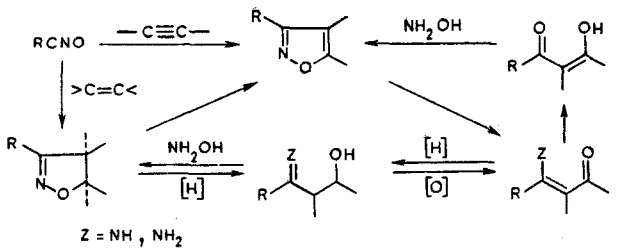
ISOXAZOLE DERIVATIVES IN THE SYNTHESIS OF BIFUNCTIONAL COMPOUNDS BY CLEAVAGE OF THE HETERORING (REVIEW)

A. A. Akhrem, F. A. Lakhvich, and V. A. Khripach

UDC 547.786'435'442'435

The pathways and methods of transformation of isoxazoles to give various acyclic difunctional derivatives (α-cyano ketones, β-diketones, imino and amino ketones, β-amino alcohols, α,β-unsaturated ketones, etc.) by opening of the heteroring are examined in the review from the point of view of latent functionality. The prospects for the application of acyclic functional derivatives of isoxazoles and 2-isoxazolines — adducts of 1,3-dipolar cycloaddition of nitrile oxides to olefins and acetylenes — for regio- and stereospecific synthesis are discussed.

Heterocyclic compounds are universal precursors of the most diverse acyclic functional derivatives [1]. This is associated with the concealed (latent) functionality [2] of the heterocyclic ring, the realization of which is achieved by opening of the heteroring and may include a number of successive chemical reactions. 1,2-Oxazole derivatives (oxazoles), which, depending on their structure and the chemical transformation conditions, can be regarded as the latent forms of cyano and imino ketones, α,β-unsaturated ketones and ketoximes, β-hydroxy ketones, β-di- and polyketones, γ-amino alcohols, and other compounds, are extremely characteristic in this respect. The isoxazole ring is stable under the conditions of many chemical reactions and makes it possible to carry out the selective chemical modification of other parts of the molecule [3]. The subsequent generation of a highly reactive bifunctional grouping is readily accomplished by, for example, reductive or base-induced cleavage of the ring at the N—O bond or, in some cases, at the C—O bond. In addition to the traditional methods of synthesis described in earlier reviews [4-7], new effective methods for the regiospecific production of isoxazoles such as those in [8, 10] and their selective conversion to various functional compounds with an open chain have recently been developed. The isoxazoles and 2-isoxazolines obtained by 1,3-dipolar cycloaddition of nitrile oxides to compounds with multiple carbon—carbon bonds [11] are of particular interest in this connection. The reaction of nitrile oxides with acetylenes and olefins makes it possible to obtain isoxazole derivatives that are selectively substituted in all of the positions of the heteroring. The nitrile oxide synthesis of isoxazoles does not, in principle, require carbonyl-containing starting substances (for example, in this case of nitrile oxides from primary nitro compounds) and is potentially a method for the generation rather than regeneration of bifunctionality, as in the case of the cleavage of isoxazoles obtained by the classical method from β-dicarbonyl derivatives and hydroxylamine. The possibility of the realization of regio- and stereospecific processes both in the formation and transformation of the cycloadducts and of the use of functionally substituted dipoles and dipolarophiles makes it possible to regard nitrile oxides and and the cycloadducts based on them as universal polyfunctional building blocks for the preparation of the most diverse organic structures.



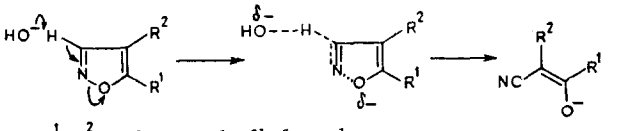
Institute of Bioorganic Chemistry, Academy of Sciences of the Belorussian SSR, Minsk 220600. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 9, pp. 1155-1173, September, 1981. Original article submitted December 30, 1980.

The aim of the present review is to give information, chiefly from the literature of the last 10-15 years that has not been dealt with in the available reviews, regarding the pathways and methods of conversion of isoxazoles to functional compounds by opening of the heteroring; particular attention is directed to 2-isoxazolines, which previously were virtually disregarded in this respect. At the same time, 2-isoxazolines are related to isoxazoles by one step involving oxidative transformation and are themselves of considerable interest for the regio- and stereoselective synthesis of functional derivatives. In the case of 2-isoxazolines obtained by 1,3-cycloaddition of nitrile oxides to olefins the orientation of the substituents in the 4 and 5 positions is dictated by the strict cis stereospecificity of the process [11], which in turn determines the stereochemistry of these centers during the subsequent cleavage of the heteroring. The general problems in the chemistry of isoxazoles have been illuminated in earlier reviews [4-7]. The conversion of isoxazoles to other heterocycles is discussed in [12]. Individual aspects of the synthetic application of isoxazoles are examined in [13-16].

Cleavage of the Isoxazole Ring

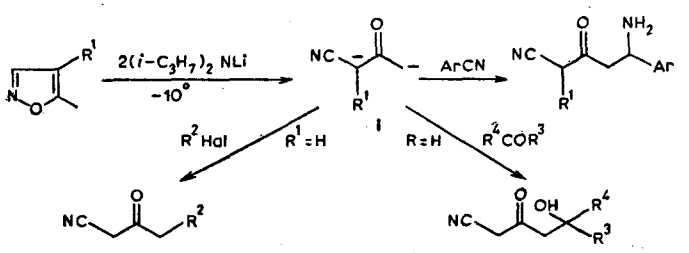
The cleavage of the heteroring of isoxazoles, which leads to functional compounds with an open chain, is widely used in organic synthesis. The use of isoxazoles in the annelation of steroid rings by the method of Johnson and Stork and in the synthesis of peptides and vitamin B_{12} precursors has become classical for the chemistry of natural compounds and has been discussed in a number of reviews [13, 15, 16]. In addition, the interest in the use of the latent functionality of the isoxazole ring is far from exhausted, as evidenced by the recent publication of a number of studies in this area. Although the action of bases and reductive cleavage are still the principal methods for cleavage of the isoxazole ring, the scope of their application has been expanded significantly, and a number of new reagents have been proposed. The substantially increasing preparative possibilities of photolytic cleavage, to the study of which a great deal of attention has recently been directed, should also be noted.

By the Action of Bases. The ease of opening of the heteroring of isoxazoles under the influence of bases and the character of the reaction products depend on the presence of substituents in the ring and their orientation. According to earlier data [6], isoxazoles that do not contain substituents in the 3 position are the most sensitive to the effect of bases; substituents in the 4 and 5 positions have a substantial effect on the rate of cleavage. In general, the stability of the isoxazole ring decreases as the electron-acceptor properties of the substituents become more pronounced [17] and on passing from 5-substituted to 4-substituted 3H-isoxazoles. Thus 4-phenylisoxazole reacts with an aqueous methanol solution of potassium hydroxide 19 times faster than 5-phenylisoxazole [18]. This fact, together with the other kinetic parameters, provides a basis for the assumption that the described reaction proceeds via a one-step concerted E_2 mechanism with a transition state of the cyanoenol anion type with localization of the partial negative charge on the oxygen atom of the isoxazole ring. The difference in rates in this case is due to the more effective stabilization of



R^1, R^2 = alkyl, cycloalkyl, aryl

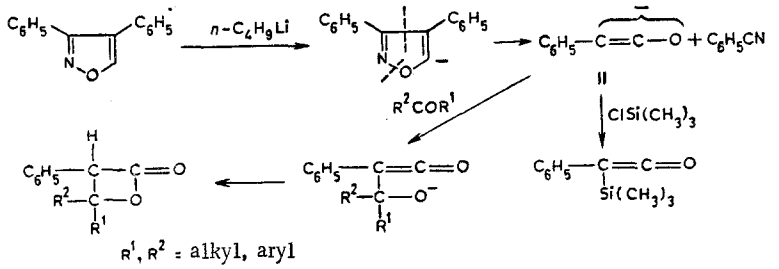
the transition state by the substituent in the 4 position. Similar results were obtained during a study of the mechanism of cleavage of benzisoxazoles by the action of aqueous alcoholic alkali and amines [19]. The reaction evidently proceeds via an E_1 mechanism with detachment of a proton from the 3 position and the formation of a carbanion under the influence of strong bases such as alcoholates, lithium diisopropylamide, and n-butyllithium. The use



R^1=H,CH_3; R^2 = alkyl, alkenyl, aryl; R^3, R^4 = H, aryl

of two equivalents of lithium diisopropylamide in the reaction with 4-methyl- and 4,5-dimethylisoxazoles leads to ring opening to give dianion I, which can be used for the preparation of polyfunctional compounds by reaction with halo derivatives, aldehydes, ketones, nitriles, etc. [20].

