SYNTHESIS, STRUCTURE, AND PROPERTIES OF 1,3-OXAZACYCLOALKANES (REVIEW)

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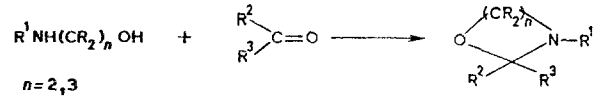
Research dealing with methods for the synthesis of 1,3-oxazacycloalkanes and their structures and homolytic and heterolytic transformations is reviewed.

Owing to their interesting physicochemical properties and high reactivities, 1,3-oxazacycloalkanes have been of constant interest to researchers since the beginning of the twentieth century. However, of the two available review publications [1, 2], one [1] has become obsolete in many respects, and only 1,3-oxazines were included in [2]. In addition, a number of papers that open up prospects for the use of 1,3-oxazacycloalkanes in organic synthesis and in the preparation of biologically active preparations have been published in the last 5-8 years. Proceeding from this, in the present review we examined the principal methods for the preparation of 1,3-oxazacycloalkanes and their structures and reactions.

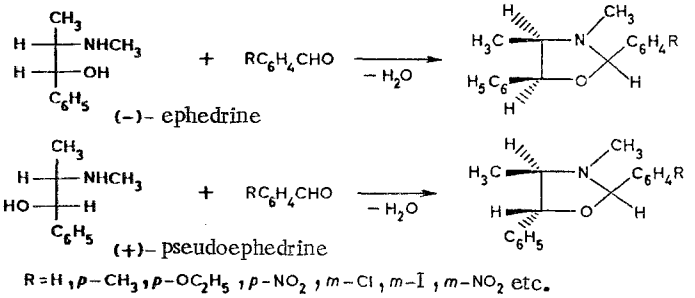
1. Synthesis of 1,3-Oxazacycloalkanes

1.1. Synthesis from 1,2- and 1,3-Amino Alcohols and Carbonyl Compounds. The first reports regarding 1,3-oxazacycloalkanes are contained in [3, 4], which are devoted to the reaction of amino alcohols with aldehydes and ketones. The cyclization of amino alcohols with carbonyl compounds is the most nearly universal and reliable method for the synthesis of 1,3-oxazacycloalkanes. This method has been used to obtain the overwhelming majority of five- [5-15] and six-membered [16-23] 1,3-oxazacycloalkanes:



In most cases cyclization is realized in solvents such as benzene, toluene, ether, alcohol, dioxane, and chloroform, but it sometimes also proceeds readily without a solvent.

Soliman and co-workers [12, 13] have synthesized a number of 2-aryloxazolidines by condensation of (−)-ephedrine and (+)-pseudoephedrine with aldehydes:



The condensation of aromatic aldehydes with (−)-ephedrine or (+)-pseudoephedrine proceeds stereospecifically with the formation of only the 2R,4S,5R-diastereomer [14], whereas condensation of (−)-ephedrine [15] with acetaldehyde gives two diastereomeric 2,3,4-trimethyl-5-phenyloxazolidine:

Ufa Petroleum Institute, Ufa 450062. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 4, pp. 435-449, April, 1982. Original article submitted September 10, 1980.

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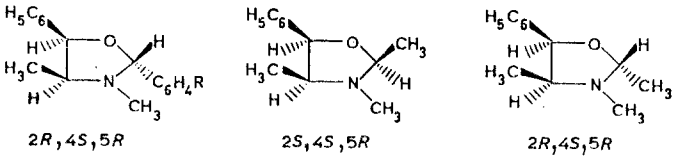
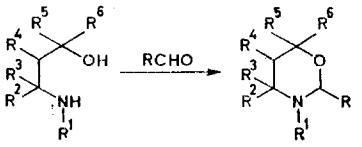


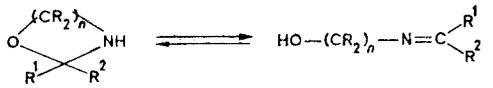
2R,4S,5R 2S,4S,5R 2R,4S,5R

A large number of polysubstituted tetrahydro-1,3-oxazines, which previously had been difficult-to-obtain compounds [21-23], were obtained only after the creation of new methods for the synthesis of γ-amino alcohols [16-20].



