SYNTHESIS OF FURAZANS BY REARRANGEMENT OF 3-ACYL-1-OXA-2-AZOLE OXIMES (REVIEW)

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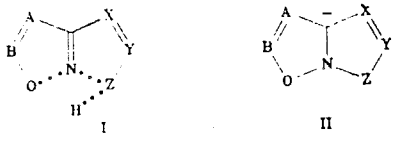
UDC 547.793.07(047)

Information on the rearrangement of the Z- and E-isomers of oximes of 3-acylisoxazoles, -1,2,4-oxadiazoles, -furazans, -furoxans, and Δ^2-isoxazolines to furazans is reviewed. The effects of basic and acidic catalysts on the course of the reaction are considered.

Rearrangements of heterocycles have attracted the attention of research workers in that, while frequently taking place under very mild conditions, they afford in many instances products with unexpected combinations of functional groups in the molecule. These rearrangements include those generalized by Boulton and Katritzky [1, 2], which are known in the literature under the rather unfortunate title of "monocyclic rearrangements of heterocycles" [3]. Essentially, the Boulton–Katritzky rearrangement is a subclass of such rearrangements [4]. The definition of these rearrangements as monocyclic (or mononuclear) is also imprecise, since in many instances they have been extended to polycyclic systems. For these reasons, we propose to use the term "rearrangement of heteromonocycles" as applied to both mono- and polycyclic systems, bearing in mind that only one ring is transformed during the rearrangement [4]. The Boulton–Katritzky rearrangement comprises rearrangements in which the original heterocycle is a 1-oxa-2-azole, the substituent in the 3-position being a heteroallyl grouping:

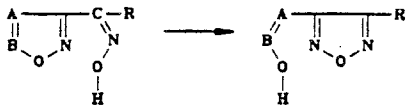
The rearrangement can, in principle, occur in three ways: 1) in the absence of a catalyst, by a concerted electrocyclic mechanism via the bicyclic transition state (I); 2) in the presence of a basic catalyst, by intramolecular nucleophilic replacement (S_Ni mechanism) at nitrogen via an intermediate or transition state (II); or 3) via the formation of acyclic intermediates [5, 6]:



I II

The route involving the formation of acyclic products has not been confirmed experimentally [7], and for the present the Boulton–Katritzky rearrangement will be considered to refer to reactions proceeding by the first two routes.

This review discusses the rearrangements of oximes of 3-acyl-1-oxa-2-azoles, which are, in most instances including azole–azole conversions, to be regarded as Boulton–Katritzky rearrangements:



Institute of Organic Synthesis, Academy of Sciences of the Latvian SSR. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 11, pp. 1443-1459, November, 1990. Original article submitted October 3, 1989.

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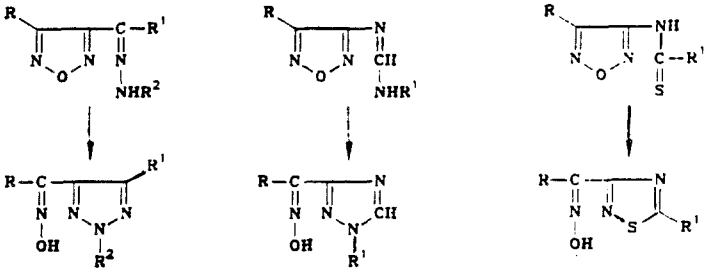
Not included here are rearrangements of Δ^2-isoxazolines involving conversion of azolines to azoles. The Boulton–Katritzky rearrangement has recently been extended to cover azole–azoline conversions, and termed the extended Boulton–Katritzky rearrangement [8]:

Following this argument, a further extension of the "extended" scheme would be inclusion of azoline–azole conversions (and perhaps subsequently azoline–azoline conversions):

Since only 1-oxa-heterocycles undergo this rearrangement, furazans are not obtained from triazole of thiadiazole oximes. In practice, in these cases the reverse reactions occur [3]:

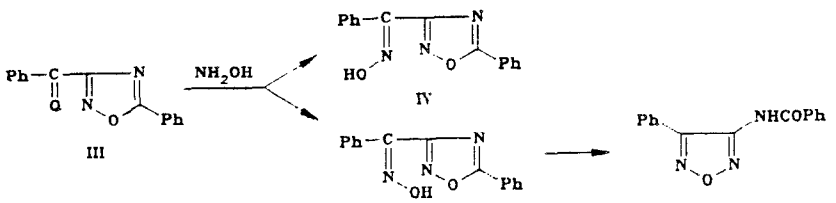


There have been no literature reports of rearrangements of oximes of 3-acyl-1-oxa-1-azines or other heterocycles.

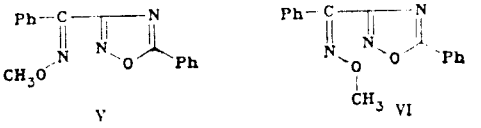
It is conventional in the literature to designate isomers of oximes in which the R group, when a hydrocarbon radical, and the OH group are located in the anti-positions as the Z-isomers, and isomers in which R is a heteroatomic substituent (NR_2, OR, halogen, SR, etc.) as the E-isomers. In order to avoid confusion, oximes in which the R and OH groups are anti-located will be termed E-isomers, and when syn-located, the Z-isomers:

3-ACYL-1,2,4-OXADIAZOLE OXIMES

A distinguishing feature of the rearrangement of 3-acyl-1,2,4-oxadiazole oximes is the low barrier to this reaction, in consequence of which E-oximes are converted during the reaction into furazans, which appears to be the reason why the E-isomers have not so far been isolated. Further, Ponzio [9] showed that oximation of 3-benzoyl-5-phenyloxadiazole resulted in the formation of a mixture of 1,2,4-oxadiazole and furazan compounds, the oxadiazole (IV) not being converted into the furazan under the reaction conditions:



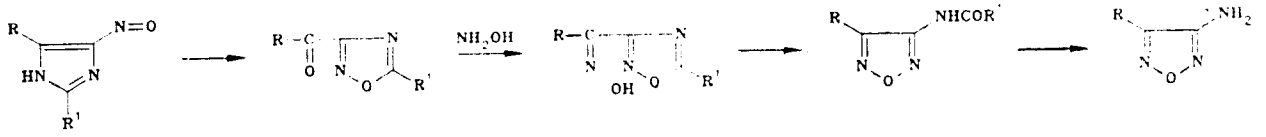
Ponzio rationalized the formation of two products as follows: Oximation gives the two isomeric oximes, one of which is unstable and rearranges to 3-phenyl-3-benzoylaminofurazan. Subsequent work confirmed this suggestion [10-13]. For example, oximation of (III) with O-methylhydroxylamine afforded a mixture of the E- and Z-isomers (V) and (VI) [12]. The O-methylated E-oxime (VI) does not undergo rearrangement.



