MOLECULAR DESIGN OF HETEROCYCLES.* 6.[†] HETARENES WITH BRIDGE NITROGEN ATOM. 4.[†] STRATEGY AND TACTICS FOR COMPUTER PREDICTION OF NEW RECYCLIZATIONS IN THE AZOLOPYRIDINE SERIES WITH BRIDGE NITROGEN ATOM

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Based on the previously developed program for computer prediction of recyclization (GREH) and analysis of literature data on ring opening in bridged azolopyridines, we propose specific types of substituted substrates capable of undergoing previously unknown classes of isomerization and recyclization. We discuss the criteria for expert assessment of the computer predictions and heuristic principles for design of the structures of such substrates (the empirical principle of the maximally alternant tree in the bicycle), increasing the probability of experimental observation of the predicted conversions.

INTRODUCTION

One of the known specific characteristics of heterocycles is their tendency toward reactions of ring transformation or recyclizations. For *non*-heterocycles (say, alicycles or arenes), the corresponding reactions of heterolytic cleavage of the ring or recyclization processes (for example, of the classical ANRORC type) are atypical. It was evidently Kekulé who first noted this distinguishing characteristic of heterocycles, comparing the heteroatom of the ring with a clasp joining the ends of a chain, and comparing the ring itself with the ancient alchemical symbol of a snake biting its ow 'ail [6]. The latter analogy, extremely graphic and quite appropriate for describing ring closure (cyclizations) and ring opening (scheme 1A), however seems unsuitable for describing recyclizations. In fact, the topological nature of processes in scheme 1A (the appearance and disappearance of the ring) is fundamentally different from the topology of recyclization processes (retention of the ring as it changes), and therefore the symbol of the "Kekulé snake" (changing its topology) is inapplicable for qualitative description of recyclizations. As an analogous representation of recyclizations, we should probably use the symbol of a many-headed (or many-tailed) dragon (scheme 1B), graphically and correctly describing the topological sequence of conversions "ring—open form—new ring."

Recyclization reactions often serve as unusual synthetic strategies in organic synthesis, where heterocycles act as the synthons [7]. In fact, recyclizations often lead to cyclic structures with unexpected distribution of heteroatoms and substituents or to compounds which are difficult or entirely impossible to obtain by other routes. Sometimes the recyclization strategy proves to be generally the only preparative approach to a whole class (or subclass) of organic compounds. (It suffices to mention, for example, the classical Hafner azulene syntheses or the synthesis of sterically hindered 2,6-disubstituted N-arylpyridinium salts by recyclization of pyrylium salts.)

^{*}Dedicated to É. Ya. Lukevits on his 60th birthday. *For communications 4 and 5, see [1, 2].

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Scheme 1. Graphic expression of the topological features of one-component processes of ring closure, ring opening, and ring transformation: A) schematic representation of the topology of cyclization and ring opening processes; B) proposed graphic scheme for the change in topology in recyclizations (for the example of isomerizations of a monocycle).

An interesting problem arises: Since recyclizations are so important and useful (and ultimately elegant), wouldn't it be possible to try to theoretically predict new, as yet unknown, ring transformations? Of course, many new recyclizations have been "discovered" quite deliberately, for example, using the principle of substrate structural analogy (we replace, add, or remove a heteroatom or an annelated ring). Nevertheless, until recently there were no approaches in which the comparison (classification) of recyclizations and prediction of really new classes of transformations were based on the principle of structural relationship between 'he reactions themselves rather than only between the substrates.

In this paper, for the first time we attempt to demonstrate the effectiveness of the principle of structural classification of recyclizations in designing new nontrivial heterocyclic transformations. Using our previously created computer program, we intend to predict some unknown families of recyclizations and rearrangements of a specific class of hetarenes in order to subsequently "discover" them experimentally.

RECYCLIZATION GRAPH MODEL

Several years ago, we suggested [8-11] a new combinatorial—topological model for describing and classifying recyclizations using graph theory methods based on the principle of structural similarity or difference of the reactions rather than the substrates. (In early classifications discussed in [8-10], recyclizations were compared only on the basis of the structure of the substrates, say, according to the sizes of the initial and final rings, the size of the "tail" involved in formation of the new ring, etc.). The central idea of our model was the principle of construction of the reaction graph, used in a number of domestic [12-14] and foreign [15-17] approaches. The reaction graph is an imaginary superposition of the starting reagents onto the products of the transformation so that identical atoms coincide and so that on the final diagram we see only those bonds which have changed their multiplicity (have formed or disappeared).