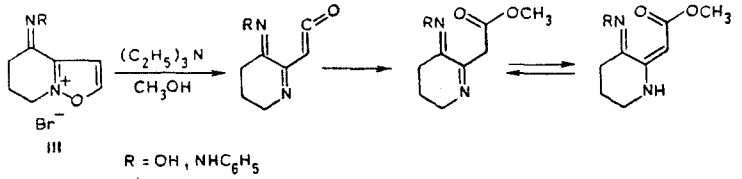
When 3,4-diphenylisoxazole is treated with n-butyllithium, a proton is detached from the 5 position with opening of the heteroring and subsequent cleavage of the carbon chain to give benzonitrile and ethynolate anion II [21], which was identified in the form of adducts with ketones or the trimethylchlorosilyl derivative.



R^1, R^2 = alkyl, aryl

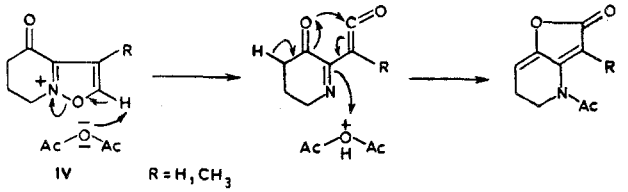
Quaternization of the nitrogen atom increases the reactivity of the isoxazole ring significantly with respect to bases [6]. Isoxazolium salts with an unsubstituted 3 position are particularly labile. They readily undergo ring opening under the influence of various nucleophiles, including carboxylate anion, and this constitutes the basis for the use of 3H-isoxazolium salts as condensing agents, as, for example, in the synthesis of peptides [13, 22-24].

In the case of 3-substituted isoxazolium salts the reaction depends on the presence of a proton in the 5 position. For example, isoxazolopyridinium salts III are readily cleaved in methanol in the presence of triethylamine [25].



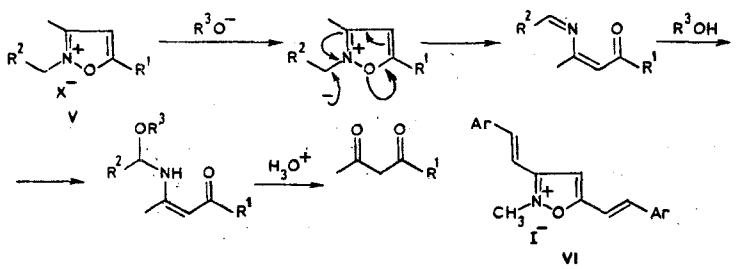
R = OH, NHC_6H_5

Salt IV undergoes cleavage when it is refluxed briefly in acetic anhydride, and the intermediate ketene undergoes cyclization [26-28]. At the same time, the heteroring is not cleaved in the case of the analogous 5-substituted derivatives.



R = H, CH_3

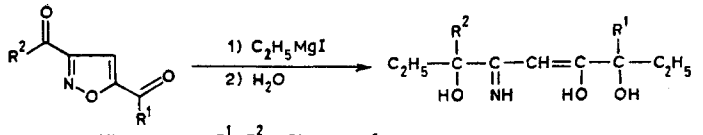
An effective method for the cleavage of 3,5-disubstituted isoxazolium salts V is the action of alkali metal alcoholates, which leads to β-aminoenones, by hydrolysis of which the corresponding β-dicarbonyl derivatives can be obtained [29]. The application of this method for the cleavage of methylisoxazolium salt VI made it possible to realize the synthesis of the natural β-diketone curcumin [29].



R^1 = t-C_4H_9, C_6H_5, $C_6H_5CH_2CH_2$; R^2 = H, CH_3; R^3 = t-C_4H_9, CH_3; X = I, ClO_4

In most cases cleavage of 3,5-di- and 3,4,5-trisubstituted isoxazoles even in the form of isoxazolium salts occurs only under the influence of strong bases. The resulting acyclic polyfunctional compounds may undergo subsequent transformations to give carbocyclic [13] and heterocyclic [12] structures.

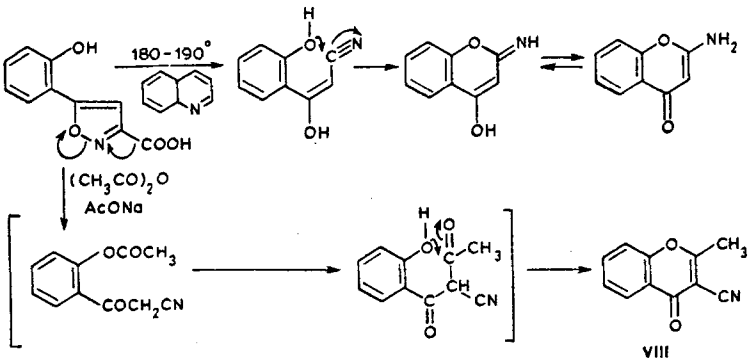
The cleavage of isoxazole by means of Grignard reagents has limited application [30]. For example, this method was used to cleave the ring of isoxazoles VII, which contain acyl substituents in the 3 and 5 positions [31].



VII $R^1, R^2 = CH_3$, aryl

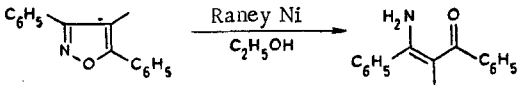
Organomagnesium compounds can be similarly used to cleave isoxazolium salts [32].

The decarboxylation of isoxazole-3-carboxylic acids displays a close analogy to the nucleophilic cleavage of the ring of 3-unsubstituted isoxazoles both with respect to the mechanism and the final products [6]. In some cases the resulting cyano ketones may undergo subsequent transformations, as, for example, in the preparation of chromone derivatives VIII [33, 34].



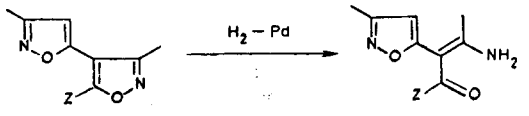
VIII

Reductive Cleavage. The most nearly universal method for exposing the bifunctionality of the isoxazole ring is reductive cleavage, since its applicability has no limitations with respect to the character of the substitution in the ring. Of the traditional methods, the action of alkali metals in alcohol or moist ether, as well as of metals in solutions of acids, is used relatively rarely. Catalytic hydrogenation with the use of platinum or Raney nickel is widely employed. The reaction gives enamino carbonyl derivatives in generally high yields via cleavage of the N–O bond. For example, the hydrogenation of 3,5-diphenyl-4-methylisoxazole over Raney nickel in ethanol gives 1-amino-1,3-diphenyl-2-methyl-3 oxopropene in quantitative yield [35].



Such transformations are widely used in various multistep syntheses for the creation in the appropriate step of a reactive enamino carbonyl grouping and subsequently for the production from it of other functional compounds with both open chains and cyclic structures.

The cleavage of isoxazole during hydrogenation on palladium catalysts is generally achieved only in the presence of bases [36, 37] or when substituents that activate the heterocyclic ring are present. In some cases hydrogenation at high pressures proves to be effective [38]. The selectivity of palladium catalysts, which is used, for example, in the reduction of ole-

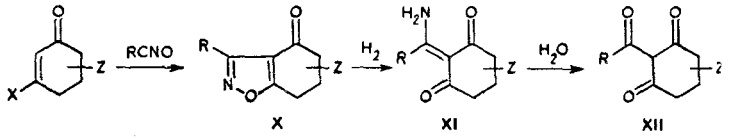


IX

Z = OAlk, NHAlk

finic bonds in compounds that contain an isoxazole ring [39], as well as in the cleavage of one of the rings of bisisoxazole IX [40], is associated with the properties noted above for them.

