FORMALIZATION AND SUBSEQUENT EXTENSION OF RULES

In the above discussion, we have examined the problematics of pyridine syntheses from only one side — by analyzing the electronic structure of the reagents. However, there is another aspect of the problem that deserves analysis: *How does the nature of the reaction centers in the reagent change upon closure of the ring?* The answer to this question may consist of two parts: 1) What changes have occurred in the reaction centers that entered into the ring as *skeletal* atoms? 2) What is the behavior of the functions that showed up as *substituents* in the ring? In order to answer these questions, we must reconsider the correspondence between the atoms of the reagents and the product of cyclization, i.e., the assembly scheme.

Assembly Schemes Taken as Reaction Graphs. Traditional schemes of assembly of heterocyclic rings (see Scheme 1) contain implicit information on the correspondence of specific atoms of the reagent (those that enter into the skeleton) to the atoms of the ring that is formed. In this sense, assembly schemes perform the function of *mapping* the atoms of the original substances into the atoms of the reaction product. In mathematical and computerized chemistry, such "mapping" objects have for many years been termed reaction graphs or graphs of reactions [1, 17].

Let us clarify this point with an example. An equation of some particular heterocyclization reaction can be represented symbolically, in the most highly simplified form, as a pair of molecular graphs after replacing the left-hand and right-hand atoms (entering into the ring or having shown up in the ring) by points or vertices of the graph, and representing the skeletal bonds of the ring (those that existed previously in the reagents and those that have newly appeared) by lines or edges of the graph. All of the other atoms and bonds are simply eliminated. Now we must number the atoms from left to right so that we will know without any error the origin of each ring atom and the fate of each atom of the reagent. Assuming that the reaction mechanism is known, this is not difficult to do: After arbitrarily numbering the atoms on the left, we adopt the same number for the atoms on the right, knowing how they correspond to the predecessors. Only now do we obtain a classical assembly scheme, after superposing the molecular graph of the ring on the graph of the acyclic predecessors in such a manner as to identify vertices with identical numbers, and so as to distinguish the newly formed bonds (edges) from the preserved bonds in some manner, for example by the use of dashed lines.

Thus, classical assembly schemes can be ultimately named as what they actually are: graphs of cyclization reactions (compare with the analogous construction of recyclization graphs [1]). Let us note that any construction of reaction graphs is particularly useful in that it permits analysis of the purely mathematical side, apart from specific carriers (for example, by studying the similarity of reactions with identical graphs, counting the number of theoretically possible graphs, and so on); this is extremely important in the use of computers in chemistry.

Utilizing the rules of alternation and heteroalternation, one would think it not difficult to introduce the concept of electrophilic and nucleophilic centers into classical methods of assembly from Scheme 1, by simply adding labels for the reaction centers. However, such assembly schemes are by no means new reaction graphs. We do not have the right to place labels of electrophilicity and nucleophilicity on the *mapping* until we have at our disposal counter-information on the nature of the reaction centers in the final product of cyclization.

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It is generally known that the structure and reactivity of the pyridine ring is described adequately in terms of alternating electrophilic and nucleophilic centers. Actually, external nucleophiles readily attack electrophilic α- and γ-positions, whereas electrophilic attack is directed at the nucleophilic nitrogen atom or at the β-position (with a less distinct nucleophilicity). Such an alternation of centers is reflected adequately, for example, by the distribution of π-charge in the pyridine ring.

Now we can carry out with confidence the "superposition" of skeletal atoms of the reagents and product, noting in some manner (let us say by solid and open circles) the nucleophilic and electrophilic centers in the original and final structures. For example, in the condensation of some enamine with some 1,3-dicarbonyl compound, the corresponding "colors" (solid or open circles) of the reagents and the product coincide:

SUPERPOSITION
(polar scheme of assembly)
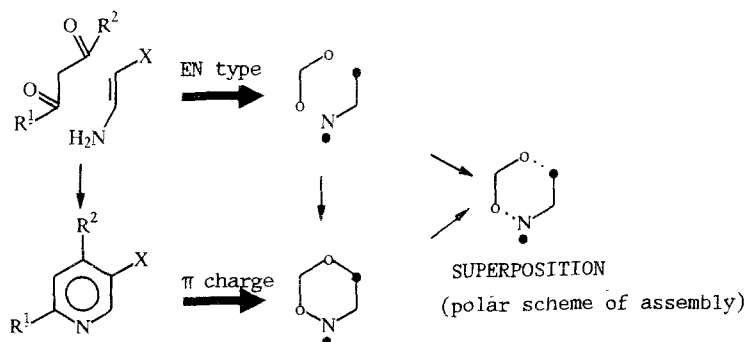
It is not difficult to see that, in the most general case as well, when an "allowed" acyclic reagent with alternating centers is superposed on a cyclic alternating system, *the nature of the reaction centers is, in effect, preserved*. And in the other direction, with an arbitrary breaking of the pyridine ring into one or two parts (a procedure equivalent to retrosynthesis), we obtain either even-membered ambiphiles or odd-membered bielectrophiles or binucleophiles. Let us note, finally, that the position of the heteroatom in the pyridine relative to the electrophilic and nucleophilic centers coincides with the heteroalternation rule. In other words, a more general rule is valid — the **rule of succession:**

The nature of the reaction centers of acyclic alternant reagents is inherited by the skeletal atoms of the even-membered conjugated pyridine ring.

In turn, in selecting optimal acyclic predecessors of the pyridine ring, one should be guided by the reverse principle — the **"structure—synthesis" magic rule:**

The optimal nature of reaction centers in acyclic reagents selected for constructing a pyridine — an even-membered ring with alternating π-charges — is determined by the principle of succession.

Just now, in view of the straight-through correspondence between the centers of the reagents and the product, we can introduce the concept of *polar schemes of assembly*, showing not only the locations of the bonds that are formed, but also indicating unambiguously the sites of the electrophilic and nucleophilic centers, for example in the form of open and solid circles* on the ends of the dashed line. Let us note that a permissible distribution of labels by a "predesigned" succession rule and hence such distinction of the labels for the ends of the dashed line can be done by a uniquely possible method. Thus, the rather uninformative Scheme 1 is transformed into a new Scheme 7 — given a clear chemical meaning — in which standard assembly schemes are replaced by polar schemes. Scheme 7 combinatorially exhausts the possibilities of allowed one- and two-component syntheses of pyridines: There can be only 12 such syntheses. Of the 12 syntheses, 11 have been actually realized experimentally (compare with data of Schemes 1 and 4). Discovery of the "last" of these syntheses should impart to the proposed scheme a certain elegance, rigor, and logical perfection.

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*An alternative expression of polar schemes of assembly is the introduction of the symbols " + " and " − " (convenient for typesetting) or vector arrows directed from the nucleophilic center toward the electrophilic center (useful for combinatorial enumeration). The symbols that we are proposing appear to be the most graphic.

