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RING CLEAVAGE REACTIONS IN THE SERIES OF AZOLOAZINES WITH A BRIDGING NITROGEN ATOM (REVIEW)

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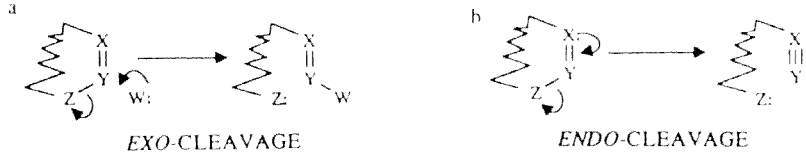
Extensive data on the opening reactions of both the five- and the six-membered fragments of the bicyclic structures of azoloazines with a bridging nitrogen atom (i.e., the aza, oxa, and thia heteroanalogs of indolizine), including the reactions leading to recyclization, are categorized systematically for the first time. A universal model is proposed for classification of the ring opening processes in azoloazines (according to the principle of endo or exo opening in heteroarenes), and an attempt is made to relate the direction of ring opening in heteroarenes to alternation (or loss of alternation) in the fragments of the heterocyclic ring.

A considerable amount of empirical data on the opening reactions of the bicyclic system has now accumulated for azoloazines with a bridging hydrogen atom (azaindolizines or their S- or O-heteroanalogs). The cleavage of various bonds in the five- or six-membered ring is possible, depending on the reaction conditions, the position of the heteroatoms in the ring, and the presence and nature of substitution, and in many cases the result is not immediately obvious. Therefore, apart from classifying the data and revealing the main trends in the cleavage of the rings, the aim of the present work was to attempt to relate the presence of one or the other structural feature of the substrate to a specific direction of opening. While striving for the first time to embrace the data in all its variety, we included in the treatment both well-studied examples and other examples of the opening reactions in heterosubstituted indolizines.

The review is assembled in the following way. First, comments essential for structuring the data are made on the general classification of the opening processes in heterosubstituted indolizines. Then, in the main part, the opening reactions themselves are discussed. Systems containing only nitrogen atoms as heteroatoms in the ring and systems containing sulfur or oxygen in addition are examined separately. Finally, a simple model is proposed to describe the various facts presented in the main part of the article in a unified manner.

I. TYPES OF RING OPENING REACTIONS

Among the polar ring opening reactions (as mentioned by Stirling, mainly for saturated systems [1]) it is possible to distinguish two main types. In the first of them ring opening is accompanied by the formation of a new bond between an atom of the former ring Y and some external atom W, which may be or may not be initially attached to the ring. The initiating stage of the process is the displacement of the unshared pair of the nucleophilic *exo* atom W; nucleophilic substitution can consequently be considered a prototype of this reaction. We will arbitrarily call this type of opening *exo cleavage*.



EXO-CLEAVAGE *ENDO*-CLEAVAGE

Scheme 1. Types of ring opening processes.

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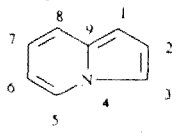
In the second type of ring opening the presence of the external nucleophile is not required: The opening of the ring at the Y – Z bond results from the formation of a new bond X – Y between the atoms of the former ring (Scheme 1b). The motivating force of the process is the displacement of the unshared pair, which must necessarily be situated at the *endo* atom X of the initial ring. The elimination process can be considered a prototype of this reaction. Thus, we will consider the most general level of the classification to be the assignment of the opening reaction to the *exo* or *endo* type. Earlier, we demonstrated the effectiveness of such a classification as applied to the opening of monocyclic heteroarenes [2].

During the presentation of data we will use designations indicating both the position of the breaking bond and the direction of cleavage, marking the direction of the shift of the electron pair by an arrow. Thus, Scheme 2 shows the simplest representative of the investigated class, i.e., indolizine. By the term "5 → 4 opening" we mean the heterolytic cleavage of the 4 – 5 bond in the skeleton of the heterosubstituted indolizine, as a result of which the electron pair moves to the $N_{(4)}$ nitrogen atom.



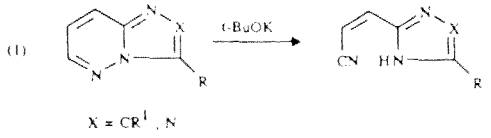
Scheme 2

Below we will use indolizine as common prototype both for naming its heteroanalogs and for numbering the atoms in them, using the generally accepted numbering of the skeletal atoms shown in Scheme 2.

II. NITROGEN-CONTAINING SYSTEMS (AZA- AND POLYAZAINDOLIZINES)

II.A. Opening of the Six-Membered Ring

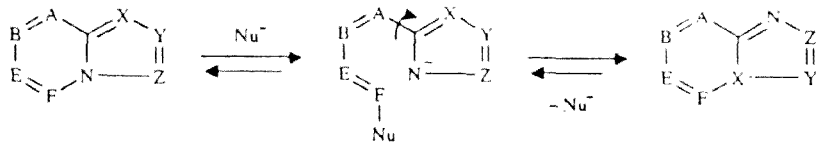
Before discussing the various forms of ring cleavage in detail, we consider it necessary to point out one interesting feature of these reactions. The six-membered ring of such bicycles is very rarely opened by the *endo* mechanism presented above in Scheme 1b. One of the few exceptions is the opening of 5-aza derivatives of azaindolizines by the action of strong bases (example **1**). In terms of our classification this reaction is characterized as 5 → 4 *endo* opening.



(1)

The reasons preventing *endo* cleavage of the six-membered rings will be examined during discussion of the theoretical model describing the opening processes in aza- and hetero-substituted indolizines (section V). At present we merely emphasize that the opening reactions of the six-membered ring in the bicycle discussed below will apply exclusively to the *exo* processes.

II.A.1. 5 → 4 Cleavage Followed by Recyclization. Most of the papers devoted to the opening and the rearrangements of azaindolizines describe the *exo* cleavage of the 5 → 4 bond. One of the most familiar examples of this type of opening is the Dimroth rearrangement, shown in Scheme 3. It represents cleavage of the 5 – 4 bond during attack by the nucleophile at position 5 and the formation of a new 5 – 1 bond with closure of a new six-membered ring. If there is a plane of symmetry in the open form (passing through the $C_{(9)}$ – A bond and the azole ring), the recyclization may be an example of a degenerate rearrangement.



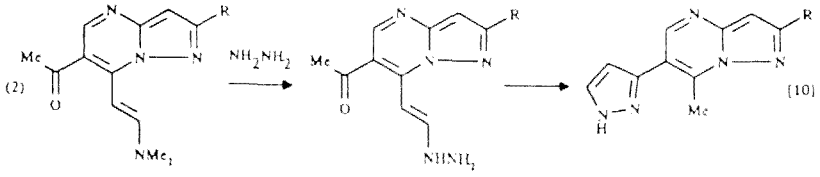
Scheme 3. Dimroth rearrangement in the series of azaindolizines with 5 → 4 *exo* cleavage.

The dependence of the ease with which this rearrangement occurs on the position of the heteroatoms and the substituents in the bicycle has been the subject of discussion in a series of papers. The main relationships governing this recyclization were summarized in the reviews [4, 5]. It was found that the rearrangement takes place most readily in the presence of aza or accepting substituents at positions 6 and 8 (i.e., at the *meta* positions of the six-membered ring in relation to the bridge atom). Thus, for example, in the series of bridged imidazoazines (Scheme 3, X = N; Y, Z = C) the alkyl-substituted imidazo[1,2-a]pyridines do not undergo rearrangement, whereas for the 6- or 8-aza-substituted bicycles the reaction takes place under fairly mild conditions. Here, the 1,6-diazaindolizines are transformed more readily than the 1,8 isomers [4]. The presence of a 6- or 8-nitro group makes rearrangement of the ring in imidazo[1,2-a]pyridines possible [6]. Alkyl-substituted 1,7-diazaindolizines, on the contrary, do not enter into the reaction.

The same relationship can be traced in the series of bridged triazoloazines (X, Y = N; Z = C), but account must be taken of the fact that for this series the rearrangement takes place more readily than in the previous case. Thus, the 1,2-diaza- and 1,2,7-triazaindolizines containing the triazole fragment (unlike the imidazo derivatives) nevertheless undergo the transformation after prolonged boiling in an aqueous solution of alkali. In other respects the situation is similar to that discussed above; the presence of the 6(8)-aza or accepting substituents makes the conditions of the rearrangement much milder [4]. It is worth mentioning that the equilibrium in this series is greatly shifted toward the formation of the 1,3-diaza derivatives (X, Z = N; Y = C).

A reaction related to the Dimroth rearrangement is the transformation of indolizines into indoles (Kost–Sagitullin), the main difference in which is the irreversible nature of the transformation of the six-membered pyridine fragment into a benzene ring (see the reviews [7-9]). An essential condition for the transformation is the presence of a nitro group at position 6 or 8. The additional presence of weak acceptors (e.g., acyl groups) at position 3 of the nitroindolizines promotes the rearrangement, while the presence of strong acceptors (a nitro group) hinders the reaction, preventing the concluding cyclization of the open form. Indolizines with acceptors only in the five-membered ring (the 1- or 3-nitro derivatives) do not enter into the recyclization, while the presence of only weak acceptors in the six-membered ring [6(8)-acetyl or cyano group] is likewise insufficient.

Other types of rearrangement (apart from the Dimroth rearrangement) in azaindolizines with 5 → 4 *exo* opening at the initial stage are less familiar. One such alternative transformation is the recently discovered recyclization of 3,8-diazaindolizine under the conditions of hydrazinolysis (example **2**). In this case 5 → 4 cleavage is accompanied by the closure of the acetyl residue at position 6 at the $N_{(4)}$ atom.



(2)

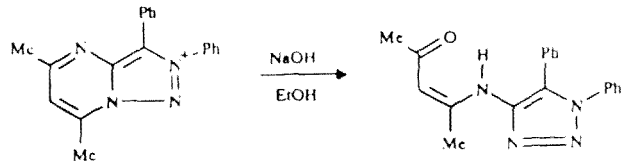
II.A.2. 5 → 4 Cleavage of Bicycles with the Formation of Monocycles. In contrast to the examples examined above in most cases a new ring is not formed after 5 → 4 cleavage, and the product is a monocyclic system. The reasons for this may be the following.

1) The substrate of the reaction is a cation; in the course of the reaction, accompanied by 5 → 4 cleavage, the charge is extinguished. The reactions of 1,2,3-triazaindolizinium cations with nucleophiles have been studied most in this respect. During the action of various reagents (alkoxide ions, amines, nitrogen heterocycles) 5 → 4 cleavage of the ring occurs with the formation of various stereoisomers of 1,4-substituted dienes (example **3**, X = N) [11-14]. Similar opening is observed in the case of 2,3-diazaindolizinium cations (X = C–Me, C–Bu-t) [12].

(3)

X = N, C-Alk; Y = H ($NaBH_4$), OR, NR_2, CN, aziridine, imidazole, indole, and others.

Similar behavior from the substrate was observed during the opening of 2,3,8-triazaindolizinium salts by the action of alkali (example **4**).

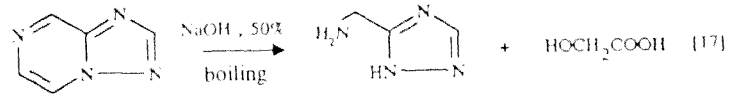


(4)

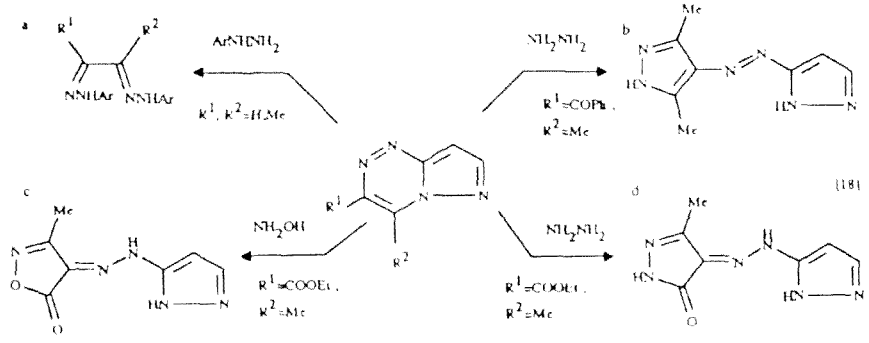
2) Nucleophilic substitution at the trigonal carbon atom $C_{(5)}$ takes place irreversibly by virtue of specific features of the nucleophile, e.g., during hydride reduction (example **5**).