As applied to recyclizations, the original reaction graph principle (mentally superposing the atoms of the reagents onto the atoms of the reaction product) was retained with only one difference: only cyclic atoms of the initial and final rings and accordingly the cyclic bonds of each of the rings were used. After imaginary superposition of the ring to be "recyclized" onto the ring formed from it, we obtained some diagram (the recyclization graph) of the redistribution of cyclic bonds. The only restriction was the requirement that there be no intermediate isomerizations of the skeleton.

Clearly if we choose a fragment in the ring and mentally superpose it onto a fragment of another ring (joining together the superimposed atoms), then we obtain some bicycle. In this bicycle, it is obvious where specifically we have rupture and formation of cyclic bonds, which can be considered the labeled (colored) edges of some bicyclic graph. It is precisely the same heteroatoms which can be considered the labels of the vertices of this graph. Finally, one version of the labels can be the electrophilic or nucleophilic nature of the atoms between which the bond is formed (is broken) in the ring. For different recyclizations, such labeled bicycles (recyclization graphs) may be different or identical, with different or identical distribution of labels.

We found that the overwhelming majority of known heterocyclic rearrangements (isomerization recyclizations) are described by a relatively small set of recyclization graphs. It is even more convenient to generate such graphs using a computer. With this goal, we developed the special program GREH (Graphs of Recyclizations of Heterocycles) [1,8], allowing us to generate complete atlases for a given type of both recyclization graph and heterocycle.

Corresponding atlases of recyclizations have been published for rearrangements of azoles [8, 9] and azines [10], and also degenerate rearrangements [11] with an indication of specifically which structural transformations already have precedents and which are unknown so far. We formulated the problem of filling in the "empty spaces" in such a classification by experimental testing of the computer predictions.

Of course, the computer program does not predict the exact empirical formula and structural formula of the compound which can serve as the substrate for the new rearrangement or recyclization. Nevertheless, the program accurately indicates specifically which functional groups present in the heterocycle are potentially capable of leading to recyclization in the required direction. Furthermore, a heuristic suggestion is given concerning the possible type (electrophilic or nucleophilic) for such key atoms. Then as needed, this should be followed by an expert assessment by an organic chemist, considering a multitude of other factors including, say, the availability of the starting compounds, the importance of the structures obtained, or (last but not least) the elegance of the expected transformation.

THEORETICAL PREDICTION OF NEW RECYCLIZATIONS

The existence of a theoretical model and its computer realization opens up broad prospects for possible experimental investigations for realization of the most interesting computer predictions. It is just this problem (the practical design of quite specific substrates taking into account the computer predictions) which is the central problem of this paper.

Rationale for Selection of the Starting Class of Heterocycles. We would like to illustrate the effectiveness of our proposed procedure for computer design of new recyclizations using the most characteristic archetypes of hetarene chemistry: the class of azoles and azines. Following the familiar principle of Occam's razor ("do not multiply entities unnecessarily"), we decided that it would be most illustrative to choose models in which both types of heterocycles (five- and six-membered) would be present simultaneously. Among them, the most interesting objects were systems of condensed azoloazines, for which (for example, azaindenes) we use the traditional term "heterocyclic nucleus."

We know that recyclizations of heterosystems with a single heteroatom are more rarely encountered than heterocycles with several heteroatoms. In this connection, investigations of new recyclizations of azoloazines with a minimum number of heteroatoms would be more attractive from the standpoint of novelty. The condensed azoloazine with the smallest number of heteroatoms is indolizine (pyrrolo-[1,2-a]pyridine), where the bridge nitrogen atom belongs to both rings. Indolizine, activated by a nitro group, is already capable of recyclizations but only with transformations of the six-membered fragment. If we consider the structure of 1-, 2- or 3-hetero-substituted indolizines (i.e., with a 1,2- or 1,3-azole fragment), then it is clear that these also represent substrates with a minimal number of heteroatoms potentially tending toward transformations of both the pyridine and azole rings.