Scheme 7. Polar schemes of assembly of pyridine skeleton
that are allowed by heteroalternation rule.
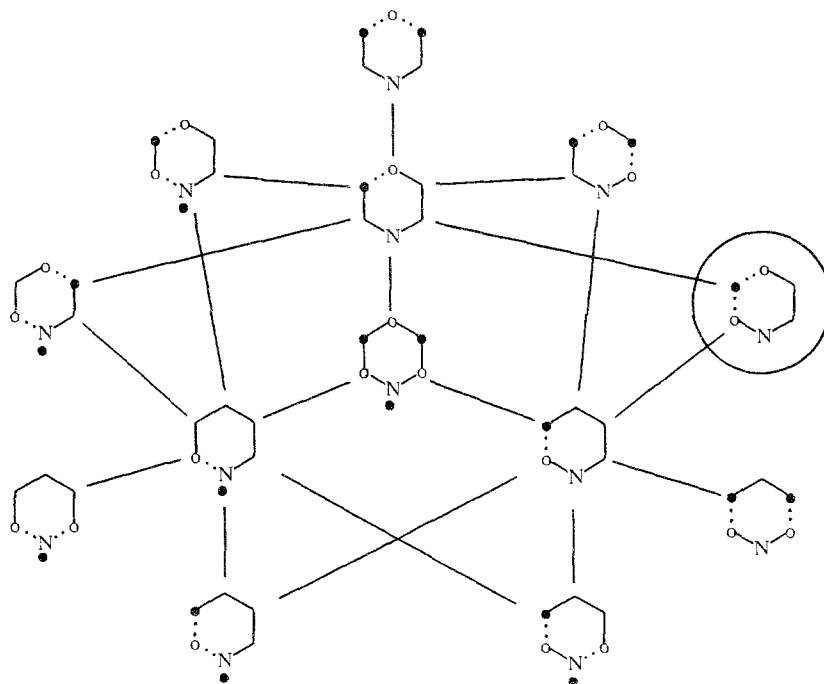
The schemes shown are those of theoretically permissible one- and two-component assemblies of the pyridine ring that correspond to experimentally observed syntheses (the unknown type of synthesis is enclosed in a circle). The small open and solid circles correspond to E- and N-centers in the reagents. In the middle of the scheme, the distribution of E- and N-centers in the pyridine ring is shown. The lines denote alternative formation of bonds when the change is made from two-component to one-component syntheses.

Extension of Rules to Functional Groups. From a superficial analysis of the experimental material on the position of functions in pyridines obtained from alternant reagents, we find evidence for the existence of a "secondary succession effect." As we considered in the above material, an alternating skeleton of the chain in the reagent allows the appearance of only those exo substituents of such a nature that the alternation in the chain is not changed. In particular, electron-donor functions of the X-type or electron-acceptor functions of the CY-type are allowed to appear only on skeletal centers of opposite nature.

Then, in view of the succession rule, the exo functional groups from the reagents pass into the cyclic structure in a way such that they are positioned on centers of opposite nature. In particular, donor groups (OH, SH, NH_2, halogens) may end up in electron-acceptor α- and γ-positions, giving rise to the corresponding α- and γ-pyridones and their heteroanalogs or their tautomers. On the other hand, electron-acceptor substituents (carboxy, cyano, or nitro groups, etc.) are "obliged" to appear in the weak-donor β-position. In fact this is specifically the type of position of the functions that is most characteristic for products of heterocyclization (see for example Scheme 4). Some exceptions from this clearly dominant trend in the principle are known, but they are not typical.

Now let us note, departing from the general theme of this review, that in addition to rules of the "structure—synthesis" type, subsequent running correlations, of the "synthesis—reactivity" type, are possible. In fact, the distinctive "genetic memory" of a reagent that has been closed into the ring is manifested in subsequent heterolytic reactions of the pyridine, for example in the selectivity of reactions of aromatic electrophilic and nucleophilic substitution. As a result, certain classes of substituted pyridines are in effect "doubly available" in heterolytic syntheses (by means of cyclization and also substitution), for example $\alpha(\gamma)$-hydroxy and amino derivatives, or β-nitropyridines. And on the contrary, in obtaining β-hydroxy and amino derivatives of pyridine or $\alpha(\gamma)$-nitropyridines, alternative paths of synthesis should be sought [21]. New prospects in this area are opened up by reactions that proceed with "reversal" of the heteroalternation rule; compare the prohibited location of functions in the product of reaction (6).

9. EXTENSION OF RULES: OTHER PYRIDINE STRUCTURES AND CYCLIZATIONS

Up to this point, our analysis has dealt with maximally unsaturated pyridines and the simplest one- and two-component cyclizations. We will now examine the applicability of the rules as we move in the reverse direction in Scheme 3.

Hydrogenated Structures of Pyridines. The rules that were obtained for aromatic structures of pyridines turn out to be clear guidelines in classifying syntheses of more-hydrogenated structures. The proposed rules are followed very clearly in two cases:

1) The initial reagents are more highly reduced but nonetheless conjugated systems. For example, among the odd-membered bielectrophiles, we can replace β-dicarbonyl derivatives by α,β-unsaturated carbonyl compounds, carboxylic acids by aldehydes, and so on. The dihydropyridines that are formed are readily oxidized (and their N-oxides are readily dehydrated) to form aromatic structures.

