REACTIONS INVOLVING THE FORMATION OF FIVE-MEMBERED MESOIONIC HETEROCYCLES (REVIEW)

V. G. Yashunskii and V. V. Ogorodnikova

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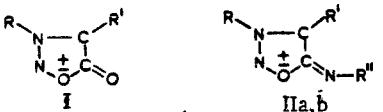
The available literature data on reactions involving the formation of five-membered mesoionic heterocycles are systematized and correlated. It is shown that the conversion of linear compounds to mesoionic heterocyclic systems is realized primarily via two pathways, viz., by dehydrocyclization and by protocyclization. These reactions are examined in greatest detail in the case of the formation of sydnones and sydnoneimines.

Azoles that contain oxygen, nitrogen, and sulfur atoms in the ring and have an exocyclic group that includes one of the indicated atoms are mesoionic five-membered heterocycles.

A characteristic peculiarity of these compounds, typical representatives of which are the widely known sydnones and sydnoneimines (I, II), is the fact that it is impossible to depict them satisfactorily by means of the generally accepted covalent formulas.



I IIa,b

IIa $R''=^{+}H_2$, b $R''=H$

Mesoionic compounds have high reactivities and display many-sided biological activity, and some of them have found application as effective medicinal preparations [1, 2].

A number of problems associated with structures and methods for the preparation of five-membered mesoionic heterocycles have been discussed in review papers [3, 4]; however, no principles of the reactions involved in the formation of these compounds were ascertained and correlated in them.

In the present review for the first time we have made an attempt to systematize and correlate the available literature data on reactions involving the formation of mesoionic five-membered heterocycles that contain nitrogen or oxygen atoms in the ring and in the exocyclic group.

The formation of such heterocycles may take place either as a result of cyclization of linear molecules or by means of conversion of ordinary heterocycles.

1. Formation of Five-Membered Mesoionic Heterocycles by Intramolecular Cyclization

As a rule, the formation of mesoionic heterocycles takes place via intramolecular cyclization of linear five-membered molecules that contain at the ends of their chains two reactive centers with unsaturated bonds; one of the latter forms an exocyclic group. Instances in which the necessary five-membered linear system is formed in the process of carrying out the cyclization reaction and its construction is a preliminary step are known.

The cyclization that leads to the formation of mesoionic five-membered heterocycles can be depicted by the scheme

a, b = C, N, O or a = b = C or a = b = c = N ; X = O or NR

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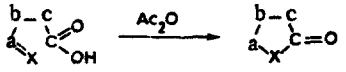
Intramolecular cyclization may be realized primarily via two pathways, viz., ring formation as a result of condensation (condensation cyclization) or under the influence of acids (protocyclization). In all cases a necessary condition for the formation of a mesoionic heterocycle is the absence of a hydrogen at atom b and the presence of a hydrogen atoms at atom c.

Several examples in which the formation of mesoionic rings does not fit into the schemes presented are known [5, 6].

1.1 Condensation Cyclization. This type of cyclization takes place formally with splitting out of simple molecules, viz., water, hydrogen halide, and ammonia. Five-membered linear compounds contain an oxygen or nitrogen atom (X = O or X = NR) at one end of the chain and a carboxy group or its derivatives (COOR, C ≡ N, and $CONH_2$) at the other. Carboxylic acid anhydrides or chlorides, as well as carbodiimides, are generally used as the cyclizing agents.

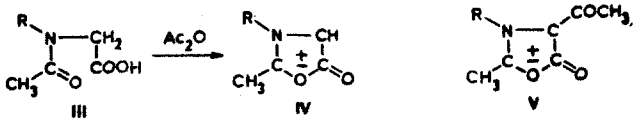
The most widely used reaction for the preparation of mesoionic five-membered heterocycles by this method is cyclization under the influence of acetic anhydride (or, less frequently, other anhydrides) of suitable linear molecules with a carboxy group at the end of the chain (Y = COOH).



Examples of the use of this reaction for the preparation of mesoionic heterocycles will be examined below.