V VI

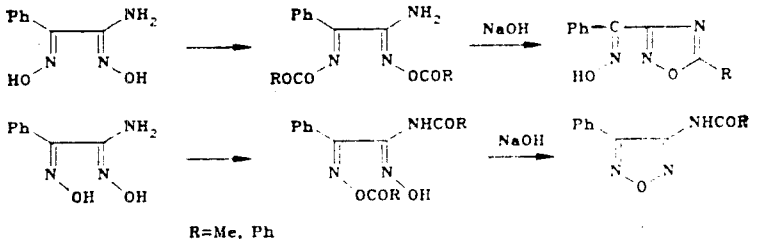
The proportions of oxime isomers formed on oximation of 3-acyl-1,2,4-oxadiazoles are dependent upon the structure of the acyl moiety. 3-Benzoyl-1,2,4-oxadiazole and its derivatives react with hydroxylamine to give mixtures of the furazan and 3-benzoyl-1,2,4-oxadiazole Z-oxime [11, 13]. The oximation product of 3-benzoyl-5-amino-1,2,4-oxadiazole, described as an oxadiazole [14], is in fact a furazan. Oximation of 3-acetyl- and 3-butyryloxadiazoles gives only the Z-oximes [14].

3-Acyl-1,2,4-oxadiazoles are known to give 4-nitrosoimidazoles on rearrangement [10, 11, 14]. If this reaction is carried out in the presence of hydroxylamine, the 5-H and 5-Me derivatives rearrange immediately to the furazans [11, 15-20]:



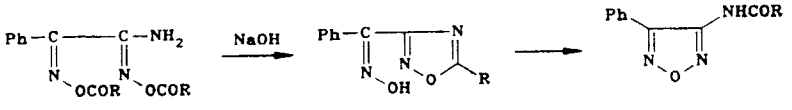
R=Ph, substituted phenyl; R^1=H, CH_3

Another example of the intermediate formation of the E-oximes of 3-acyl-1,2,4-oxadiazoles is the cyclization of amphi-phenylaminoglyoxime diacetates and dibenzoates. These compounds are known to give aminofurazans on heating with alkali [18, 21-24], whereas their isomers, the anti-aminoglyoximes, give oxadiazoles under these conditions. Ponzio therefore considered diacyl-amphi-aminoglyoximes to be O,N-diacyl compounds, and diacyl-anti-aminoglyoximes the O,O'-diacyl derivatives [21, 24]:*

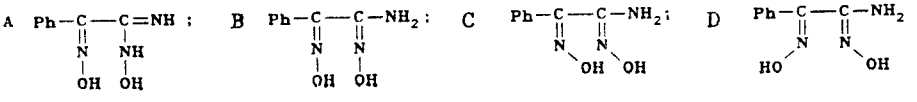


R=Me, Ph

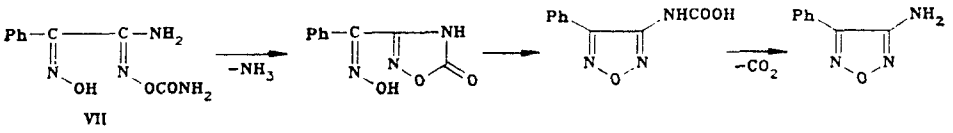
It has recently been shown, however [26] that the diacyl derivatives of both the amphi- and the anti-isomers are the O,O'-diacyl derivatives. Accordingly, the formation of N-acylaminofurazans from O,O'-diacyl-amphi-aminoglyoximes is due to the fact that they, like the anti-isomers, cyclize in the presence of alkali to 1,2,4-oxadiazoles, but the oxime group in these compounds has the E-configuration, in consequence of which they immediately undergo rearrangement:



*Ponzio considered that the isomers of aminoglyoximes differ in the structure of the amidoxime group [24]. He assigned structure A to the α-isomers, and structure B to the β-isomers. It has now been found [25] that the isomers differ in the configuration of the ketoxime moiety, the α-isomer having the amphi-configuration C, and the β-isomer the anti-configuration D.

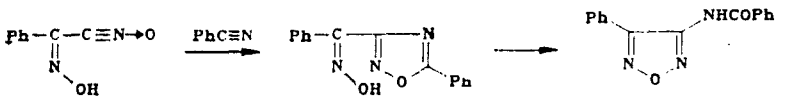


It is likely that this route is also followed in the cyclization of the carbamate (VII) [24], which is accompanied by the evolution of carbon dioxide and ammonia:



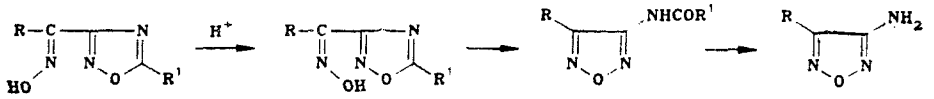
VII

The E-oxime of 3-benzoyl-5-phenyl-1,2,4-oxadiazole is an intermediate in the long-known, but hitherto unrationalized formation of 3-benzoylamino-4-phenylfurazan from α-aminophenylacetonitrile oxide [27, 28]:



The first step involves cycloaddition of benzonitrile (formed by decomposition of α-aminophenylacetonitrile oxide [28]) to the nitrile oxide group to give the E-oxime, which then rearranges to the furazan.

