SYNTHESIS, CHEMICAL TRANSFORMATION, AND APPLICATION OF ISOXAZOLE DERIVATIVES IN THE TOTAL CHEMICAL SYNTHESIS OF NATURAL COMPOUNDS (REVIEW)

F. A. Lakhvich, E. V. Koroleva, and A. A. Akhrem

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New data (1981-1988) on the production and chemical transformations of isoxazoles and 2-isoxazolines and the regio- and stereochemical aspects of the formation, modification, and cleavage of the heterocycle are examined. Advances and problems in the use of the isoxazole strategy for the synthesis of natural compounds and their analogs are discussed.

Heterocyclic compounds possessing latent functionality are widely used in organic synthesis. Isoxazoles and their 1,2-dihydro derivatives (2-isoxazolines) are very important in this respect. As a result of the intensive development of the "nitrile oxide" technique they provide an accessible and effective means for the construction of the carbon skeleton of various types of organic compounds. Here, realization of the latent functionality of the isoxazole ring by cleavage of the heterocycle provides a route to such important compounds as β-diketones, enamino ketones, enones, β-hydroxy ketones, enoximes, γ-amino alcohols, and others.

The increasing interest in the chemistry of isoxazole derivatives and their use in the synthesis of natural compounds and their analogs, including prostanoids [1-6], antibiotics [7-9], antitumor substances [10-13], vitamins [14], nucleosides [15], and alkaloids [16-19], has been partly reflected in reviews [20-22]. Nevertheless, the progress made in this region in recent years necessitates a further systematic review of the information on the production and chemical transformations of isoxazoles and 2-isoxazolines. The formation and cleavage of the isoxazole ring takes place with some degree of regio- and stereoselectivity; syntheses through oxazole derivatives are stereocontrolled. This is very important in the total synthesis of compounds containing several chiral centers.

The present review is a logical continuation of the review published in this journal in 1981 [23]. Individual aspects of the chemistry of isoxazole derivatives will therefore be discussed extremely briefly in the light of the information contained in the previous review.

1. REGIOCONTROL AND STEREOCONTROL IN THE NITRILE OXIDE SYNTHESIS OF ISOXAZOLES AND 2-ISOXAZOLINES

In the synthesis of natural compounds and their analogs the derivatives of isoxazole are used for the construction and/or elongation of a carbon chain [2 5, 6], the construction of a polycyclic molecule [16, 19], and the functionalization of the olefinic fragments of a molecule [24]. The strategy of the isoxazole (nitrile oxide) method for the synthesis of an organic compound (or its fragment) consists of three stages [21]: 1) Synthesis of the heterocycle (I) by 1,3-dipolar cycloaddition of the nitrile oxide (II) in situ (during the dehydration of a nitroalkane [25] or dehydrochlorination of an oxime chloride [26]) to an unsaturated compound; 2) modification of the molecule of (I) by the introduction of alkyl substituents or functional groups either into the ring or at an exocyclic position; 3) opening of the ring, leading to the bifunctional derivative (III). (Formula, top, following page.)

The first stage (1,3-dipolar cycloaddition) can be realized by an intramolecular mechanism [the unsaturated C—C bond (the dipolarophile) and nitrile oxide (dipole) are parts of one molecule] or an intermolecular mechanism (the heterocycle is formed from two different molecules, i.e., the dipole molecule and the dipolarophile molecule). Intermolecular cyclo-

Institute of Bioorganic Chemistry, Academy of Sciences of the Belorussian SSR, Minsk.
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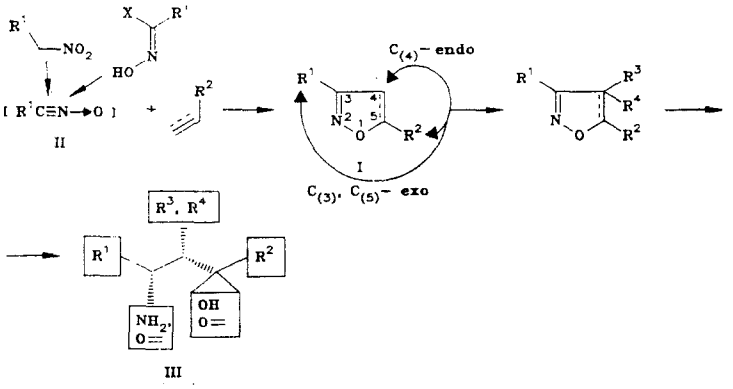
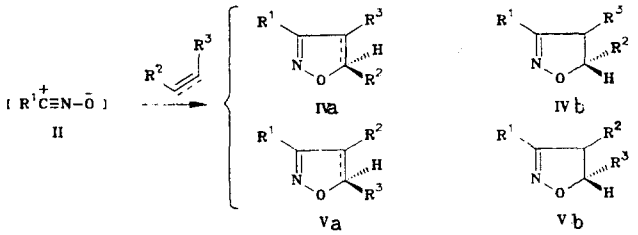


addition is used for the convergent synthesis of natural compounds from ready-made units containing the necessary functions (or their equivalents) in the substituents R^1 and R^2 [27-29].

The availability of isoxazole derivatives with various structures is secured by the almost unlimited range of 1,3-dipolar cycloaddition reactions, which take place under mild conditions and give high yields of the cyclic adducts from various unsaturated compounds and nitrile oxide precursors. An important advantage of cycloaddition is its cis-stereospecificity. Selectivity problems arise in the nitrile oxide synthesis on account of the possibility of the formation of two regioisomeric oxazoles or 2-oxazolines (IV, V) in the reaction. In addition, in the reaction with alkenes the dipole (nitrile oxide) can approach the dipolarophile on both sides of the plane of the double bond, and the formation of a diastereomeric pair (a, b) of isoxazolines can therefore be expected, while a preference for either side for attack leads to some degree of diastereoselectivity.

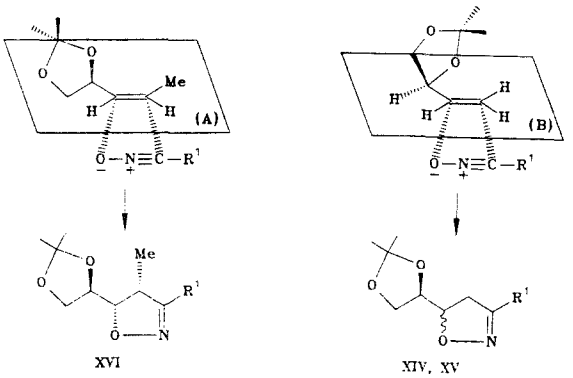


Realization of the synthesis under stereocontrolled conditions even at the first stage of the isoxazole method is a prerequisite for a high yield of the stereochemically uniform intermediates and final products of the synthesis.