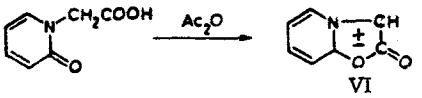
A. Reaction Center X = O

1,3-Oxazol-5-ones IV (a–b–c = C–N–C). These compounds are formed by heating N-alkyl-N-acetylglycines (III) with acetic anhydride[7]:

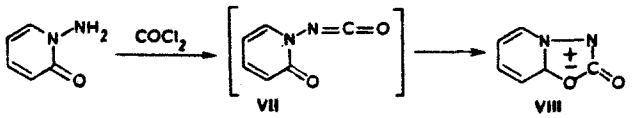


Under the influence of trifluoroacetic anhydride, acylation product V was isolated along with oxazolone IV [8]. More severe conditions — heating to 90°C in a mixture of acetic anhydride with acetic acid — are required for the cyclization of aryl derivatives III [9].

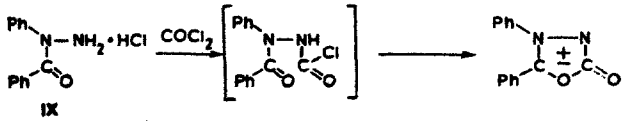
Condensed oxazolone VI was obtained in the same way as IV from 2-pyridon-1-ylacetic acid [10]:



1,3,4-Oxadiazol-5-ones (Isosydnones) VIII (a–b–c = C–N–N). These compounds are formed by the action of phosgene in chloroform on 1-amino-2-pyridone. It is assumed that isocyanate VII is formed in the first step [1]:

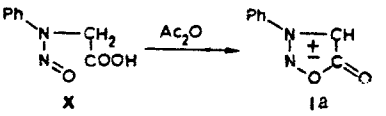


Monocyclic aryl-substituted isosydnones are obtained under more severe conditions — in refluxing toluene [12]:



A mixture of oxadiazoles with mesoionic and normal structures is formed in the case of N-alkyl derivatives of the IX type [13].

1,2,3-Oxadiazol-5-ones (Sydnones) I (a–b–c = N–N–C). These compounds are among the first obtained and most thoroughly studied mesoionic five-membered heterocycles. The first representative of the series —3-phenylsydnone (Ia) — was first obtained in 1935 [14] by the action of acetic anhydride on N-nitroso-N-phenylglycine (X):



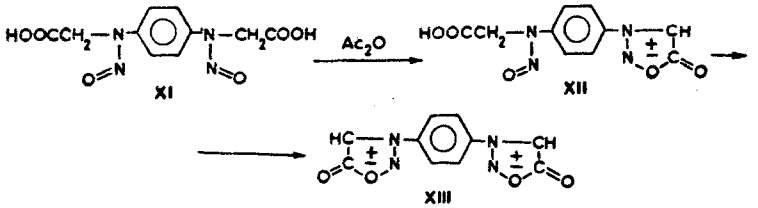
The formation of the sydnone ring in excess acetic anhydride takes place at room temperature in 0.5-1 months; heating accelerates the process, and the reaction is complete after 2 h at 100°C [15]. The addition of a few drops of 70% perchloric acid also accelerates the cyclization significantly [16].

Other dehydrating agents in addition to acetic anhydride have also been used. The cyclization takes place more smoothly and considerably more rapidly with trifluoroacetic anhydride, and the reaction is sometimes complete after a few minutes [17].

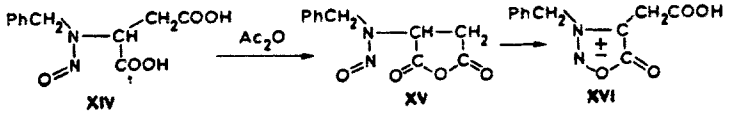
Ring closing of substituted N-nitrosoglycines to give sydnones can be realized under the influence of carboxylic acid chlorides [18], benzenesulfonyl chloride in a mixture with phosgene [19], phosgene in chloroform [20], and thionyl chloride in pyridine [21]. Sydnone Ia is formed in rather high yield when X is heated with phenyl isocyanate [22]. Cyclization also proceeds successfully in the presence of dialkyl- or diarylcarbodiimides [23].

Although the character of the substituents attached to the nitrogen atom or the α-carbon atom in nitrosoamino acid X generally does not have a substantial effect on the cyclization, examples in which the cyclodehydration is hindered or does not take place at all are known.