In the rearrangement of Z-oximes, the first step must involve Z–E isomerization. The isomerization of oximes is catalyzed by acids, so that many Z-oximes of 3-acyl-1,2,4-oxadiazoles rearrange in dilute acid to give N-acylaminofurazans. This method of synthesis of furazans was developed by Ponzio [9, 21, 23, 29], and subsequently used for the synthesis of a variety of 3-amino-4-phenylfurazans substituted in the benzene ring [11, 17, 18, 30, 31]:

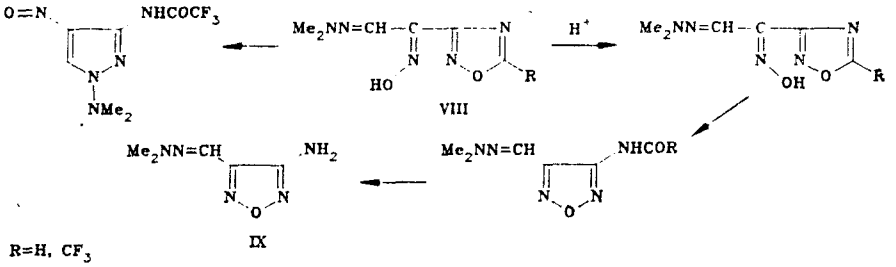


R=Me, Ph, substituted phenyl; R' = Me, Ph

With the Z-oximes of 3-benzoyl- and 3-p-toluoyl-5-phenyl-1,2,4-oxadiazole, rearrangement is accompanied by competitive hydrolysis of the oxime group [9, 10, 32].

In many cases, the rearrangement of Z-oximes takes place on heating to their melting points [9, 11-13, 21], but 3-acetyl-5-methyl-1,2,4-oxadiazole oxime remains unchanged under these conditions [9].

The rearrangement of the oxime hydrazone (VIII) (R = CF_3) can follow two routes. In the presence of acid, this compound is converted into the furazan (IX), but in the absence of a catalyst it undergoes gradual, spontaneous rearrangement involving the hydrazone rather than the oxime moiety of the molecule [33]:



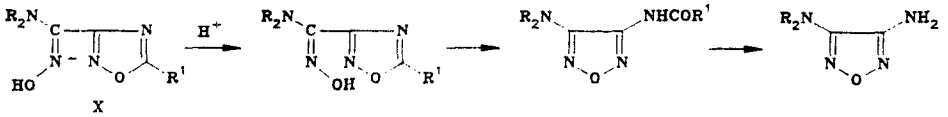
VIII

IX

R=H, CF_3

The oxadiazole (VIII), which has no substituent in the 5-position, is stable and does not undergo rearrangement to the nitrosopyrazole.

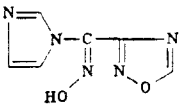
Z-N,N-Disubstituted amidoximes of 1,2,4-oxadiazole-3-carboxylic acid on treatment with acid isomerize readily, even at room temperature, to the thermodynamically more stable E-amidoximes, which rearrange to diaminofurazans [34, 35]:



X

R_2N=pyrrolidinyl, piperidyl; R^1= H, CF_3

Z-isomers of amidoximes containing a 1-azolyl ring as the amine function are not converted to the E-isomers in acid solution, so that rearrangement of the imidazole derivative (XI) does not take place under these conditions [35].

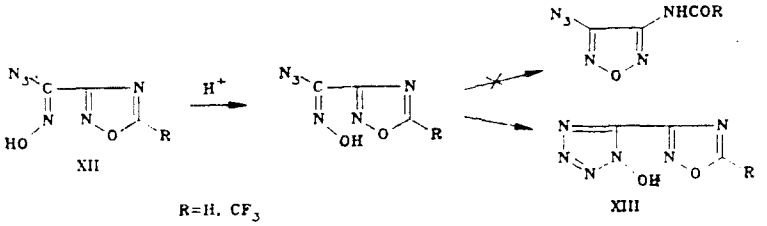


XI

Since the barrier to Z–E isomerization in N,N-dialkylamidoximes is low (21-25 kcal/mole) [36, 37], compound (X) spontaneously isomerizes and rearranges gradually to the furazan on standing at room temperature [34, 35].

The barrier to isomerization for N-monoalkylamidoximes is even lower (19.9-21.5 kcal/mole) [37], so that they rearrange spontaneously more rapidly, despite the fact that the Z–E equilibrium is strongly shifted toward the Z-isomer. Acid catalysis does not in this instance promote the reaction, since the Z–E isomerization barrier is low even in its absence.

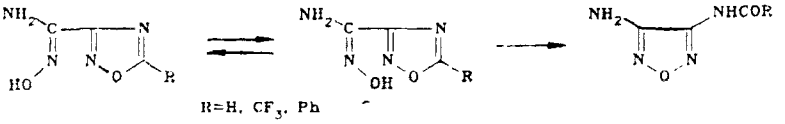
No rearrangement products are formed on isomerization of Z-azidooximes (XII), since the E-oximes cyclize to the hydroxytetrazole (XIII) [38]:



XII R=H, CF_3 XIII

Complications arise in the rearrangement if the E-oxime is thermodynamically much less stable than the Z-oxime. In such a case, on acid-catalyzed Z–E isomerization the proportion of the E-isomer in the equilibrium mixture is so small that rearrangement hardly occurs. This situation is encountered in compounds in which the oxime group is substituted by groups such as halogen, amino, imidazolyl, or aziridinyl rings. On heating these compounds in acid, only degradation of the oxime moiety takes place.

However, rearrangement of amidoximes with an unsubstituted amino-group can occur if bases are used as catalysts [35, 39, 40]:



R=H, CF_3, Ph

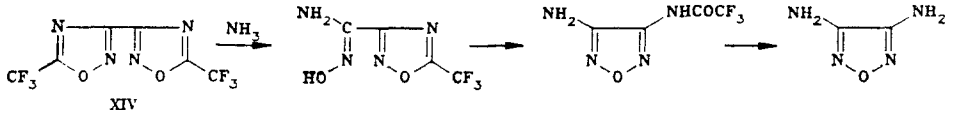
The rearrangement of monosubstituted amidoximes is also base-catalyzed [34, 35]. The occurrence of the reaction in this case is due to the fact that in unsubstituted and monosubstituted amidoximes the Z–E isomerization barrier is very low, so that isomerization can occur even in basic media. The observed reaction constant (k) for such a two-step reaction is given by the expression [41]:

$$k = K \cdot k_2,$$

where K is the Z–E equilibrium constant, and k_2 the rate constant for the second stage of the reaction (rearrangement).