Analysis of the literature has shown [5] that in a number of bridged azoloazines (including the azolopyridines we have selected), the transformations are quite numerous and diverse. Moreover, derivatives of 1-hetero-substituted indolizines (for example, those presented in Scheme 2) are the most preparatively available, and we have both neutral (imidazo[1,2-a]pyridines) and cationoid (oxazolo- or thiazolo[3,2-a]pyridines) azolopyridines or their mesoionic (such as 2-oxo) derivatives.



Despite the easy availability and relatively extensive previous study for representatives of this class, there is practically no data available on recyclizations (except for isolated examples discussed below). So we decided to concentrate specifically on the problem of searching for unknown ring transformations in bridged 1-heteroindolizines. For such substrates, we can expect both concurrent and sequential transformations of the five-membered and six-membered fragments. The possibility of sequential recyclizations (first the azole, then the pyridine fragment) is especially attractive because it has been little studied previously, and they also do not take us beyond the scope of our predictions. In addition, our early experimental investigations in the area of recyclizations concerned specifically 5+6 hetarenes [18, 19].

Thus based on a number of reasonable factors, we settled on derivatives of bridged azoloazines, mainly the structures of 1-hetero-substituted indolizines.

Analysis of Precedents and Analogs. The final selection of prospective transformations was preceded by a lengthy literature search [5]. First of all, we were interested in isomerizations and recyclizations with insertion/elimination of very simple ring fragments. We found that the only type of isomerization of neutral 1-heteroindolizines (in particular, imidazo[1,2a]pyridines and indolizines themselves) is Dimroth and Kost—Sagitullin transformations of the six-membered ring (Scheme 3a) [5, 19]



Opening of the five-membered ring for neutral structures of imidazopyridines is apparently unknown. Nevertheless, we know of a pair of individual reactions (Scheme 3b [20, 21]), the superposition of which (as is not realized as a "one pot" conversion) might serve as the sole example of transformation of the imidazole fragment. For N-alkylimidazopyridinium cations, we have an unconfirmed observation by Chichibabin in the 1920's about possible opening of the imidazole fragment [22]. For the thiazolo[3,2-a]pyridinium cation, relatively recently opening of only the pyridine ring has been shown [23], although its benzo analogs open the five-membered ring [24] (Scheme 3c). In the considered series, the most typical is opening

of the oxazole ring for 1-oxaindolizines: the oxazolo[3,2-a]pyridinium cation and its 2-oxo-substituted mesoionic derivative. Let us consider in more detail what precisely is known about opening of bridged oxazolopyridines.

Mesoionic derivatives of 2-oxo-3-acyloxazolo[3,2-*a*]pyridine were first obtained at the end of the 1950's [25, 26]. The unusual facility of opening of the oxazole ring in these systems when treated with very simple N- and O-nucleophiles (Scheme 3d) was observed repeatedly and even served as the subject of kinetic investigations within the last decade [27, 28]. Facile hydrolytic cleavage of such structures with decarboxylation and formation of $1-(\beta-oxoalkyl)-2$ -pyridones was observed a uarter of a century ago [29].

The first synthesis of oxazolo[3,2-*a*]pyridinium cations by acid cyclization of 1-(β -oxoalkyl)-2-pyridones was accomplished by Bradsher in 1964 [30]. Later an alternative strategy was proposed for synthesis of this heterocycle: reaction of 1-(β -oxoalkyl)-2-halopyridinium salts with bases [31]. Practically immediately the possibility was noted of reversible opening of the oxazole ring of this system when treated with base and the sole example of recyclization by treatment with butylamine was accomplished, with formation of the 1-butylimidazo[1,2-*a*]pyridinium salt [32] (Scheme 3e). Later Katritzky somewhat expanded the range of aliphatic amines capable of inducing recyclization [33], and recently German researchers have demonstrated the possibility of transformation of the oxazolopyridinium oxazole ring by treatment with phosphorus- and arsenic-containing nucleophiles [34]. Oddly enough, the simplest nucleophiles (ammonia, sulfide ion) or carbanions have never been used for such transformations. Such reactions have been noted only once, for the structurally related oxazolo[3,2-*a*]pyridazinium heterosystem, for which opening of the oxazole fragment when treated with sulfide ion and recyclizations to indolizines when treated with malonic acid derivatives have been observed [35]. Thus the only known example of recyclizations in the 1-oxaindolizine series remains transformation according to the Yur'ev type of reaction (Scheme 3e).