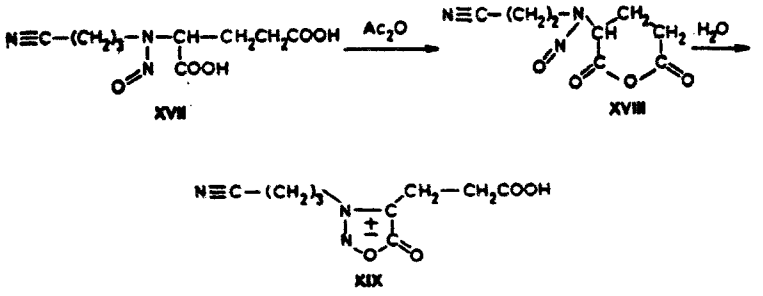
Thus the stepwise formation of sydnone rings is observed when dinitroso derivative XI is treated with acetic anhydride. Monocyclic derivative XII, which was converted to bissydnone XIII by reaction with acetic anhydride, was isolated when the reaction mixture was allowed to stand for many days [24].



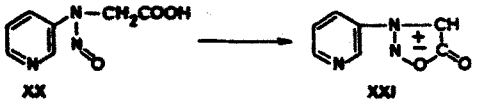
Stewart [25] has observed that when there is a carboxymethyl group attached to the α-carbon atom as in N-benzyl-N-nitrosoglycine (XIV), cyclization to a sydnone ring does not occur under the influence of acetic anhydride, and the product is anhydride XV, which upon prolonged refluxing in water is converted to the corresponding sydnone XVI:



This reaction proceeds similarly in the case of carboxyethyl derivative XVII, but six-membered anhydride XVIII proved to be less stable and underwent rearrangement to a sydnone in water at room temperature [26].

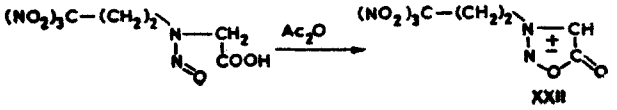


It has been found completely unexpectedly [27] that, in contrast to N-nitroso-N-(3-pyridyl)glycine (XX), which forms sydnone XXI with acetic anhydride, although at high temperatures, its analog – N-nitroso-N-(4-pyridyl)glycine – does not undergo cyclization under these conditions.



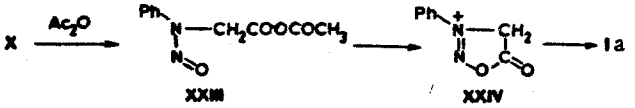
XX XXI

Attempts to bring about the cyclization of an N-nitrosoglycine with a trinitroethyl substituent to a sydnone were also unsuccessful [28]. Removal of the nitrogroups in the γ position relative to the nitrosoamino group leads to a normal reaction:



XXII

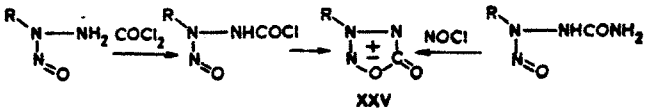
Baker and Ollis [29] have proposed that the first step in the reaction of acetic anhydride with N-phenylglycine is the formation of mixed anhydride XXIII, which is converted to cyclic product XXIV; the subsequent detachment of a proton leads to mesoionic heterocycle Ia:



XXIII XXIV

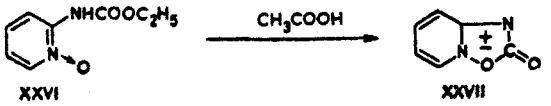
On the basis of recent kinetic studies [30] it has been shown that this reaction is second-order overall in the reagents and that electron-acceptor substituents in the phenyl ring significantly lower the rate of cyclization, while such substituents attached to the α-carbon atom increase it. When acid chlorides are used, the process also depends on the polarity of the solvent. The scheme for the process proposed by the authors does not differ fundamentally from the scheme previously presented in [29].