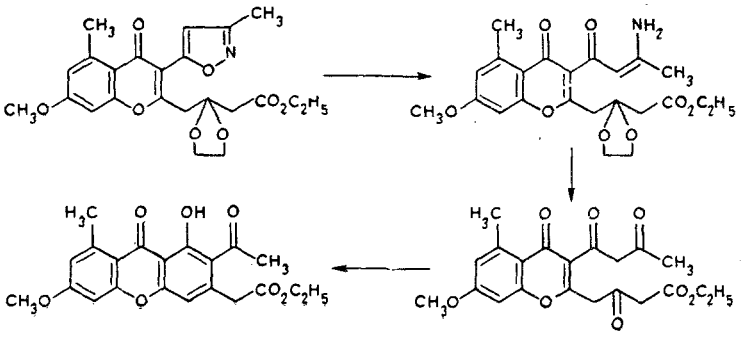
Activation of the isoxazole ring due to conjugation with the carbonyl group make it possible to realize the process under mild conditions in the absence of a base. Thus the hydrogenation of isoxazoles X, which are obtained as a result of regiospecific 1,3-cycloaddition of nitrile oxides to cyclohexane-1,3-diones and their derivatives [10, 41-43], in the presence of 5% $Pd/BaSO_4$ gives enamino diketones XI and subsequently (after hydrolysis) β-triketones XII in quantitative yields. This sequence of transformations represents a general method for the synthesis of 2-acylcyclohexane-1,3-diones XII [43, 44], which find wide application in the preparation of polycyclic and heterocyclic structures, including natural compounds and compounds related to them. In particular, it has been successfully used in a new approach of the total synthesis of glutarimide antibiotics and their analogs [45, 46].



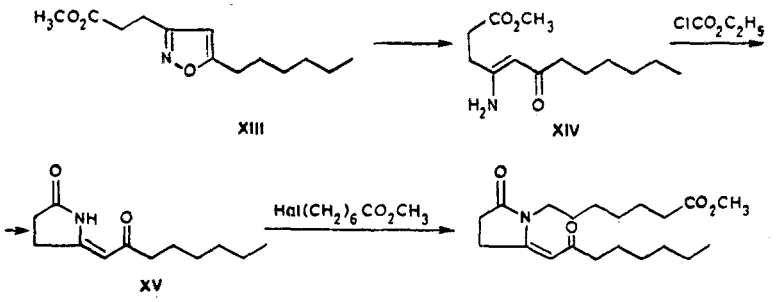
X XI XII

R = alkyl, aryl, arylalkyl, heterocycloalkyl; X = OH, OCH_3, $OCOCH_3$, NH_2, Hal etc..; Z = alkyl, H

The application of the catalytic hydrogenation of isoxazole derivatives for the preparation of α,β-unsaturated ketones [47], β-di- and polyketones [48-50], as well as 1,3-phenylenediamines [51] and acylresorcinols [49, 50, 52], which are formed as a result of cyclization of the corresponding enamino ketones or their hydrolysis products, has been described. A new approach [53] to the synthesis of the natural xanthone bicaverine and its analogs may serve as an illustration.



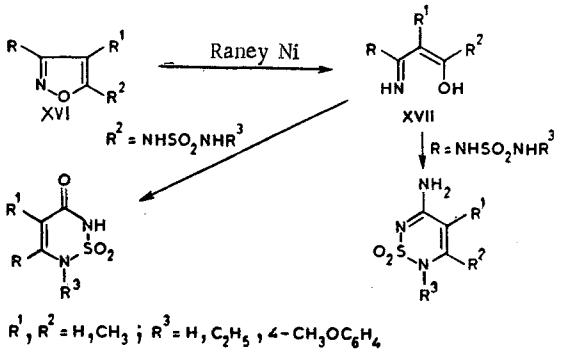
The number of applications of reductive cleavage of isoxazoles is associated with the subsequent transformation of the enamino carbonyl grouping to heterocyclic structures [12]. Thus the recently proposed approach [54, 55] to the synthesis of 8-azaprostaglandins includes reductive cleavage of isoxazole XIII by hydrogenation over platinum and cyclization of enamino ketone XIV to pyrrolidinone XV.



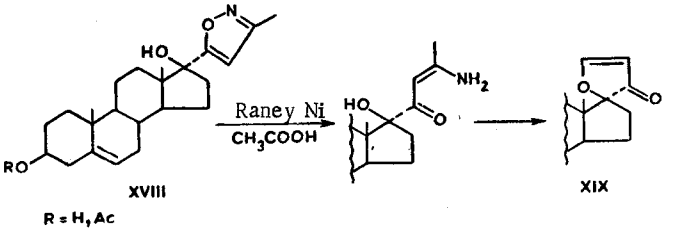
XIII XIV XV

Thio analogs of thymine and cytosine were obtained by hydrogenation of isoxazoles XVI and subsequent cyclization of iminoenols XVII [56].

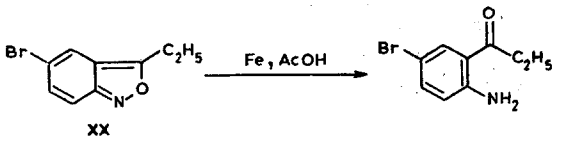
An interesting variant of the reductive cleavage of isoxazoles is the one-step conversion of 17-isoxazolylsteroids XVIII to 17-spirofuran derivatives XIX by hydrogenation over Raney nickel in acetic acid [57]. The reaction includes an intermediate step involving

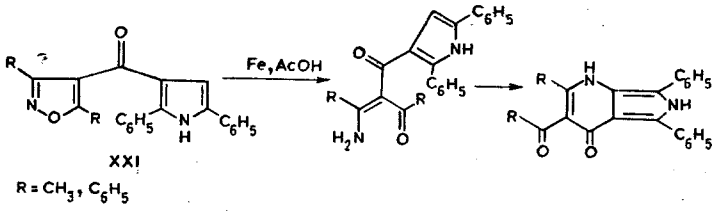


cleavage of the isoxazole ring at the N—O bond, hydrolysis of the resulting enamino ketone to give a β-dicarbonyl derivative, and acid-catalyzed intramolecular cyclodehydration of the enol form of the latter to give a spirofuranone.

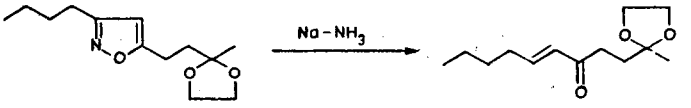


Cleavage of the N—O bond also occurs in the case of the action of hydrogen *in situ* on isoxazoles. For example, treatment of isoxazole XX with iron in acetic acid leads to ring opening to give 2-amino-5-bromopropiophenone [58]. In the case of isoxazole XXI the enamino carbonyl grouping that is formed under similar conditions undergoes subsequent cyclization [59, 60].

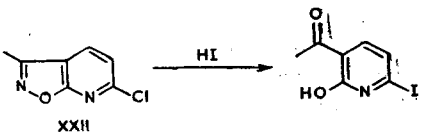




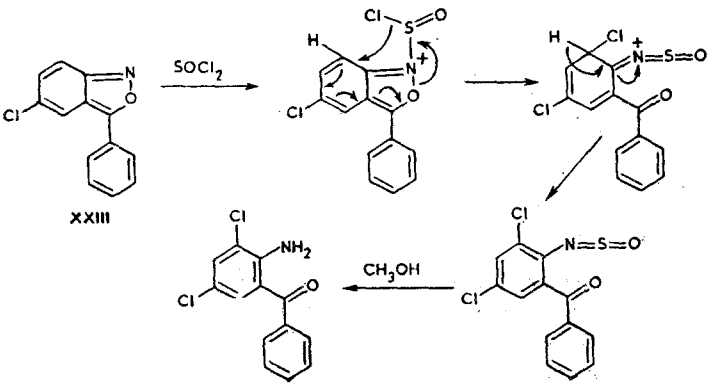
The reductive cleavage of isoxazoles under the influence of sodium in a mixture of liquid ammonia and tert-butyl alcohol is of considerable interest. The resulting β-amino ketones are converted to α,β-unsaturated ketones by treatment with acidic catalysts such as p-toluenesulfonic acid or dry HCl [13]. This method was recently used successfully for the preparation of dihydrojasmone [61].



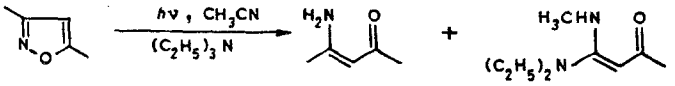
The cleavage of isoxazoles can also be realized by the action of hydriodic acid, as, for example, in the case of condensed isoxazolopyridines XXII [62] or by means of electrochemical reduction [63]. However, the latter is not of preparative value.



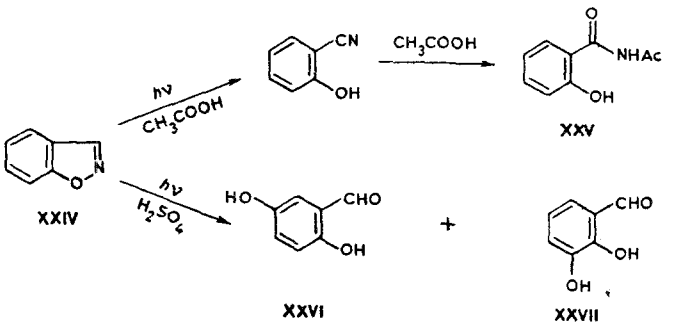
An original preparative method for the cleavage of 2,1-benzisoxazoles to give 2-aminobenzophenones by the action of thionyl chloride was recently described [64] in the case of XXIII.