Thus, literature data suggest (a) lack of previous studies of recyclizations for the entire class of 1-heteroindolizines and (b) the facility of processes of ring opening in the 1-oxaindolizine series, allowing us to expect the occurrence of recyclizations in an appropriate way on substituted substrates.

Computer Prediction of Recyclizations. As a rule, opening of the heteroaromatic ring is accompanied by closure when closure of the new ring is energetically favorable, in particular when the new ring is again heteroaromatic. Of course, recyclization of only one of the nuclei of the bicycle may occur both with disappearance of the original type of coupling of the two nuclei and with retention of the unified annelation π -system. Those recyclizations over the course of which the 10π -electron aromatic system of the bicycle will be restored seem more attractive, even if only because they include rearrangements and isomerizations. This is precisely why for computer prediction of new recyclizations we selected processes with retention of the original 5+6 type of annelation in the bicycle.

Above we mentioned that the computer program GREH is capable of generating all possible types of recyclization graphs, and consequently also pairs of skeletons (the initial and final rings) with the necessary functional groups allowing the required transformation to occur. The program is constructed hierarchically: in the initial step, we can indicate the size of the initial and final rings, and then the size of the cyclic fragment common to both rings. Then the possible alternatives for the relative position of the broken and formed cyclic bonds are sorted, and in the final step the possible ways for arrangement of the heteroatoms in the recyclization graph are sorted. A suitable search option for the last step is specification of the structures of the initial (final) heterocycles with an indication of specifically which bond (bonds) in the ring is broken (formed). Such a template search is also a means for enumerating recyclizations of a specific heterocycle. Since the current version of the GREH program is designed only for generation of recyclizations of monocycles (azoles and azines), generation of possible recyclizations of bicyclic azolopyridines was a rather nontrivial problem.

In order to avoid the combinatorial explosion effect, we used generation with the following logical constraints: (1) retain the size of the opened ring; (2) do not use recyclization graphs with a spiro structure (corresponding to a large number of unlikely transformations, see [8-10]). An additional constraint was reduction of the size of the fragment to be inserted (displaced). We decided on only rearrangements (when nothing is inserted into the heterocycle and nothing is displaced from it) and very simple insertions and eliminations of monovalent groups (water, ammonia, etc.). The problem of going from monocycles to bicycles was solved by selecting those substituted monocycles (respectively pyridine and 1,3-azole) in which annelation of the 1,3-azole and pyridine nuclei at the CN bond is possible. For designing recyclizations, we required unambiguous indication in the template of specifically which bond is broken in the initial ring. Based on literature data (compare with Scheme 3), we should expect three possible directions for bond breaking in the bicycle (Scheme 4):

(a) breaking of the $C_{(5)}$ -N bond of the pyridine fragment, for example, in neutral heterocycles,

(b) breaking of the $C_{(9)}-X_{(1)}$ bond in the azole fragment, for example, the oxazolyl cation (X = O),

(c) breaking of the $C_{(2)}$ - $X_{(1)}$ bond in the azole fragment of mesoionic 2-oxo derivatives:



In this connection, the final selection of recyclizations was made only for those structures where rupture in the monocycle corresponds to rupture in the bicycle in Scheme 4. As a result of application of the enumerated constraints, the number of possible transformations was reduced from several hundred to a few tens. The most interesting of them (16 examples) were selected and are presented in Scheme 5. The overwhelming majority of them are unknown, and many seem

Scheme 5. Computer prediction of new recyclizations of bridged azolopyridines. On the left is indicated the recyclization graph for the transformation. The equation for the recyclization is represented symbolically with indication of the skeletons of the initial heterocycle, the hypothetical open form, and the final heterocycle. The oxygen heteroatom indicated in most of the initial structures is chosen only as one of the most likely heteroatoms.





quite reasonable and rather elegant. As noted above, the 1-oxaindolizines have the greatest tendency toward opening of the azole ring; accordingly, the heteroatom in the 1 position for the substrates in reactions (1)-(12) in Scheme 5 is labeled as an oxygen atom.