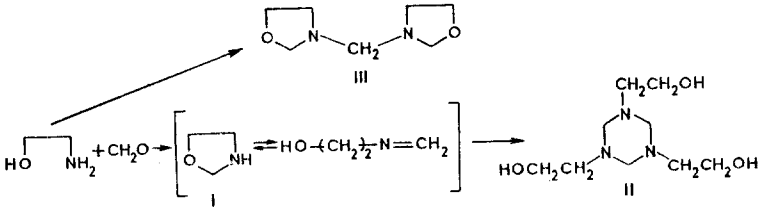
2,3-Dimethyl-6-alkyl-6-phenyltetrahydro-1,3-oxazines were synthesized in 25-36% yields by refluxing solutions of the hydrochlorides of amino alcohols with excess paraldehyde in anhydrous toluene [20]. The condensation of stereoisomers that contain asymmetric centers in the 1 and 2 or 1 and 3 positions with formaldehyde leads to individual geometrical isomers of tetrahydro-1,3-oxazines [24].

The formation of a tautomeric linear form, viz., a Schiff base, is possible in addition to the formation of cyclic products in the condensation of amino alcohols that contain a primary amino group with carbonyl compounds:



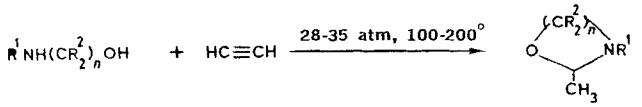
A number of papers have been devoted to the study of this tautomeric equilibrium by means of IR spectroscopy [7, 25], ^{1}H NMR spectroscopy [26], and mass spectrometry [27]. As a rule, this equilibrium is shifted to favor the cyclic product, but in some cases, primarily in the condensation with ethanolamine, primarily Schiff bases are formed. The tautomeric equilibrium is shifted to favor the Schiff base particularly readily in the cyclization of unsubstituted amino alcohols with aromatic aldehydes [28].

The condensation of monoethanolamine with formaldehyde almost always leads to a "trimer" — 1,3,5-tris(2-hydroxyethyl)hexahydro-s-triazine [29] — or to a methylene-N,N'-bisoxazolidine [30]:



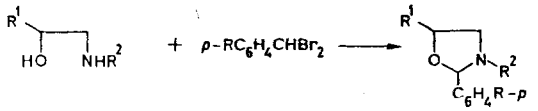
The yield of the latter increases as the percentage of CH_2O in the reaction mixture is increased and reaches quantitative levels when the ratio of monoethanolamine to formaldehyde is 1:1.5. However, the rapid condensation of ethanolamine with formaldehyde gives unsubstituted oxazolidine I, which undergoes slow polymerization to give triazine II at −20°C and, in the absence of moisture, can be stored for several weeks [28]. Tetrahydro-1,3-oxazine is more stable; however, it also undergoes polymerization during storage.

1.2. Other Methods of Synthesis. Both γ- and β-amino alcohols are converted to 2-methyl-substituted oxazolidines and tetrahydro-1,3-oxazines in 30-70% yields by the action of acetylene [31]:

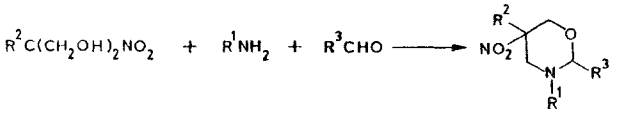


3-Aryloxazolid-2-ones and 1,4-diarylpiperazines were synthesized by the condensation of N-β-hydroxyethylarylamines with trichloroacetyl chloride and ethyl trichloroacetate [32].