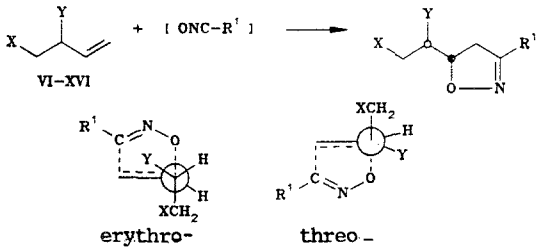
The main factors which determine the regioselectivity of the nitrile oxide synthesis are the degree of polarization of the unsaturated system and the size of the substituents R^2 and R^3. Here the oxygen of the nitrile oxide is attached to the more positively charged and sterically hindered end of the double or triple C—C bond. This rule is closely fulfilled in the special case of monosubstituted or "terminal" unsaturated compounds; in the transition to unactivated olefins and acetylenes the steric factors play a deciding role [30, 31].

The factors which control the diastereoselectivity of the reaction were established during investigation of the addition of various nitrile oxides to derivatives of 3-buten-2-ol and 3-buten-1,2-diol (VI-XVI) [31, 32]. In this case the theoretical prerequisite for control of the diastereoselectivity was antiperiplanar addition, where the nitrile oxide approaches the C—C bond from the side opposite the allyl substituent OR; here the nonbonding interactions between the oxygen and R^1 of the nitrile oxide are reduced to a minimum, and the oxygen atom at the allylic position occupies the most favorable orthogonal orientation to the plane of the C—C bond [31]. (Formula, top, following page.)

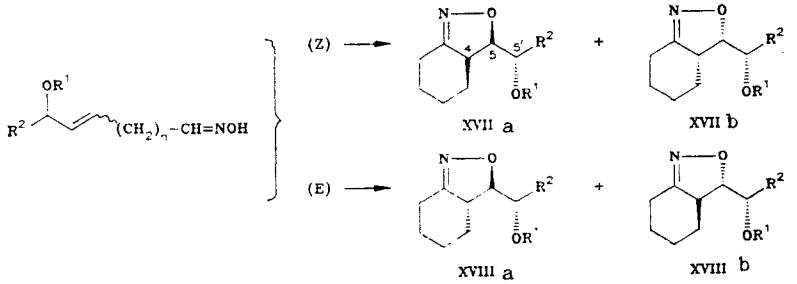
However, it follows from the experimental data (Table 1) that this suggestion is only fulfilled for cis-substituted olefins such as compound (XVI). For terminal and trans-disubstituted olefins it is necessary to consider not only the transition state (A) with the orthogonal oxygen atom at the allylic position but also the conformation (B) with the substituent inclined to the plane on the C=C bond, which makes it possible to explain the appreciable selectivity of addition in these cases (XIV, XV). The directing effect of the "allylic" oxygen shows up in conjunction with other factors in the structure of the allylic substituent. Thus,



it is necessary to take account of the size of the substituent at the C=C bond [cf. compounds (VI, IX, XI, XIV)] and the presence of the allylic chiral center, which gives rise to asymmetric induction. During the addition of benzonitrile oxide to α-chiral olefins the ratio of the diastereomeric isoxazolines varies in relation to the structure of the olefin, reaching considerable magnitude in the presence of the five-membered ring at the allylic position [32] [cf. compounds (VI, IX, XIV)]. According to data from calculations on models of the transition state, the conformation with the antiperiplanar arrangement of the CH_2X group is preferred for any (erythro or threo) diastereomer, since the steric effect of the substituent X does not appear in this case. However, the problem is the position of the substituent Y, i.e., "inside" (as in the erythro isomer) or "outside" (as in the threo isomer). The stereochemical result changes greatly with increase in the size of the substituent Y [cf. (XII) and (XIII), Table 1]; the amount of the more favorable erythro-isomer is increased, since the steric factor of Y must have a larger effect in the threo-conformation.

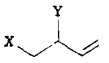
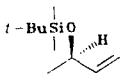
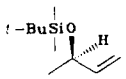
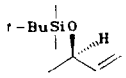
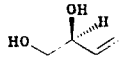
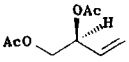
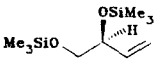
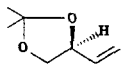
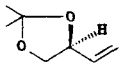
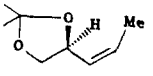


The stereochemical result from intramolecular cycloaddition is determined by a combination of many factors in the structure of the substrate. For monosubstituted terminal alkenes the stereoselectivity is controlled by the strain in the bicyclic system which forms [4, 10, 20]. For disubstituted alkenes one of the factors of stereoselectivity control is the configuration of the double bond, and irrespective of the nature of the substituent the Z-alkenylnitrile oxides give the $C_{(4)}/C_{(5)}$-syn-cycloadducts (XVII) preferentially, while the E-alkenylnitrile oxides give the $C_{(4)}/C_{(5)}$-anticycloadducts (XVIII) [35, 36]. Irrespective of the configuration of the double bond and the substituents at this bond, the cycloadducts (XVIIa) and (XVIIIa) with the $C_{(5)}/C_{(5')}$-anti-orientation of the substituents predominate in the stereoisomeric mixture.



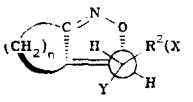
The anti-directing effect of the allylic asymmetric center with a bulky substituent close to it, observed for intermolecular cycloaddition, does not appear to an appreciable degree dur-

TABLE 1. The Diastereoselectivity in the Reaction of Derivatives of 3-Buten-2-ol and 3-Butene-1,2-diol with Various Nitrile Oxides [29, 31-34]

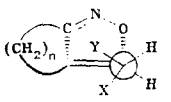
Compound		R¹CNO	Ratio of stereoisomers of cyclic adducts, erythro: threo
VI		PhCNO	50 : 50
VII		MeCNO	52 : 48
VIII		EtO_2CNO	71 : 29
IX		PhCNO	75 : 25
X		$THPOCH_2CNO$*	81 : 19
XI		PhCNO	61 : 39
XII		PhCNO	53 : 47
XIII		PhCNO	75 : 25
XIV		PhCNO	83 : 17
XV		$THPOCH_2CNO$*	95 : 5
XVI		EtCNO	100

*THP is the tetrahydropyranyl group.

ing intramolecular cycloaddition [16, 18]. According to the data from calculation of models of the transition state, the preferred conformation for Z-alkenes is the conformation (XIXa) with the "inside" arrangement of the smallest substituent of the allylic chiral center in relation to the forming C—O bond; the diastereoselectivity is mainly controlled by steric factors. For the double bond of E-alkenes having smallest steric hindrances it is assumed that the medium-size group Y is "inside," since a dependence of the stereoselectivity on the electronic factors of the substituents Y and X is observed [35, 36].



XIX a



XIX b

Here, if one of the substituents of the allylic stereocenter is a heteroatom, the stereoselectivity of the intramolecular cycloaddition is greatly increased. Thus, the high stereoselectivity exhibited by allyl ethers based on glyceraldehyde is attributed to the electronic effects of both (allylic and homoallylic) oxygen atoms. Thus, the effect of the alkoxyl group Y at the allylic stereocenter ("inside alkoxy effect") on the stereoselectivity of both intermolecular and intramolecular cycloaddition is clearly due both to the electronic effect of the heteroatom and to the size of the whole RO group [36-38].