2) The acyclic chain is completely (or partly) saturated, but it is made up of conjugated alternant reagents. For example, in reaction (7), the saturated chain of the original type of reagent is obtained from alkyl acrylates and amines (in accordance with the rule), and the overall reaction is subject to the principle of heteroalternation [45]:
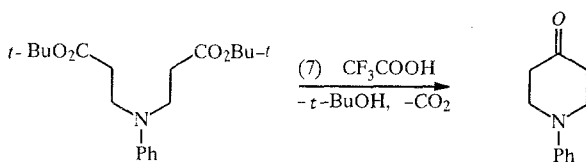
If the functions in the saturated chain are nonalternant (created on the basis of one or more nonalternant predecessors), the "prohibited" synthesis of the pyridine skeleton is frequently accompanied by the expected competitive formation of an odd-membered ring. A good example is reaction (8) [25, 45]:
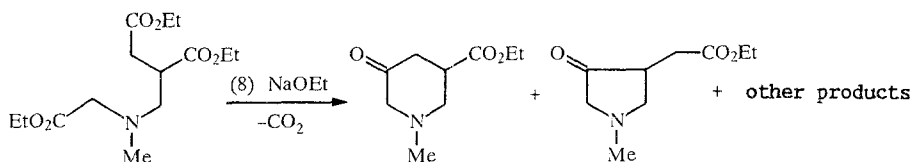

in which the acyclic predecessor was obtained from a "prohibited" 1,3-ambiphilic glycine. An even clearer example of the use of a nonalternant reagent with mismatched functionality in the synthesis of pyridines was demonstrated by Cohen [47]:
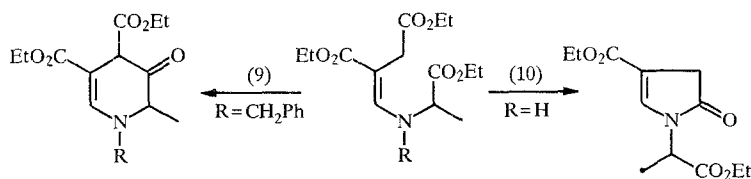

Reaction (9) proceeds with violation of the heteroalternation principle, leading (after oxidation) to pyridinium salts. An attempt to perform this same reaction with an N-unsubstituted substrate for the formation of nonquaternized pyridine led to the expected formation of a pyrrole ring, i.e., reaction (10).

Multicomponent Syntheses of Pyridines. The profusion of multicomponent syntheses of pyridines (see for example the review [48]) is fully compensated by the simplicity of their interpretation: The rules are followed rigidly in the overwhelming majority of cases. The "apparent simplicity and alchemy" noted for these syntheses [5, p. 38] have long been reflected in the naming of these reactions for their discoverers. In fact, the rules proposed in this review are fully observed in the Hantzsch, Chichibabin, Petrenko—Kritschenko, and Reddelien four-component syntheses and the Gattermann—Skita, Meyer—Moore, and Guareschi—Thorpe three-component syntheses [49, 50] in which alternant reagents, like beads of opposite colors, form an alternating pyridine skeleton. One example of multicomponent assembly is reaction (11) [51]. The stages of the proposed mechanism include both the formation and cleavage of C—C bonds of the reagent:
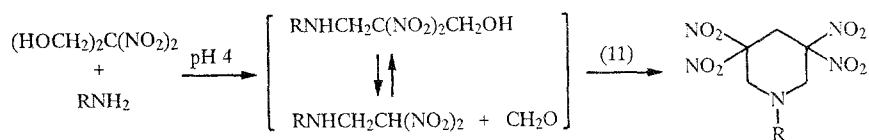
The "prohibited" α-haloketone was the first to appear explicitly among the group of three-component syntheses. This reagent was used by Feist as far back as 1902 [52] in reaction (12) with oxaloacetic ester and ammonia:
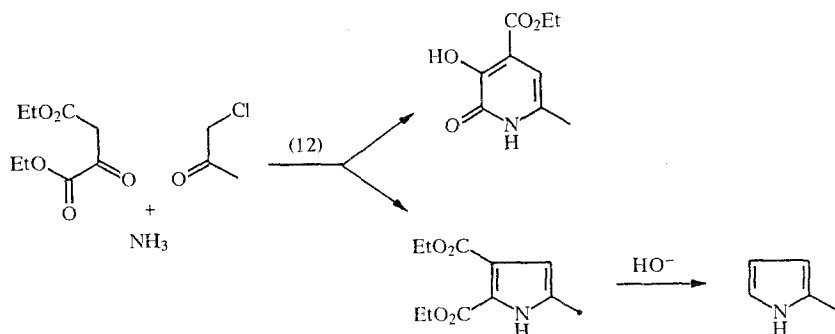
As expected, a pyrrole derivative was formed as a byproduct (recovered in the form of a product of decarboxylation). Let us note that the attitude of Feist himself to this synthesis is unambiguous: The paper is titled "Syntheses of Pyrroles and Furans."