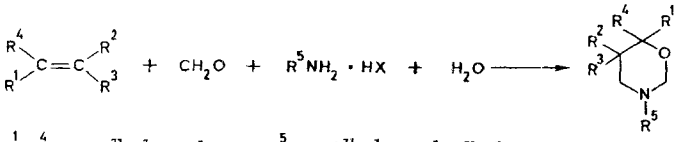
A number of oxazolidines were obtained by the reaction of p-subtituted dibromobenzylidenes with β-amino alcohols in refluxing ether or dioxane [33]:



The preparation of 3,5-dialkyl-5-nitrotetrahydro-1,3-oxazines by heating a mixture of formaldehyde, a primary amine, and a nitroalkanediol has been described [34]. Urbanski and co-workers [25, 35, 36] have used this method to synthesize a series of 3,5-dialkyl-5-nitrotetrahydro-1,3-oxazines:



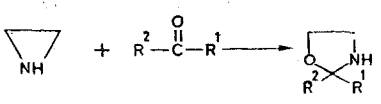
Substittuted tetrahydro-1,3-oxazines can be synthesized by the reaction of olefins, formaldehyde, and hydrohalides of ammonia and primary amines [37, 38]. In addition to tetrahydro-1,3-oxazines, bis(tetrahydro-1,3-oxazino)methanes and formaldimines are obtained in this reaction.



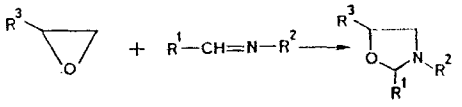
R^1-R^4 = H, alkyl, aryl, etc.; R^5 = H, alkyl, cycloalkyl, aryl, OH, etc.

A series of 1-alkyl-6-aryltetrahydro-1,3-oxazines were similarly obtained along with 1-alkyl-4-aryl-4-piperidinols [39, 40]. Similarly [41], the reaction of diaryl olefins, formaldehyde, and ammonium chloride leads to 6,6-diaryltetrahydro-1,3-oxazines.

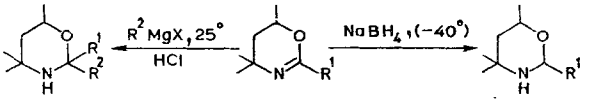
2-Substituted oxazolidines are formed in 55-57% yields in the reaction of ethyleneimine with aldehydes or ketones [42]:



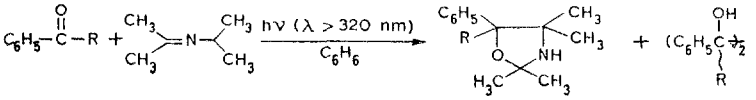
The addition of aliphatic epoxides to Schiff bases at 10-20°C in CCl_4 leads to substituted oxazolidines [43] in 8-10% yields; the yields can be improved to 20-50% by the addition of catalytic amounts of BF_3 or $SnCl_4$.



The reduction of 5,6-dihydro-4H-1,3-oxazines under mild conditions leads to tetrahydro-1,3-oxazines [44, 45], while their reaction with Grignard reagents makes it possible to synthesize 2-substituted tetrahydro-1,3-oxazines [44]:



The possibility of the photochemical synthesis of oxazolidines from aromatic ketones and aliphatic imines [46] in 40-45% yields has been demonstrated (for two subjects):

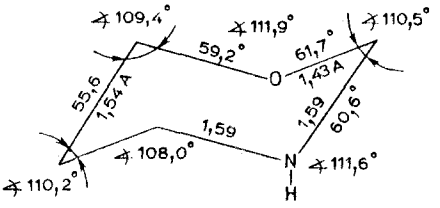


2. Stereochemistry of 1,3-Oxazacycloalkanes

In contrast to 1,3-dioxa-, 1,3-dithia-, and 1,3-oxathiacyclanes, the presence of a nitrogen atom in 1,3-oxazacyclanes is responsible for their greater conformational diversity because of the possibility of inversion of the pyramid of bonds at the nitrogen atom.

2.1. Tetrahydro-1,3-oxazines. Methods such as measurement of the dipole moments [47-51], IR spectroscopy [47], ^{1}H NMR spectroscopy [23, 52-65], and ^{13}C NMR spectroscopy [23, 65] have been used to investigate the three-dimensional structures and conformational behavior of these compounds. It has been shown by the dipole moment method and NMR spectroscopy that the chair form is the principal conformation of tetrahydro-1,3-oxazines.