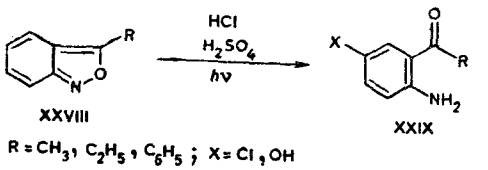
Photolysis. The action of light on the isolated isoxazole ring generally leads to rearrangements to other heterocycles (usually oxazoles or azirines) [12, 65-68]. The formation of bifunctional acyclic structures is possible in some cases [12], as, for example, in the photoinduced cleavage of 3,5-dimethylisoxazole in the presence of triethylamine [69].

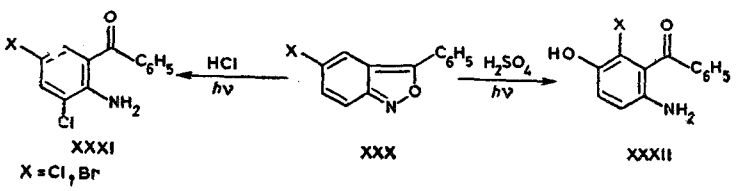


Brief irradiation of 1,2-benzisoxazole XXIV in glacial acetic acid gives salicylamide XXV as a result of successive ring opening and the addition of a molecule of the solvent [68]. The photolysis of XXIV in concentrated sulfuric acid leads to a mixture of formylresorcinols XXVI and XXVII in 64 and 17% yields, respectively; the introduction of a substituent in the 5 position has a substantial effect on the reaction in that it leads only to compounds of the XXVII type [70] in very low yields.

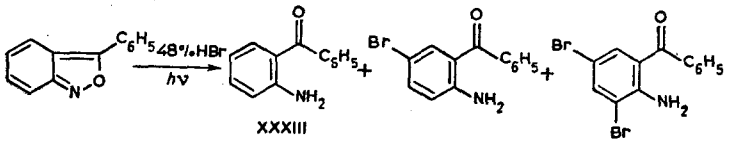


The photolysis of 2,1-benzisoxazoles XXVIII in concentrated hydrochloric or sulfuric acid leads to amino ketones XXIX as the principal reaction products [71]. At the same time, 5-halo-substituted isoxazoles XXX display different behavior in the case of photolysis in the same acids in that they give aminobenzophenones XXXI and XXXII [71].



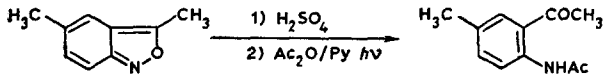


The photolysis of XXVIII (R = C_6H_5) in hydrobromic acid solution, which leads to reduction product XXXIII in addition to mono- and dibromo derivatives, differs somewhat from the photolysis described above [72].



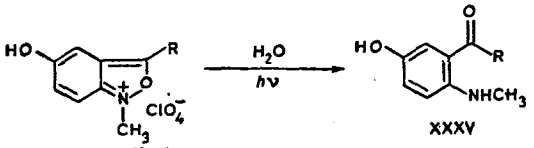
XXXIII

A similar result was obtained in [73] in the photolysis of isoxazole XXXIV in diulte sulfuric acid and of isoxazole XXVIII (R = CH_3) in acetonitrile in the presence of sulfuric acid and benzene or its homologs [74].



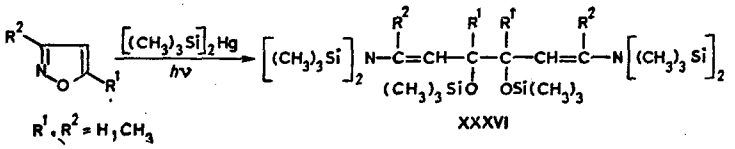
XXXIV

The photolysis of aqueous solutions of N-alkyl-2,1-benzisoxazolium perchlorates leads to amino ketones XXXV in high yields [75].



R = H, alkyl

The cleavage of isoxazoles under the influence of bis(trimethylsilyl)mercury [76] occupies a special place, since it represents a new ring-opening mechanism and unusual products are associated with it. The reaction takes place in benzene when the mixture is irradiated with a fluorescent lamp and leads to 1,5-hexadiene derivatives XXXVI in close-to-quantitative yields. The proposed reaction mechanism includes the participation of the free radicals that are formed in the decomposition of bis(trimethylsilyl)mercury in the cleavage of the heteroring.

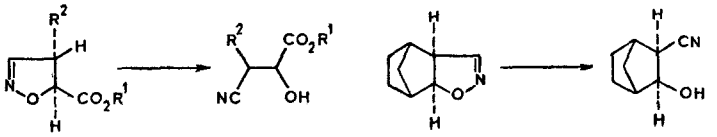


$R^1, R^2 = H, CH_3$

XXXVI

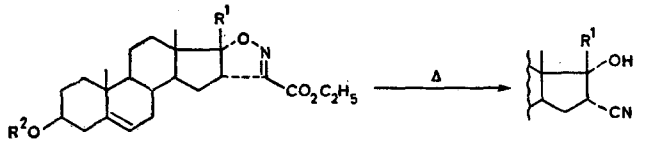
Cleavage of 2-Isoxazolines

By the Action of Bases. 3-Unsubstituted 2-isoxazolines undergo ring opening at the N–O bond under the influence of bases to give β-hydroxy nitriles [77]. For example, the cycloadducts of formonitrile oxide with esters of acrylic and crotonic acids, as well as with norbornene when they are treated with triethylamine, react in this way [78].



R^1 = alkyl ; $R^2 = H, CH_3$

The reaction of 3-carboxyisoxazolines proceeds similarly under the influence of bases and under pyrolytic decarboxylation conditions. 16α-Cyano-17α-hydroxysteroids in the pregnane [79, 80] and androstane [80-82] series were synthesized by this method from condensed 16,17-isoxazolinosteroids XXXVII.

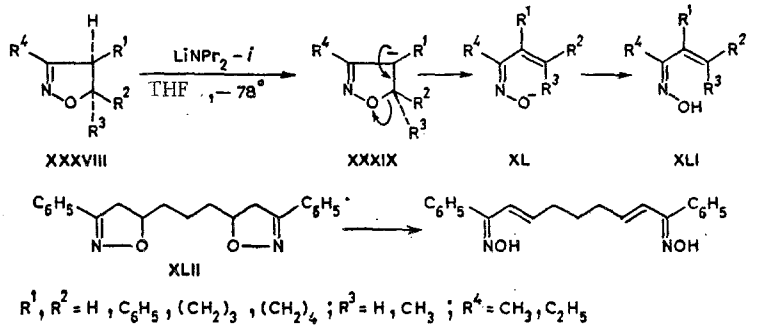


XXXVII

$R^1 = COCH_3, OCOCH_3$; $R^2 = COCH_3$

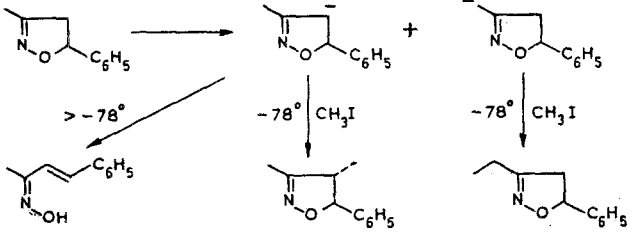
The resulting hydroxy nitriles retain the stereochemistry of the starting 2-isoxazolines in the 4 and 5 positions of the heteroring. Thus the reaction of formonitrile oxide or oxaalic acid mononitrile oxide with olefins and subsequent cleavage of the resulting 2-isoxazolines constitutes a simple regio- and stereospecific synthesis of compounds with a vicinal hydroxy nitrile grouping. However, it should be noted little study has been devoted to the possibility of the synthesis of functional compounds with an open chain by cleavage of 2-isoxazolines with bases and that this possibility was not described at all with respect to 3-substituted derivatives prior to 1976.

Jäger and Grund [83] have shown that 3-substituted isoxazolines XXXVIII undergo cleavage under the influence of lithium diisopropylamide to give enoximes XLI. This reaction also proceeds similarly in the case of bisisoxazoline XLII [84]. All of the enoximes were obtained in the form of one of the four possible stereoisomers and have an E configuration with

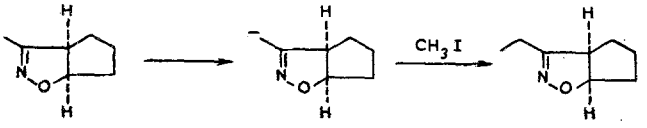


respect to the C=C bond. The oxime group retains the orientation (E or Z, depending on the substituents) of the C=N—O bond in the starting isoxazoline. In the case of 3,5-diphenyl-2-isoxazoline it has been shown that opening of the heteroring in the indicated direction also occurs under the influence of butyllithium or ethylmagnesium bromide. However, the yields of the enoxime are considerably lower in this case. The utilization of potassium hydroxide or potassium tert-butoxide for this purpose did not give positive results [84].