A serious test for our rules is the rather unusual three-component cyclization (13), which was detected for the *aci* forms of 2,2-dinitroethanol and its 2-nitro-2-cyano analog [53], leading to 2,4,6-substituted N-oxides of pyridine. No reaction mechanism was proposed, but we can assume that the reaction follows the alternation rule (the reagents are unambiguously alternant):

$$X = NO_2, CN$$
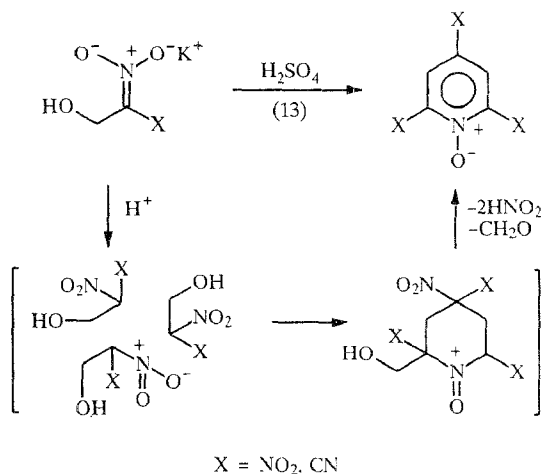
Our proposed scheme explains the unusual ("prohibited") position of the functions (implying electrophilicity of the nitrogen atom of the nitro group and elimination of a one-carbon fragment), and the scheme is consistent with the experimentally observed evolution of nitrogen oxides. Meanwhile, the proposed polar scheme of assembly III for this process, analogous to reaction (6), is in effect inverse to the principle of heteroalternation.

Heterocycles Containing an Annelated Pyridine Ring. For the synthesis of binuclear structures containing a pyridine fragment, the case that is of interest to us, the splicing of a pyridine ring onto an existing ring, is quite frequently encountered. New tactical approaches in this currently active field of synthesis were proposed by Molina [54-56], literally in the last year or two (for earlier work, see the review [35]). We will be interested in searching for explicit correlations of the "structure—synthesis" type for such systems, and in a comparison with the rules that have been found for pyridines. Let us examine very briefly the simplest case of an annelated benzene ring (syntheses of quinolines and isoquinolines).

It would seem that there is no natural polarization in the benzene ring, and hence we can expect that polar schemes of assembly of quinolines and isoquinolines should reproduce the corresponding schemes for pyridines. At the same time, benzene is generally known to be susceptible to processes of electrophilic substitution; nucleophilic substitution is typical only for certain activated systems. This weak factor, nonetheless, not only is the key influence on the frequency of encountering prohibited "pyridine" syntheses for benzopyridines, but also leads to a clear violation of the rules for isoquinolines.

In obtaining isoquinolines, two groups of syntheses are possible [14, 25, 57], including the formation of two different types of C—C bonds with the benzene ring. In the first case, a bond is formed by the $C_{(1)}$ atom corresponding to the α-position in the pyridine fragment. In the reagent, therefore, it must correspond to an electrophilic center. In the second case, the bond is formed by the $C_{(4)}$ atom, corresponding to the β-position in the pyridine fragment. Consequently, its prototype in the reagent must have a nucleophilic nature with respect to the benzene fragment. Meanwhile, in view of the noted specific susceptibility of the benzene ring to S_E reactions, the first case proves to be matched, the second case mismatched.