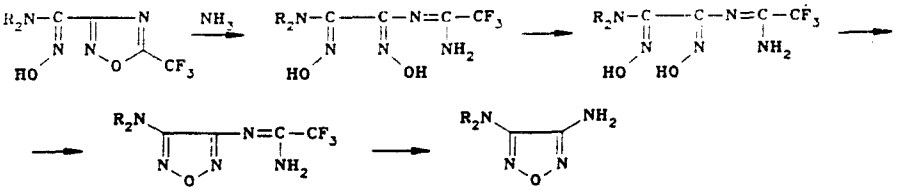
Hence, in this instance the overall reaction rate is dependent on the rate of rearrangement, the function of the base being to catalyze this stage. The rate K is greater for monosubstituted amidoximes than for the unsubstituted compounds, so that the overall reaction rate is greater, and these amidoximes are unstable, undergoing spontaneous conversion into furazans. As already pointed out, the conversion of Z-monosubstituted amidoximes into furazans is not catalyzed by acids. In fact, the expression for the observed reaction rate does not include the rate constant for the first stage (isomerization of the oxime group).

The bisoxadiazole (XIV) rearranges on treatment with ammonia to give a diaminofurazan [40, 42]:

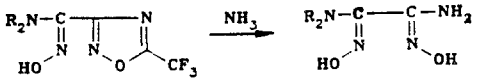


XIV

The first step involves cleavage of one of the oxadiazole rings with the formation of an amidoxime group. Bearing in mind the ease of cleavage of the 5-trifluoromethyl-1,2,4-oxadiazole ring, it was assumed to be possible that the rearrangement of these compounds could involve the formation of intermediate acyclic products [40]:

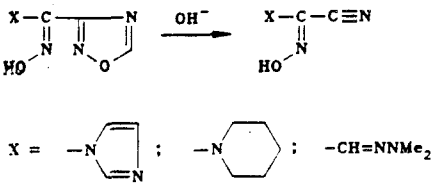


This scheme does not include the stage of isomerization of the amidoxime group, so that the overall reaction rate should not be dependent on this step. However, further work failed to confirm this. Compounds in which the Z–E barrier is high (amidoximes containing aziridine or imidazole rings are the amine function) on treatment with ammonia undergo cleavage of the oxadiazole ring, but do not cyclize to furazans:



It follows that bases catalyze the rearrangement of those Z-amidoximes which have a low Z–E isomerization barrier, which is evidence in support of the above reaction scheme involving the initial isomerization of the Z-amidoxime group, followed by base-catalyzed rearrangement.

Rearrangement of the Z-oximes of 5-substituted 3-acetyl- and 3-benzoyl-1,2,4-oxadiazoles fails to occur in basic media, due to the high isomerization barrier in alkaline media. Oxadiazoles unsubstituted in the 5-position undergo ring-opening under these conditions with the formation of cyano-oximes [33, 35]:

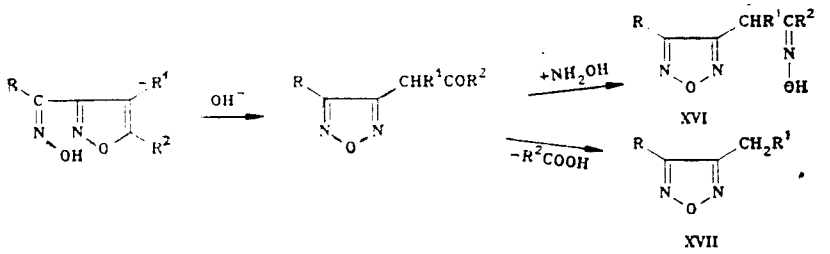


Hence, the E-isomers of 3-acyl-1,2,4-oxadiazole oximes are unstable, undergoing spontaneous rearrangement on formation without base catalysis. The Z-isomers on treatment with acids, which catalyze the isomerization of oximes, undergo rearrangement when the amounts of the E-isomer in the equilibrium mixture are sufficiently high for the rearrangement to proceed at a rate which is greater than that of degradation of the oxime group (or is at least comparable with this rate). If the equilibrium is strongly shifted toward the Z-isomer, the use of basic catalysts enables the rearrangement to be carried out in those cases in which the barrier to isomerization of the oxime group is so low that it can occur even in alkaline solution.

3-ACYLISOXAZOLE OXIMES

The E-oximes of 3-acyloxazoles, unlike the 1,2,4-oxadiazoles discussed above, are stable, and under the usual conditions do not rearrange in the absence of a basic catalyst. For this reason, oximation of 3-benzoylisoxazoles affords mixtures of the Z- and E-oximes, while 3-acetylisoxazoles give a single isomer only, which, according to Vivona et al. [7], has the Z-configuration. Previously, the E-oximes of 3-benzoylisoxazoles had been erroneously assigned the furazan structure [7, 43-46].

On treatment with base, the E-oximes undergo extremely facile rearrangement to ketofurazans. The reaction frequently proceeds even at room temperature, or on brief heating in alcohol:

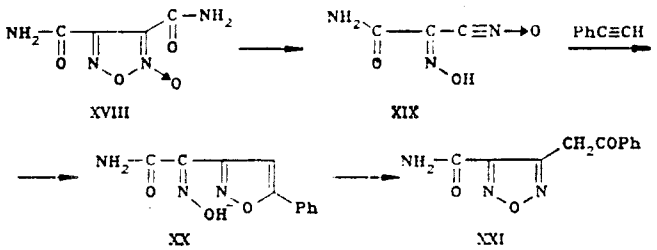


XVI XVII

R=Ph, R^1=H, R^2=Me [7, 47—49]; R=Ph, R^1=H, R^2=Ph [7, 50, 51]; R=R^1=R^2=Ph [7, 43, 44, 46]; R=Ph, R^1=PhCO, R^2=Ph [51]; R=$C_5H_{10}N$, R^1=H, R^2=H [52]; R=$C_5H_{10}N$, R^1=H, R^2=Ph [52]; R=3-isoxazolyl, R^1=H, R^2=H [53, 54]

The ketofurazans (XV) may undergo deacylation in the alkaline medium, so that the final products are the alkylfurazans (XVII) [7, 43, 44, 46, 50, 51]. When the rearrangement is carried out in the presence of hydroxylamine, the product is isolated as a mixture of the E- and Z-isomeric oximes (XVI) [7, 47-50, 52-56].