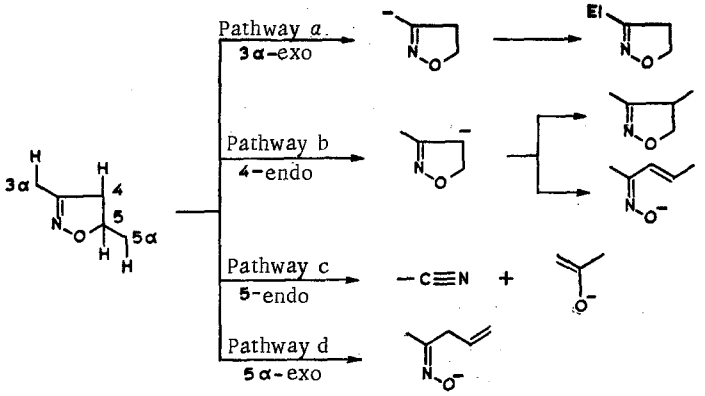
The opening of the ring of 2-isoxaolines XXXVIII and the formation of enoximes XLI proceed through a step involving detachment of the allyl proton in the 4 position and subsequent isomerization of the resulting XXXIX carbanion to enoximate anion XL. Protonation of the latter gives an unsaturated ketoxime, which can then be converted to the corresponding enone and other functional compounds by known methods. The direction of the deprotonation is confirmed by deuterolysis or by C alkylation of the XXXIX carbanion at −78°C to give 4-deutero and 4-alkyl derivatives. In the case of 3-methyl-5-phenylisoxazoline, in addition to the examined 4-deprotonation, detachment of the 3α-hydrogen atom to give a mixture of "endo" and "exo" anions in a ratio of (1.5-2):1. The former undergoes both C alkylation on treatment with alkyl halides at low temperatures and cleavage to give an unsaturated ketoxime when it is heated. The exo anion does not undergo cleavage of the heteroring and can be subjected to C alkylation in the side chain.



The formation of an exo anion becomes the dominant process in the case of 3-methyl-4,5-cyclopentanoisoxazoline, for which the corresponding oxime is not obtained at all, whereas C alkylation of the 3-side chain gives the alkylation product in high yield. Upon the whole, the pathway of deprotonation of 3-substituted 2-isoxazolines under the influence of bases and



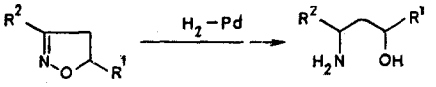
the possible pathways of the transformations of the resulting carbanions can be represented by the general scheme [84]



El-electrophile

The realization of pathways *a* and b was examined above. Pathway c, which is characteristic for 5-acylisoxazolines [85-87], includes ring opening with cleavage of the carbon skeleton of the molecule and is therefore not discussed in detail here. Pathway d is realized partially in the case of 5-alkyl-5-phenylisoxazolines [84] and is more pronounced in the case of 5-halomethyl derivatives [88].

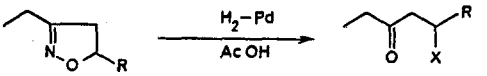
Reductive Cleavage. In contrast to the isoxazoles examined above, relatively little study has been devoted to opening of the 2-isoxazoline ring under catalytic hydrogenation conditions. The preparation of hydroxy amino carboxylic acids and other γ-hydroxy amino derivatives by hydrogenation of 3,5-disubstituted isoxazolines on a palladium catalyst in alcohol has been described [81,91]



$R^1, R^2 = C_6H_5, CO_2C_2H_5$

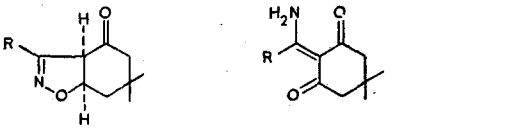
Similar results were obtained by the action of sodium amalgam in methanol [89]. In both cases the reaction proceeds nonstereospecifically, and a mixture of diastereomeric γ-amino alcohols is obtained.

The hydrogenation of 3-ethyl-5-carbomethoxyisoxazoline in solution in acetic acid gives the corresponding β-hydroxy ketone. In the case of the related 5-phenylisoxazoline the reaction proceeds with hydrogenolysis of the OH group [92].

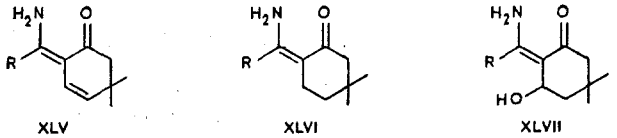


$R = CO_2CH_3, C_6H_5$; X = H, OH

Of considerable synthetic interest in this respect are condensed 4,5-cyclohexanoisoxazolines of the XLIII type, the cleavage of which at the N–O bond should lead to β-trifunctional compounds XLVII with selective modification of all of the functional groups [43-46]. With this in mind, Akhrem and co-workers [93] studied the behavior of the indicated compounds under the various catalytic hydrogenation conditions. Isoxazoline XLIII is stable under the



XLIII XLIV

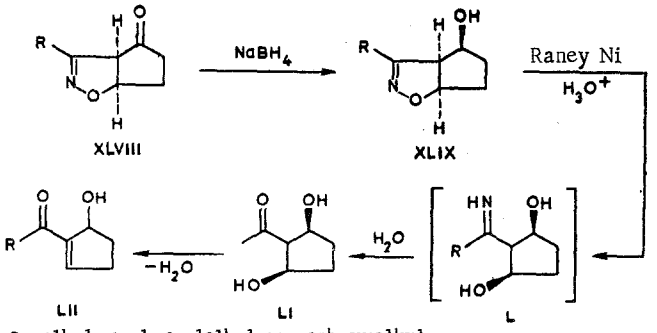


XLV XLVI XLVII

R = aryl, alkyl, arylalkyl, heterocycloalkyl

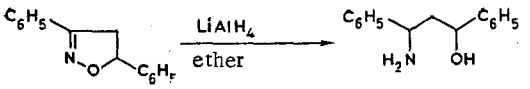
usual conditions of hydrogenation over 5% $Pd/BaSO_4$; however, enamino diketone XLIV was obtained in high yield under the same conditions in the presence of triethylamine. Hydrogenation over Raney nickel gives enamino ketone XLVI in virtually quantitative yield. The same compound was obtained in lower yield when 30% $Pd/SrCO_3$ was used. Hydrogenation on a rhodium or nickel catalyst in the presence of bases makes it possible to obtain dienamino ketone XLV. The formation of enamino diketone XLIV is evidently due to intermediate dehydrogenation of isoxazoline XLIII to give the corresponding isoxazole and its subsequent reductive cleavage, which was examined above. The formation of XLV and XLVI is associated with cleavage of the N–O bond and proceeds through an intermediate step involving unstable β-hydroxy enamino ketone XLVII, which undergoes spontaneous dehydration to give dienamino ketone XLV. The latter can be reduced to enamino ketone XLVI. The examined reductive cleavage of isoxazolines — the cycloadducts of β-glutarimidylacetonitrile oxide and substituted 2-cyclohexenones — has been used successfully in a new approach to the total synthesis of glutarimide antibiotics [45, 46].

In contrast to the cyclohexane analogs, 4,5-cyclopentanoisoxazolines XLVIII are extremely resistant to both opening of the heteroring under catalytic-hydrogenation conditions and to the action of other reducing agents. It has been observed that isoxazoline XLIX, which was obtained in [94] by reduction of oxo derivative XLVIII with sodium borohydride, undergoes ring opening under the influence of Raney nickel in aqueous solutions of strong acids (trifluoroacetic, hydrochloric, sulfuric, and perchloric acids) to give 2-acyl-2-cyclopenten-1-ol (LII) as the final product. This process does not take place under the usual conditions of catalytic hydrogenation over Raney nickel or under the influence of the latter in solutions of weak acids such as acetic acid [95]. Depending on the conditions under which the reaction is carried out, in addition to eneketol LII, cis-ketodiol LI (the precursor of LII), which retains the configuration of the starting isoxazoline, can be isolated. The reaction evidently proceeds as reductive cleavage at the N–O bond (activated as a result of protonation of the nitrogen atom) to give iminodiol L, which is readily hydrolyzed to ketodiol LI under the reaction conditions. The reaction can evidently be regarded as an unusual case of catalytic ionic hydrogenation [96], the first step of which is protonation of the nitrogen atom with subsequent cleavage of the N–O bond and neutralization of the oxonium ion by means of detachment of a hydride anion from the in situ hydrogen obtained by the action of the acid on the Raney nickel. The catalytic action of nickel is also important, since the reaction does not occur in the case of the action on isoxazoline XLVIII of other metals (Zn, Fe) in a solution of a strong acid [95]. Similar results were obtained in the cleavage under the indicated conditions of cyclohexanoisoxazolines and some monocyclic 2-isoxazolines. The resulting ketodiols LI and eneketols LII, as well as their six-membered analogs, depending on the R substituents, are important intermediates in the total synthesis of steroids and prostaglandins [97].