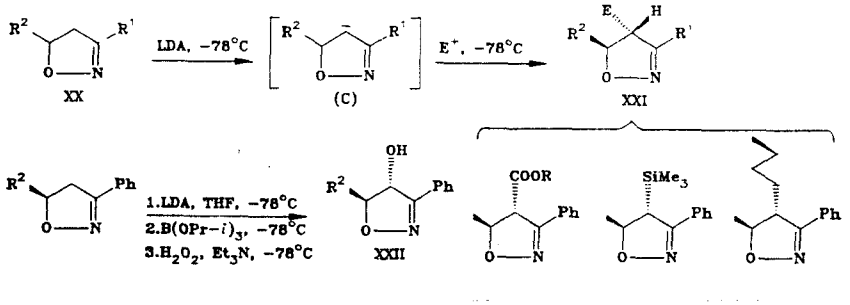
In conclusion it should be noted that the structure of the olefin plays a deciding role in the stereocontrol of the nitrile oxide synthesis. A number of cases have been described [39, 40] where the addition of nitrile oxides having extremely complicated structures to simple olefins takes place without appreciable selectivity, and some transfer of chirality is only observed when the optically active nitrile oxides are used [34]. The nitrile oxides are therefore regarded as relatively small cycloaddends [41], and only for a bulky and optically active nitrile oxide can it be supposed that cycloaddition will take place with greater stereoselectivity the better the conditions for the realization of stereoselectivity in a specific olefin.

The use of information on the factors involved in the stereocontrol of the nitrile oxide synthesis led to the successful stereoselective synthesis of the isoxazoline precursors of 2-deoxy-D-ribose [24, 33], the key intermediate in the synthesis of carbohydrates "compactin lactone" [42, 43], the metabolite of the antibiotic antimycin (blastmycinone) [31], and other natural compounds.

2. MODIFICATION OF ISOXAZOLE DERIVATIVES

The isoxazole ring is resistant to the action of many of the reagents normally employed in synthesis, e.g., strong acids, mild reducing agents, and strong oxidizing agents. A positive feature of the latent functionality of the isoxazole ring is the fact that it is possible to introduce functional groups at various functions of the molecule or to modify existing groups without affecting the heterocycle itself. Here the small geometric size and the compactness of the heterocycle do not create obstacles for the reactions.

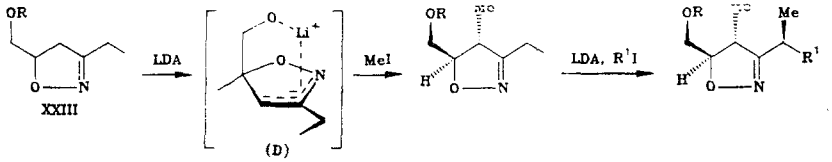
The principal method for the modification of 2-isoxazolines is based on their ability to enter into substitution reactions. Under the influence of strong bases one of the allylic protons either at the $C_{(4)}$ of the ring (4-endo-deprotonation) or in the substituent at $C_{(3)}$ of the ring (3-exo-deprotonation) is removed with the formation of an anion, stable at −60 to −80°C, which can react with various electrophiles [31, 44-46]. Thus, under the influence of lithium diisopropylamide (LDA) in THF at −78°C 3,5-diphenylisoxazoline (XX) forms the 4-endo-anion (C), the alkylation of which takes place trans-stereoselectively in relation to the substituent at $C_{(5)}$. This method makes it possible to obtain 4-trans-R-isoxazolines (XXI) [21], which are not always obtainable by nitrile oxide addition to trans-alkenes on account of its low selectivity. The potential precursors of amino sugars, 4-hydroxyisoxazolines (XXII), cannot be obtained by the nitrile oxide synthesis, since in cycloaddition the OR substituent of the alkene occupies position 5 of the heterocycle, but they can be obtained by trans-selective 4-endo-hydroxylation [46].



The hydrogen atom at the tertiary $C_{(4)}$ atom in 4-methyl-isoxazoline (XXI) (E = Me) can be removed again, and due to this it is possible to obtain 4-gem-dimethylisoxazoline [45]. It was established for 3-alkyl-substituted isoxazolines that alkylation of the substituent at $C_{(3)}$ takes place after alkylation of the ring, i.e., the 4-endo-proton has higher kinetic acidity and is deprotonated first [31]. For 3,4,5-trisubstituted isoxazolines and for 3-alkyl-4,5-cyclopentanoisoxazolines, in particular, the preferred 3-exo-alkylation is explained by the lower kinetic acidity of the endo-methine hydrogen compared with the exo-methyl hydrogen [44]. The regioselectivity of deprotonation depends, however, on the employed solvent; regiospecific 3-exo-deprotonation is observed in nonpolar solvents [47]. A significant increase of regioselectivity is obtained with the use of the more bulky lithium amide base [48].

The stereoselectivity factors in endo-alkylation of the heterocycle were studied for the case of isoxazolines (XXIII), and it was established that an oxygen-containing substituent at the $C_{(5)}$ atom directs the alkyl substituent preferentially at the trans position. It is assumed that the transition complex (D) is formed in the reaction. In this complex the

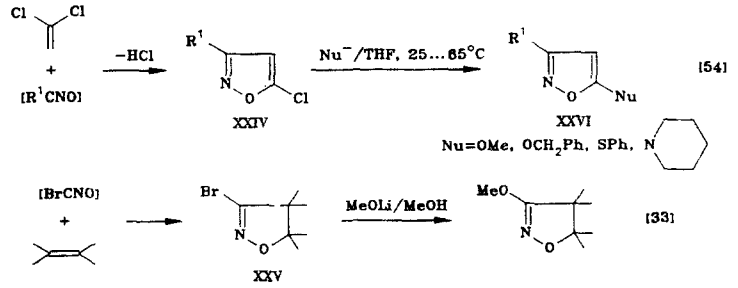
oxygen of the substituent OR at $C_{(5)}$ is chelated with the lithium cation coordinated with the 4-endo-anion, and the syn side of this complex is thereby closed for attack by the electrophilic particle. This secures preferential introduction fo the new alkyl group opposite OR even in the case of 4-methyl-5-alkoxyisoxazoline [31].



The main factor in the stereocontrol of 3-exo-alkylation is the substituent at the $C_{(4)}$ atom of the isoxazoline, in a relation to which substitution takes place preferentially trans-stereoselectively [44]. The deprotonation of 3,5-dimethylisoxazoles takes place regioselectively at first at the methyl group at the $C_{(5)}$ atom and then at the methyl at $C_{(3)}$, so that it is possible with successive substitution to obtain various 3,5-disubstituted isoxazoles [49].

The mobility of the allylic protons at positions 3 and 5 of the isoxazole and at positions 4 and 5 of isoxazoline can be used for the introduction of various functional groups [50-52]. For example, 3,5-dimethyl-4-nitroisoxazole was used in the synthesis of coumarinic acid as the CH-acid component in the Perkin reaction [50]. In the synthesis of lankacidin a method was developed for single-stage successive acylation and alkylation of the isoxazoline ring at the $C_{(4)}$ atom [51].

Synthetically useful modifications can be achieved on the basis of halogen-substituted isoxazoline and isoxazoles, which are obtained by a nitrile oxide synthesis with α-halogen-substituted olefins or nitrile oxides. Such derivatives of isoxazole (XXIV, XXV) enter readily into nucleophilic substitution, securing a route to a wide range of derivatives (XXVI) having various functions in the substituents of the heterocyclic ring [33, 53, 54].