The geometry of the tetrahydro-1,3-oxazine ring calculated by means of minimization of the strain energy [66] is presented below:



Primarily the spin–spin coupling constants of the ^{3}J vicinal type have been used in the determination of the configurations and preferred conformations of tetrahydro-1,3-oxazines [23, 53, 54, 58, 59]. The constants of this type, which range from 9.5 to 13.0 Hz, belong to constants of the $^3J_{aa}$ form, whereas values ranging from 2.2 to 4.0 Hz are typical for constants of the $^3J_{ae}$ form. Ring inversion is retarded at −80 to −90°C, and the 2-H protons couple with N–H with SSCC $^3J_{2a3a}$ = 13.1 Hz and $^3J_{2e3a}$ = 2.9 Hz [63]. The magnitude of the geminal $^2J_{HH}$ constant in the N–CH_2–O fragment depends on the orientation of the unshared pair of electrons of the nitrogen atom [52-54]. The ^{2}J constant for the chair conformation is −7.7 Hz in the tetrahydro-1,3-oxazine system for the methylene group located between the oxygen atom and the nitrogen atom with an axial pair, whereas ^2J = −10.5 Hz in the case of an equatorial orientation of the orbital of the unshared pair of the nitrogen atom [54].

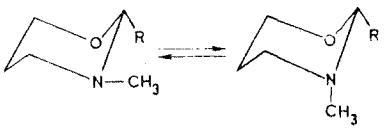
The relative changes in the nuclear magnetic shielding constants ($\Delta\sigma$) of the geminal protons for various preferred conformations of the oxazine ring were estimated and the effect of an aromatic solvent on the proton chemical shifts was studied in [59] in order to obtain additional stereochemical information. It was shown that the $\Delta\delta_{2a2e}$ value is greater in the case of an equatorial orientation of the N–Me substituent than in the case of an axial orientation. A chair conformation was confirmed for the overwhelming majority of the investigated compounds.

The chemical shifts in the ^{13}C NMR spectra of substituted tetrahydro-1,3-oxazines depend substantially on the character and orientation of the substituents in the ring and attached to the nitrogen atom [23, 65].

2.2. Barriers to Inversion in Tetrahydro-1,3-oxazines. The activation parameters for ring inversion were determined in [67] by ^{1}H NMR spectroscopy in the case of 3-methyl- and 3,6,6-trimethyltetrahydro-1,3-oxazines. It was shown that $\Delta G^{\neq} \approx 10$ kcal/mole, which is close to the $\Delta G^{\neq}$ values for 1,3-dioxane, cyclohexane, and 1,3-dithiane.

The conformational behavior of 3-alkyltetrahydro-1,3-oxazines has been studied by the dipole moment method [48] and ^{1}H NMR spectroscopy [56]. The results of measurements by means of both methods showed that the percentage of the isomer with an equatorial orientation of N–R increases from 58% (R = CH_3) to 100% (R = tert-C_4H_9) as the size of the substituent attached to the nitrogen atom increases. The barrier to inversion [48, 56] ranges from 0.2 to 1.1 kcal/mole.

The inversion of the pyramidal nitrogen atom in 2-alkyl-3-methyl-tetrahydro-1,3-oxanes was studied in [57]:

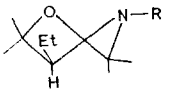


Measurement of the ^{1}H NMR spectra of tetrahydro-1,3-oxazines at 34°C indicates rapid inversion of the nitrogen atom. (The signal of the N—Me groups shows up in the form of a singlet.) Rapid ring inversion (the 2-H signal is a singlet) is also observed in the spectrum of 3-methyl-1,3-tetrahydrooxazine. Ring inversion is retarded at —80°C, and the signal of the protons of the CH_2 group shows up in the form of a quartet. Inversion of the nitrogen atom is retarded only at —130 to —140°C, and the N—CH_3 protons give two separate signals corresponding to both conformations [57]. The results of determinations of the conformational equilibrium of 2-alkyl-3-methyltetrahydro-1,3-oxazines by ^{1}H NMR spectroscopy are in good agreement with the results of determinations by the dipole moment method for these compounds [57]. It was shown that the percentage of the axial conformer increases with the size of the 2-alkyl substituent in the order CH_3, C_2H_5, iso-C_3H_7, tert-C_4H_9.