Prediction of the Polarity of the Functional Groups in the Substrates. As we see from the data in Scheme 5, a purely structural requirement for the occurrence of recyclizations of 1-heteroindolizines is the presence of suitable substituents in the 2, 3, 5, and 6 positions of the bicycle. An interesting problem arises: is it possible to draw any *a priori* conclusion concerning the polarity of the functional groups in the 2, 3, 5, and 6 positions which would simultaneously favor both stages of ring opening and stages of ring closure (cyclization)? We note that the stage of ring opening (for example, one of the three presented in Scheme 4) is the usual process of heterolytic bond breaking. The cyclization stage in turn also may be the usual polar process, including reaction of electrophilic and nucleophilic centers of the open form.

Detailed analysis of the possible distribution of polar functional groups in the initial substrates of reactions (1)-(16) in Scheme 5 leads to a curious conclusion. It seems that the most promising distribution of polarities of the functional groups in the starting compounds should follow a simple alternation principle. Although a 5+6 system on the whole is nonalternant, the presence of a pyridine fragment (with pronounced alternation) and an oxygen atom induces alternation of the donor—acceptor nature of the atoms both in the five-membered ring and in all the adjacent groups [5]. We may assume that the "node" (the coincidence of two minus signs) is strictly localized and falls on the C—N bond of the five-membered ring. This does not contradict our preliminary data from quantum chemical calculations. In other words, in the nonalternant graph of a bicyclic system, we can isolate an alternant acyclic fragment (tree), the arrangement of alternating donor—acceptor centers in which will occur in a "consonant" fashion [36]. (Let us recall that consonance means the possibility of placing labels of two colors so that electronegative heteroatoms have the same color.)

It seems that it is specifically such a distribution of polarities which will to the greatest degree stabilize both the initial and final ring. If we take this claim as a working hypothesis, then we can suggest that substrates potentially capable of the expected transformations should have a donor substituent at the $C_{(2)}$ and $C_{(5)}$ atoms and an acceptor group at the $C_{(3)}$ and $C_{(6)}$ atoms (Scheme 6). In this case, the "bicycle—open monocyclic form—bicycle" transformation will occur so that the original



Scheme 6. Alternant acyclic fragment in the initial nonalternant structure. Black and white labels correspond to nucleophilic and electrophilic atoms respectively. The arrows indicate the possibility of rotation of the fragments about the axes (passed through specific bonds of the open forms) and correspond to the different ways for closing the new ring.

alternation pattern (in Scheme 6) is also preserved in the bicycle formed. In fact, the placement of the labels in the open forms in Scheme 6 (and the requirement of heterolytic closure of the stable five-membered or six-membered ring) does not retain the open intermediates of the other alternative, except to form a 5+6 bicycle with the same distribution of polarities as in the initial structure. We note that such a rule for retention of the alternant (consonant) fragment in a previously nonalternant (dissonant [36]) structure may serve as a generalization of the previously formulated rules for polar control in heterocyclizations [37, 38].

Thus in designing structures of specific substrates for reactions (1)-(16) in Scheme 5, we should be guided by comparing them with the template (polar pattern) of Scheme 6.

DESIGN OF PREDICTED TRANSFORMATIONS

The final expert assessment of the transformations (1)-(16) to be designed should include selection of specific substrates for which occurrence of the expected recyclizations is most probable. It is not difficult to understand how we can go from the skeletal diagrams in Scheme 5 to real structures. First of all, the heteroaromaticity of the rings requires additions to the skeleton of the bicycle of the maximum number of multiple bonds (and specifically, four) and additional bonds to the exo substituents in the 3 and 6 positions. Secondly, comparison of the substituted structure with the donor—acceptor pattern of Scheme 6 gives a heuristic suggestion about the polar nature of the substituents. Finally, comparison of the initial structures in Scheme 5 with the structures in Schemes 2 and 4 allows us to unambiguously assign a neutral, cationoid, or mesoionic type to the initial bicycle. (We note in this connection that reactions (1)-(12) in Scheme 5 are numbered so that the even numbers correspond to cations while the odd numbers correspond to mesoionic structures; reactions (15) and (16) should be characteristic for neutral heterocycles.)