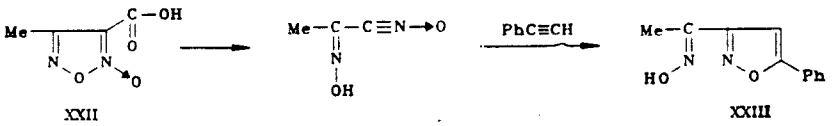
The nitrile oxide obtained on thermolysis of the furoxan (XVIII) reacts with phenylacetylene to give the isoxazole (XX), which under the reaction conditions (a boiling mixture of xylene and DMF) rearranges to the furazan (XXI) [57].



XVIII XIX XX XXI

It appears that the oxime group in the nitrile oxide (XIX) and in the isoxazole (XX) retains the same configuration as it has in the furoxan.

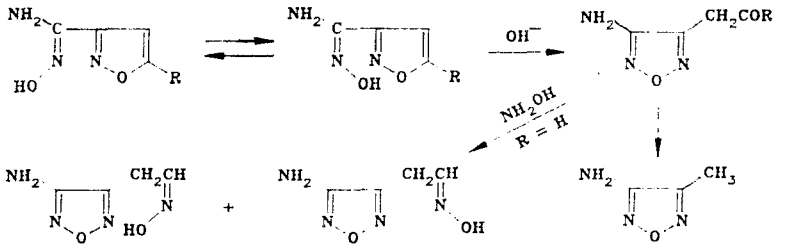
In contrast, the nitrile oxide generated from the furoxan (XXII), on reaction with phenylacetylene gives as the final product not a furazan, but the oxime (XXIII) [58], which is identical in its properties to the isomer with the Z-configuration [7]:



XXII XXIII

It is clear that even at an early stage in the reaction (formation of the nitrile oxide), isomerization of the oxime group occurs, and as a result of cycloaddition an oxime is formed, the configuration of which is unfavorable for rearrangement.

The rearrangement of Z-oximes is complicated by the fact that the first step involves Z–E isomerization, which is catalyzed by acids. If the E-isomer is thermodynamically more stable than the Z-isomer, as may be the case with N,N-disubstituted amidoximes, then the reaction presents no particular difficulties. First, the Z-isomers are converted to the E-isomers in the presence of acid, and these are then rearranged in an alkaline medium [52]. If, however, the Z-isomers are more stable than the E-isomers, both stages occur simultaneously, and the situation arises in which the first step requires acid catalysis and the second, basic catalysis. In this case, the occurrence of a reaction is dependent on the Z–E isomerization barrier for the oxime. As already pointed out, with unsubstituted amidoximes this barrier is low, and isomerization can occur without a catalyst, or even in alkaline media. Consequently, the Z-amidoximes of isoxazoles, as in the case of 1,2,4-oxadiazoles, undergo facile rearrangement to furazans on treatment with base [56]:



R = H, Ph

When R = H, the aldehyde formed on rearrangement undergoes deformylation, but when the reaction is carried out in the presence of hydroxylamine a mixture of the Z- and E-oximes is obtained.

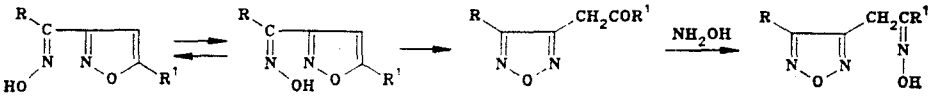
The situation is more complex when the Z–E isomerization barrier is high. This is the case with the Z-oximes of 3-acetyl- and 3-benzoylisoxazoles. The rearrangement of these compounds has been examined by Ajello [43-45, 47, 50, 51]. More recent studies of some of these reactions [7] have shown that despite the findings of Ajello, in no case did the Z-oximes rearrange in the presence of alkali [1, 7]. It is apparent that under basic conditions Z–E isomerization of these oximes, like that of the previously discussed 1,2,4-oxadiazole compounds, does not occur. Likewise, the oximes (XXIV) and (XXV) fail to rearrange in the presence of base [59, 60], which may be regarded as evidence in support of the Z-configuration of the oxime group in these compounds.

XXIV XXV

R = H, Me

In contrast to 3-acetyl- and 3-benzoyl-1,2,4-oxadiazoles, the Z-oximes of which undergo isomerization on treatment with acid, followed by rearrangement to furazans, the analogous derivatives of isoxazole undergo hydrolysis under these conditions to give the desoximated products (ketones) [44, 45, 47, 48, 58, 61-63]. This is rationalized as being due to the fact that in isoxazoles the second stage of the reaction (rearrangement) occurs with greater difficulty, requires basic catalysis, and does not occur in acid media.

The rearrangement of these Z-oximes can be successfully effected by boiling in the presence of a large excess of free hydroxylamine [47, 64]:

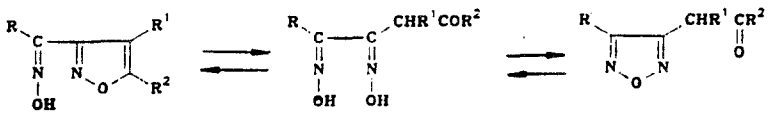


R=Me, Ph; R'=Me, Ph

The reaction becomes possible since in weakly basic media the oxime is not ionized and, consequently, Z–E isomerization occurs more readily than in strongly basic media. At the same time, a weakly basic medium is sufficiently favorable for the recyclization to occur. Hence, there is an optimum pH of the medium at which rearrangement of the Z-oximes of 3-acetyl- and 3-benzoylisoxazoles takes place at the greatest rate.