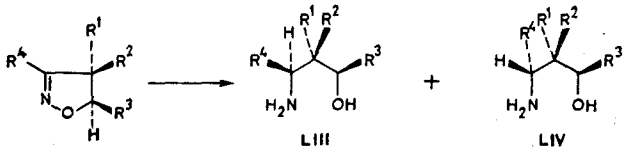
R = alkyl, aryl, arylalkyl, ω-carboxyalkyl

In 1957 Perold and Reiche [98] described the reduction of 3,5-diphenyl-isoxazoline by means of lithium aluminum hydride in refluxing ether; 1,3-diphenyl-3-aminopropanol was obtained in 62% yield in the form of a single diastereomer. This reaction was later used for the reduction of other substituted 2-isoxazolines, and the corresponding amino alcohols were obtained in high yields [99-102].



The reduction of 3-phenyl-5-methylisoxazoline with diborane or sulfonated sodium borohydride was described in [103]. However, the authors did not discuss the structure of the γ-amino alcohol obtained.

Jäger and co-workers [104-106] recently made a detailed study of the stereochemical pathway in the conversion of 3,5-, 3,4-, and 3,4,5-substituted isoxazolines to the corresponding γ-amino alcohols with two or three vicinal chiral centers, the stereoselectivity of various reducing agents [$LiAlH_4$, H_2—Pd, Na—Hg—H_2O, Na—C_2H_5OH, Na—tert-C_4H_9OH, $(CH_3)2S\cdot BH_3$, and $NaAlH_2(OCH_2OCH_3)_2$], and the degree of asymmetric induction due to the substituents in the 4 and 5 positions. The ratio and relative β and α configurations of the resulting diastereomeric amino alcohols LIII and LIV (in the case of simpler compounds with two chiral centers the β series corresponds to the erythro configuration, while the α series corresponds to the threo configuration) were determined by ^1H and ^{13}C NMR spectroscopy.

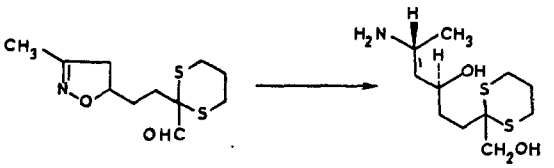


LIII LIV

$R^1 = H, CH_3$; $R^2, R^3 = H$, alkyl, cycloalkyl, aryl ; R^4 = alkyl, aryl

It has been shown that lithium aluminum hydride is the most suitable reagent from the point of view of both the overall yields of amino alcohols and the stereoselectivity of the process [105]. Thus, for example, the reduction of 3,5-diphenyl- and 3-phenyl-5-methylisoxazolines to the corresponding γ-amino alcohols by means of lithium aluminum hydride proceeds virtually quantitatively to give the β and α isomers in ratios of 95:5 and 85:15, respectively. In the case of reduction with borane·dimethyl sulfide this ratio is 60:40, as compared with a ratio of 40:60 for both isoxazolines in the case of reduction with sodium or sodium amalgam in aqueous alcohol. The substituents in the 4 and 5 positions of isoxazoline have a substantial effect on the stereoselectivity of the reaction; the effect of the substituent in the 5 position (1,3-asymmetric induction) surpasses that of the substituent in the 4 position (1,2-asymmetric induction) [105, 106].

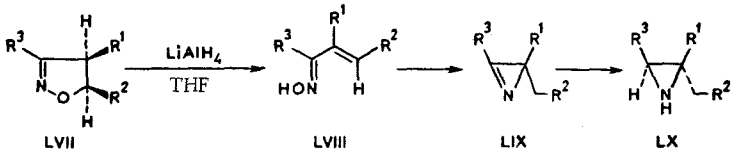
The stereospecific reduction of 3,5-disubstituted isoxazoline LV to give γ-amino alcohol LVI, which proceeds quantitatively under the influence of diisobutylaluminum hydride, has been successfully used [107] in the total synthesis of the macrolipid antibiotic vermiculine.



LV LVI

The examined regio- and stereoselective reductive cleavage of 2-isoxazolines, which are accessible through 1,3-dipolar cycloaddition of nitrile oxides to olefins, is of great preparative value for the synthesis of the pharmacologically valuable γ-amino alcohols, including those of natural origin [108-110].

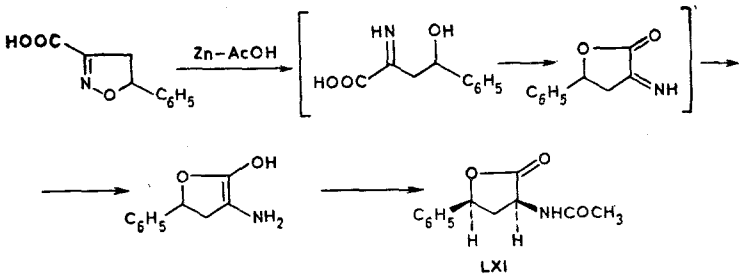
Replacement of ether by tetrahydrofuran (THF) in the reaction of lithium aluminum hydride with 2-isoxazolines LVII leads to the formation of cis-aziridines LX as the principal reaction products through intermediate steps involving unsaturated ketoxime LVIII and 2H-azirine LIX [111, 112]. The reaction is stereospecific and proceeds by means of detachment of the allyl proton in the 4 position by a hydride anion with subsequent cleavage of the C—O bond and the formation of an enoximate anion. The latter under the influence of lithium aluminum hydride undergoes cyclization to an azirine, which is subsequently reduced to a cis-aziridine. γ-Amino alcohols were isolated in very low yields in this case, and their formation includes cleavage of the N—O bond. This sequence of the transformations of the heteroring is confirmed by the production of aziridines by the action of lithium aluminum hydride on α,β-unsaturated ketoximes [113] and by the formation of the latter in the above-examined reaction of 2-isoxazolines with lithium diisopropylamide [83, 84].



LVII LVIII LIX LX

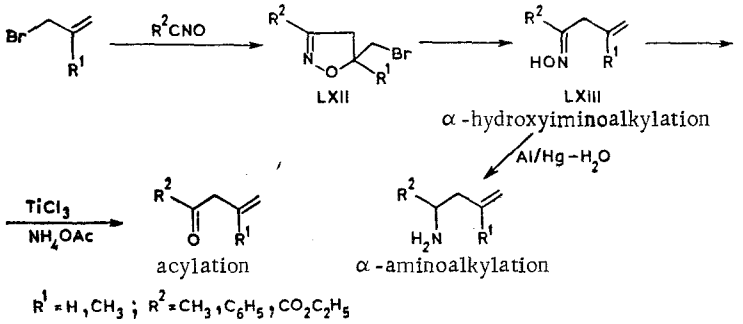
$R^1, R^2 = H$, alkyl, aryl ; R^3 = alkyl, aryl

The reduction of 3-carboxy-5-phenyl-2-isoxazoline with zinc in acetic acid proceeds stereospecifically with the formation of N-acetamidolactone LXI with a cis orientation of the phenyl and acetamido groups as the final product [114].

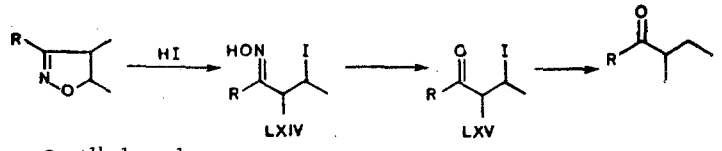


LXI

An interesting method for the preparation of acyclic functional compounds has been proposed [115] on the basis of the cycloadducts of 1,3-dipolar cycloaddition of nitrile oxides to allyl bromides. The cleavage of 5-bromomethyl-2-isoxazolines LXII proceeds under the influence of zinc in alcohol or a zinc–copper couple in dimethylformamide to give β,γ-unsaturated ketoximes LXIII, which are subsequently converted to the corresponding enones or are reduced to give unsaturated amines. The indicated transformations are formally classified as γ substitution of allyl bromides by α-functionalized alkyl residues.