Actually, the first case, i.e., electrophilic attack by the $C_{(1)}$ atom, corresponds to "prohibited" reagents and reactions; it is directly analogous to syntheses of pyridines, and it is widely represented in syntheses of quinolines (Bischler—Napiral'skii, Pictet—Gams, Pictet—Spengler syntheses), for example reaction (14)
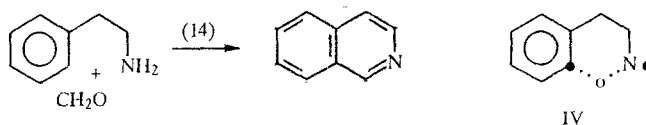
The second type under discussion is nucleophilic substitution in benzene by a $C_{(4)}$ carbanion center; although this type of reaction is known, for example reaction (15) [58], it is completely atypical [57] for the synthesis of isoquinolines:
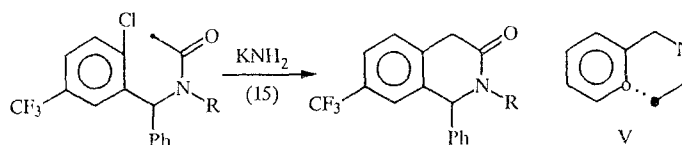
In place of this, a group of Pomeranz—Fritsch syntheses (or modifications) is known, in which "prohibited" reagents are used, namely glyoxal derivatives (in reactions with benzylamine) or α-aminoketones (in reactions with benzaldehyde), reaction (16):
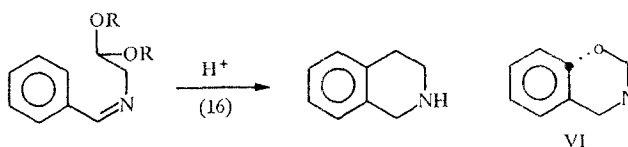

It is obvious that these syntheses, which are prohibited by the rules for pyridines, proceed unambiguously in the isoquinoline series as a result of alternation (not taken into account in the rules) of latent nucleophilicity of the benzene ring — which is preserved even in the *ortho* position of the molecule of the original benzaldehyde, reaction (16).

Thus, annelation of a benzene ring at the γ-bond to a pyridine ring introduces certain corrections into the "structure—synthesis" rules for isoquinolines. In addition to the usual polar schemes of assembly of the type of IV or V, we should consider the manifestation of nonstandard diagrams of the type of VI, due to the typical 1,2-binucleophilicity of the benzene ring. Let us note that such manifestation of electrophilicity of the γ-position leads to disappearance of a number of allowed reactions and hence depletes the syntheses of isoquinolines to some extent.

In the case of syntheses of quinolines, a β-annelated benzene ring acts as a matched-position substituent with respect to the π-system of the annelated pyridine. Only one carbon atom can form a C—C bond with the benzene ring, and the nature of the $C_{(4)}$ atom that is required for electrophilic attack is consistent with alternation in the pyridine fragment.

Scheme 8. Polar schemes of assembly of pyridine fragment of quinoline nucleus.
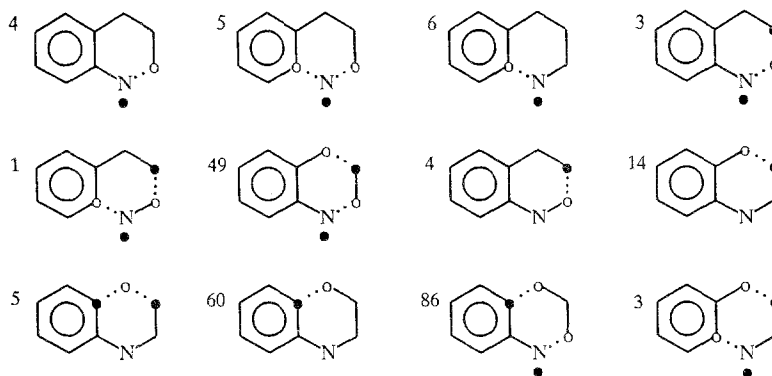

The known one- and two-component methods of quinoline synthesis are shown in this scheme. The open and solid circles correspond to E- and N-centers in the reagents. The numbers (from the review [18]) show the number of references for each type of synthesis.