Thus, the possibility of structural modification of isoxazoles and 2-isoxazolines extends the applicability of these universal heterocycles in the synthesis of a large range of polyfunctional molecules.

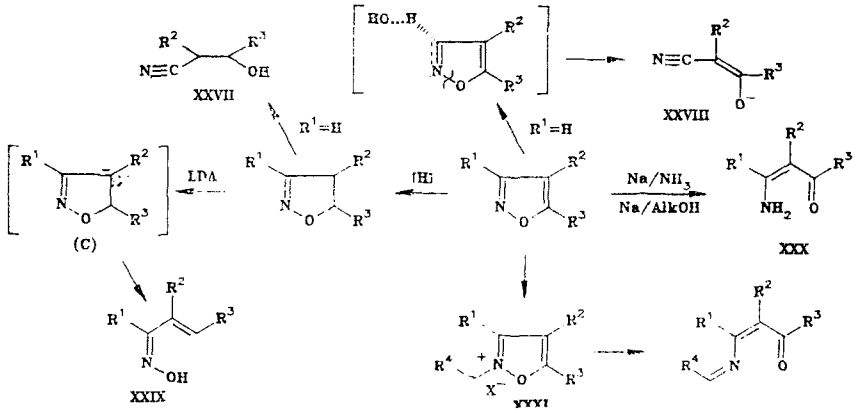
3. CLEAVAGE OF ISOXAZOLE DERIVATIVES AS A METHOD FOR THE GENERATION OF BIFUNCTIONALITY

The synthetic potential of the isoxazoles and their derivatives is achieved by ring opening under the influence of mainly two types of reagents (reducing agents and bases).

3.1. Cleavage with Bases

To summarize the information from a large number of researches into the cleavage of isoxazoles and 2-isoxazolines by bases, which was set out in detail in [23], it can be stated that the production of an unambiguous result is problematical on account of the strong dependence of the direction of ring opening on the structure of the substrate, the base, and the reaction conditions. Many reactions take place under the influence of some bases and do not take place under the influence of others. The anion of type (C), formed by the action of bases (see subsection 2) at room temperature, is cleaved, and the direction and ease of ring opening depend very much on the structure of the isoxazole derivative, since it is the structure which determines the point of deprotonation and its accessibility to the base. In isoxazoles and isoxazo-

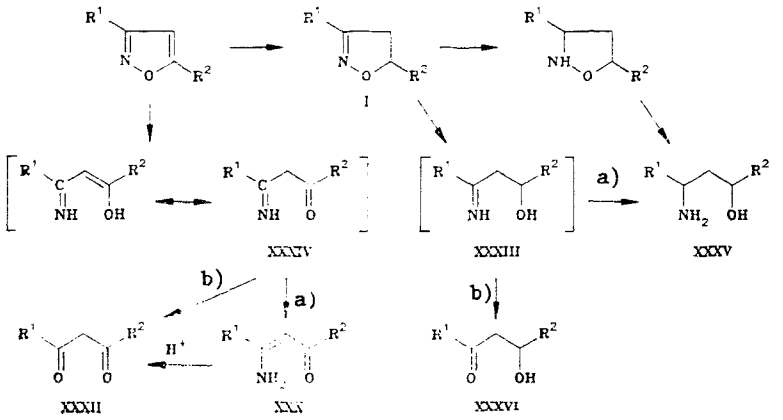
lines unsubstituted at $C_{(3)}$ ring opening takes place at the N–O bond with conversion into nitriles and their derivatives (XXVII, XXVIII). 3-Substituted isoxazolines are cleaved at the C–O bond with the formation of enoximes (XXIX) [45, 55, 56]. The enoximes can then be converted into α,β-enones, reduced to amines, or submitted to recyclization [23]. 3-Substituted isoxazoles are cleaved by bases with the formation of enamino ketones (XXX) [57]. The cleavage of isoxazolium salts (XXXI) takes place under mild conditions (0°C), and such a method of ring opening is therefore most suitable for the labile derivatives of isoxazole [58, 59]. An interesting preparative method was recently proposed [60] for the cleavage of isoxazolinium salts by bases.



As seen from the scheme, the degree of unsaturation of the heterocycle determines both the regiochemistry of cleavage and the degree of oxidation of the cleavage products; 2-isoxazolines mainly give the enoximes (XXIX) as products, while the stronger heteroaromatic ring is opened at the N–O bond.

3.2. Reductive Cleavage of Isoxazoles and 2-Isoxazolines

The general scheme for the hydrogenolysis of 2-isoxazolines and isoxazoles at the N–O bond presupposes the intermediate formation either of the hydroxyimine (XXXIII) [61] or of the keto imine (XXIV) [62] respectively, while the final products are formed as a result of the further reduction (path a) or hydrolysis (path b) of these intermediates. Hydroxyimines, which were for a long time considered hypothetical intermediates, were recently isolated, and their structures were demonstrated [63, 64]. Ketoimines are quite stable [62].



The direction of the subsequent transformation of the hydroxyimine into the amino alcohol (XXXV) or the hydroxy ketone (XXXVI) and of the ketoimine into the enamino ketone (XXX) or diketone (XXXII) is determined by the nature of the reducing agent and by the reaction conditions. In some cases, considered in subsection 3.2.2, the formation of the amino alcohol during the reduction of 2-isoxazolines takes place through the isoxazolidine. The formation of other products from the reduction of isoxazole derivatives in each particular case is due to specific characteristics of the structure of the specific initial compound. This shows up either at the ring opening stage or in the subsequent transformations of the initial hydrogenolysis products, and this will be discussed below.

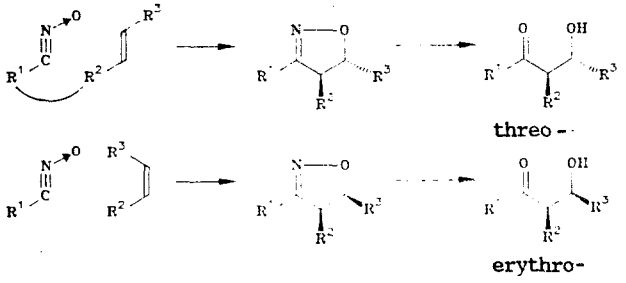
3.2.1. Reductive Cleavage of 2-Isoxazolines to β-Hydroxy Ketones. The hydroxy ketones (aldols) (XXXVI) are the initial and main products from the hydrogenolysis of isoxazoline and subsequent hydrolysis of the intermediate hydroxyimine (XXXIII). A fairly large number of methods have been proposed for the production of the hydroxy ketones, and they can be divided into two main groups.

1. Methods of catalytic hydrogenation of 2-isoxazolines with palladium and nickel catalysts. An important position among these methods belongs to the reductive cleavage of 2-isoxazolines by the action of Raney nickel in an acidic medium. The general cleavage of isoxazolines to β-hydroxy ketones or their dehydration products (α,β-unsaturated ketones), which we described first in 1979 [65], has subsequently been used widely in various procedure modifications [15, 27, 30, 31, 61, 66]. It is considered that stereospecific opening of the ring is secured in the presence of a strong acid [31, 67, 68]. The nonstereospecific cleavage observed in the case of 3,4,5-substituted isoxazolines is due to the fact that the hydrolysis rate of the hydroxyimine (XXXIII) is reduced in the presence of a bulky substituent at the $C_{(3)}$ atom, and epimerization at $C_{(4)}$ is possible through the tautomeric transformation of (XXXIII) to the enamine [68].