1,2,3,4-Oxatriazol-5-ones XXV (a–b–c = N–N–N). These compounds are formed by the action of phosgene in chloroform at room temperature of N-nitroso-N-substituted hydrazines [1] or by the action of nitrosyl chloride on N-nitrososemicarbazides [32]:



XXV

1,2,4-Oxadiazol-5-one XXVII (a–b–c = N–C–N). This compound was obtained by cyclization of 2-[N-(ethoxycarbonyl)amino]pyridine N-oxide (XXVI) under the influence of acetic acid [33]:

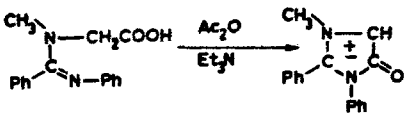


XXVI XXVII

B. Reaction Center X = NR

An imino group may be found in place of a carbonyl group as the terminal group in a linear molecule that undergoes cyclization to a five-membered mesoionic ring.

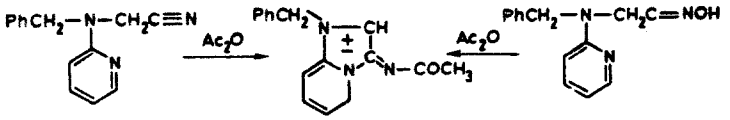
1,2-Diphenyl-3-methylimidazol-5-one XXIX (a–b–c = C–N–C). This compound was isolated by prolonged refluxing of anil XXVIII with acetic anhydride and triethylamine in xylene [34]:



XXVIII XXIX

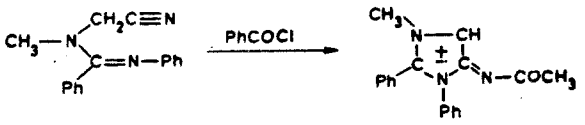
The cyclization of N-(2-benzyliminodihydropyridine)- and N-(2-benzyliminodihydroquinoline)acetic acids proceeds similarly [35].

A carboxy group at the other end of the chain in the starting linear molecule can be replaced by a nitrile or oxime group. Heterocycles with an exocyclic imino group are formed in these cases. Thus condensed imidazoleimine XXX is formed in good yield when N-benzyl-substituted 2-pyridylaminoacetonitriles or 2-pyridylaminoacetaldoxime are heated with acetic anhydride in pyridine to 70°C [36]:



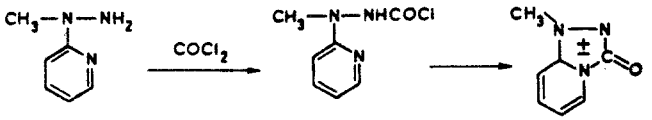
XXX

Imidazole XXXII was obtained from N-methyl(N-phenylbenzimidoyl)aminoacetonitrile (XXXI) by treatment with benzoyl chloride in dry benzene [37]:



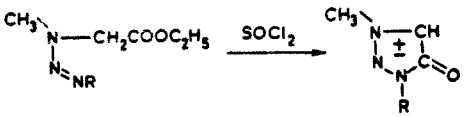
XXXI XXXII

1,3,4-Triazol-5-ones (a–b–c = C–N–N). These compounds are formed in the same way as isosydnones by the action of phosgene on acylhydrazines. Thus N-methyl-N-(2-pyridyl)hydrazine undergoes cyclization to triazole XXXIII under mild conditions [38]:



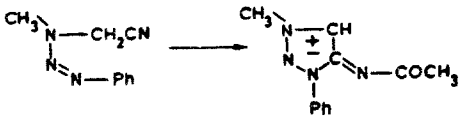
XXXIII

1,2,3-Triazol-5-ones XXXV (a–b–c = N–N–C). These compounds were obtained by cyclization of triazeneacetic esters under the influence of thionyl chloride in the presence of pyridine in the cold [39]:



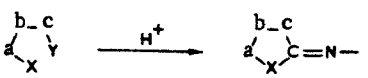
XXXV

Exocyclic nitrogen analog XXXVII is formed by heating the corresponding nitrole XXXVI with acetyl chloride [40].