The cleavage of 2-isoxazolines under the influence of hydriodic acid, which was used to establish the structures of the cycloadducts of 1,3 cycloaddition of nitrile oxides to various olefins, has been described [116, 117]. The reaction includes steps involving the formation of β-iodo oxime LXIV and β-iodo ketone LXV, which leads to substituted propanone LXVI as the final cleavage product.



R = alkyl, aryl

In contrast to the action of bases and reducing agents, the cleavage of 2-isoxazolines during irradiation with UV light leads chiefly to products of rearrangements [118-121] to other heterocycles, and the formation in some cases of functional compounds with an open chain is not of preparative value.

A number of important synthetic applications of 2-isoxazolines are associated with their oxidation to isoxazoles, the methods for the conversion of which to bifunctional compounds with an open chain were examined in the first part of this review. It should be noted that of the various methods for the dehydrogenation of 2-isoxazolines to isoxazoles, oxidation with N-bromosuccinimide [122] and active manganese dioxide [123] is of preparative value. High yields of isoxazoles were obtained in some cases by dehydrogenation of isoxazolines with chloranil [43].

LITERATURE CITED

1. A. I. Meyers, Heterocycles in Organic Synthesis, Wiley, New York–London (1974).
2. D. Lednicer, Adv. Org. Chem., 8, 179 (1972).
3. C. Kashima, Heterocycles, 12. 1343 (1979).

4. R. Barnes, in: Heterocyclic Compounds, Vol. 5, R. Elderfield, et. Wiley (1957).
5. A. Quilico, The Chemistry of Heterocyclic Compounds, Vol. 17, A. Weissberger, ed., Academic Press, New York (1963).
6. N. K. Kochetkov and S. D. Sokolov, in: Advances in Heterocyclic Chemistry, Vol. 2, Academic Press, New York (1963), p. 365.
7. C. Grundmann, Synthesis, No. 7, 344 (1970).
8. L. S. Crawley and W. J. Fanshawe, J. Heterocycl. Chem., 14, 531 (1977).
9. G. N. Barber and R. A. Olofson, J. Org. Chem., 43, 3015 (1978).
10. A. A. Akhrem, F. A. Lakhvich, V. A. Khripach, and A. G. Pozdeev (Pozdeyev), Synthesis, No. 1, 43 (1978).
11. C. Grundmann and P. Grünanger, The Nitrile Oxides, Springer Verlag, Berlin (1971), p. 96.
12. T. Nishiwaki, Synthesis, No. 1, 20 (1975).
13. C. J. Subrahmanyam, Sci. Ind. Res., 33, 304 (1974).
14. S. D. Sokolov, Usp. Khim., 48, 533 (1979).
15. T. Kametani and H. Nemoto, Heterocycles, 10, 349 (1978).
16. T. Kametani and K. Fukumoto, Heterocycles, 10, 469 (1978).
17. V. Bertini, A. Munno, and P. Pino, Gazz. Chim. Ital., 97, 185 (1967).
18. A. Munno, V. Bertini, and F. Lucchesini, J. Chem. Soc., Perkin Trans. II, No. 9, 1121 (1977).
19. M. L. Casey, and D. S. Kemp, K. G. Paul, and D. D. Cox, J. Org. Chem., 38, 2294 (1973).
20. P. J. Vinick and H. W. Gschwend, Tetrahedron Lett., No. 44, 4221 (1978).
21. I. Hoppe and U. Schölkopf, Lieb. Ann., No. 2, 219 (1979).
22. D. S. Kemp, S. —W. Wang, R. C. Mollan, S. —L. Hsia, and P. N. Confalone, Tetrahedron, 30, 3677 (1974).
23. D. S. Kemp, S. —W. Wang, J. Rebek, R. C. Mollan, C. Banquer, and G. Subramanyam, Tetrahedron, 30 3955 (1974).
24. D. S. Kemp, S. J. Wrobel, S. —W. Wang, Z. Bernstein, and J. Rebek, Tetrahedron, 30, 3969 (1974).
25. G. Jones and J. R. Phipps, J. Chem. Soc., Perkin Trans. I, No. 11, 1241 (1976).
26. R. H. Good, G. Jones, and J. R. Phipps, Tetrahedron Lett., No. 7, 609 (1972).
27. R. H. Good, G. Jones, and J. R. Phipps, J. Chem. Soc., Perkin Trans. I, No. 19, 2441 (1972).
28. G. Jones and J. R. Phipps, J. Chem. Soc., Perkin Trans. I, No. 1, 158 (1974).
29. C. Kashima, N. Mukai, Y. Yamamoto, Y. Tsuda, and Y. Omote, Heterocycles, 7, 241 (1977).
30. N. K. Kochetkov and S. D. Sokolov, Zh. Obshch. Khim., 33, 1442 (1963).
31. M. I. Shevchuk, A. F. Tolochko, M. G. Bal'on, and M. V. Khalaturnik, Zh. Org. Khim., 14, 2003 (1978).
32. I. Adachi, K. Harada, R. Miyazaki, and H. Kano, Chem. Pharm. Bull, 22, 61 (1974).
33. Z. Jerzmanowsak and W. Basinski, Roczn. Chem., 51, 2283 (1977).
34. W. Basinski and Z. Jerzmanowska, Pol. J. Chem., 53, 229 (1979).
35. S. Auricchio, O. V. Pava, and E. Vera, Synthesis, No. 2, 116 (1979).
36. J. W. Scott and G. Saucy, J. Org. Chem., 37, 1652 (1972).
37. J. W. Scott, R. Borer, and G. Saucy, J. Org. Chem., 37, 1659 (1972).
38. C. Skotsch, I. Kohlmeyer, and E. Breitmaier, Synthesis, No. 6, 449 (1979).
39. G. Stork and J. E. McMurry, J. Am. Chem. Soc., 89, 5464 (1967).
40. P. Caramella, R. Metelli, and P. Grünanger, Tetrahedron, 27, 379 (1971).
41. A. A. Akhrem, V. A. Khripach, and F. A. Lakhvich, Khim. Geterotsikl. Soedin., No. 7, 901 (1974).
42. A. A. Akhrem, F. A. Lakhvich, V. A. Khripach, and A. G. Pozdeev, Dokl. Akad. Nauk Belorussk. SSR, 20, 1007 (1976).
43. A. A. Akhrem, F. A. Lakhvich, V. A. Khripach, and I. B. Klebanovich, Khim. Geterotsikl. Soedin., No. 3, 329 (1975).
44. A. A. Akhrem, F. A. Lakhvich, V. A. Khripach, and I. B. Klebanovich, Dokl. Akad. Nauk SSSR, 216, 1645 (1974).
45. A. A. Akhrem, F. A. Lakhvich, V. A. Khripach, and I. B. Klebanovich, Tetrahedron Lett., No. 44, 3983 (1976).
46. A. A. Akhrem, F. A. Lakhvich, V. A. Khripach, and I. B. Klebanovich, Khim. Geterotsikl. Soedin., No. 2, 230 (1979).
47. C. Kashima, J. Org. Chem., 40, 527 (1975).
48. G. Casnati, A. Quilico, A. Ricca, and P. Vita-Finzi, Chim. Ind., 47, 993 (1965).
49. S. Auricchio and A. Ricca, Gazz. Chim. Ital., 103, 37 (1973).