During the reduction of isoxazolines with complex structures at Raney nickel, it was found that it is of great advantage to conduct the reaction at pH 5-7 in the case of compounds having substituents sensitive to reduction; here the cleavage is not complicated by side processes. Attention is drawn to the procedural developments using boric acid and other compounds of boron as acidic agents; this guarantees the retention of protecting groups sensitive to acids (acetyl, tetrahydropyranyl, silyl) [30, 61]. A procedure with ozonolytic cleavage of isoxazolines was proposed to preserve groups sensitive to reduction and to acids [67].

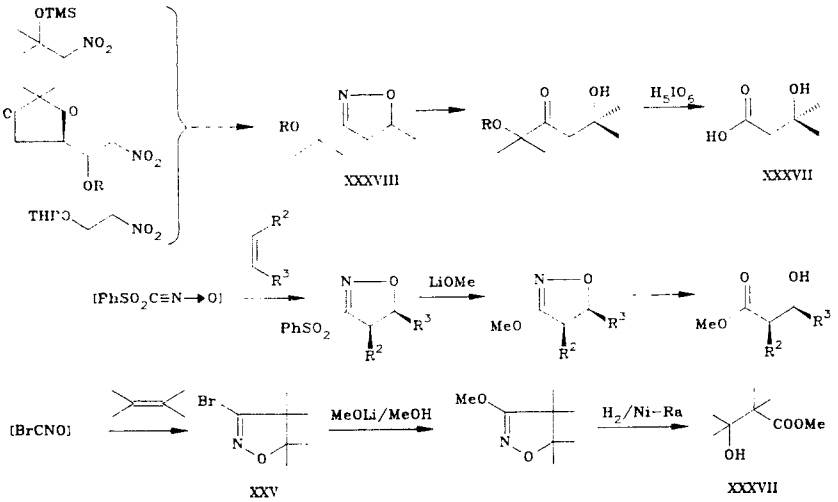
2. The use of exotic reducing systems is justified when there are unsaturated substituents in the isoxazoline, since all the methods of hydrogenolysis using Raney nickel do not guarantee retention of the unsaturated groups [69-71]. New reducing agents $Mo(CO)_6$, $Fe(CO)_5$ [11, 72], and H_2/Rh-Al [73], having substantial advantages and distinguished by higher selectivity, have recently been proposed.

It was established by numerous investigations that the cleavage of isoxazolines to hydroxy ketones takes place without inversion of the configuration and is stereospecific from the initial olefin [61]. Thus, the geometry of the olefin is directly translated into the geometry of the final alicyclic compound.

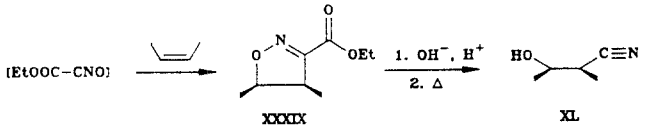


Such a stereocontrolled two-stage method for the production of the aldol fragment is attractive for use in organic synthesis. A convenient path to various types of polyfunctional molecules is provided by the cleavage of functionally 3,4,5-substituted isoxazolines. Both nitrile oxides containing hydroxy, alkoxy, cyano, and alkoxycarbonyl substituents and α-functionalized olefins are used for their synthesis. Thus, methods have been developed for the synthesis of β-hydroxy acids (XXXVII) from protected nitroalkyls through 3-alkoxymethylisoxazolines (XXXVIII) [34, 68]. Benzenesulfonylnitrile oxide has also been used for this purpose, and the benzenesulfonyl group is easily substituted by a methoxy group in subsequent transformations [68]. Recently a simpler version of the synthesis through 3-halogenoisoxazolines (XXV) was proposed [33]. (Formula, top, following page.)

Methods for the production of hydroxynitriles were developed with the use of cyanonitrile oxide and ethoxycarbonylnitrile oxide: 3-alkoxycarbonylisoxazolines (XXXIX) are readily sapon-

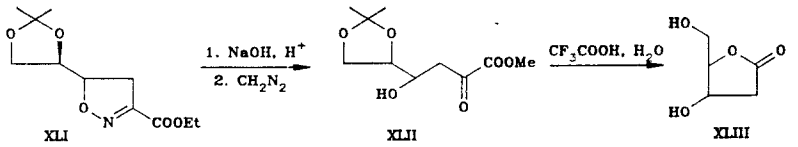


ified to 3-carboxyisoxazolines, and the latter can be pyrolyzed with simultaneous cleavage to the hydroxynitriles (XL) [74].

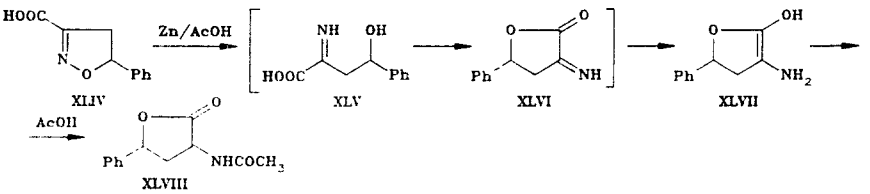


cis-Cyanohydroxylation on the basis of 3-benzenesulfonylisoxazolines was recently proposed [75].

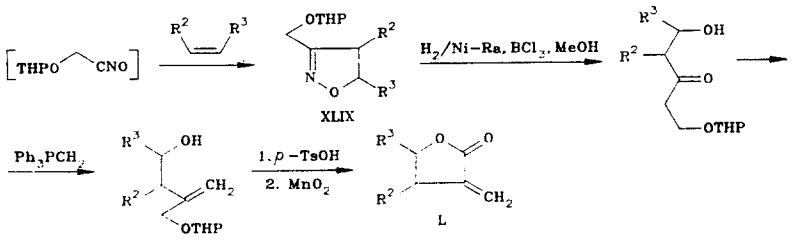
3-Alkoxycarbonylisoxazoline (XLI) is cleaved by diazomethane to the γ-hydroxy acid (XLII). The latter undergoes recyclization to the lactone (XLIII) under the influence of trifluoroacetic acid [24].



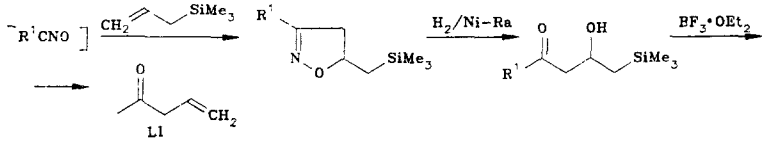
3-Isoxazoline acids (XLIV) are cleaved by the action of zinc in acetic acid by the usual mechanism, but the carboxy group gives rise to cyclization of the intermediate hydroxyimine (XLV) to the lactone (XLVI), which is then reduced to (XLVII) and acylated with the formation of N-acetylaminolactone (XLVIII) [76].