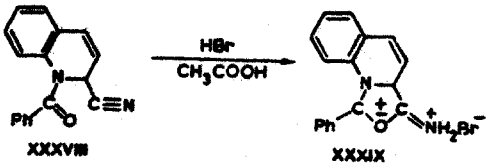
XXXVI XXXVII

1.2. Protocyclization. Another type of reaction for the formation of five-membered mesoionic heterocycles is cyclization under the influence of acids, which catalyze this process. The resulting heterocycles contain an exocyclic imino group. As in the case of condensation cyclization, one of the terminal reaction centers (X) may be an oxygen or nitrogen atom, while the other (Y) may be a carboxy function (most often a nitrile function):



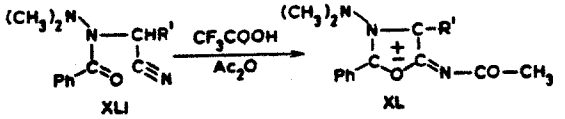
A. Reaction Center X = O

Condensed 1,3-Oxazole-5-imine XXXIX (a–b–c = C–N–C). This compound was obtained [41] by treatment of nitrile XXXVIII with hydrogen bromide in acetic acid at 20°C:



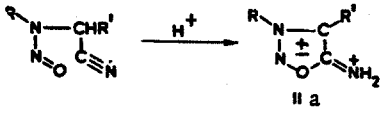
XXXVIII XXXIX

Monocyclic oxazoles XL can be formed by the action of trifluoroacetic acid in acetic anhydride on N-substituted N-benzoylhydrazinoacetonitroles XLI [42]. Cyclization does not occur if the acyl group contains a strong electron-acceptor substituent.



XLI XL

1,2,3-Oxadiazole-5-imines (Sydnoneimines) (a–b–c = N–N–C). These nitrogen exocyclic analogs of sydnones were obtained by cyclization of N-nitrosoaminoacetonitriles with hydrogen chloride in alcohol, methylene chloride, ether, dioxane, and dichloroethane at 0-5°C [43, 44].



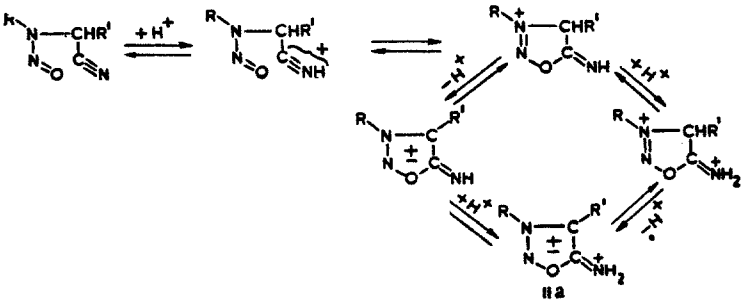
II a

The formation of a sydnoneimine ring also occurs in dilute mineral acids [45, 46]. The possibility of autocyclization catalyzed by carboxy group protons was demonstrated in the case of N-nitro-N-carboxymethylaminoacetonitrile [47], whereas cyclization takes place in water in the absence of acids in the case of N-adamantyl-N-nitrosoaminoacetonitrile [48].

A large number of salts of sydnoneimines with various substituents in the 3 and 4 positions have been synthesized by protocyclization of N-nitrosoaminoacetonitriles [49, 50]. As a rule, the character of the substituents in the starting molecule has no effect on the conditions under which the cyclization is carried out; however, side reactions have been observed in a number of cases in the cyclization of nitroso nitriles in acidic media. One such side reaction is elimination of a nitroso group. This reaction proved to be the dominant process in the case of N-tert-butyl [51] and methyl [52] substituents. Migration of a nitroso group with the formation of C-nitroso derivatives is also possible in acidic media [53]. The presence of strong electronegative substituents such as three nitro groups in the α position of the hydrocarbon chain attached to the amine nitrogen atom hinders the formation of a sydnoneimine ring [28]. N-Nitrosoaminoacetonitriles that contain an arylacetyl [54] or sulfonyl [55,56] group do not undergo cyclization.

A scheme for the cyclization of N-nitrosoaminoacetonitriles was proposed in [43]; according to this scheme, the first step in the process is protonation of the nitrile group, and this is followed by cyclization and detachment of a proton from the heteroring to give a mesoioinic ring.