(5)

3) During azasubstitution in the six-membered ring in addition to 5 → 4 cleavage another bond is cleaved with the formation of a shorter chain. The type of associated cleavage is determined by the position of the aza substituent. Thus, in 7-aza-substituted bicycles not containing heteroatoms at positions 5 and 6 the most likely associated cleavage will be 6 → 7 cleavage (examples **6** and **7a**). It is worth mentioning that if bidentate nucleophiles are used and there are *exo* substituents capable of condensation in the initial heterocycle the formation of a new ring can be observed instead of the associated cleavage (examples **7b-d**).

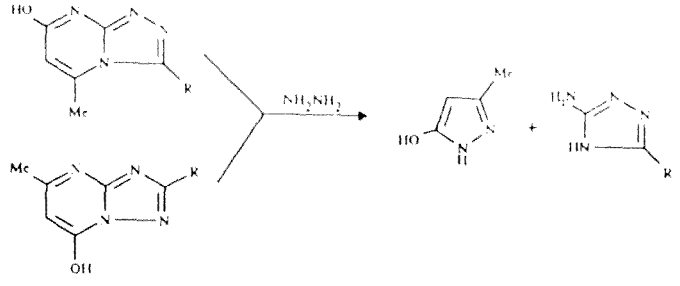


(6)

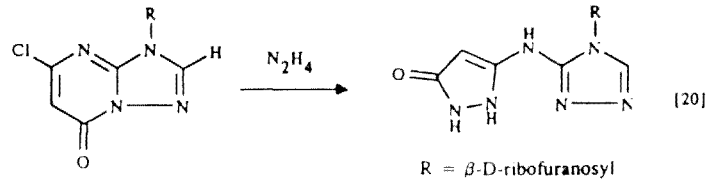


(7)

The associated 7 → 8 cleavage is most probable in the reaction of nucleophiles with 8-aza-substituted bicycles. Aminoazoles and a three-carbon chain, substituted at the terminal positions by the residues of the nucleophile, are formed as a result of the reaction. In the case of a bidentate nucleophile a new heterocycle is formed (examples **8-10**).



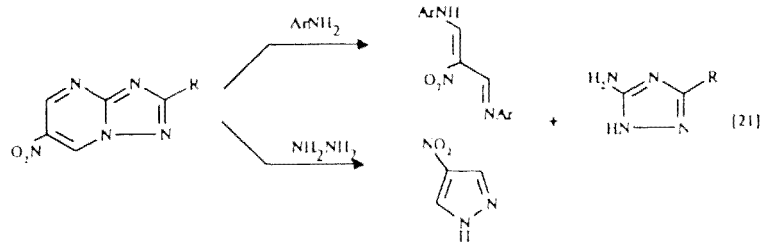
(8)



[20]

(9)

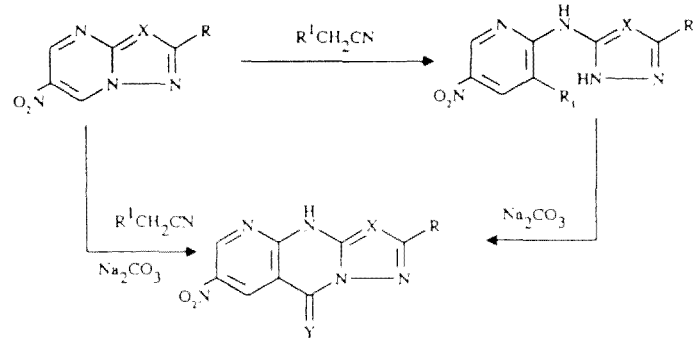
R = β-D-ribofuranosyl



[21]

(10)

A similar reaction takes place when malonic acid derivatives are used as bidentate nucleophiles. The reaction product readily closes a ring, and this was used in an elegant rearrangement, during which a tricyclic structure with the inserted four-atom block of the former nucleophile is formed (example **11**):

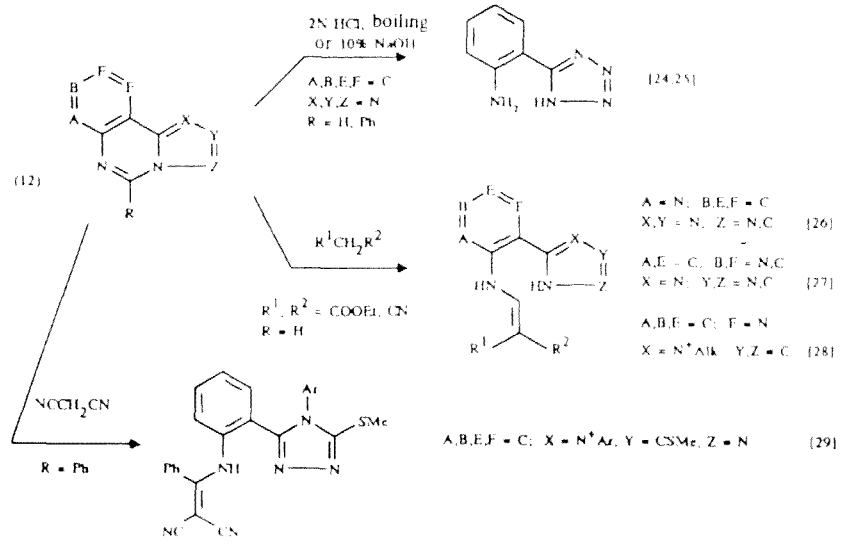


[22,23]

(11)

R = H, Alk, Cl, CF_3, SMe, NH_2NMe_2; X = N, CCOOEt, CNO_2; R^1 = $CONH_2$, $CSNH_2$, CN; Y = O, NH

The question as to which of the cleavages takes place first cannot always be resolved unambiguously in favor of the 5 → 4 process. Thus, for the last reaction (example **11**) it is possible on the basis of the structure of the obtained compounds to propose a mechanism according to which the nucleophilic center of the reagent attacks the $C_{(7)}$ atom, and 7 → 8 cleavage takes place before or at least simultaneously with 5 → 4 cleavage.



[24,25]

[26]

[27]

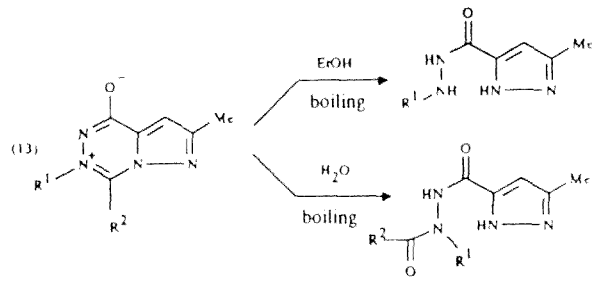
[28]

[29]

(12)

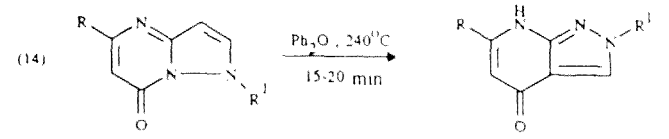
In the series of tricyclic structures the opening reactions for azoloquinazolines and their aza analogs under the influence of nucleophiles have been studied most. Here, the associated 5 → 6 cleavage (example **12**) can be observed alongside 5 → 4 cleavage. It is worth noting, however, that such bond cleavages only take place readily in the presence of three or four nitrogen atoms in the five-membered ring. The derivatives of imidazoquinazolines are not cleaved under analogous conditions; opening requires quaternization of the $N_{(1)}$ atom in the five-membered ring [28]. The authors explain this fact by the weak ability of the imidazole ring to draw off electron density.

Thus, the presence of the heteroatom at position 6 promotes both 5 → 4 opening and the associated 5 → 6 cleavage. This fact can be illustrated in the case of the opening of the mesoionic pyrazolotriazinone under the conditions of hydrolysis or by the action of alcohol (example **13**).

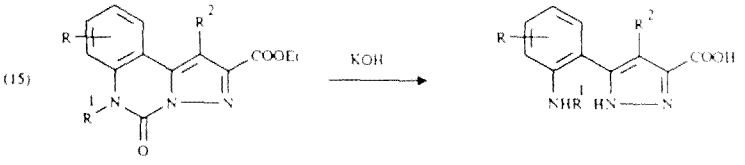


(13)

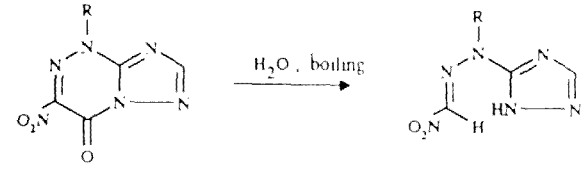
In addition, the 5 → 4 cleavage is greatly facilitated if the 5-4 bond is an amide bond, i.e., in the series of 5-oxo derivatives of azaindolizines. Some reactions of such tri- and bicyclic substrates are represented by examples **14-18**. Depending on the structure and the experimental conditions, the cleavage products can undergo cyclization again by a rearrangement of the Dimroth type (example **14**) or undergo further degradation (examples **15-17**).



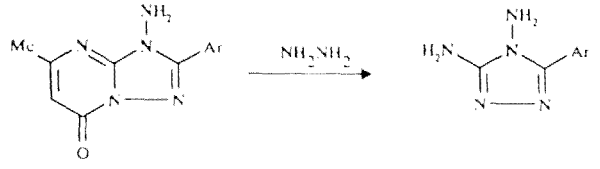
(14)



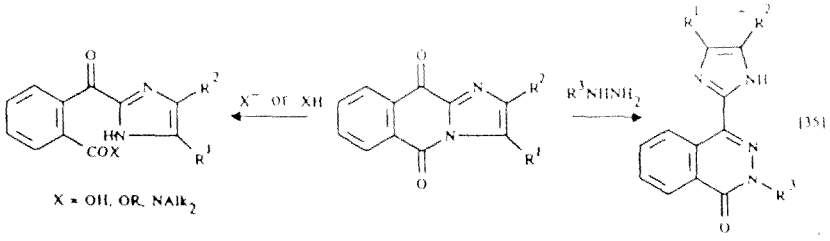
(15)



(16)

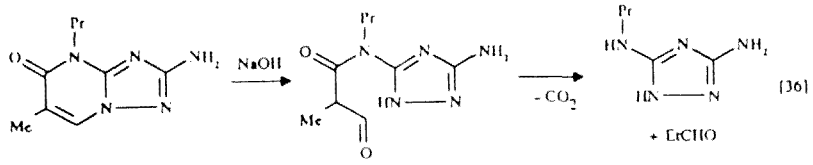


(17)



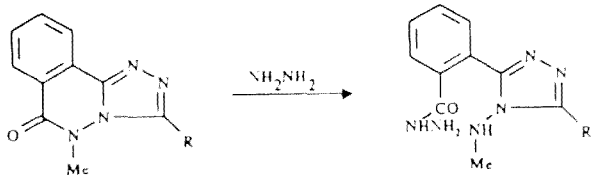
(18)

It is interesting to note that in certain cases the presence of an oxo group at position 7 of the bicycle also promotes 5 → 4 opening (example **19**):

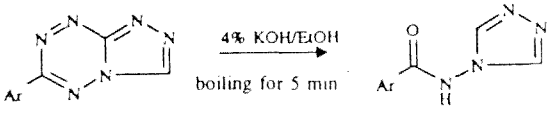


[36] (19)

II.A.3. Opening Reactions of the Six-Membered Ring Not Accompanied by 5 → 4 Cleavage. Alternative forms of cleavage of the bonds in the six-membered ring not accompanied by 5 → 4 cleavage are encountered quite rarely. An essential condition for this is the presence of heteroatoms at position 5 or 7. Such a structure in the substrate can result, for example, in 6 → 5 (example **20**) and 6 → 7 (example **21**) opening.

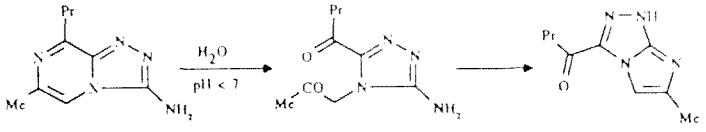


[37] (20)

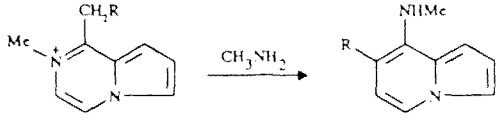


[38] (21)

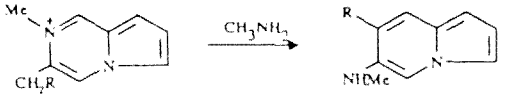
Protonation (example **22**) or quaternization (examples **23** and **24**) at these positions also promotes alternative forms of opening. Thus, the transformation of quaternized 7-azaindolizines into indolizines results from initial 6 → 7 cleavage (example **23**) or 8 → 7 cleavage (example **24**) followed by recyclization.