2.3. Stereochemistry of 1,3-Oxazolidines. As in the case of their heterocyclic analogs (1,3-dioxolanes and 1,3-dithiolanes), two conformations, viz., "envelope" and "half-chair," are possible for 1,3-oxazolidines. However, it has been shown in a number of studies [68-70] that the "envelope" conformation is preferred.

It has been shown by *ab initio* calculations [68] that of the five possible "envelope" conformations for unsubstituted 1,3-oxazolidines, the conformation with the nitrogen atom jutting out above the plane of the ring has the minimal energy, while the conformations with the C_5, C_4, O, and C_2 atoms at the apexes of the "flap" have energies of 1.9, 3.8, 4.1, and 4.3 kcal/mole, respectively.

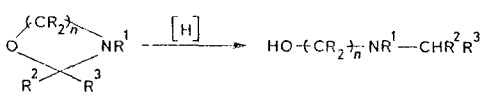
According to ^{1}H NMR data, the most preferred conformation in series of substituted 4-ethyloxazolidines [69] is the conformation with minimal eclipsing with respect to the C—C bond, and the N—Me and N—Et groups occupy a pseudoequatorial orientation. The dihedral angles between the C_4—H and C_5—H bonds are ~30 and 150°:



The structure of a number of N-phenyl- and N-alkyloxazolidines (R = C_2H_5, C_3H_7, iso-C_4H_9, and cyclo-C_6H_{11}) and their 2-substituted derivatives has been studied by ^{1}H and ^{13}C NMR spectroscopy [70]. 2-Unsubstituted oxazolidines exist in a state of rapid pseudorotation at 20°C. The introduction of an alkyl or aryl substituent in the 2 position leads to an increase in the nonequivalence of all of the protons attached to C_4 and C_5, as a consequence of which a complex multiplet of four protons at 2.8-4.0 ppm is observed in the spectra [70].

3. Heterolytic Reactions of 1,3-Oxazacycloalkanes

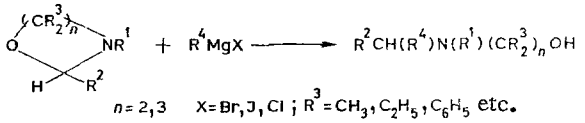
3.1. Reactions That Take Place with Ring Opening. Under the influence of reducing agents 1,3-oxazacycloalkanes are converted to amino alcohols with the same number of carbon atoms:



When there are no substituents attached to the nitrogen atom, the cyclization and reduction process can be repeated to give N,N-dialkyl derivatives in which the two alkyl groups can be both the same or different. Variants of the reduction of 1,3-oxazocycloalkanes include reduction with lithium aluminum hydride in anhydrous ether or tetrahydrofuran [24, 71] and with sodium borohydride in methanol [24, 44], catalytic hydrogenation on Raney nickel at

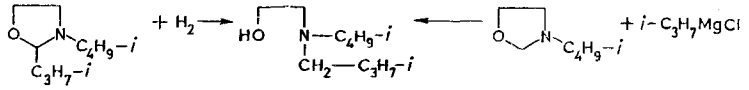
100°C and 70 atm [72-75], on palladium or charcoal [76], and on an Adams catalyst [77], and reduction with an aluminum [78] or sodium [79] amalgam. Formic acid can be used as the reducing agent. Thus the reduction of N-methyl-1,3-oxazolidines by means of HCOOH formed by heating $5HCOOH \cdot 2(CH_3)_3N$ was investigated in [77]. N,N-Dimethylaminoethanol is formed as a result of the reaction, and CO_2 is evolved. The authors proposed a mechanism that specifies nucleophilic substitution of the ether group by formate ion in the first step, as a consequence of which an unstable ester, which is rapidly decarboxylated to give methylaminoethanol, is formed.

A special case of reduction (or reductive alkylation) is the reaction of 1,3-oxazacycloalkanes with organomagnesium compounds, as a result of which opening of the ring at the C_2—O bond also occurs [76, 80, 81]. The yield of the amino alcohol in some cases reaches 80%.

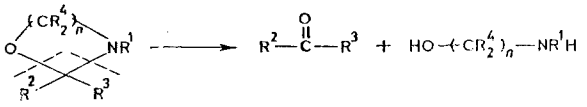


$n = 2,3$ X=Br, J, Cl; $R^3 = CH_3, C_2H_5, C_6H_5$ etc.