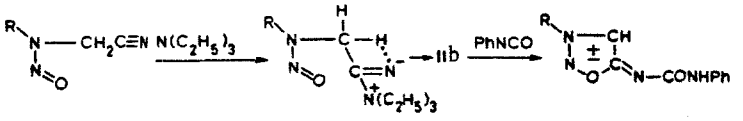
A detailed spectrophotometric study of the kinetics of the acidic cyclization of N-nitrosoaminoacetonitriles [48] showed that this reaction is first-order in the nitroso nitrile and second-order in protons. A correlation analysis of the dependence of the reaction rate constants on the character of the substituents made it possible to evaluate the quantitative contribution of the electronic and steric effects. A possible mechanism for the formation of a sydnoneimine ring was proposed on the basis of the experimental data obtained and is represented by the scheme



IIa

Protonation of the nitrile group is also proposed as the first step; this is followed by cyclization to an imino ester diazotate, which may form a sydnoneimine cation via two pathways — through a dication or through the sydnoneimine base (IIb). The existence of the free sydnoneimine base in several transformations of salts of sydnoneimines has been demonstrated by spectral methods [57].

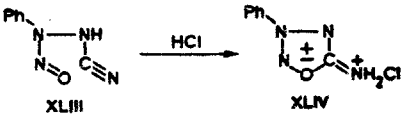
The previously unknown possibility of the formation of a sydnoneimine ring by cyclization of N-nitrosoaminoacetonitriles in the presence of bases with isocyanates or acylating agents (such as carboxylic acid anhydrides or chlorides) was recently observed [58]. It was shown that the cyclization of N-nitrosoaminoacetonitriles with triethylamine and phenyl isocyanate in benzene is first-order relative to triethylamine and phenyl isocyanate. A quantitative dependence of the rate constants on the character of the substituents attached to the amine nitrogen atom in N-nitrosoaminoacetonitriles was established. A mechanism was proposed on the basis of a study of the kinetics of this process [57]; cyclization of N-nitrosoaminoacetonitrile to sydnoneimine IIb is evidently realized through intermediate complex XLII:



XLII

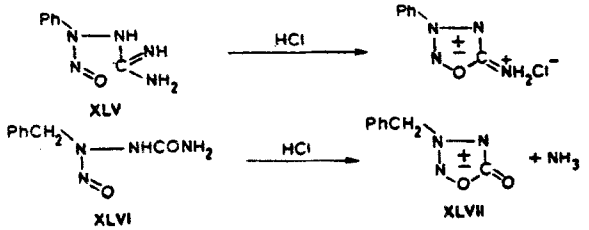
The interconversion of two ring-chain tautomeric forms of the triad-prototropic type, which can be catalyzed by both acids and bases, lies at the basis of the proposed mechanisms for the cyclization of N-nitrosoaminoacetonitriles both by the action of hydrogen chloride and in the presence of bases [59].

1,2,3,4-Oxatriazole-5-imines (a–b–c = N–N–N). These compounds are formed in the same way as sydnoneimines. Thus an oxatriazole hydrochloride (XLIV) was isolated in high yield by treatment of N-nitroso-N-phenylhydrazinonitrile (XLIII) with hydrogen chloride in methanol at 5°C [60]:



XLIII XLIV

The formation of an oxatriazole from amidine XLV requires heating with hydrochloric acid to 50°C, and amide derivative XLVI undergoes a cyclization under the same conditions [61]; however, ammonia is split out, and exocyclic derivative XLVII is formed:



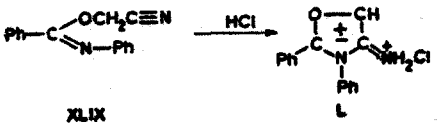
XLV XLVI XLVII

Both reactions have condensation cyclization character but proceed under the influence of acids.

B. Reaction Center X = NR

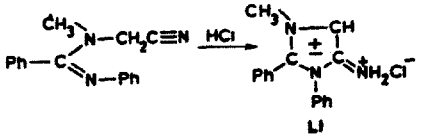
Just as in the first type of reaction, linear molecules in which an amino group or its derivatives (X = NR) may be found in place of a carbonyl group or its derivatives (X = O) at the ends of the chain participate in the protocyclization.