[39] (22)



[40] (23)

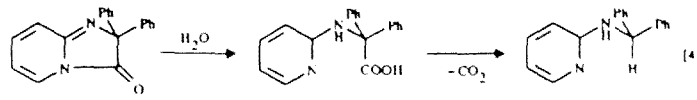


[41] (24)

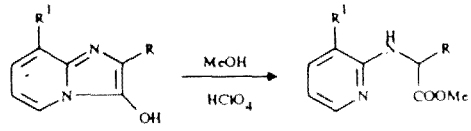
II.B. Opening of the Five-Membered Ring

Just as 5 → 4 cleavage is most typical for the opening of the six-membered ring of the bicycle, cleavage of the bond adjacent to the bridging nitrogen atom, i.e., 3 → 4 cleavage, takes place most often in the case of the opening of the five-membered ring in azaindolizines. Here, however, in contrast to the openings of the six-membered part of the bicycle cleavages of both *exo* and *endo* type take place equally often.

II.B.1. 3 → 4 Cleavage of the *exo* Type. As also in the case of the six-membered ring, *exo* openings take place readily if the center of the substrate undergoing nucleophilic attack contains a donating (oxo) substituent. Thus, under the influence of nucleophiles 3-hydroxy(oxo)imidazo[1,2-a]pyridines quickly cleave the five-membered ring at the 3-4 bond with the formation of a pyridine ring (examples **25** and **26**):



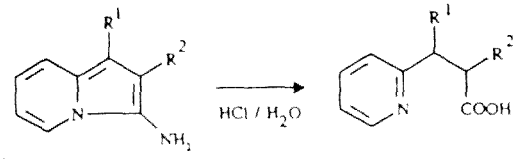
[42] (25)



[43] (26)

R = Me, Ph; R^1 = OCH_2Ph, NO_2

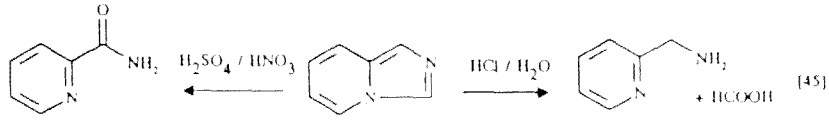
Analogous opening is observed during the hydrolysis of 3-aminoindolizines (example **27**).



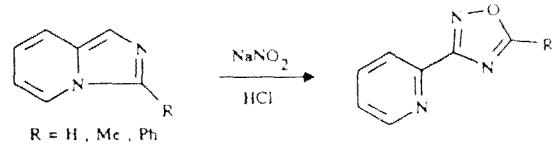
[44] (27)

R^1, R^2 = H, Ph

In the case of imidazo[1,5-a]pyridines, however, additional activation of position 3 is not required. In an acidic medium the hydrolysis of such structures takes place fairly readily (example **28**). Moreover, the formation of 3-(α-pyridyl)-1,2,4-oxadiazoles is observed during the diazotization of these substrates (example **29**).



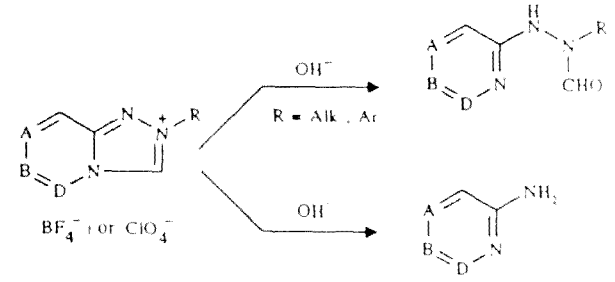
[45] (28)



R = H, Me, Ph

[46] (29)

Quaternization at the nitrogen atom at position 2 also activates azaindolizines to 3 → 4 *exo* opening. Thus, 1,2,4-triazoloazinium salts quaternized in a similar way are easily opened by the action of alkalis with the formation of aldehydes or, in some cases, aminoazines (example **30**).

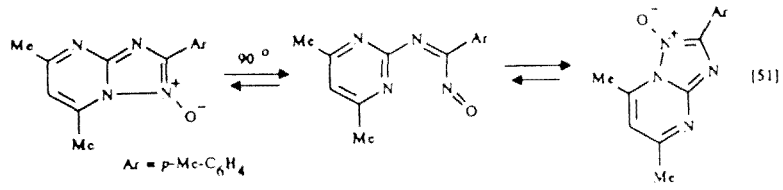


R = R^1COCH_2, $NCCH_2$, R^1OOCCH_2

A = CH, B, D = CH or C - benzo [47]
A = N; B, D = C - benzo [48]
A,B = C - Alk, Ar, D = N [49]
B = C - Ar; A, D = N [50]

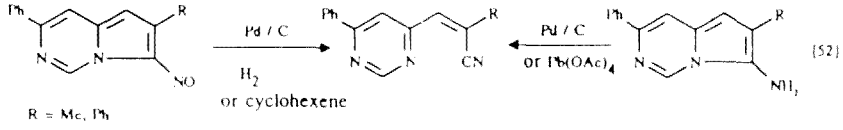
(30)

Another interesting case of 3 → 4 *exo* cleavage is the equilibrium opening of substituted 1,2,4-triazolo[1,5-a]pyrimidine 3-oxide at elevated temperature, studied by NMR (example **31**):

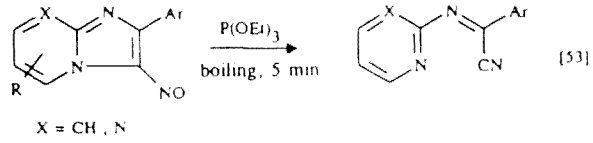


(31)

The examples presented above show that the presence of a 3-donating substituent (in particular) or a 2-aza substituent promotes 3 → 4 *exo* cleavage. There is, however, another process of cleavage in the five-membered ring, which can be assigned formally to the 3 → 4 *exo* type but which is not nevertheless the result of nucleophilic substitution. It is the deoxygenation of the 3-nitroso derivatives of azaindolizines (examples **32** and **33**). In this case the specific character of the substituent in the substrate, which assists 3 → 4 *exo* cleavage under the influence of nucleophiles, does not probably play a determining role.

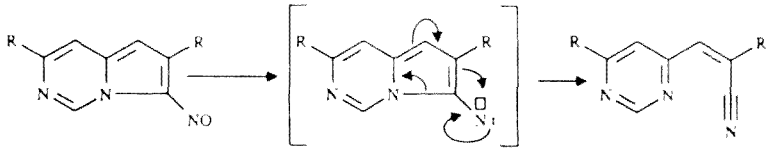


(32)



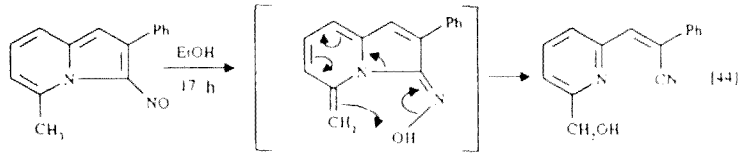
(33)

It is supposed that in this case the reaction takes place through the formation of nitrene at position 3 of the bicycle (Scheme 4). Such ring-opening processes in the presence of a carbene or nitrene center at the α position to the breaking bond are well-known for mononuclear five-membered heterocycles (see the reviews [54, 55]).



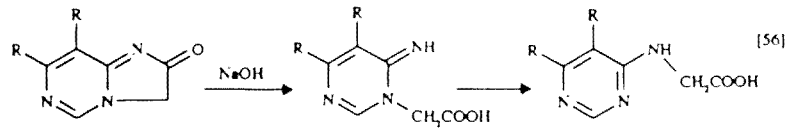
Scheme 4

It is interesting to note that for 3-nitroso-5-methylindolizines, as supposed, intramolecular oxidation of the methyl substituent at position 5 is observed under the conditions of ethanolysis. In this case too the process can be represented as 3 → 4 *exo* cleavage (example **34**).



(34)

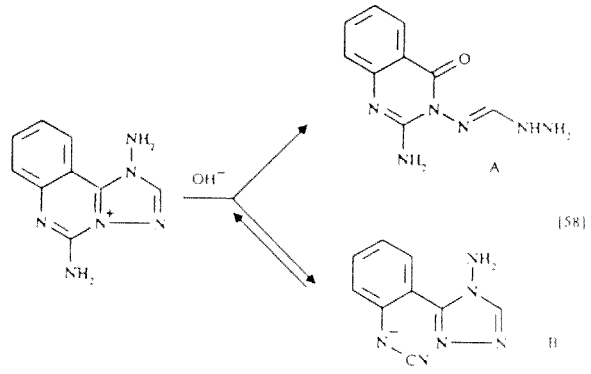
II.B.2. Alternative Forms (2 → 1 and 9 → 1) of the *exo* Cleavage of the Five-Membered Ring. Other forms of the *exo* opening of the five-membered ring can be observed with a donating substituent (e.g., oxo) at position 2 of the bicycle and with the presence of a heteroatom at position 1. With a substrate having such a structure *exo* cleavage of the 2 → 1 type is possible under the influence of nucleophiles. The formation of N-(4-pyrimidyl)glycine during the alkaline cleavage of imidazo[1,2-c]pyrimidin-2-ones was interpreted from this standpoint (example **35**). The first stage, according to the interpretation by the authors in [56], is 2 → 1 *exo* opening of the cyclic system, and the second stage is a Dimroth rearrangement in the pyrimidine ring.



R = H or [c]pyrazolo

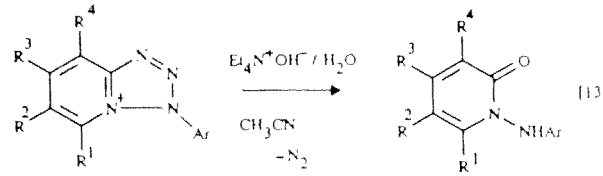
(35)

Another possible path for the opening of the five-membered ring, 9 → 1 cleavage, has also been observed quite rarely in the azaindolizine series. In this connection we note that there is the single observation (not confirmed or refuted by anyone) by Chichibabin that the salts of 1-azaindolizines open the imidazole ring under the influence of alkalis [57]. On the other hand, 5 → 4 opening is observed in most cases during the action of nucleophiles on 1-aza-substituted substrates containing additional nitrogen atoms in the bicycle. If the 9 → 1 cleavage does occur, concurrent 5 → 4 cleavage frequently accompanies it. Thus, during kinetic investigations of the alkaline hydrolysis of substituted 1,2,4-triazolo[1,5-c]quinazolinium (example **36**) the reversible formation of the anion (B) as a result of 5 → 4 cleavage of the six-membered ring was established in addition to the formation of the product of 9 → 1 opening (A), isolated as a result of the reaction.



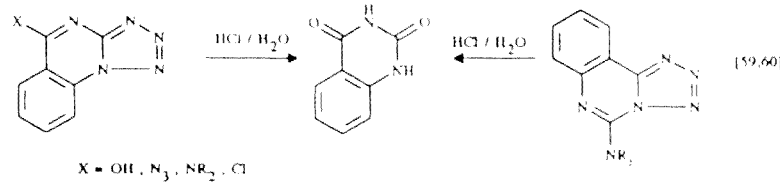
(36)

In addition, it was found that the benzo derivatives of 3-aryltetrazolo[1,5-a]pyridiniums, unlike the unannellated analogs studied in the early papers (example **3**), undergo 9 → 1 opening with the ejection of a nitrogen molecule under the influence of alkalis (example **37**). A similar type of cleavage was observed earlier during the acid hydrolysis of various tetrazoloquinazolines (example **38**).



a R^1, R^2 = benzo; R^3, R^4 = H; b R^3, R^4 = benzo; R^2 = Br, R^1 = H; c R^1, R^2 and R^3, R^4 = benzo

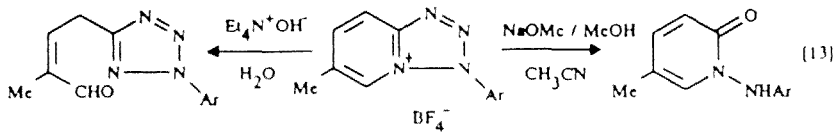
(37)



X = OH, N_3, NR_2, Cl

(38)

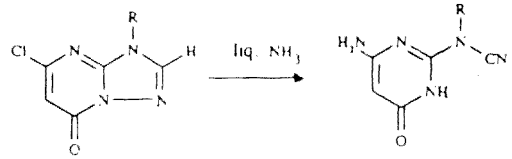
This fact prompted the authors in [13] to reexamine the previously obtained results on the opening of bicyclic substrates. In fact, it was found that both 5 → 4 and 9 → 1 cleavage can occur preferentially under the various reaction conditions. The most convincing evidence for such ambident reactivity was obtained for the 6-methyl derivative (example **39**).