In addition, rearrangement of the Z-oxime of 3-acetyl-5-methylisoxazole occurs when it is melted in the presence of copper powder [1]. The function of the catalyst in this reaction is not clear, but, as in the preceding example, the reaction takes place under conditions not too far removed from neutral.

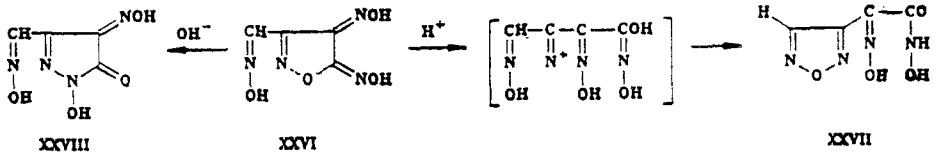
Ajello considered that the rearrangement of 3-acylisoxazole oximes involved hydrolytic ring cleavage:



Moreover, the E-oxime was assumed by Ajello to be the product of the rearrangement of the furazan. Since on heating with acid it was converted into 3-acylisoxazole, it was concluded erroneously that the rearrangement was reversible [50, 65].

The observed decisive effect of the configuration of the oxime grouping on the occurrence of the rearrangement is a weighty argument in favor of the reaction proceeding via intramolecular nucleophilic substitution at nitrogen.

The mechanism of the rearrangement of pericyanilic acid (XXVI) is not entirely clear [66-68]. The reaction requires the presence of acid, and results in the formation of α- and β-epicyanilic acids (XXVII), which differ in the configurations of the oxime groups. It is assumed that the reaction proceeds via an acyclic intermediate [68]. The configuration of the oxime group in the starting acid (XXVI) is unknown.



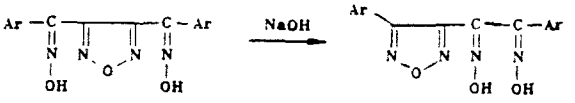
XXVIII XXVI XXVII

The rearrangement of pericyanilic acid in the presence of base follows a different course, to give erythrocyanilic acid (XXVIII) [66, 69], a derivative of 1-hydroxypyrazole [70].

It follows from the above that the rearrangement of the E-isomers of 3-acylisoxazole oximes is extremely facile in the presence of base. The Z-oximes in acid media either undergo hydrolysis, or they isomerize to the E-oximes, if the latter are more stable, but in this case no rearrangement occurs. In alkaline media, only those Z-oximes with a low Z–E isomerization barrier rearrange. For the rearrangement of the Z-oximes of 3-acetyl- and 3-benzoylisoxazoles, there is an optimum pH of the medium, approximating to weakly basic. In strongly acidic and strongly basic media, these compounds do not undergo rearrangement.

3-ACYLFURAZAN OXIMES

3-Acylfurazan oximes rearrange under very severe conditions. This was first reported by Ponzio for the diaroylfurazan dioximes (XXIX) [71]:

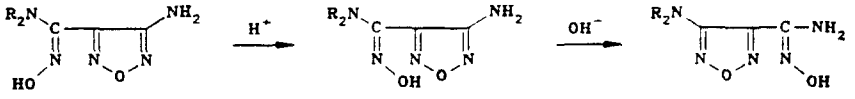


XXIX

Ar=C_6H_5; p-$CH_3C_6H_4$

The reaction took place when the dioxime was fused, on or boiling in 20% aqueous sodium hydroxide. The starting dioxime (XXIX) was obtained by oximating the appropriate diketone, but its configuration is not known. On boiling in hydrochloric acid, the dioxime (XXIV) is hydrolyzed to the starting ketone.

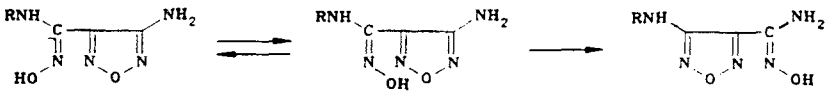
The Z-isomers of N,N-disubstituted amidoximes (XXX) undergo isomerization in the presence of acid at room temperature to give the E-oximes [72]. The structures of both isomers have been confirmed by x-ray diffraction examination [73]. The E-oximes (XXXI) rearrange in alkali at 120-140°C to the isomeric oximes (XXXII) [72]:



XXX XXXI XXXII

R_2 = Me_2, $(CH_2)_5$, $(CH_2)_6$

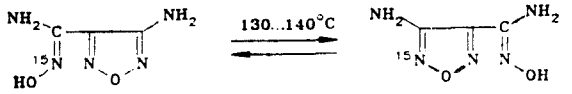
Since the barrier to the isomerization of amidoximes is low, but the conditions for rearrangement fairly severe,, the Z-amidoximes also undergo this reaction to give the same products. For this reason, N-monosubstituted amidoximes, in which the Z-form is thermodynamically favored, undergo rearrangement:



R = i-Pr, $PhCH_2$

It is clear that the rearrangement of furazans can be reversible, but in all cases mono- and disubstituted amidoximes rearrange completely, no equilibrium being established.

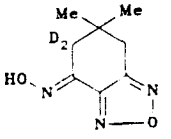
When the same substituents are present in the oxime group and the furazan ring, the rearrangement must be degenerate. In fact, in the case of the oxime nitrogen-labeled amidoxime (XXXIII), it has been shown that on carrying out the reaction under the above conditions the labeled nitrogen is incorporated into the ring to give a mixture of (XXXIII) and (XXXIV) in equal amounts [74]:



XXXIII XXXIV

In unsubstituted amidoximes, the Z–E equilibrium is strongly shifted toward the Z-isomer and, therefore, rearrangement of (XXXIII) takes place only at 130-140°C, whereas the E-isomer (XXXI) rearranges in boiling aqueous or alcoholic alkali, even if less rapidly.

In contrast, it did not prove possible to carry out the degenerate rearrangement of the oxime (XXXV) [2]. The configuration of the oxime group in this compound is unfavorable for rearrangement [75], the Z–E isomerization barrier for ketoximes is higher than that for amidoximes, and isomerization of the oxime under the reaction conditions does not appear to take place.