2,3-Diphenyl-1,3-oxazole-4-imine L (a–b–c = C–O–C). This compound was obtained by treatment of imino ester XLIX with hydrogen chloride in dry benzene [62]:



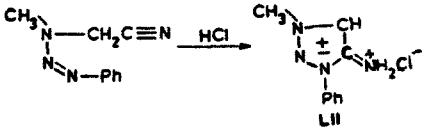
XLIX L

1,2-Diphenyl-3-methyl-1,3-imidazole-5-imine LI (a–b–c = C–N–C). This compound is readily formed by cyclization of amidines under the influence of hydrogen chloride in dry ether at 0-5°C [63]:



LI

1-Phenyl-3-methyl-1,2,3-triazole-5-imine LII (a–b–c = N–N–C). This compound was isolated by cyclization of triazenoacetonitriles under the same conditions [64]:



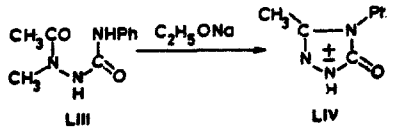
LII

The examples presented above constitute evidence that protocyclization reactions that lead to the formation of five-membered mesoionic heterocycles from linear molecules take place under conditions similar to those in the formation of sydnoneimines, for which this reaction has been studied in detail. It may be assumed that the basic principles and mechanism of the formation of a sydnoneimine ring are also common to other protocyclization reactions that lead to exocyclic imine mesoionic heterocycles.

2. Other Types of Cyclization

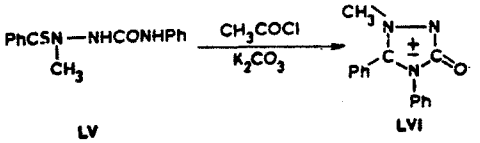
In addition to the two principal types of formation of mesoionic five-membered heterocycles, other types that do not fit completely into the proposed systemization are known. One of them is cyclization of linear molecules in which the future exocyclic group is already present.

Thus 1,2,4-triazol-5-one LIV was synthesized by the action of sodium ethoxide in alcohol on substituted acetylsemicarbazone LIII [65]:



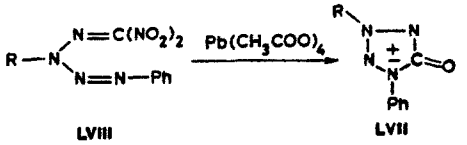
LIII LIV

Semicarbazide derivative LV undergoes cyclization to mesoionic triazolone LVI under the influence of acetyl chloride by heating to 80°C in the presence of potassium carbonate [66]:



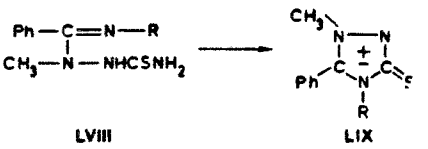
LV LVI

Tetrazolone LVII was isolated in the oxidation of LVIII with lead tetraacetate [67]:



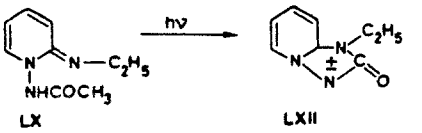
LVIII LVII

Cyclization with the formation of mesoionic five-membered heterocycles can also occur under thermolysis conditions and during irradiation. For example, during heat treatment thiosemicarbazide LVIII undergoes cyclodehydration to give 1,3,4-triazole-2-thione LIX [68]:



LVIII LIX

1,3,4-Triazole-5-one LXII was isolated in very low yield in the case of prolonged UV irradiation of a pyridine derivative (LX) [69]:

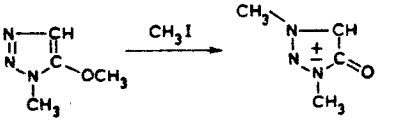


LX LXII

3. Formation of Mesoionic Compounds from Heterocycles with Normal Structures

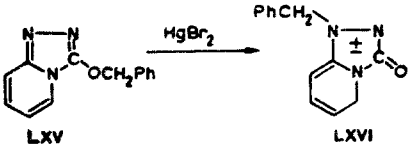
As we have already pointed out, in addition to formation by cyclization reactions, mesoionic five-membered heterocycles may also be formed via conversion of ordinary heterocycles.