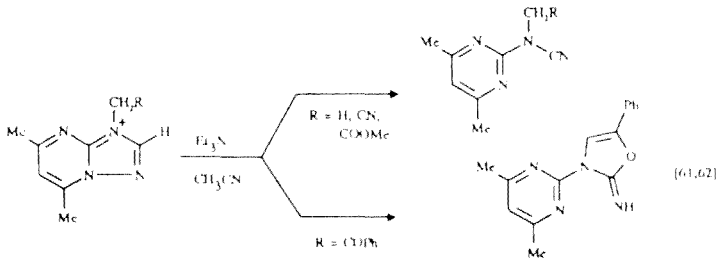
(39)

II.B.3. 3 → 4 *endo* Opening of the Five-Membered Ring in Azaindolizines. The main difference in the reactivity of the five-membered ring of azaindolizines from the six-membered part of the heterocycle is the ability to undergo *endo* cleavage of the ring [2]. We recall that the motivating force of cleavage in this case is the transformation of the unshared pair at the *endo* atom of the ring into a new bond between the atoms of the former ring (Scheme 1b). Such reactions are not a rarity for monocyclic five-membered heterocycles (see the review [54]), and it is not surprising that this type of cleavage is also encountered among the opening reactions of azaindolizines.

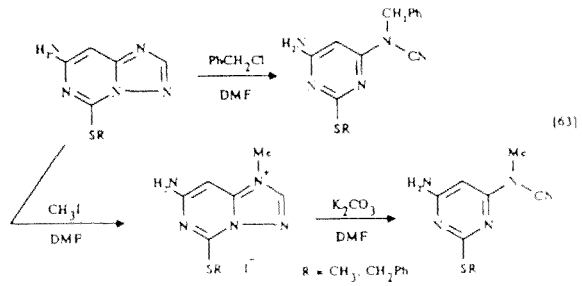
The *endo* cleavage of the 3 → 4 type is most often encountered among the investigated structures. Thus, the derivatives of 1,3,4-triazoloazines not substituted at position 2 easily undergo 3 → 4 *endo* cleavage under the influence of bases (examples **40-42**). Opening does not occur in the case of the 2-alkyl derivatives [62].



(40)



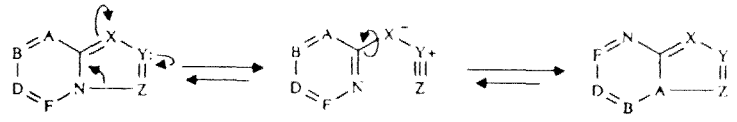
(41)



(42)

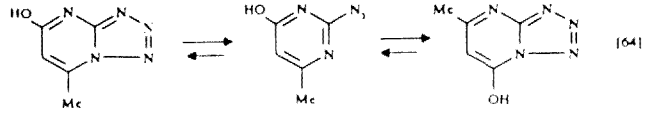
In addition, there may be a nitrogen atom with an unshared pair at position 2 of the bicycle. The best-known example of 3 → 4 *endo* opening in such structures is the azidotetrazole equilibrium observed for various tetrazoloazines (e.g., see [5]).

In the case of 8-aza-substituted structures, however, *endo* opening can be the first stage in various rearrangements of the Dimroth type in a five-membered ring according to Scheme 5:

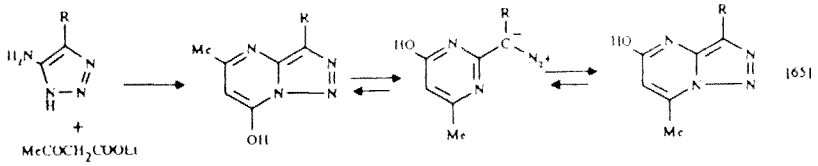


Scheme 5. Dimroth rearrangement of the five-membered fragment of azaindolizines with 3 → 4 opening.

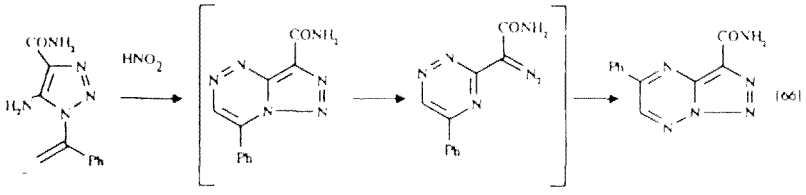
The rearrangements of certain tetrazolo- and triazoloazines (examples **43-45**) take place in such a way. We note that the yield of the product from rearrangement of the triazole derivatives is fairly high if there is an accepting substituent at position 1 [65].



(43)

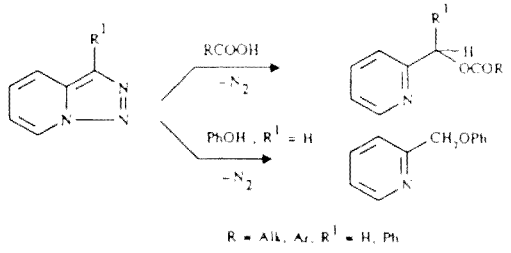


(44)



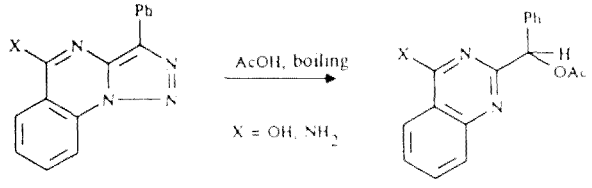
(45)

In addition 3 → 4 *endo* cleavage is probably the main stage in a wide range of reactions of 1,2,3-triazoloazines (derivatives of 2,3-diazaindolizines) with electrophiles with the ejection of molecular nitrogen. One of the first examples of such processes was the reaction of 1,2,3-triazolo[1,5-a]pyridines with carboxylic acids [67]. Here, it was noticed that the elimination of nitrogen was accompanied by the fairly exotic 1,1-addition of the reagent, in which the role of electrophile was played by the proton and the role of nucleophile was played by the anion of the acid. It is noteworthy that a similar reaction also occurred under the influence of phenol, which exhibits both acidic and nucleophilic characteristics (example **46**):



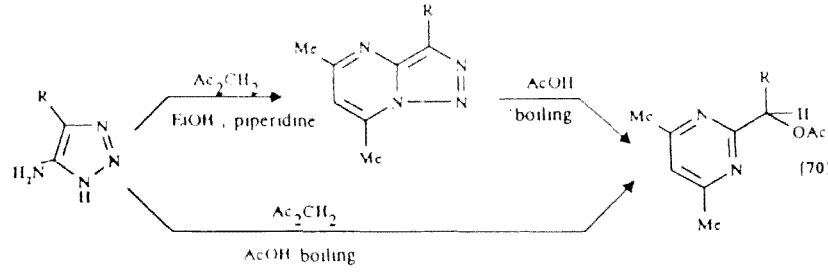
(46)

Analogous reactions were also observed for a series of tricyclic substrates. Thus, the derivatives of 1,2,3-triazolo[1,5-a]quinazolines also decomposed with the release of nitrogen when boiled in acetic acid (example **47**):



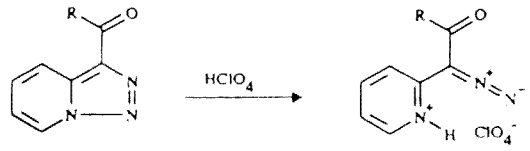
(47)

The analogous reaction of substituted 1,2,3-triazolo[1,5-a]pyrimidines served as the basis for a one-pot synthesis of the pyrimidine ring from the triazole ring (example **48**, R = Ph). It is interesting to note, however, that the opening reaction with the release of nitrogen did not occur if there was an accepting substituent at position 1 (example **48**, R = $CONH_2$).



(48)

In spite of the synthetic significance of this type of reaction there was no common opinion about their mechanism. Thus, according to the IR spectra, 1-COR-substituted 2,3-diazaindolizinium perchlorates exist in the cationic diazo form (example **49**):



[71] (49)

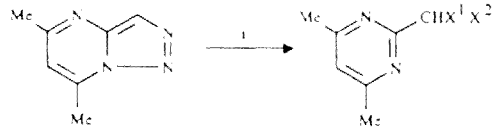
In this connection it was suggested that reactions of type **46–48** take place through an open diazo intermediate. Nevertheless, the open diazo form was not detected (the PMR spectrum in sulfuric acid) during investigation of the mechanism of the reactions of thienotriazolopyrimidines with acids (example **50**). As a result direct attack by the nucleophile at position 1 of the protonated heterocycle without prior cleavage of the 3-4 bond was considered more likely.

[72]

a in dil H_2SO_4, X = OH
b in conc. HCl (HBr), X = Cl (Br)
c in glacial AcOH, X = OAc

(50)

Simultaneously with this the reactions of 2,3-diazaindolizines with standard electrophilic reagents were studied. It was found that 1,1-addition with the ejection of a nitrogen molecule also occurs readily under the influence of electrophiles that are not too strong electron acceptors (halogens, etc.) (examples **51** and **52**):



[73] (51)

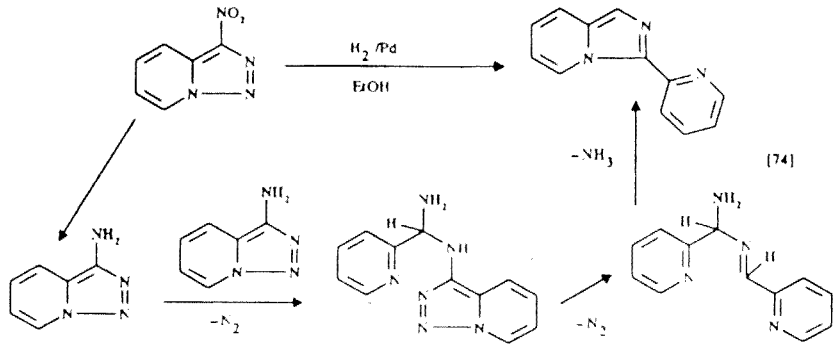
a in bromosuccinimide, $X^1=X^2=Br$
b in chlorosuccinimide, $X^1=X^2=Cl$
c in ICl, $X^1=I$, $X^2=Cl$
d in Br_2/EtOH, X^1 and X^2 = Br or OEt

[74] (52)

a in Cl_2 or Br_2, $X^1=X^2=$ Cl or Br
b in $Hg(OCOR)_2$/RCOOH, X^1 = HgOCOR, X^2 = OCOR, R = Me, Et

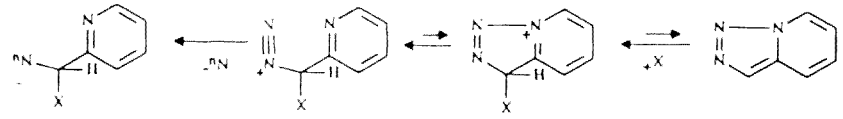
If, however, the electrophile is at the same time a strong acceptor, the usual electrophilic substitution takes place instead of ring cleavage. Thus, the nitration and formylation of 2,3-diazaindolizines (the substrates of reaction **52**) take place at position 1 without cleavage of the ring [74]. It was, therefore, supposed that the presence of a strong electron-accepting group at position 1 of the bicycle promotes stabilization of the open diazo intermediate, which as a result does not decompose further and can undergo cyclization back to the closed form [see also examples **48** (R = $CONH_2$) and **49**]. If there is no strong acceptor at position 1, the elimination of nitrogen takes place readily, and the reaction represents 1,1-addition (examples **46-48** and **50-52**).