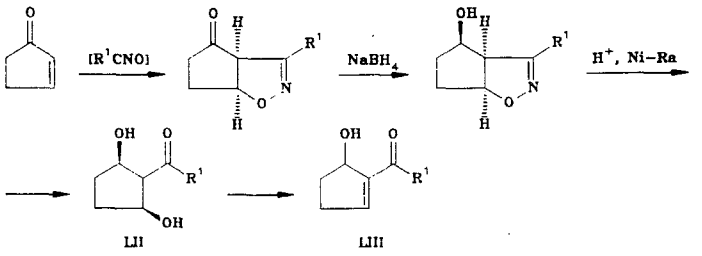
A method was developed by means of which α-methylenelactones (L) were obtained from 3-hydroxymethylisoxazolines (XLIX) through the hydroxy ketones [77].



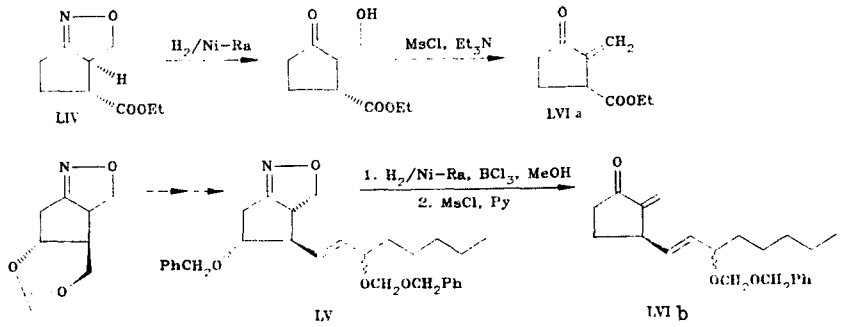
The recently proposed nitrile oxide approach to β,γ-unsaturated ketones (LI) is promising [78].



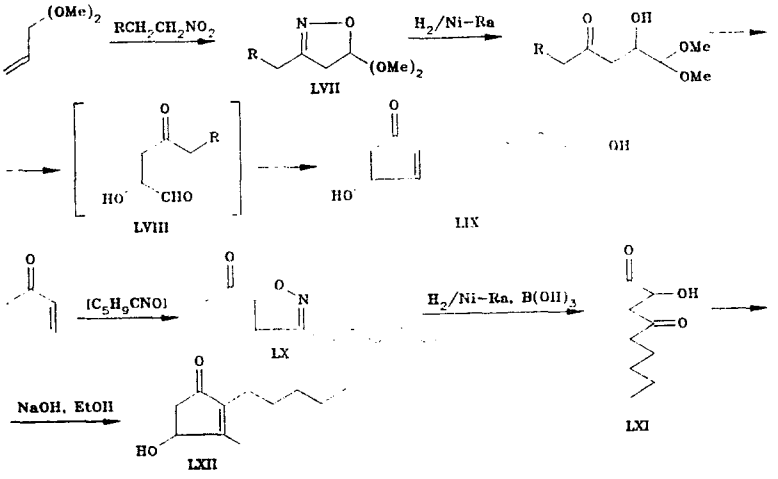
Preparative methods for the synthesis of cyclic ketodiols (LII) and eneketols (LIII), which are key compounds in the total synthesis of steroids, prostanoids, and other biologically active molecules, represent an example of the isoxazole method for the functionalization of cycloalkanes [79-83].



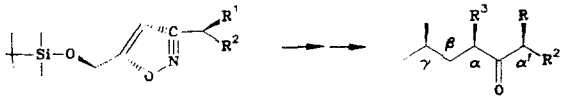
The key stage in isoxazole methods for the synthesis of prostanoid precursors (methylenecyclopentanones) is cleavage of the isoxazolines (LIV) and (LV) by hydrogenation over Raney nickel under mild conditions with the formation of hydroxy ketones and their subsequent dehydration to α,β-unsaturated ketones (LVIa, LVIb) [4, 10].



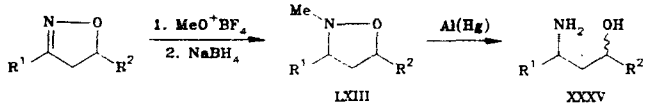
A scheme was developed for the synthesis of functionalized precursors of prostanoids (LIX, LXII), in which the key reactions are the formation and cleavage of the isoxazolines (LVII, LX), and the condensation of the γ-ketone aldehydes (LVIII) or diketones (LXI) [3].



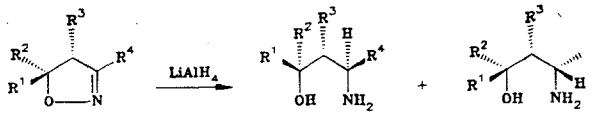
A similar approach was used for the synthesis of prostanoid synthons from acrolein diethyl acetal [84]. The isoxazole method for the generation of the hydroxy ketone fragment is widely used in the synthesis of other natural compounds and their analogs [27, 28, 42, 82, 85]. An example of the use of all stages of the isoxazole strategy in the synthesis of natural compounds is the total synthesis of blastmycinone [31], where the choice of substrates and reagents secured occurrence of the reactions under conditions with stereocontrol. If a nitrile oxide with an α-asymmetric center and an alkene with an alkoxy substituent at the allylic position are used, stereoselective synthesis of the isoxazoline is achieved. After alkylation it was converted by hydrogenolysis into the hydroxy ketone with given stereochemistry at the α'-, α-, β-, and γ-centers.



3.2.2. Reductive Cleavage of 2-Isoxazolines to γ-Amino Alcohols. The hydrogenolysis of isoxazolines to amino alcohols is the key stage in the synthesis of many natural compounds such as hydroxyamino acids, amino sugars, and others [7, 21, 29, 86-90]. It is assumed that the cleavage of the isoxazoline to the amino alcohol can take place through the hydroxyimine (XXXIII) or isoxazolidine (LXIII), depending on the nature of the reducing agent. The first path represents hydrogenolysis of the ring to the hydroxyimine, the further reduction of which leads to the amino alcohol (XXXV) [29, 86, 87]. The second path provides for the preliminary total saturation of the ring, which can be realized in practice through its methylation with the formation of an isoxazolinium salt and reduction to the isoxazolidine (LXIII) with a metal hydride. An aluminum amalgam in aqueous solutions was used for the cleavage of the isoxazolidine [18, 51, 91].



The stereochemistry of the transformations of substituted isoxazolines to amino alcohols, the stereoselectivity of the various reducing agents, and other factors concerned in the stereocontrol of the reaction were investigated in detail [21, 29, 89, 90]. The best reducing agent from the standpoint both of the yield of the amino alcohol and of the selectivity was lithium aluminum hydride, which promotes "erythro" selectivity in the reaction [86, 92].