In order to accomplish the designed transformations, we need to have at our disposal substrates (especially oxazolopyridine derivatives) with a wide range of variation in functional groups in the 2, 3, and 5 positions. We note that synthesis of such functional derivatives of oxazolopyridines (especially 5-substituted) is an extremely weakly developed area of heterocyclic synthesis. So it is not surprising that the predicted transformations of substituted oxazolopyridines have not yet been observed. In this connection, discussing specific substrates capable of new recyclizations, we have attempted to also give an assessment of the strategies for their synthesis.

Design of Reaction (1). In accordance with the alternation hypothesis, the oxazolopyridinium cation should be substituted in the 3 position by an acceptor group, such as acyl. The expected transformation may look like the following (Scheme 7):

Scheme 7



Obviously the case R' = R'' would correspond to an unknown degenerate rearrangement. An example of a transformation of this type has been described for neutral 4-acyl(carboxy)oxazoles [39]. Nevertheless, such a rearrangement is unknown for oxazolium cations or for structures annelated at the C—N bond (as in ot case). The 3-acyl oxazolopyridinium cations required for experimental confirmation of this reaction are not yet known. For their synthesis, we can suggest a strategy involving expansion of the oxazole ring by an NCO fragment of 2-pyridone through the oxygen atom. We know that the reaction of 2-pyridone salts with acetylene leads to formation of 2-vinyloxypyridines, which when treated with bromine may undergo cyclization to an oxazolopyridinium cation. We assume that ketones of the acetylene series, methyl(aryl)ethynylketones, might enter into an analogous reaction with pyridone. Then on cyclization of the corresponding O-vinyl derivatives, the required 3-acyl derivatives might be formed, capable of reversible ring opening with formation of isomeric (also 3-acyl) cations in accordance with Scheme 7. Based on the alternation rule, we may assume that the driving force for the process (from left to right) would be the donor character of the R'' group compared with the R' group. It is of interest to assess the driving forces of this transformation from the standpoint of quantum chemistry.

Design of Reaction (2). In accordance with the alternation hypothesis, the one-carbon fragment to be eliminated (the $C_{(2)}$ atom of the initial system) should be electrophilic, i.e., may be represented by, for example, a carbon dioxide molecule. Then the starting compounds are known mesoionic 2-oxo-3-acyloxazolopyridines, which might be transformed to oxazolopyridinium cations (Scheme 8):

Scheme 8



The only problem is how easily this process will occur as a "one-pot" conversion.

Design of Families of Reactions (3). The Yur'ev reaction (exchange of the heteroatom in furan and its analogs) may serve as the prototype for such a family of recyclizations. As already noted, it is specifically for this family of recyclizations that a precedent is known when the X group is a primary amine. First of all, it is reasonable to study the prospects for rather simple reactions of exchange of the oxazolopyridinium oxygen heteroatom for a new heteroatom (nitrogen or sulfur) with formation of respectively bridged imidazopyridines or thiazolopyridinium compounds. Possibly selenide and telluride ions may prove to be promising nucleophiles. Secondly, a less trivial transformation will be substitution of the oxygen atom by a carbon (binucleophilic) center, say when using alkyllithium or alkylmagnesium reagents, anions of nitromethane, DMSO (possibly malonic acid), the Reformatskii reagent, etc. The resulting compounds obviously appear to be 1-substituted indolizines.

Design of Reaction (4). This rearrangement (a "pure" case of the Dimroth rearrangement in the azole series) is the least likely. Nevertheless, there exists a precedent for its occurrence for the mesoionic aza analog of the considered system: 2-methylimino-oxa-3,4-diazolo[3,2-*a*]pyridine [40]. Accordingly, we may also expect an analogous isomerization for the case of the mesoionic 2-alkylimino derivative of oxazolo[3,2-*a*]pyridines. Synthesis of the original structure probably requires N-alkylation of 2-pyridone by bromoacetamide derivatives followed by cyclization.