The formation of 3-(α-pyridyl)imidazo[1,5-a]pyridine during the reduction of 1-nitro-2,3-diazaindolizine was explained from the same standpoint (example **53**). The dimerization of the obtained 1-amino derivative with the ejection of two molecules of nitrogen and ammonia is most likely:



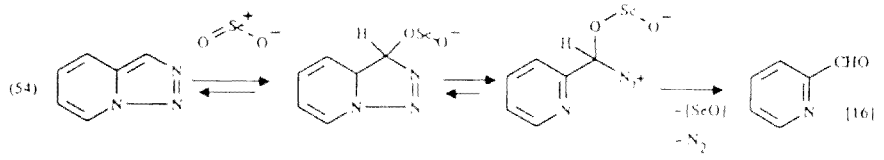
[74] (53)

Thus, a mechanism involving the addition of the electrophile at position 1 and 3 → 4 *endo* opening of the bicycle was proposed for the reactions of 2,3-diazaindolizines with electrophiles with the ejection of molecular nitrogen (Scheme 6) [16]:



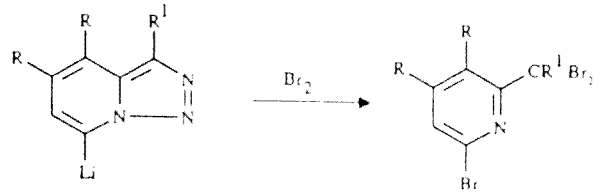
Scheme 6. The *endo* cleavage of the 3-4 bond in the reaction of 2,3-diazaindolizines with electrophiles.

The authors [16] also consider that a similar mechanism is realized during the oxidation of these substrates by the action of selenium dioxide (example **54**):



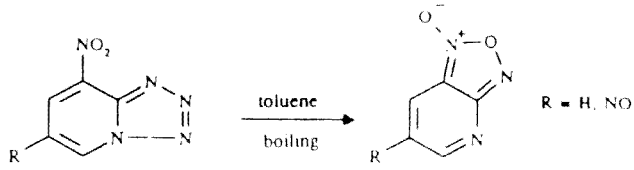
[16] (54)

The analogous cleavage reactions of the benzo analogs (triazoloquinolines and triazoloisoquinolines) by the action of electrophiles were examined in [16, 75]. It is interesting to note the behavior of the lithiated triazolopyridines and triazoloisoquinolines. In the absence of a strong acceptor at position 1 the action of bromine leads not only to replacement of the lithium by the halogen but also to cleavage of the triazole ring with the formation of the dibromo derivative (example **55**):



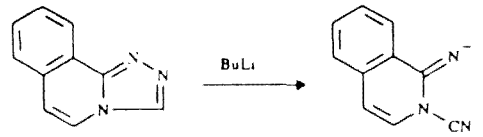
[76,77] (55)

Thus, 3 → 4 *endo* opening is an important part of the chemistry of azaindolizines and the principal stage in various transformations. In addition, it probably determines the occurrence of certain rearrangements under the influence of a formal nucleophilic center. An example is the recyclization of 8-nitrotetrazolopyridines to condensed furazans, where the formal nucleophilic center is the oxygen of the nitro group (example **56**):

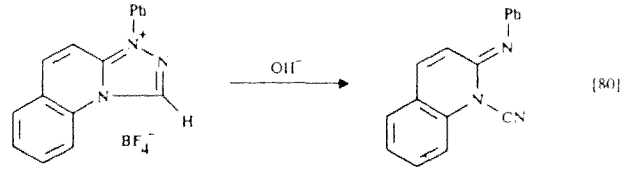


[78] (56)

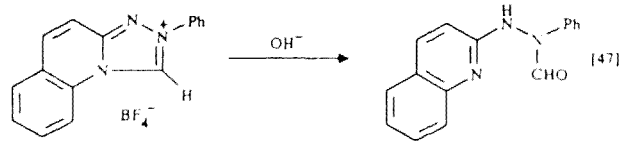
II.B.4. Other Types of *endo* Opening of the Five-Membered Ring. The other types of *endo* opening of the five-membered ring in azaindolizines are less familiar. Thus, 2 → 1 *endo* opening can occur in the series of 1,2,4-triazoloazines under the influence of bases (examples **57** and **58**). It is worth mentioning the significant role of the position of the quaternized center. One and the same substrate, depending on the position of the quaternization center, can undergo both 2 → 1 *endo* cleavage (example **57**) and 3 → 4 *exo* cleavage (example **59**).



[79] (57)



[80] (58)



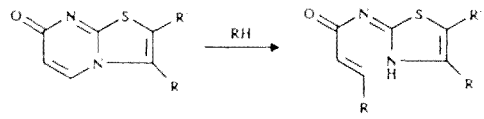
[47] (59)

III. OPENING OF THE THIA AND OXA DERIVATIVES OF INDOLIZINES

III.A. 1-Thia and 1-Oxa Derivatives of Indolizines

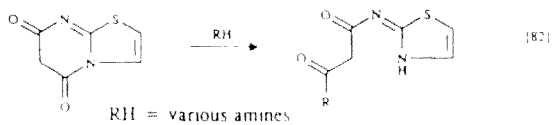
The presence of oxygen or sulfur as additional heteroatoms in the skeleton of the azaindolizine molecule can substantially alter the nature of the cleavage of the structure. Thus, in the presence of sulfur or oxygen at position 1, 9 → 1 and 2 → 1 cleavages are also possible in addition to the usual 5 → 4 and 3 → 4 opening for azaindolizines. These four types of cleavage often compete with each other, leading to mixtures of reaction products. In this case even small changes in the structure of the substrate can become determining for the selectivity of opening.

III.A.1. Concurrent Openings in the Series of 1-Thia Derivatives of Azaindolizines. In the presence of oxo substituents at positions 5 and 7 in the series of 1-thia derivatives (as also in the case of azaindolizines) the probability of 5 → 4 *exo* opening is increased substantially. (Here, however, it is desirable that the possibility of *endo* opening in the five-membered ring should be absent.) This type of 5 → 4 *exo* cleavage is represented by examples **60-63**.

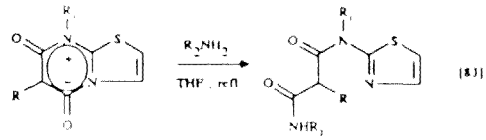


[81] (60)

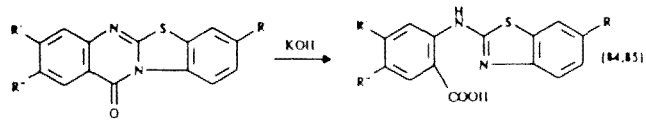
R, R' = H, benzo; R = EtNH, BuNH, morpholino



[82] (61)

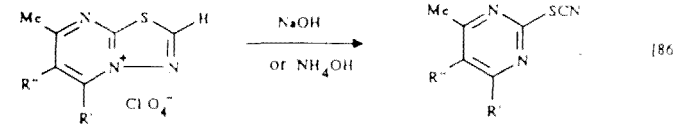


[83] (62)

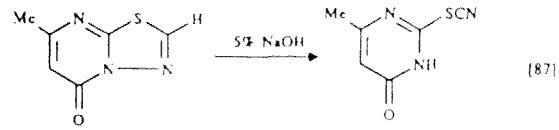


(63)

In most cases, however, opening of the five-membered ring occurs. Here, the most likely processes are 3 → 4 *endo* cleavage (3 → 4 *exo* cleavage is not very characteristic of the 1-thia- and 1-oxaazaindolizines) and 9 → 1 and 2 → 1 *exo* cleavage. In this respect the cleavage of substrates containing 1,3,4-thiadiazole as five-membered fragment is significant. In the absence of a substituent at position 2 of the bicycle under the influence of bases cleavage of the N – N bond occurs under mild conditions, and a thiocyanate-substituted six-membered ring is formed (examples **64** and **65**). We note that the *endo* opening in example **65** takes place even in the presence of a 5-oxo group. It was also shown [86] that thiadiazolopyridinium salts are opened by the action of weaker bases than the neutral substrates.

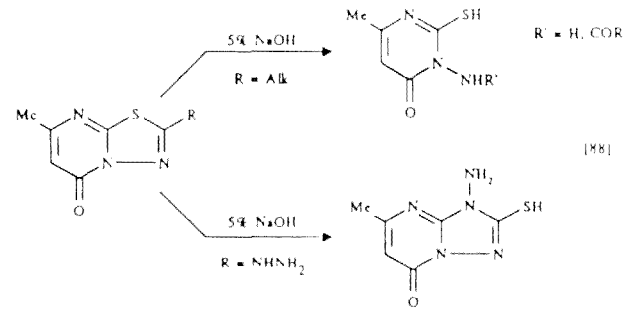


[86] (64)



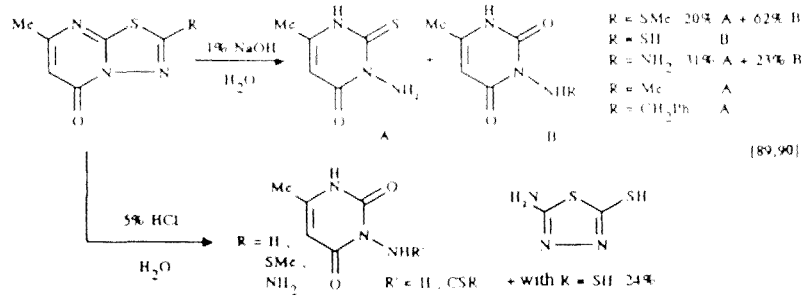
[87] (65)

However, for the substrate of example **65** under the same reaction conditions the authors of [88] observed the formation of 6-methylthiouracil, and they explained this fact by the hydrolysis of the thiocyanate. According to their observations, the product from *endo* opening was produced by the action of liquid ammonia. Under the influence of aqueous alkali in the presence of a 2-alkyl substituent, however, 2 → 1 cleavage occurred also with the formation of derivatives of 6-methylthiouracils (example **66**). Under the same conditions the 2-hydrazino-substituted bicycle underwent rearrangement, the first stage of which was probably 9 → 1 cleavage.



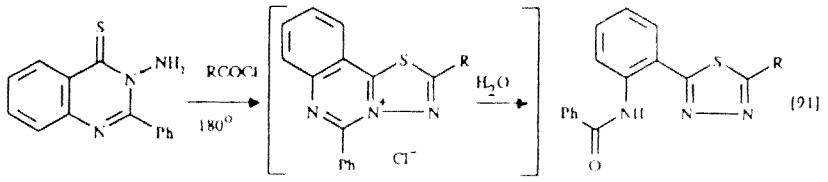
[88] (66)

A detailed study of the various possibilities for cleavage of substituted 1,3,4-thiadiazolo[3,2-a]pyrimidin-5-ones under the influence of both alkaline and acidic reagents was made in [89, 90]. Here, it was shown that both 2 → 1 (A) and 9 → 1 (B) cleavage can be observed during alkaline opening (example **67**). The ratio of the obtained open forms is determined by the nature of the substituent at position 2. During acid cleavage 9 → 1 cleavage mainly occurs, and in the case of the 2-SH derivative it is accompanied by 5 → 4 (and also 7 → 8) opening with the formation of a five-membered ring.

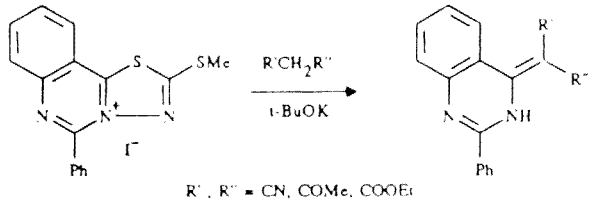


[89,90] (67)

1,3,4-Thiadiazolo[3,2-c]quinazolinium derivatives are also capable of opening both the six- and the five-membered ring, depending on the reaction conditions. Thus, the given substrates (formed during the condensation of 3-amino-4-quinazolinethiones with acyl chlorides) cleave the six-membered ring by the 5 → 4 *exo* mechanism under the influence of the water released during the reaction (example **68**). At the same time 9 → 1 cleavage of the five-membered ring can take place under the influence of C-nucleophiles (example **69**). It is interesting to note that the 1-aza analogs of the substrates of example **69** under the same conditions undergo 5 → 4 cleavage (see example **12** above).