The conversion of methoxytriazole LXIII by mesoionic 1,2,3-triazol-5-one LXIV by the action of methyl iodide in refluxing chloroform may serve as an example of this [70]:



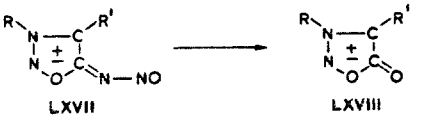
LXIII LXIV

The conversion of a normal heterocycle to a mesoionic heterocycle also occurs in the case of intramolecular transalkylation. Thus when pyridotriazole LXV is heated, the benzyl grouping migrates from the exocyclic oxygen atom to the nitrogen atom to give mesoionic system LXVI [71]:



LXV LXVI

The conversion of one mesoionic system to another by replacement of an exocyclic group has been described [72]: the corresponding sydnone LXVIII is formed when N-nitrososydnoneimine LXVII is heated in DMSO or butyl alcohol:



LXVII LXVIII

The examples of the formation of five-membered mesoionic heterocycles presented above constitute evidence for the absence of specificity in reactions that are characteristic only for mesoionic systems.

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MASS-SPECTRAL BEHAVIOR OF SUBSTITUTED 2-ALKYLAMINOBENZOXAZOLES AND 3-METHYL-2-ALKYLIMINOBENZOXAZOLINES

P. B. Terent'ev, V. A. Shmorgunov,
K. Davidkov, D. Simov,
and A. N. Kost*

UDC 543.51:547.787

Schemes that reflect the peculiarities of each of the investigated groups of compounds and make it possible to distinguish the amino and imino forms are given on the basis of a study of the dissociative ionization processes of 18 2-alkyl(dialkyl)-aminobenzoxazoles and six 3-methyl-2-alkyliminobenzoxazolines. A qualitative relationship between the electronic properties of the substituents in the aromatic ring and the formation of the imino forms of the molecular ions in the gas phase was found.

The problem of the possibility of the use of mass spectrometry as a method for the determination of the existence of tautomeric equilibria in various organic compounds has been discussed repeatedly [1-3]. Relatively recently Ogura and co-workers [4] described the mass spectra of a series of N-alkylaminobenzothiazoles. In a comparison of some peculiarities of the mass-spectral behavior of 2-methylaminobenzoxazole and 3-methyl-2-iminobenzoxazoline (as well as their thiazole analogs) they erroneously concluded that the mass spectra of these compounds are virtually identical, whereas a more thorough analysis of the mass spectra† presented in [4] makes it possible to note that higher stability of the molecular ions, a higher probability of the loss of a hydrogen atom or a CH_3N fragment by the molecular ion, and a lower probability of elimination of H_2CN or $CH_3N{-}CN$ fragments are characteristic for the 2-methylamino derivatives as compared with the isomeric 2-imino compounds.

In order to find distinctive features that are characteristic for the mass spectra of 2-alkylaminobenzoxazoles (I) and 2-alkyliminobenzoxazolines (II) we studied the dissociative ionization of a large series of Ia-r and IIa-f compounds that contain electron-donor or electron-acceptor substituents in the benzene ring.

The synthesis of these compounds [5] and their IR spectra [6] have been previously described. A comparison of the mass spectra of Ia,l,n,q that we obtained with the spectra presented in [4] showed good agreement for the peaks with intensities greater than 90%, and this

*Deceased.

†The mass numbers of the ions in the mass spectra of these and many other compounds published in [4] are frequently presented, but the intensities of their peaks are not indicated. In addition, the presence in them of $[M-12]^+$, $[M-13]^+$, and $[M-24]^+$ ion peaks and the increased (as compared with the theoretically possible values) intensities of the $[M+1]^+$ ion peaks make it possible to assert that some of the investigated compounds were not sufficiently pure for mass-spectral analysis.

M. V. Lomonosov Moscow State University, Moscow 117234. K. Okhridskii Sofia University, Sofia, Bulgaria 1126. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 3, pp. 304-308, March, 1981. Original article submitted September 24, 1980.

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