Design of the Family of Reactions (5)-(8). As follows from the data in Scheme 5, in reactions (5)-(8) the group X initially located in the 5 position of the initial oxazolopyridine is involved in formation of the new azole ring. According to the alternation rule, this group should be a donor group, and in the open form it proves to be an a substituent on the pyridine ring and consequently its nucleophilic properties should be rather pronounced. Examples of such a substituent might be NH₂, OH, SH groups and even a methyl group. In the latter case (Scheme 9), recyclization would make it possible to go to the as yet unknown class of 5-substituted indolizines, as for example in the reaction (5):

Scheme 9



We have already synthesized the 5-methyloxazolo[3,2-a] pyridines required for such a reaction [3]. It is quite likely that such recyclization may also occur in the case of thiazolo- and imidazolopyridinium cations.

Design of the Family of Reactions (9)-(12). A distinguishing feature of this family of recyclizations is the requirement for closure of the new ring at the $C_{(5)}$ atom of the original system. According to the alternation rule, the $C_{(5)}$ atom of the original bicycle should be electrophilic. It is reasonable to suggest that for facile formation of the new bond at the $C_{(5)}$ atom, this atom might contain some leaving group Y, displaced during recyclization. (This group is not indicated on the diagrams for Scheme 5, since in contrast to all the rest of the atoms, it is not included in either of the rings.) An example of such a transformation for reaction (1) might look like the following (Scheme 10):

Scheme 10



The nucleophilic group X may either be an external nucleophile (for example, an ammonia or amine molecule), as in reactions (9), (10), or be present in the side chain of the original substrate in reactions (11), (12).

Obviously, we need to synthesize the starting oxazolopyridines with a leaving group (such as a halogen atom) in the 5 position. We have currently developed a synthesis route for such oxazolopyridines (both mesoionic and cationoid), using 2,6-substituted pyridines (2,6-dihalo-, 2,6-dialkoxy-, 2-halo-6-alkoxypyridines) as the original substrates in reaction with halocar-

bonyl compounds. More available substrates are the thio analogs of the indicated oxazolopyridines; however, it is less likely that the C-S bond undergoes such a facile heterolysis as the CO bond (compare Schemes 3c,e).

Characteristic features of reactions (13)-(16). Both cationoid or mesoionic structures (Y = O) and uncharged imidazopyridine structures (Y = N) might serve as substrates for recyclizations (13), (14). In the first two cases (Y = O), the initial stage should be opening of the oxazole ring, while in the case Y = N the initial stage may be closure of the azacyclazine structure (as in the known reaction on Scheme 3b) followed by hydrolytic cleavage of such a tricyclic intermediate with formation of a new bicycle.

Recyclization according to the reaction type (16) is known only for monocyclic 3-cyanopyridine. Attempts to realize this reaction in the 6-cyanoindolizine series have not yet been successful [41], and for the case of 6-cyano derivatives of imidazo[1,2-*a*]pyridine derivatives it has not been attempted at all. A possible substrate for the reaction might be 6-cyano-8-nitroindolizine, sufficiently activated for nucleophilic attack, or its 1-aza analog. Rearrangement (15) is a known example of the classical Dimroth (X = N) or Kost—Sagitullin (X = CH) rearrangement (compare with Scheme 3a). This reaction does not present fundamental novelty, but its occurrence as a sequential process, accompanying another recyclization (see below), is of specific interest.

DEGENERATE, PARALLEL, AND SEQUENTIAL RECYCLIZATIONS

Degenerate recyclizations. Earlier we formulated a simple symmetry criterion for which recyclization of a given heterocycle may be degenerate or "almost degenerate" (quasidegenerate) [11]. This criterion involves the presence of specific symmetry elements in the recyclization graph, or more precisely, the characteristics of the automorphism group of such a graph. It is not difficult to see that this principle is easily generalized from the case of monocycles to the case of bicyclic heterocycles. For this, we should look for symmetry elements in the structure of the recyclization graph shown on the left-hand column of Scheme 5. The required symmetry elements are present in the graphs of reactions (1), (3), (4), (6), (8), (9), (11), (15), (16) and are missing in the rest of the graphs. (Of course, we need to identify the labels of the heteroatoms, replacing as necessary the pairs of heteroatoms of the set (X, Y, N, O) by identical ones.) For the enumerated cases, it is theoretically possible to have both degenerate recyclizations (when the structures of the initial and final structures are indistinguishable) and quasidegenerate recyclizations (when the difference between the structure of the initial and final systems involves only the presence of a "label," a substituent or heteroatom).