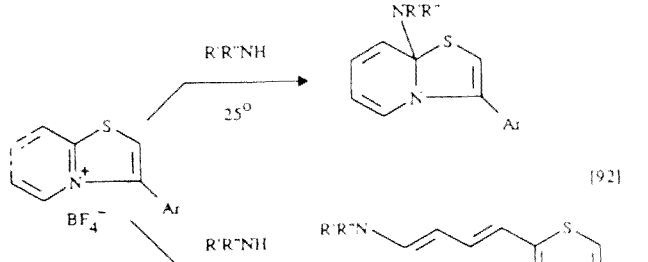


[91] (68)

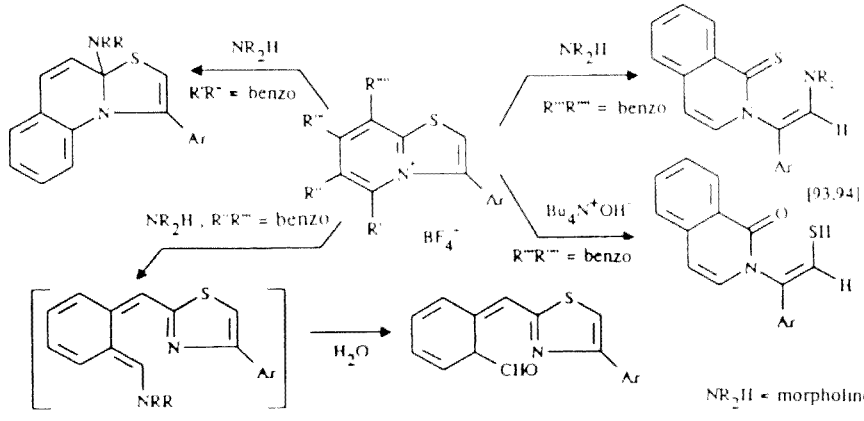


[29] (69)

Unexpected types of ring opening were found in the series of the simplest 1-thiaindolizines — thiazolo[3,2-a]pyridinium cations and their benzo derivatives. Thus, depending on the reaction conditions, the action of secondary cyclic amines on the salts of the bicyclic cations led either to attack at the bridging position with the formation of an adduct or to 5 → 4 opening (example **70**). Various directions of reaction, depending on the structure of the substrate, were also observed during the action of nucleophilic reagents on the tricyclic benzo derivatives (example **71**). The 5,6-benzo derivative, for example, forms a stable 9-adduct with morpholine, whereas the action of this amine on the 7,8-analog leads to 2 → 1 opening. It is interesting that if the nucleophile is the hydroxide ion 9 → 1 cleavage is observed in the case of the 7,8-benzo derivative. The reaction of the 6,7-annellated bicycle with morpholine also takes place in a nonstandard manner: The product of 5 → 4 opening is unstable, and after the addition of water an aldehyde is isolated from the reaction mixture.

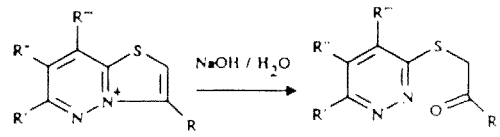


[92] (70)



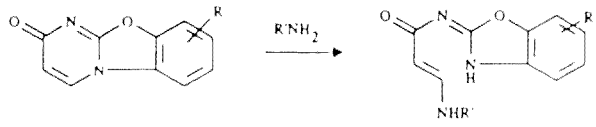
[93,94] (71)

It is interesting in this respect to note that, according to data in [95], 3 → 4 *exo* cleavage (which is uncharacteristic of the 1-thiaazaindolizine class) is observed in the case of the derivatives of thiazolo[3,2-b]pyrazinium salts (example **72**).



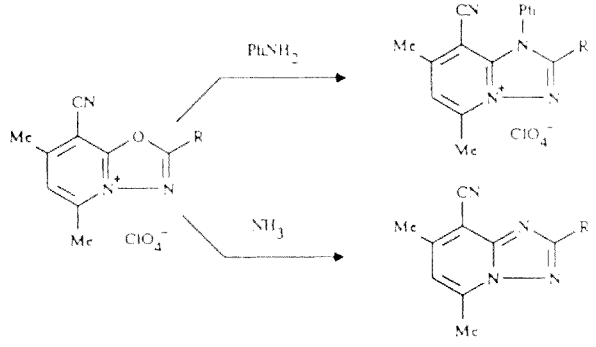
[95] (72)

III.A.2. Cleavage of the Rings in 1-Oxaazaindolizines. Cleavage of the rings in 1-oxaazaindolizines also takes place ambiguously. As in the case of the aza and thia analogs, activating substituents (e.g., the oxo group) in the six-membered ring can promote 5 → 4 opening (example **73**).



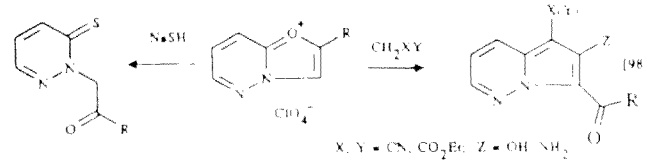
[96] (73)

The 2 → 1 *exo* opening of the five-membered ring is assisted by a donating substituent, such as an oxo group, at position 2. The main type of cleavage in such structures is probably 9 → 1 cleavage, although in a number of cases (realized by recyclization with the inclusion of an external nucleophile) it is difficult to distinguish between 9 → 1 and 2 → 1 opening from the final structure of the reaction products. Thus, for example, 1,3,4-oxadiazolo[3,2-a]pyridinium salts undergo recyclization to the 1-aza derivatives under the influence of amines or ammonia (example **74**):



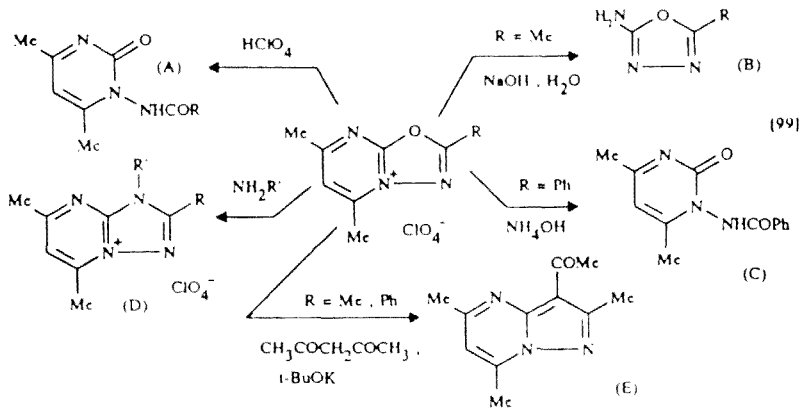
[97] (74)

The presence of an aza group at position 5 (example **75**) does not fundamentally alter the indicated direction of opening. The corresponding oxazolo[3,2-b]pyridazinium cations readily undergo 9 → 1 cleavage under the influence of S-nucleophiles, while in the reaction with malonic acid derivatives opening of the oxazole fragment followed by closure of a pyrrole ring is observed:



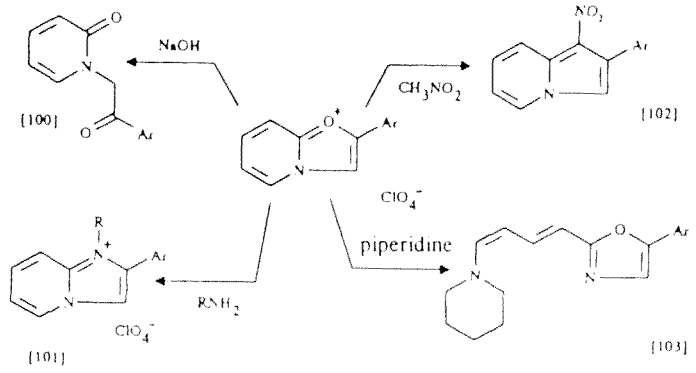
[98] (75)

With stronger activation of the six-membered ring, e.g., in 1,3,4-oxadiazolo[3,2-a]pyrimidinium salts, the opening of the rings takes place ambiguously (example **76**). Whereas cleavage of the five-membered ring (A) is observed in an acidic medium, in an alkaline medium even small differences in the polarity of the substituent at position 2 can determine the opening both of the six-membered ring (B) and of the five-membered ring (C). During the recyclization of such substrates by the action of various nucleophiles (D, E) 9 → 1 cleavage probably occurs at one of the initial stages. Indirect evidence for this is provided by the result of the rearrangement (E), during which one and the same compound is obtained both from the 2-methyl and from the 2-phenyl derivative.



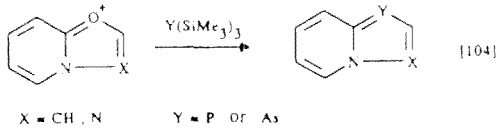
(76)

The oxazolo[3,2-*a*]pyridinium derivatives similarly undergo 9 → 1 cleavage under the influence of O- and N-nucleophiles and also (as we were able to discover recently [102]) under the influence of carbanions. However, in some cases, e.g., during the action of cyclic secondary amines, opening of the six-membered ring with 5 → 4 cleavage occurs (example **77**).



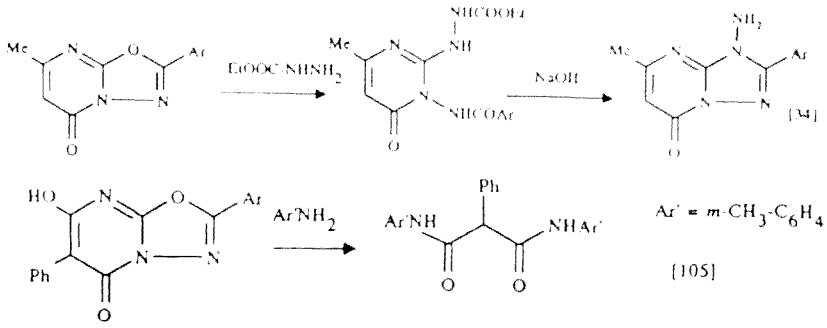
(77)

It is worth mentioning that the important 1-phospha and 1-arsa analogs of these bicycles were obtained by the recyclization of oxazolo[3,2-a]pyridiniums and 1,3,4-oxadiazolo[3,2-a]pyridiniums (through a stage with opening of the five-membered ring) (stage **78**).



(78)

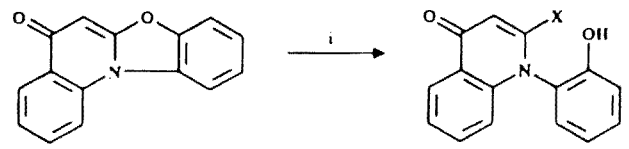
Unlike the 5-oxoazaindolizines, their 5-oxo-1-oxa analogs do not always undergo cleavage only in the six-membered ring. Thus 9 → 1 opening is observed in the case of 5-oxo-substituted 1,3,4-oxadiazolo[3,2-a]pyrimidine (example **79**), whereas the 1-aza analog undergoes 5 → 4 cleavage (see example **17** above). Only in the case of the 5,7-dioxo derivatives does cleavage of the six-membered ring with cleavage of the 5-4 and 7-8 bonds occur (example **80**).



(79)

(80)

The same relationship is observed in the reaction of the dibenzo derivative of oxazolopyridinone with nucleophilic reagents (example **81**). In spite of the presence of the oxo substituent 9 → 1 opening of the substrate takes place in the six-membered ring:

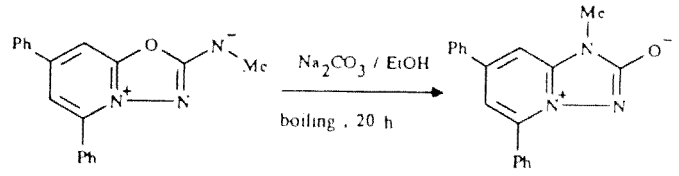


[106]

(81)

a i KOH / ROH, X = OR; b i NaCN / DMSO, X = CN; c i $NaCH(COOEt)_2$, X = $CH(COOEt)_2$

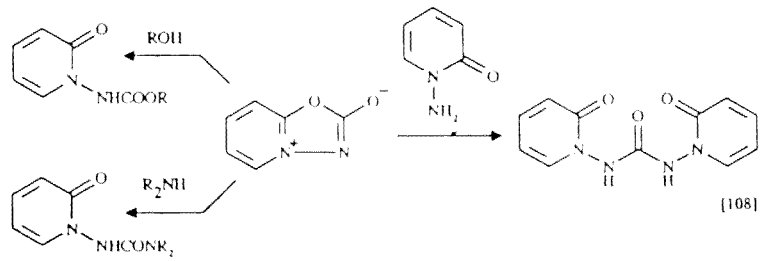
According to the authors of [107], 9 → 1 cleavage is also the first stage in the rearrangement of the mesoionic derivative of 1,3,4-oxadiazolo[3,2-a]pyridine to 1,2,4-triazolo[1,5-a]pyridine (example **82**).