As a result, the distribution of quinoline syntheses by class (excluding electrocyclization of oximes) that is shown in Scheme 8 provides complete support of the "structure—synthesis" rules that were formulated for pyridine. Perhaps the only exception is reaction (2) (see Scheme 8), though the main direction of this reaction (called the Madelung indole syntheses [49, 50]) is the formation of an odd-membered ring.

Let us note that the two-component scheme of (3+3)-condensation of the pyridine ring VII corresponds in the quinoline series to two different assembly schemes VIII and IX, differing in whether the benzene ring is positioned in a bielectrophilic or binucleophilic fragment:
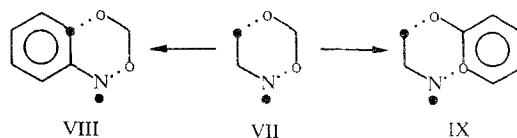
The first of these schemes (VIII) corresponds to the most widely encountered syntheses of quinolines [14, 18, 25] — the condensation of anilines with 1,3-bielectrophiles (Skraup, Conrad—Limpach, and Knorr syntheses). The second type of assembly (IX) is considerably less characteristic, owing to the previously noted weak tendency for the benzene ring to undergo nucleophilic substitution; however, the introduction of electron-acceptor groups makes such a reaction path possible [59], reaction (17):
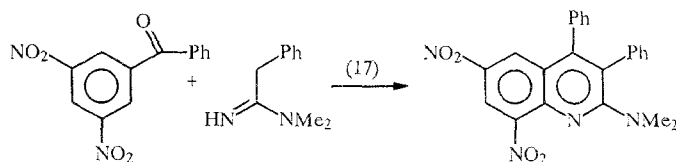

Completing our examination of reactions leading to pyridines and related structures, in the light of the proposed rules, let us note that certain methods of synthesis that are not heterocyclizations but are very closely related to heterocyclization still remain beyond the scope of this review. Undoubtedly, the idea of heteroalternation can be applied fruitfully in analyzing regioselectivity in obtaining pyridines by reactions of cycloaddition, and also by recyclization (the latter problem was discussed in the preceding communication of this series [1]).

10. APPLICATION OF RULES TO SYNTHESES OF OTHER HETEROCYCLES. HETEROALTERNANT SYSTEMS

The rules proposed in this review are based on principles (alternant π-systems, combinatorial control of parity of the ring that is formed, examples of preservation of the nature of the reaction center in heterolytic processes) that are too general to be used solely in designing syntheses of the pyridine ring. It is reasonable to assume that replacement of the heteroatom in pyridine, i.e., the replacement of nitrogen by oxygen or sulfur, should not produce any substantial changes in the formulations of the rules we have discussed. Moreover, it is possible to change the pyridine ring by introducing new nitrogen atoms in the *meta* position (through an even number of bonds) without violating the rule of heteroalternation. Finally, the above examples of benzene analogs of pyridine suggest that annelation of a benzene fragment (in particular through the β-bond, as in quinoline) to heteroanalogs of pyridine will also expand the sphere of compounds and reactions in which the rules are operative.

Let us apply the term *heteroalternant* to heterocycles obtained by imaginary modification of an original pyridine in the three directions indicated above. The structure of such systems includes monocycles and β-annelated bicycles; and in most general form, the structure is reflected by the following types (group A):

X, Y, Z: C, N, O, S
A, B: N, O, S
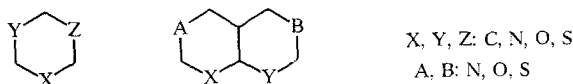
We will segregate in a different category (group B) heteroalternant bicycles containing rings that are annelated to the pyridine nitrogen atom through γ-bonds (isobenzo structures) or through α-bonds (for example, quinolizines):


A, B, X, Y: C, N, O, S
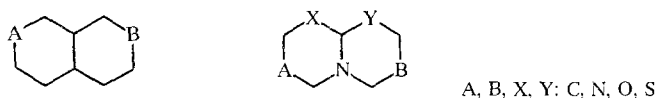
Other heterocycles in which there is even one example of adjacency of heteroatoms or their *para* position, i.e., a contradiction of the heteroalternation rule, will be classed as nonheteroalternant.