Parallel Recyclizations. In a number of cases, the original substrates of the reactions in Scheme 5 either differ only in the number/location of the functional groups, or are generally identical in structure. In such cases, we cannot draw *a priori* conclusions concerning the direction of recyclization. We can only expect an unambiguous direction of opening, but the selectivity of closure of the new ring is not quite definite. This situation is most graphically represented for the open forms in Scheme 6, where the lines with arrows indicate the possible axes of rotation for the acyclic fragments before closure of the new ring, and the presence of several axes is equivalent to the occurrence of parallel processes. In particular, parallel processes are most likely in reaction of cationoid substrates, as for example in reactions (1), (5), (7), (9), (11), (13), when treated with an external nucleophile. In these reactions, the concurrent process may occur according to the type of reaction (3) (the Yur'ev reaction) with simple exchange of the heteroatom in the 1 position for the external nucleophile. Analogously, in the case of opening of 3- and/or 5-substituted mesoionic systems at the $C_{(2)}$ —O bond, a polydentate system is formed, capable of concurrent closures of a new azole ring (compare reactions (6), (8), (10), (12), (14)). Finally, concurrent closure of the six-membered ring is also possible in the case of the reaction pair (15), (16).

A more interesting case is sequential recyclizations, when the recyclization product formed is a suitable substrate for a new recyclization.

Double Recyclization of the Azole Ring. We have high hopes for the possibility of the occurrence of sequential recyclizations using mesoionic 3-acyl-substituted structures. The first recyclization may be transformation according to reaction (4) with formation of an oxazolopyridinium cation, tending toward new recyclizations in various directions, such as according to reaction (3) (Scheme 11):



As we know, the classical synthesis route for oxazolopyridinium cations includes reaction of pyridone with haloketones, while the expected recyclization (3) of mesoionic systems (obtained from pyridone, haloacetic acid, and acid halides) allows us to synthesize such cations with broader variation in the functional groups R in the 2 position. In turn, the carboxylic acid residue R will enter into the structure of further products of new recyclizations.

Sequential Recyclization of Oxazole and Pyridine Rings. We attach exceptional importance to the possible reaction of exchange of the oxazolopyridinium oxygen atom for a carbon atom with possible formation of indolizine-1-carboxylic acids (and their esters), which will occur according to Eq. (4) (X — carbon atom). It is well known that such acids of the indolizine series tend toward very facile (acid and base) decarboxylation. If we can accomplish a similar insertion of a carbon atom in the example of 6(8)-nitro-substituted oxazolo[3,2-*a*]pyridines, then the 6(8)-nitroindolizines formed or their 1-carboxy derivatives will be capable of further Kost—Sagitullin transformation to 5(7)-nitroindoles, i.e., according to Eq. (15) (Scheme 12).





It is not difficult to imagine a unique "ternary recyclization" (superposition of Schemes 11 and 12), where the mesoionic system (a) would be converted to a cation, (b) the cation would be converted to indolizine and (c) the indolizine would be converted to indole. Accordingly, special interest is aroused by the possibility of synthesis and study of the reactivity of the starting 2-oxo-3-acyl-6(8)-nitro de ivatives of oxazolopyridines. It is not difficult to foresee that as far as reactivity is concerned, these systems and the cations formed from them may be ambident with respect to nucleophiles, opening the oxazolium or pyridinium ring. The chemical structure of the cationoid system may be symbolically represented as a tightly compressed spring in the form of the letter S, the ends of which (pressed against the CN bond of the bicycle on different sides) may straighten out in any direction. Synthesis of such derivatives is not yet known, although their direct precursor, 1-carboxymethyl-5-nitro-2-pyridone, is described in the literature.

CONCLUSION

In the first communication in this series [10], we limited ourselves to classification of simple transformations of heterocycles and enumeration of "missing" recyclizations of monocyclic hetarenes, addressing these predictions to a wide circle of organic chemists. In this communication, we added computer sorting of interesting and as yet unknown recyclizations of bridged 5+6 heterocycles with our expert assessment of the probability of their occurrence, declaring our own intention to observe the predicted reactions experimentally. Representative results of our experimental investigations have proven to be rather encouraging [42,43], and will be the subject of later publications.

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