[107]

(82)

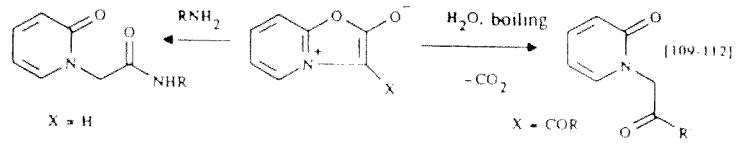
Nevertheless, it has been shown in many papers that the presence of donating substituents (oxo) at position 2 of such substrates promotes 2 → 1 cleavage of the five-membered ring. Thus, 2 → 1 cleavage was observed during the nucleophilic opening of the mesoionic 2-oxooxadiazolo[3,2-a]pyridine (example **83**).



[108]

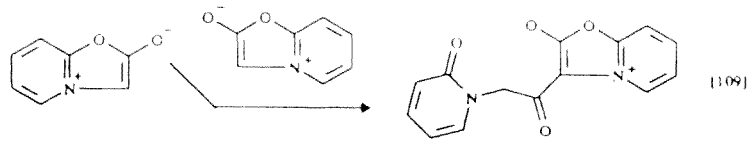
(83)

A similar type of opening was observed during the reaction of mesoionic 2-oxooxazolo[3,2-a]pyridines with nucleophiles (example **84**). We note that in the absence of an external nucleophile such substrates can dimerize, where the reaction process includes 2 → 1 cleavage of one of the molecules (example **85**). The formation of coumarin during the reaction of the given structure with salicylaldehyde (example **86**) also involves cleavage of the 2-1 bond at one of the stages of the reaction.



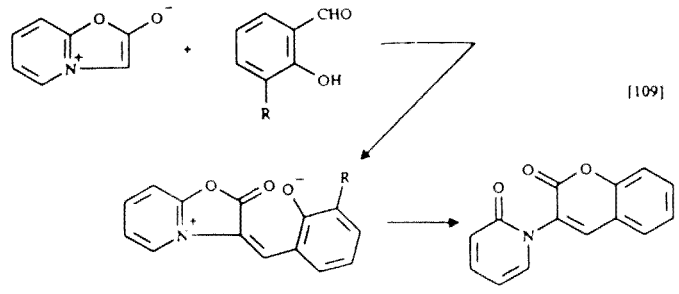
[109-112]

(84)



[109]

(85)

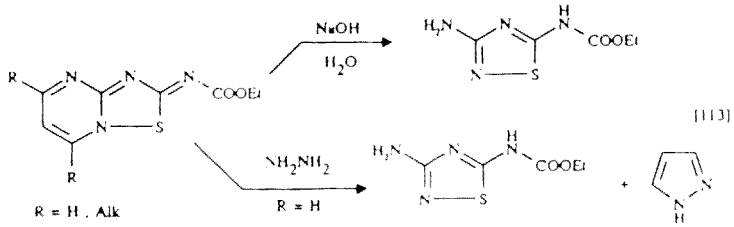


[109]

(86)

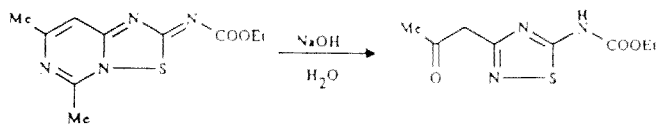
III.B. Features of the Opening of 3-Thia- and 3-Oxaazaindolizines

The data on the opening of this type of thia- and oxaindolizines are more fragmentary, but it has been shown in a number of papers that the preferred direction of the reaction is determined by the fine structure of the substrate and by the presence of one or the other substituents. Thus, under the influence of nucleophiles the derivatives of thiadiazolopyrimidines undergo cleavage in the six-membered ring. This is due to a combination of 5 → 4 and 7 → 6 (or 7 → 8) cleavages as a result of the presence of the 6(8)-aza group (examples **87** and **88**).



[113]

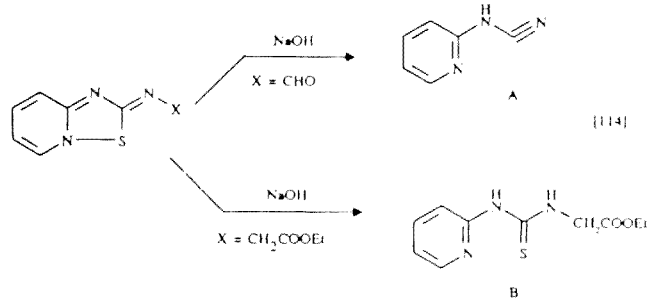
(87)



[113]

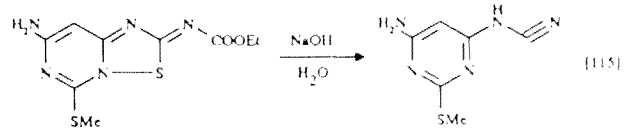
(88)

At the same time, if the six-membered part of the bicycle is a pyridine, pyrazine, or pyridazine system or even a 5-RS-substituted pyrimidine fragment, the five-membered ring is opened (examples **89-92**). In terms of the employed approach the data can be interpreted formally as 2 → 3 *exo* opening (examples **89**A and **90**) or as 4 → 3 opening (examples **89**B, **91**, and **92**).



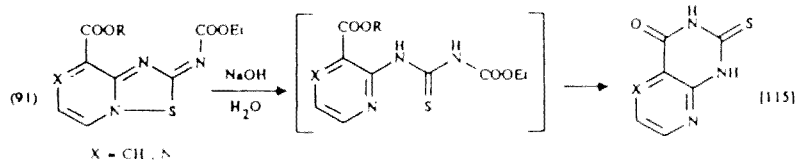
[114]

(89)



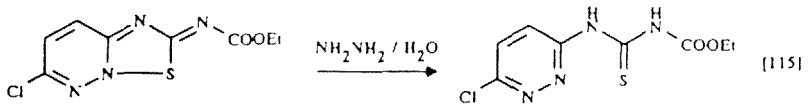
[115]

(90)



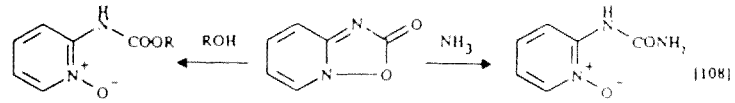
[115]

(91)

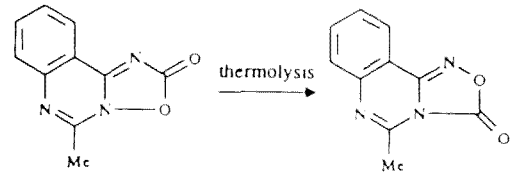


(92)

A similar alternative possibility with opening of the five- or six-membered ring depending on the position of the substituents in the substrate is also characteristic of the derivatives of 3-oxaindolizines. For example, 2 → 3 opening with the formation of derivatives of pyridinium N-oxide takes place during the action of nucleophiles on 2-oxo-1,2,4-oxadiazolo[2,3-a]pyridine (example **93**). The presence of a 6-aza substituent leads to a Dimroth rearrangement with 5 → 4 cleavage at the first stage (example **94**), although cleavage of the 2-3 and 3-4 bonds also occurs, according to [116], during thermolysis.

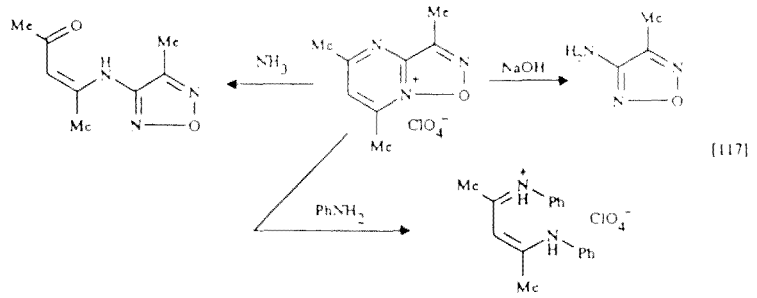


(93)

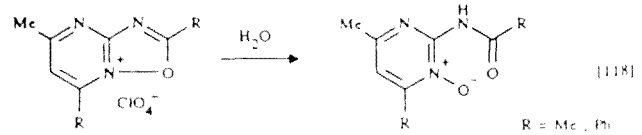


(94)

During the action of nucleophiles 1,2,5-oxadiazolo[2,3-a]pyrimidinium salts open the six-membered ring (example **95**), whereas 2 → 3 cleavage is observed for the isomeric 1,2,4-oxadiazolo[2,3-a]pyrimidinium salts (example **96**).

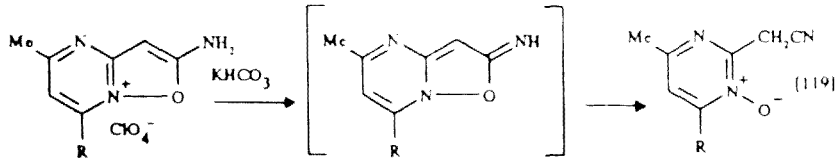


(95)

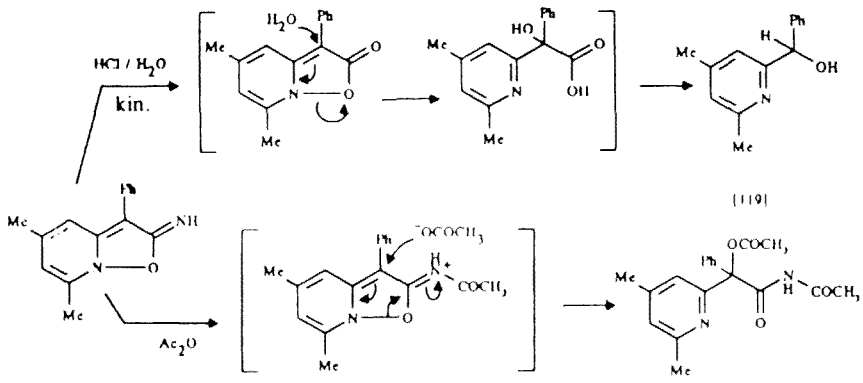


(96)

The action of weak bases on 2-aminoisoxazolo[2,3-a]pyridinium salts leads to 2 → 3 cleavage of the intermediately formed imino form with the formation of pyrimidinium N-oxide (example **97**). In the case of the 1-phenyl derivatives the imino form is resistant to alkalis, but it is decomposed by the action of nucleophiles in an acidic medium. It was suggested in [119] that one of the first stages of this process is 4 → 3 opening (example **98**).



(97)

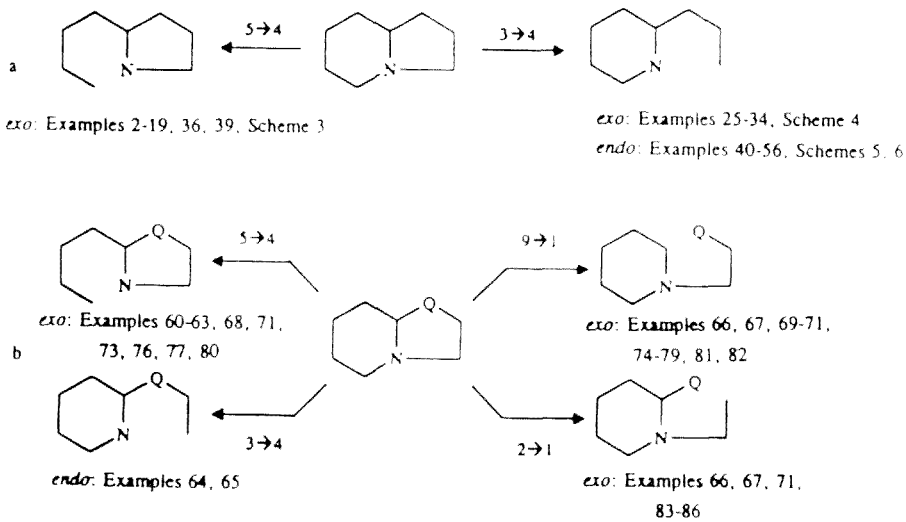


(98)

[119]

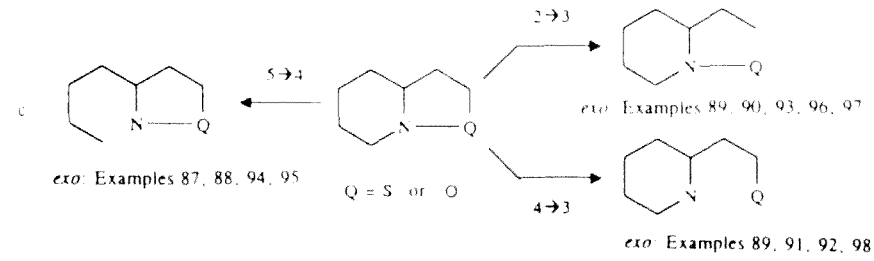
IV. RESULTS

The empirical material set out above makes it possible to reach the following conclusions about the preferred directions of opening in bridged azoloazines under the influence of polar reagents:



Scheme 7a, b. Main types of opening: a) in the series of azaindolizines; b) in the series of 1-oxa(thia) derivatives, Q = O, S.