XXXV

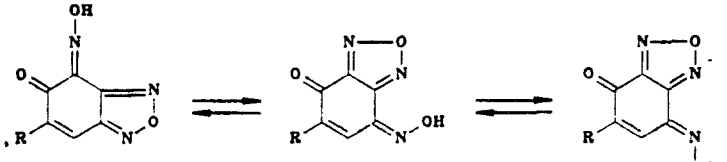
Nor was it possible to rearrange the oxime (XXXVI), the configuration of which has not been established [2]. The reason for the lack of success could be the same as in the previous case, but it is also possible that the starting furazan (XXXVI) is thermodynamically more stable than its isomer (XXXVII).

XXXVI XXXVII

The rearrangement of benzofurans takes place with great ease [76-79]. The reaction proceeds at near-ambient temperatures, and is catalyzed by bases.

In the case of the keto-derivative (XXXVIII) the rearrangement is reversible, and can be carried out either with the isomer (XXXVIII), or isomer (XL) [79].

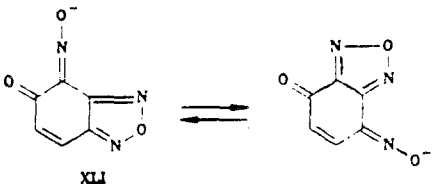
In acid media, no rearrangement takes place, although in the case of the furazan (XL) an equilibrium is established between the Z- and E-isomers of the oxime. The oxime (XXXVIII) is invariably obtained as a single isomer, the configuration of which has not been established.



XXXVIII XXXIX XL

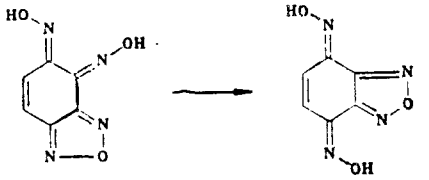
R = H, Me, Cl

The rearrangement is extremely slow in dioxane. In aqueous dioxane, equilibrium is reached after 48 h, but in DMSO, pyridine, and a mixture of dioxane and triethylamine it is reached within 10 min. The composition of the equilibrium mixture is independent of the solvent. The proportions of (XXXVIII) are 11-12, of (XXXIX) 65-70, and of (XL) 17-23%. In solution in aqueous alkali, the equilibrium between the ionized forms of the oximes is shifted in the opposite direction. The content of the isomer (XLI) in the equilibrium mixture was around 80% [79].



XLI

The rearrangement of the dioxime (XLII) proceeded similarly, but in this case the reaction went to completion [78]:



XLII XLIII

The kinetic reaction product is the dioxime (XLIII), in which one of the groups has the Z-, and the other the E-configuration. The configuration of the α-oxime group in the starting furazan (XLII) has not been established.

Thus, the rearrangement of monocyclic furazans takes place under severe conditions, and is catalyzed by bases. The rearrangement may proceed to an equilibrium. When the same substituents are present in the ring and oxime group, the rearrangement becomes degenerate. The Z-isomers rearrange when Z–E isomerization of the oxime group is possible under the reaction conditions. In benzofurazans, the Z–E isomerization of the oximes and rearrangement are extremely facile. The rearrangement is catalyzed by bases, and does not occur in the presence of acid.

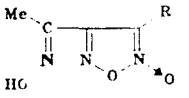
5-ACETYLFUROXAN OXIMES

The voluminous experimental material on the reactions of acetylfuroxan oximes was first reviewed in a monograph [80].

The E-oxime of 5-benzoyl-3-methylfuroxan (XLV) on treatment with alkali at room temperature rearranges rapidly to a furazan derivative [81, 82]:

XLIV

This reaction was first reported by Ponzio [81], but it is only recently that the precise structures of the starting material and product have been established [82]. The 5-acetylfuroxan oximes (XLV) are stable toward alkali [83, 84], possibly as a result of the Z-configuration of these compounds, which is unfavorable for rearrangement. The structure of (XLV) (R = CH_3) has been established by x-ray crystallography [85].

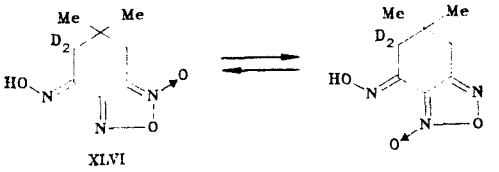


XLV

R = Me, Ph

On heating in hydrochloric acid solution, oximes (XLIV) and (XLV) undergo hydrolysis to the corresponding ketones [81, 83, 84].

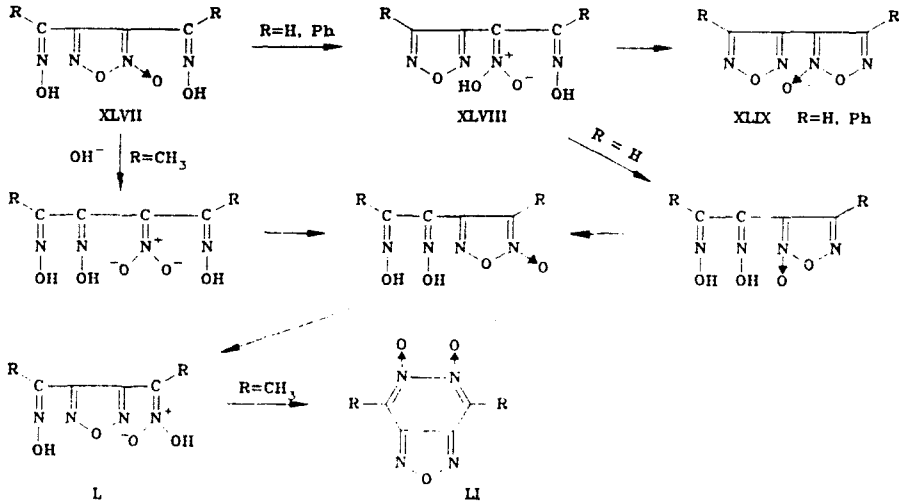
Neither does the furoxan (XLVI) rearrange [2], in which the oxime group also has the Z-configuration [86, 78]. On heating, this compound merely undergoes isomerization of the furoxan ring, the configuration of the oxime group being retained:



XLVI

The rearrangement of 3,4-diacylfuroxan dioximes is complex. The correct structures of the products of these reactions were established only recently [68, 88], but their mode of formation remains largely unclear.