50. S. Auricchio, S. Morrocchi, and A. Ricca, Tetrahedron Lett., No. 33, 2793 (1974).
51. S. Auricchio, A. Ricca, and O. V. Pava, Chim. Ind., 58, 699 (1976).
52. T. Hiraoka, M. Yoshimoto, and Y. Kishida, Chem. Pharm. Bull., 20, 122 (1972).
53. I. Iijima, N. Taga, M. Miyazaki, and T. Tanaka, J. Chem. Soc., Perkin Trans. I, No. 12, 3190 (1979).
54. A. Barco, S. Benetti, and G. Pollini, Synth. Commun., 8, 219 (1978).
55. A. Barco, S. Benetti, G. P. Pollini, P. G. Baraldi, D. Simoni, and C. B. Vicentini, J. Org. Chem., 44, 1734 (1979).
56. H. A. Albrecht, J. F. Blount, F. M. Konzelmann, and J. T. Plati, J. Org. Chem., 44, 4191 (1979).
57. A. A. Akhrem, F. A. Lakhvich, and V. A. Khripach, Zh. Obshch. Khim., 45, 2572 (1975).
58. S. S. Mochalov, T. P. Surikova, and Yu. S. Shabarov, Khim. Geterotsikl. Soedin., No. 7, 886 (1976).
59. G. Dattolo, E. Aiello, S. Plescia, G. Cirrincione, and G. Daidone, J. Heterocycl. Chem., 14, 1021 (1977).
60. E. Aiello, G. Dattolo, G. Cirrincione, S. Plescia, and G. Daidone, J. Heterocycl. Chem., 15, 537 (1978).
61. A. Barco, S. Benetti, G. P. Pollini, P. G. Baraldi, M. Guarneri, and C. B. Vicentini, J. Org. Chem., 44, 105 (1979).
62. A. Camparini, F. Ponticelli, and P. Tedeschi, J. Heterocycl. Chem., 14, 435 (1977).
63. I. G. Markova, M. K. Polievktov, and S. D. Sokolov, Zh. Obshch. Khim., 46, 398 (1976).
64. R. C. Boruah, J. S. Sandhu, and G. Thyagarajan, J. Heterocycl. Chem., 16, 1087 (1979).
65. D. J. Anderson and A. Hassner, Synthesis, No. 8, 495 (1975).
66. K. Dietliker, P. Gilgen, H. Heimgarther, and H. Schmid, Helv. Chim. Acta, 59, 2074 (1976).
67. M. Nakagawa, T. Nakamura, and K. Tomita, Agric. Biol. Chem., 38, 2205 (1974).
68. J. P. Ferris and R. W. Trimmer, J. Org. Chem., 41, 14 (1976).
69. T. Sato and K. Saito, Chem. Commun., No. 19, 781 (1974).
70. T. Doppler, H. Schmid, and H. —J. Hansen, Helv. Chim. Acta, 62, 314 (1979).
71. E. Giovannini and B. F. S. E. Sousa, Helv. Chim. Acta, 62, 185 (1979).
72. E. Giovannini and B. F. S. E. Sousa, Helv. Chim. Acta, 62 198 (1979).
73. T. Doppler, H. Schmid, and H. —J. Hansen, Helv. Chim. Acta, 62, 271 (1979).
74. T. Doppler, H. Schmid, and H. —J. Hansen, Helv. Chim. Acta, 62, 304 (1979).
75. N. F. Haley, J. Org. Chem., 42, 3929 (1977).
76. T. N. Mitchell and B. Kleine, Tetrahedron Lett., No. 25, 2173 (1976).
77. R. Huisgen and M. Christl, Chem. Ber., 106, 3291 (1973).
78. R. Huisgen and M. Christl, Angew. Chem., 79, 471 (1967).
79. G. W. Moersch, E. L. Wittle, and W. A. Newklis, J. Org. Chem., 30, 1272 (1965).
80. G. Gerali, G. Sportoletti, G. Parini, and A. Ius, Farm. Sci. Ed., 24, 112 (1969).
81. G. Gerali, G. Parini, G. Sportoletti, and A. Ius, Farm. Sci. Ed., 24, 231 (1969).
82. G. Gerali, G. Parini, A. Ius, and G. Sportoletti, Farm. Sci. Ed., 24, 299 (1969).
83. V. Jäger and H. Grund, Angew. Chem., 88, 27 (1976).
84. H. Grund and V. Jäger, Lieb. Ann., No. 1, 80 (1980).
85. G. Bianchi, R. Gandolfi, and P. Grünanger, J. Heterocycl. Chem., 5, 49 (1968).
86. G. Bianchi, A. Gamba-Invernizzi, and R. J. Gandolfi, J. Chem. Soc., Perkin Trans. I, No. 15, 1757 (1974).
87. R. G. Shotter, D. Sesardic, and P. H. Wrigt, Tetrahedron, 31, 3069 (1975).
88. H. Grund and V. Jäger, J. Chem. Res. (Synop.), No. 2, 54 (1979); Chem. Abstr., 91, 91541 (1979).
89. W. Stühner and W. Heinrich, Chem. Ber., 84, 224 (1951).
90. G. Drefahl and H. H. Hörhold, Chem. Ber., 97, 159 (1964).
91. T. Kusumi, H. Kakisawa, S. Suzuki, K. Harada, and C. Kashima, Bull. Chem. Soc. Jpn., 51, 1261 (1978).
92. K. Torsell and O. Zeuthen, Acta Chem. Scand., B32, 118 (1978).
93. A. A. Akhrem, F. A. Lakhvich, V. A. Khripach, and I. I. Petrusevich, Khim. Geterotsikl. Soedin., No. 7, 891 (1976).
94. A. A. Akhrem, F. A. Lakhvich, V. A. Khripach, I. B. Klebanovich, and A. G. Pozdeev, Khim. Geterotsikl. Soedin., No. 5, 625 (1976).
95. A. A. Akhrem, F. A. Lakhvich, V. A. Khripach, and I. B. Klebanovich, Dokl. Akad. Nauk SSSR, 244, 615 (1979).
96. D. N. Kursanov, Z. N. Parnes, M. I. Kalinkin, and N. M. Loim, Ionic Hydrogenation [in Russian], Khimiya, Moscow (1979), p. 167.

97. A. A. Akhrem, F. A. Lakhvich, V. A. Khripach, and I. B. Klebanovich, USSR Inventor's Certificate No. 607832 (1978); Byull. Izobret., No. 19, 59 (1978).
98. G. W. Perold and F. V. K. Reiche, J. Am. Chem. Soc., 79, 465 (1957).
99. N. Barbulescu and A. Quilico, Gazz. Chim. Ital., 91, 326 (1961).
100. P. Grünanger and M. R. Langella, Gazz. Chim. Ital., 91, 1112 (1961).
101. N. Barbulescu, P. Grünanger, M. R. Langella, and A. Quilico, Tetrahedron Lett., No. 2, 89 (1961).
102. R. Paul and S. Tchelitcheff, Bull. Soc. Chim. Fr., Nos. 11-12, 2215 (1962).
103. M. V. Kashutina, S. L. Ioffe, and V. A. Tartakovskii, Dokl. Akad. Nauk SSSR, 218, 109 (1974).
104. V. Jäger, V. Buss, and W. Schwab, Tetrahedron Lett., No. 34, 3133 (1978).
105. V. Jäger and V. Buss, Lieb. Ann., No. 1, 101 (1980).
106. V. Jäger, V. Buss, and W. Schwab, Lieb. Ann., No. 1, 122 (1980).
107. K. F. Burri, R. A. Cardone, Wen Yean Chen, and P. Rosen, J. Am. Chem. Soc., 100, 7069 (1978).
108. T. Wieland, Naturwissenschaften, 59, 225 (1972).
109. A. Gieren, P. Narayanan, W. Hoppe, M. Hasan, K. Michl, T. Wieland, H. O. Smith, G. Jung, and E. Breitmaier, Lieb. Ann., No. 10, 1561 (1974).
110. H. V. Secor and E. B. Sanders, J. Org. Chem., 43, 2539 (1978).
111. K. Kotera, Y. Takano, A. Matsuura, and K. Kitahonoki, Tetrahedron Lett., No. 55, 5759 (1968).
112. K. Kotera, Y. Takano, A. Matsuura, and K. Kitahonoki, Tetrahedron, 26, 539 (1970).
113. K. Kitahonoki, K. Kotera, Y. Matsukava, S. Miyazaki, T. Okada, H. Takahashi, and Y. Takano, Tetrahedron Lett., No. 16, 1059 (1965).
114. G. S. King. P. D. Magnus, and H. S. Rzepa, J. Chem. Soc., Perkin Trans. I, No. 3, 437 (1972).
115. V. Jäger, H. Grund, and W. Schwab, Angew. Chem., Int. Ed., 18, 78 (1979).
116. G. W. Perold and F. V. K. Reiche, J. South Afr. Chem. Inst., 10, 5 (1957); Chem. Abstr., 52, 1145 (1958).
117. G. S. Alcontres and G. L. Vecchio, Gazz. Chim. Ital., 90, 1239 (1960).
118. Y. Ito and T. Matsuura, Tetrahedron, 31, 1373 (1975).
119. H. Saiki, T. Miyashi, and T. Mukai, Tetrahedron Lett., No. 52, 4619 (1977).
120. O. Sechimoto, T. Kumagai, K. Shimizu, and T. Mukai, Chem. Lett., No. 10, 1195 (1977); Curr. Abstr., 68, 265237 (1978).
121. H. Kaufmann and J. Kalvoda, Chem. Commun., No. 6, 210 (1976).
122. G. Bianchi and P. Grünanger, Tetrahedron, 21, 817 (1965).
123. A. Barco, S. Benetti, and G. Pollini, Synthesis, No. 12, 837 (1977).