1) In the series of azaindolizines most of the reactions amount to 5 → 4 and 3 → 4 cleavage of the bond adjacent to the bridging nitrogen atom (Scheme 7a). Among the 3 → 4 openings there are both *exo* and *endo* cleavages, whereas *exo* cleavage is mostly characteristic of the 5 → 4 openings.



Scheme 7c. Main types of opening in the series of bridged 3-oxa(thia) derivatives of azoloazines.

2) The appearance of S or O atoms at position 1 reduces the probability of 3 → 4 *exo* opening in the bicyclic ring and at the same time promotes 9 → 1 and 2 → 1 *exo* opening (Scheme 7b).

3) The appearance of S or O atoms at position 3 of the bicycle removes the possibility of both types of 3 → 4 opening, promoting 2 → 3 and 4 → 3 *exo* cleavages (Scheme 7c).

V. DISCUSSION

In this section of the paper we propose a simple model, which combines the empirical data presented above and shows how the distribution of the polar centers in a bicyclic (5+6) structure with a bridging nitrogen atom affects the cleavage of one or the other bond in the heterocycle. According to this model, the direction of opening is determined by two factors. One of them is the *local* distribution of the polarities, the requirements for which for *exo* and *endo* openings differ. The other factor is the *a priori* distribution of the polar centers in the bicyclic (5+6) system as a *whole*, due to the presence of the nitrogen bridge.

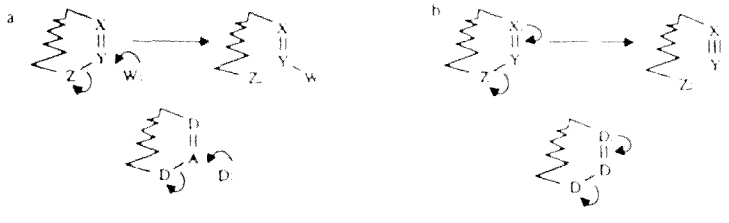
Both the local and the global distribution of the polarities in the chains and rings of organic compounds have recently found their own reflection in the principle of alternating polarities. (For greater detail, see the reviews [120-123].) We recall briefly that a fully (or partially) saturated molecule is called consonant (normal, alternant), if it does not contain odd rings and there is an odd number of atoms between the pair of heteroatoms. The consonant structure can be drawn in two colors so that the heteroatoms will have the same color. In the opposite case (the presence of an odd ring, the presence or absence of an even chain between the heteroatoms) the structure is considered dissonant (containing "umpoling"). As a rule the methods of synthesis and the reactivity of consonant systems are fully predictable (the principle of "inherited polarities" [122] or "conserved alternation" [123]), which cannot be said of the dissonant systems.

The definitions of consonant and dissonant systems were refined in terms of the evenness or oddness of the chain between the centers of Lewis acidity and basicity [123]. We will fashion further discussion on this position.

A. Rule of Polar Assemblies for *endo* and *exo* Opening

Earlier [2] we demonstrated the existence of a relationship between the type of opening of the heterocycle (*endo* or *exo*) and the presence of triatomic fragments of consonant or dissonant nature in it. Here we will briefly repeat the rules that we formulated for monocyclic structures.

***exo* Openings (Scheme 8a).** The assembly in this type of cleavage reaction consists of four atoms: the initiating center of the reagent W and the three atoms of the ring — the center of the direction of external attack Y and the two neighbors. Eventually the unshared pair of the initiating agent will go to one of the neighboring atoms (Z), and the other will participate in its delocalization in the intermediate. Opening takes place most readily in an assembly with a *consonant* structure. This means that its three outer atoms (X, Z, and W in Scheme 8a) must be polar in nature, while the central atom Y is opposite in nature. For the most frequently encountered case of the opening of heterocycles under the influence of nucleophiles (W) this condition is fulfilled if the atoms of the trio X, Y, and Z have the nature of D, A, and D respectively. Here "D" signifies a center of donating type (a relative excess of electron density); "A" signifies a center of accepting type (a relative deficiency of electron density).



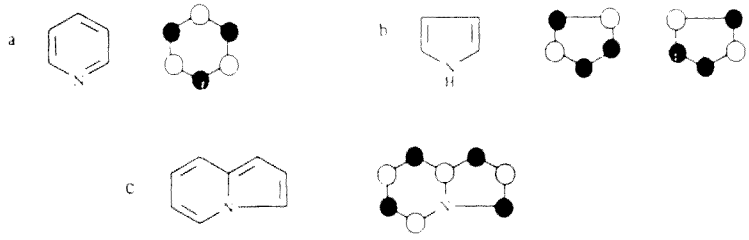
Scheme 8. Distribution patterns of the polarities for the assemblies in *exo* (a) and *endo* (b) opening.

endo **Opening (Scheme 8b).** The assembly of the reaction consists of three atoms of the ring. The unshared pair passes from terminal atom (X) to the other (Z). Opening takes place most readily in an assembly with *dissonant* structure. This means that all three atoms must have identical polar nature. During opening by bases the nature of the trio X, Y, and Z must correspond to the pattern D, D, and D.

As seen from analysis of the empirical data presented in the present review, these rules are strictly fulfilled both for *exo* and for *endo* opening of the investigated bicycles. However, the probability of cleavage of a specific bond bears a relation to the general distribution of the polar centers as a whole.

B. Effect of the Nitrogen Bridge on the Distribution of the Polar Centers in the (5 + 6) Bicycle

The prototype of the class of substrate under discussion (indolizine) contains the consonant pyridine ring (with clearly defined alternant polarities) (Scheme 9a) and the dissonant (odd) pyrrole ring. The latter does not determine the polar nature of the other centers in a clear manner; an attempt to place labels of two colors will lead to the result that in every case two labels of one color will be adjacent (Scheme 9b). Nevertheless, with fusion of the six-membered ring (with stable alternant distribution of the polar centers) and the five-membered ring alternation can be induced in the latter by the neighboring ring. Indeed this feature shows up clearly for indolizine (Scheme 9c). In conjunction with the π-deficiency of the six-membered ring and the π-excess of the five-membered ring such "induction" of pseudoalternation leads to the clearly defined donating nature of positions 1 and 3 of the bicycle and to the accepting nature of positions 5 and 7. Such a pattern is confirmed as a whole by the results of quantum-chemical calculations [124]. In other words the polarity of the skeletal atoms of the indolizine ring can be approximated roughly by the alternant sequence of its carbon atoms (Scheme 9c).



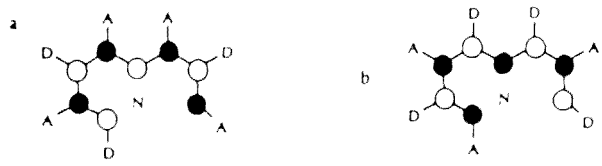
Scheme 9. Distribution of polarity in the skeleta of alternant and nonalternant heterocycles. (The donating centers are black, and the accepting centers are white.)

C. Features of the *exo* Processes

In nearly all the reactions involving the opening of hetero-substituted indolizines the unshared pair goes to the heteroatom Z. The ability to undergo opening here increases in the order:

$$Z = N_{ring} << N_{bridge} < S < O$$

In the simplest case of azaindolizines the unshared pair goes to the bridging nitrogen atom during both 5 → 4 and 3 → 4 opening. In both cases the *exo* process requires a consonant trio of ring atoms (6, 5, and 4 or 2, 3, and 4 respectively). In the mean time during 5 → 4 opening the consonant nature of the local trio is superimposed on the consonant pattern of the general distribution of the polarities in the bicycle. In the case of 3 → 4 opening, however, the consonant nature of the local trio does not correspond to such a pattern. From this it is easy to derive the principles governing the effect of the substituents in the bicycle on the preferred type of *exo* opening (5 → 4 or 3 → 4). Any effect of the substituents that increases the initial alternation on the bicycle will assist 5 → 4 opening (Scheme 10a). On the other hand any substitution that increases the reverse chain of alternation (Scheme 10b) will assist 3 → 4 *exo* opening.



Scheme 10. Normal (a) and reverse (b) alternation of the chain in bridged azoloazines.

In other words, 5 → 4 *exo* opening is promoted by the donating nature (aza substitution, the presence of an external acceptor) of positions 6, 8, 1, and 3 in the bicycle and by the accepting nature (the presence of external donating and oxo substituents) of positions 5, 7, 9, and 2. It is clear that the chain atoms closest to the opening assembly (primarily 5 and 6 and then 7 and 8 and so forth) have the greatest effect. It should be emphasized that quaternization of the molecules, by increasing the general activity of the substrate toward Lewis bases, at positions 1 and 3 also represents a means for accentuating the alternation of the chain in Scheme 10a. In addition, we note that during the Dimroth rearrangement of 1,2,4-triazoloazines the equilibrium is always shifted toward the formation of the triazolo[1,5-a] derivatives [5], i.e., the structure that corresponds most in its five-membered part to the pattern represented in Scheme 9c and is most favorable thermodynamically.

Since the alternation in the chain for 3 → 4 *exo* opening (Scheme 10b) is the reverse of the initial distribution of polarities in the bicycle, openings of this type for azaindolizines are more rare. However, they occur with strong accentuation of the necessary alternation sequence, represented in Scheme 10b — the donating nature of atoms 2, 7, and 5 and the accepting nature of atoms 3, 1, 8, and 6. As in the previous case, the polarity of the centers of the chain closest to the opening assembly, i.e., the atoms of the five-membered ring, is most significant.

The appearance of sulfur or oxygen at position 1 results in the following changes in the nature of the *exo* openings.

1) Being a strong donating center, the S or O atom increases the initial chain of alternation of the polarities in the bicycle (Scheme 10a) and weakens the reverse chain (Scheme 10b). Therefore, 3 → 4 *exo* openings are hardly encountered at all for the 1-thia and 1-oxo derivatives of indolizines.

2) The comparability of the S and O atoms with the bridging N atom in the order of preference of the heteroatoms gives rise to the possibility of concurrent *exo* processes: 5 → 4, 9 → 1, and 2 → 1. It is possible to increase the probability of each of them by accentuating the constant nature of the atoms of the given opening assembly. Thus, for example, the 5 → 4 cleavage is promoted by 5-oxo- and 6-aza-substitution, while 2 → 1 cleavage is promoted by 2-oxo- and 3-aza-substitution. With other conditions equal 9 → 1 cleavage is probably favored by the realization of the reactions with the salts (the analog of quaternization at position 1) as a means of increasing the accepting nature of position 9.

The presence of a sulfur or oxygen atom at position 3 of the bicycle does not contradict the initial chain of alternation in the system (Scheme 10a). Therefore, 5 → 4 openings are also probable in this case. At the same time the possibility of localization of the charge at the S and O atoms that arises during cleavage of the five-membered ring leads to the realization of both alternative 2 → 3 and 4 → 3 opening mechanisms to an equal degree.

D. Features of the *endo* Processes

In the case of the *endo* processes, as seen, the required presence of a dissonant trio is not consistent with the pattern of alternation in Scheme 9c. Consequently, the determining factor in the occurrence of *endo* cleavages will be the correspondence of the polar nature of the atoms to the dissonant pattern (Scheme 8b). Since the dissonant nature is incorporated in the very nature of the odd ring, it is not surprising that it is the five-membered ring of the investigated type of structures that is most susceptible to *endo* opening.

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