Our experience shows that for heteroalternant systems of group A, *in the rules given above, the word "pyridine" in the name of a specific heterocycle can be replaced,* without any serious loss of correctness. In group B heteroalternant systems, along with the "allowed" reagents, appearances of "prohibited" reagents are fully justified. In nonheteroalternant systems, the heteroalternation rule will be violated by definition, and the alternation rule will be manifested only in rare cases. For odd-membered rings, it is not at all obvious whether any rules are followed.

Let us note that in the syntheses of nonheteroalternant nuclei, it is not at all rare to observe competitive formation of odd-membered rings. Thus, in reactions of hydrazine with 1,4-dicarbonyl compounds, derivatives of both pyridazines and N-aminopyrroles may be formed. Analogously, reactions of 1,4-diamines with 1,2-dicarbonyl compounds may lead to both pyrazines and imidazoles.

Meanwhile, in syntheses of nonheteroalternant systems, it is possible to avoid the very possibility of forming an odd-membered ring by making use of the alternation rule. In syntheses of (let us say) cinnoline, this can be done by using alternant pairs of reagents, for example by the method of Borsche [60], where the EN type of reagent corresponds to 1,1-bielectrophilic nitrogen and a 1.5-binucleophilic chain [reaction (18)], or, on the other hand, by the method of Baumgarten [61] on the basis of 1,1-binucleophilic nitromethane and a 1,5-bielectrophilic chain [reaction (19)]:
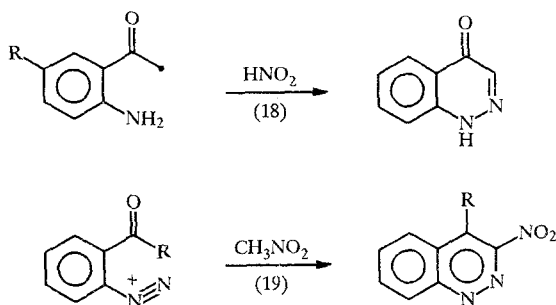
11. UTILIZATION OF "STRUCTURE—SYNTHESIS" RULES
IN THE DESIGN OF NEW HETEROCYCLIZATIONS

The rules that we have examined in this review pertain only to heterolytic processes, and this determines all of the advantages and disadvantages of the approach. Naturally, such rules are useful in reviewing diverse material, in setting up databases, in teaching, and in computer-aided or conventional planning of syntheses. Three aspects of the application of these rules in experimental practice are of central importance.

In the first place, we refer to the wider involvement of "prohibited" reagents in syntheses of heteroalternant nuclei, and, on the other hand, the use of alternant reagents in syntheses of nonheteroalternant systems.

In the second place, research must be pursued vigorously in discovering syntheses similar to reaction (6) or (13), i.e., syntheses that proceed with reversal of the heteroalternation rule. In these two particular cases we should expect to find syntheses leading to unusual combinations of functionalities in the products.

In the third place, certain classical syntheses that follow the rules of heteroalternation, — promising reactions that have remained "undiscovered" only by chance, should be discovered experimentally, thus filling in gaps in the theoretically allowed sets of assembly schemes. For example, we can state with confidence that one last two-component synthesis of pyridines (and quinolines) allowed by the heteroalternation rules still remains undiscovered. The polar scheme of assembly for this unknown type (enclosed in a circle in Scheme 7) demonstrates unambiguously how an EN type of reagent should be selected for realization of this scheme. Designation of specific substituents or annelated rings is not central to this problem. Our next communication will be devoted to experimental discovery of this type of conversion.

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