The Z,Z-furoxandialdoxime (XLVII) (R = H, α-isocyanilic acid) on brief heating in water undergoes rearrangement to the α-nitroxime (XLVIII) (R = H, β-isocyanilic acid), which then undergoes dehydration to 3,3-difurazanyl 2-oxide [68, 69, 89]:

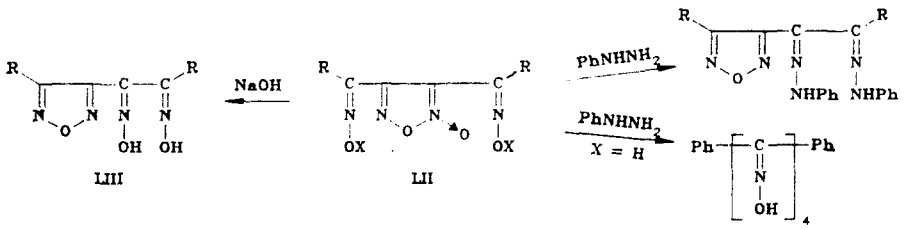


XLVII XLVIII XLIX R=H, Ph L LI

Dibenzoylfuroxan rearranges similarly on boiling in hydrochloric acid, or on fusion [90]. In this case, the intermediate α-nitro-oxime (XLVIII) was not isolated, the final product being 4,4-diphenyl-3,3-difurazanyl 2-oxide (XLIX) (R = Ph).

The reaction proceeds differently in alkali. The Z,Z-dioxime (XLVII) (R = H) was converted via the α-nitro-oxime (XLVIII) into the furazan (L) [66, 68, 69, 89]. The proposed reaction sequence includes reactions involving cleavage and closure of the heterocycles [68]. On treatment with alkali, the diacetylfuroxan Z,Z-dioxime undergoes complex reactions to give the furazanopyridazine (LI) [88, 91, 92]. The scheme proposed for its formation [88] also includes formation of the intermediate (L) (R = CH_3), albeit by a somewhat different route.

Rearrangement of the dioxime (LII) in alkali is accompanied by reduction to give the dioxime (LIII) [90], which is identical with the product obtained on rearrangement of the furazan analog [71]:



LIII LII

R=Ph, p-Tol; X=H, CH_2CO; PhCO

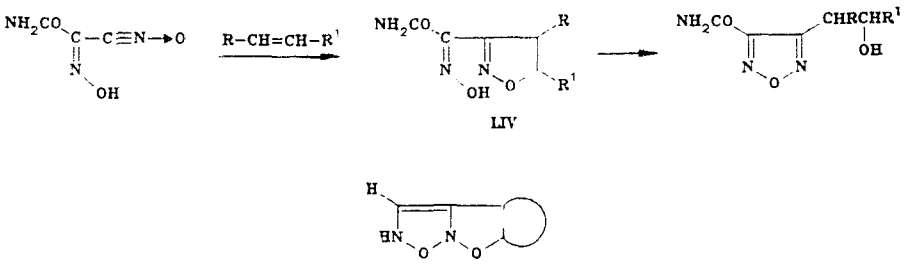
Reduction also occurs in the reaction of diacyl derivatives of the dioxime (LII) with phenylhydrazine [90]. In this case, in addition to rearrangement, the oxime groups are replaced by hydrazone groups. The nonacylated dioxime on reaction with phenylhydrazine gives only the reduction product, with cleavage of the furoxan ring [93]. This provides indirect support for the view that the rearrangement of the dioximes (LII) involves reduction cleavage of the furoxan ring followed by closure of the furazan ring.

On boiling with acids, the dioximes (XLVII) (R = H, CH_3) decompose [66, 92].

3-ACYL-Δ^2-ISOXAZOLINE OXIMES

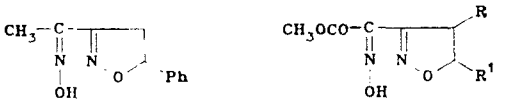
Of the dihydro-derivatives of azoles, only Δ^2-isoxazolines have so far been shown to rearrange.

The nitrile oxide generated by thermolysis of furazandicarbonamide adds to olefins to give the E-oxides (LIV), which then rearrange to furazans [57]:



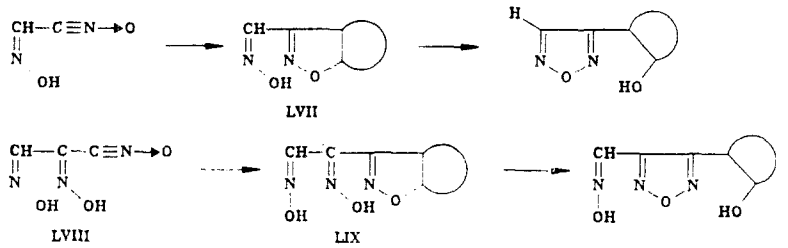
LIV

However, oximes (LV) and (LVI), obtained in a similar way, are not converted into furazans under these conditions [57, 58]:



LV LVI

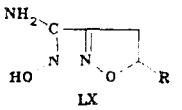
The isoxazolines obtained by reaction of fulminic dimer and trimer (LVIII) with cyclic olefins rearrange with great ease [94, 95]*:



LVII LVIII LIX

The E-isomers (LVII) and (LIX), which are the kinetic products of the cycloaddition reaction, are unstable, rearranging in alkali (and sometimes directly on their formation) into furazans. In acid media, the E-oxides isomerize to the thermodynamically more stable Z-oximes [94, 95], and under more severe conditions they undergo hydrolysis [96]. Rearrangement also takes placed on brief heating to 210°C, but in this case the Z-oximes are formed in addition to furazans [94].

The Z-amidoximes (LX) on treatment with bases such as ammonia and 1,8-diazabicyclo[5.4.0]undec-7-ene are unaffected, but in the presence of caustic alkali they decompose [56]:



LX

R = C≡N; $CONH_2$

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*The rearrangement products have been assigned the Δ^3-1,2,5-oxadiazoline structure [94].

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