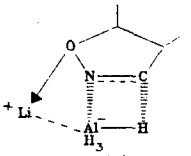


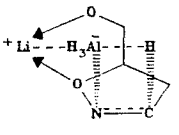
The stereoselectivity of the lithium aluminum hydride reduction is appreciably reduced with the mutual 4,5-trans-arrangement fo the substituents in the heterocycle and is increased in the presence of alkoxy substituents at the $C_{(5)}$ atom (Table 2). In the transition from the hydroxy to the alkoxy substituent the stereoselectivity is appreciably reduced [cf. (LXVIII) and (LXXII), (LXX) and (LXXI)]. An anti-directing effect was found for alkyl and aryl substituents at $C_{(5)}$, while substituents with a hydroxy group were syn-directing [29, 90]. The small reactive lithium aluminum hydride is sensitive to the structure and the size of the substituents in the heterocycle because it coordinates through chelation of the lithium and the oxygen of the ring; here the aluminum and the hydrogen lie above the C=N bond on the most accessible side, and the overall antistereoselectivity of the reduction process is increased. In substrates containing alkyl and phenyl substituents the antidirection is controlled by the size of the substituent, and the transition state (E) can be proposed for the transfer of hydrogen from the aluminate anion. In the case of substrates with hydroxy functions an additional co-

TABLE 2. The Diastereoselectivity of the Reductive Cleavage of the Isoxazolines (LXIV-LXXV) by Lithium Aluminum Hydride [21, 29, 89]

Initial isoxazoline	Substituents				Ratio of stereoisomers of amino alcohols, β:α
	R^1—$C_{(5)}$	R^2—$C_{(5)}$	R^3—$C_{(4)}$	R^4—$C_{(3)}$	
LXIV	Me	H	Me	H	72:28
LXV	H	Me	Me	H	90:10
LXVI	Me	Ph	H	H	82:18
LXVII	$C_{14}H_{29}$	H	H	Me	88:12
LXVIII	$C_{14}H_{29}$	H	H	CH_2OH	58:42
LXIX	Me	CH_2OH	H	H	82:12
LXX	CH_2OH	H	H	Me	37:63
LXXI	CH_2OTHP	H	H	Me	72:28
LXXII	$C_{14}H_{29}$	H	H	CH_2OTHP	78:22
LXXIII	H	H	OH	Ph	90:10
LXXIV		H	H	Ph	90:10
LXXV	Alk	H	OH	H	95:5

ordination complex appears, and hydride transfer from the alkoxyaluminate complex (F) is preferred. Substituents of such a type are therefore syn-directing.


(E)


(F)

A high degree of diastereoselectivity is observed in the reduction of isoxazolines containing a dioxolane group at the $C_{(5)}$ atom [29, 88] and also of furo- and dihydrofuroisoxazolines, in which the oxygen-containing substituent is rigidly fixed in the [3.3.0]bicyclic system [89]. The degree of asymmetric induction of the ring substituents under the conditions of lithium aluminum hydride reduction was also investigated, and it was found that hydroxymethyl substituents at the $C_{(3)}$ and $C_{(5)}$ atoms reduce the degree of asymmetric induction, and the substituent at $C_{(5)}$ has the largest effect [86, 90]. It was also found that the effect of the substituent at $C_{(5)}$ predominates during comparison of the effects of the substituents at $C_{(4)}$ and $C_{(5)}$; 1,3-induction predominates over 1,2-induction. By promoting stereoselective opening of the ring, the dioxolane substituent gives rise to a decrease in the degree of asymmetric induction.

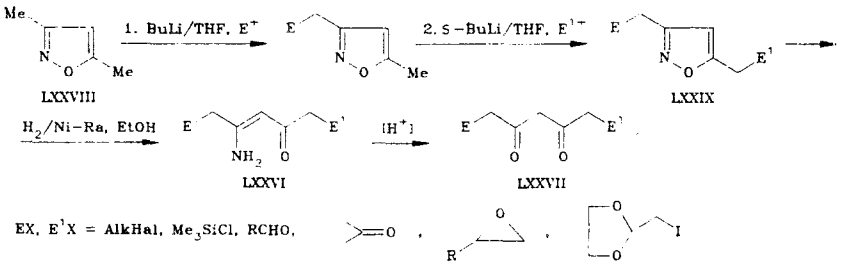
Investigation of successive reduction through isoxazolidine showed [18] that reducing agents of medium strength (sodium borohydride) or very reactive bulky agents (L-selectride) are insensitive to the ring substituents, but they approach the isoxazoline molecule from the most accessible side. The reduction of isoxazolines by hydrogen in the presence of amalgams takes place nonstereospecifically on account, evidently, of the initial cleavage of the ring at the N—O bond with subsquent reduction of the C=N bond [20]. The same nonstereospecific opening, leading to a stereoisomeric mixture of amino alcohols (3:2) is also observed during hydrogenation over Adams catalyst [7].

3.2.3. Reductive Cleavage of Isoxazoles. Opening of the isoxazole ring takes place during catalytic hydrogenation; the usual catalysts are palladium on supports, Raney nickel, and platinum oxides, and the yields are preparative. β-Enamino ketones (XXX) or β-diketones (XXXII) are formed, depending on the reduction conditions [15, 49, 93, 94].

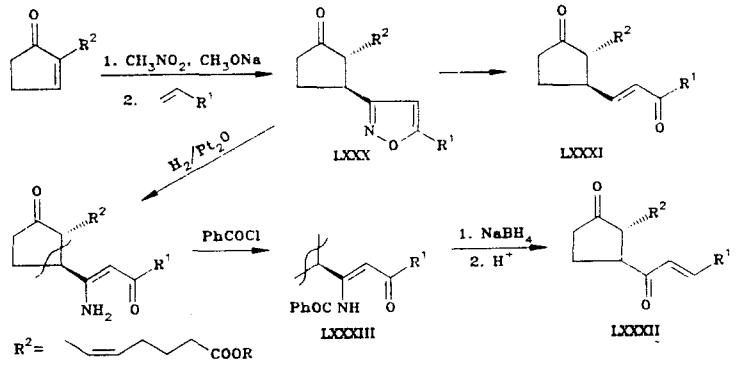
Work on the reductive cleavage of isoxazoles carried out up to 1980 was considered in [23]. We will give mainly the data from recent investigations on new reagents, new transformations of isoxazoles, and the use of these transformations in the synthesis of natural compounds and their analogs.*

*During the preparation of the present review for the press a review was published on the application of isoxazoles in the synthesis of natural compounds [95].

The synthesis of polyfunctional enamino ketones (LXXVI) and β-diketones (LXXVII) was realized from isoxazoles (LXXVIII) by successive modification of the substituents at the $C_{(3)}$ and $C_{(5)}$ atoms and reductive cleavage of the ring in the derivatives (LXXIX); the diketones were obtained by acid hydrolysis of the enamino ketones [49].



The transformation of the isoxazoles into α,β-unsaturated ketones (LXXXI) and (LXXXII) by Birch cleavage followed by deamination or catalytic hydrogenolysis of the ring and subsequent production of the acylated derivative (LXXXIII) was used successfully in the synthesis of prostaglandins [5, 94]. The use of the isoxazole strategy for the construction of the ω-chain of prostanoids was based on the synthesis of isoxazole-substituted cyclopentanones (LXXX), in which cleavage of the heterocycle gives the natural prostaglandin chain [1, 5, 96].



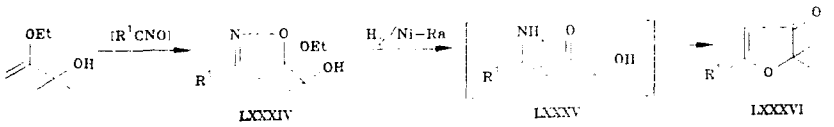
Recyclization of enamino ketones or their derivatives at the carbonyl group opens up the possibility of the synthesis of other nitrogen-containing heterocycles [57, 97-100]. Such a path was used to develop a method for the synthesis of 8-azaprostanoids [101].

A method was developed recently for the direct opening of isoxazoles to β-diketones by hydrogenation in the presence of Raney nickel in an acidic medium under conditions similar to the conditions for the cleavage of 2-isoxazolines to β-hydroxy ketones [15, 42]. Such a process takes place with retention of the protecting groups, and the yields of the desired products are close to quantitative. The diketones (XXXII) are clearly both products from hydrolysis of the enamino ketones (XXX) and products from hydrogenolysis–hydrolysis of the isoxazoles through the intermediate ketoimines (XXXIV) [49, 62].

New more selective methods have been found for the reduction of isoxazoles to enamino ketones [102-105]. Successful researches into the synthesis of a series of natural compounds [9, 11, 12, 62, 106] among the applied synthetic investigations of recent years employing the isoxazole → enamino ketone → diketone scheme demonstrate the procedural advantages of the given strategy.

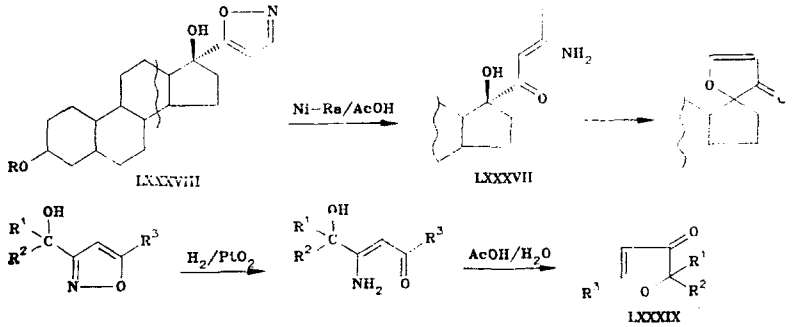
In recent years the attention of investigators has been attracted to methods of reductive cleavage of isoxazoles to amino alcohols or hydroxy ketones [107] or of 2-isoxazolines to enamino ketones or diketones [13], which make it possible to manipulate the structure of the heterocycle, e.g., removing the problem of the stereochemistry of cleavage of the isoxazolines during the synthesis of amino alcohols. On the other hand, it is possible to increase the yield substantially at all stages of the isoxazole scheme by means of the more preparative and selective syntheses through 2-isoxazolines.

The reductive cleavage of 5-hydromethyl-5-alkoxyisoxazolines (LXXXIV) during hydrogenation over Raney nickel in a water–methanol solution evidently takes place through the intermediate formation of enamino ketones (LXXXV). This method opens up a three-stage path from the olefin to dihydrofuranones (LXXXVI) [13].



LXXXIV LXXXV LXXXVI

A similar process to the recyclization of α-hydroxyketoenamines (LXXXVII) from the isoxazole derivatives of steroids (LXXXVIII) is the single-stage catalytic reduction of the latter over Raney nickel in acetic acid, which we described earlier [108]. In recent years methods have been developed on the basis of this reaction for the synthesis of dihydrofuranones (LXXXIX), which are the central structural fragments of a whole series of natural compounds [11-13, 106, 109].



LXXXVIII LXXXVII LXXXIX

The results from investigations of recent years reflect to a fairly full extent both the advantages and the problems of the isoxazole strategy for the synthesis of functionalized organic molecules. Various structural factors in the stereocontrol of the formation, modification, and opening of the isoxazole ring have been revealed, selective reagents have been found, a method has been developed for the selection of protecting groups during the synthesis of polyfunctional compounds, and it has been possible in a number of cases to realize stereoselective preparative synthesis. For molecules in which the specific weight of the isoxazole fragment is substantial there is experience on the prediction of the stereoselectivity of the reactions, and electronic and steric complication of the molecule up to a certain limit increases the stereoselectivity at all stages of the synthesis. We find just such a situation in the synthesis of natural compounds, where the fairly large volumes of the whole molecule and of the substituents in the heterocycle are stereocontrol factors; however, these factors have not so far prevented the possibility of reaction. The stereochemical problems of the isoxazole method are mostly connected with the development of new selective reagents and techniques for the selective reactions. At the present time advances in the total synthesis of natural compounds and in the synthesis of analogs are ensuring vigorous progress in this field.

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2-BENZOPYRYLIUM SALTS.

34.* REACTIONS OF 3-CARBOXY-2-BENZOPYRYLIUM SALTS WITH AMINES. SYNTHESIS OF CYCLIC KETOLS

Yu. A. Zhdanov, V. G. Brovchenko, M. A. Klyuev, and E. V. Kuznetsov

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3-Carboxy-2-benzopyrylium salts form 3-carboxyisoquinolinium salts, their decarboxylated analogs, or products of contraction of the heterocycle, namely, cyclic ketols, depending on the nature of the amine and solvent. Upon treatment with acids, these ketols are demethylated through the intermediate formation of α-acylcarbenium ions and are converted to quinonemethides.

The presence of functional groups in the heterocycle of the pyrylium cation has a definite effect on the nature of its reaction with nucleophiles [2, 3]. Thus, monocyclic α-carboxypyrylium salts react with primary amines to convert to pyridinium salts with decarboxylation [4, 5].

We have found that 1-aryl-3-carboxy-2-benzopyrylium salts Ia and Ib react with primary amines in ethanol or chloroform to give 3-carboxyisoquinolinium salts IIa-IId in 90-97% (method A) and in benzene to give their decarboxylated analogs, IIIa-IIId in 52-62% yield (method A1) [6].

We may propose that salts II are formed as intermediates in benzene and are then converted to III either by thermal decarboxylation [7] or by recyclization due to addition of a nucleophile with simultaneous decarboxylation as found in the case of their monocyclic analogs [5]. However, the direct decarboxylation of isoquinolinium salts IIa-IId under these conditions leads to a sharp decrease in the yields of IIIa-IIId (40-12%, method B). On the other hand, "degenerate recyclization" products were not found in the reaction mixture upon carrying out this reaction with primary amines having substituents at the nitrogen atom different from those in isoquinolinium salts II (method B1) [5, 8]. Thus, if the formation of salts III under the conditions examined proceeds by thermal decarboxylation of acids II, the contribution of this pathway is only slight.

The most likely reason for the different reaction courses lies in the effect of the solvent on the site of nucleophile addition to the 2-benzopyrilium cation, which, in contrast to its monocyclic analogs, has two nonequivalent α-positions. In ethanol, a primary amine, upon addition to $C_{(1)}$, causes recyclization without affecting the carboxyl group. A pyruvic acid enamine fragment capable of facile decarboxylation [9] arises upon addition to $C_{(3)}$ in

*For communication 33, see [1].

Physical and Organic Chemistry Research Institute, M. A. Suslov Rostov State University, Rostov-on-Don 344071. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 454-459, April, 1989. Original article submitted August 4, 1987.