The same bond cleavage was also observed in the reduction of 1,3-oxazacyclopentanes with hydrogen and in their reaction with Grignard reagents [76]:

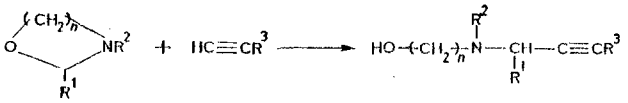


1,3-Oxazacycloalkanes undergo both alkaline and acidic hydrolysis to give the starting amino alcohol and the carbonyl compound [6, 13, 72, 82]. Individual representatives are hydrolyzed even in the absence of acids and alkalies; this is true for ethanolamine and cyclopentanone derivatives, for example [72].

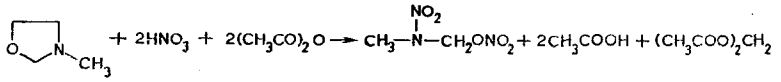


The kinetics of the hydrolysis of 2-aryl-3-ethyloxazolidines in concentrated HCl and NaCl solutions at 30°C were studied in [82] by a spectrophotometric method. At high pH values the rate constants for the formation of aldehydes do not depend on the pH and correlate well with the Hammett σ constants. Two reactions, viz., a fast reaction involving the formation of an intermediate and a slow reaction involving the hydrolysis of the latter to give the corresponding aldehyde, take place in solutions with moderate HCl concentrations. The step involving the formation of the intermediate is catalyzed in buffer solutions (formate, acetate, and imidazole solutions). The mechanism of the hydrolysis consists in slow protonation of the oxygen atom with cleavage of the C—O bond [82].

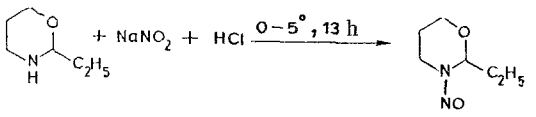
Opening of the 1,3-oxazacycloalkane ring by monosubstituted acetylenes to give acetylenic amino alcohols has been described [83, 84]. In the case of tetrahydro-1,3-oxazines the reaction is carried out in dioxane in the presence of Cu_2Cl_2 at room temperature and 3-5 atm [84].



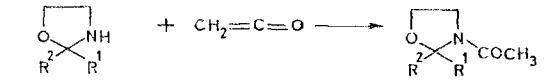
The nitration of 3-methyloxazolidine and bisoxazolidine with nitric acid in acetic anhydride proceeds with opening of the oxazolidine ring [85]:



3.2. Reactions That Take Place without Ring Opening. Treatment of 2-ethyltetrahydro-1,3-oxazine with sodium nitrite in concentrated HCl leads to 2-ethyl-3-nitrosotetrahydro-1,3-oxazine [86]:

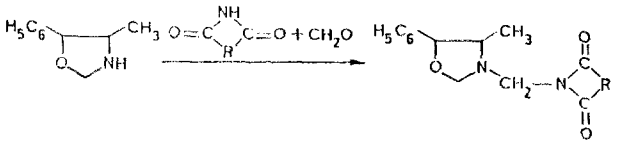


N-Acetyloxazolidines were obtained in 60-80% yields by acetylation of oxazolidines with ketene [87]:

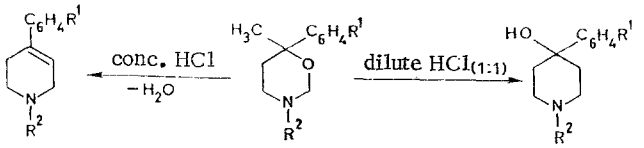


$R^1 = H, CH_3, C_2H_5, C_6H_5, m\text{-}NO_2C_6H_4, o\text{-}HOC_6H_4$; $R^2 = H, CH_3$

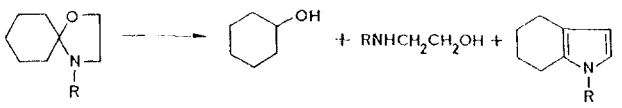
4,5-Disubstituted oxazolidines were converted to 4,5-disubstituted 3-imidomethyloxazolidines, which display diversified biological activity [88]:



The possibility of acidic rearrangement of tetrahydro-1,3-oxazines in the presence of hydrochloric acid is examined in studies by Schmidle and Mansfield [39, 40]. It is shown that tetrahydro-1,3-oxazines that have an aromatic substituent in the 6 position undergo the reaction

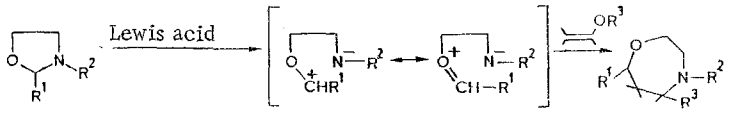


When cyclohexanespiro-2-(1-alkyloxazolidines) are heated with traces of potassium tert-butoxide, they undergo disproportionation to give cyclohexanol, an amino alcohol, and a 1-alkyl-4,5,6,7-tetrahydroindole [89]:



The polymerization of 3-phenyloxazolidines in the presence of acidic catalysts (for example, $PhNMe_2 \cdot HCl$) leads to polyether imines with low molecular weights [90]. 3-Alkyloxazolidines are not polymerized under these conditions. If the oxazolidines have chloromethylene groups, polymerization takes place readily even in the absence of a catalyst.

1,3-Oxazolidines undergo 1,5-dipolar cycloaddition in the presence of Lewis acids with enol ethers, dihydrofuran, dihydropyran, and cyclohexane [sic] to give the corresponding perhydro-1,4-oxazepines in 60-75% yields [91-93].

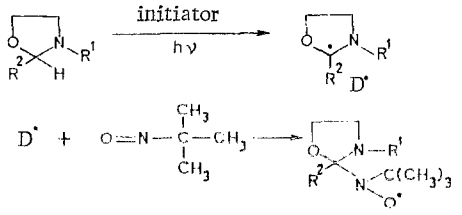


$R^1, R^3 = alkyl, C_6H_5$; $R^2 = Alk$

4. Liquid-Phase Homolytic Transformations of 1,3-Oxazacycloalkanes

1,3-Oxaza-2-cyclopentyl radicals are formed selectively from oxazolidines at 20°C under the influence of free radicals (RO•). 2-Methyl-2-nitrosopropane was used to record them by

EPR spectroscopy. Signals of nitroxyl radicals that contain a 1,3-oxaza-2-cyclopentyl residue are recorded in the EPR spectra [94-96].



Thus oxazolidines behave like 1,3-dioxa-, 1,3-oxathia-, and 1,3-dithiacyclanes [94-96].

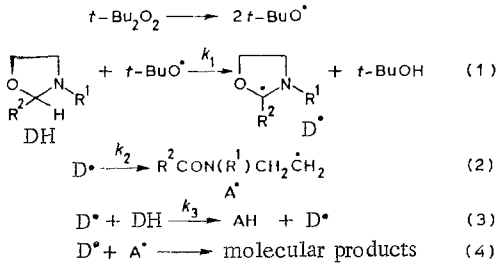
Signals of heterocyclic radicals ($D^{\bullet}$) were observed in the spectra when oxazolidines (DH) were treated with hydroxyl radicals in the cell of the EPR spectrometer [96-98]:

$$DH + HO^{\cdot} \rightarrow D^{\cdot} + H_2O.$$

The presence of a bulky alkyl substituent attached to the nitrogen atom gives rise to the development of radicals with an unpaired electron on the alkyl substituent in addition to 1,3-oxaza-2-cyclopentyl radicals.

It has been established that oxazolidines display higher reactivities in the detachment of a hydrogen atom by tert-butoxyl radicals than their oxygen-containing analogs [64, 96]. The increased activity of oxazolidines as compared with 1,3-dioxanes and 1,3-dioxolanes is explained [64, 96] by the more favorable combination of polar factors in the transition state of the detachment of a hydrogen atom by the electrophilic tert-$BuO^{\bullet}$ radical.

In the case of thermal (120-150°C) decomposition of tert-butyl peroxide in 1,3-oxazacyclopentanes the latter undergo isomerization to N,N-disubstituted amides of carboxylic acids [64, 96, 99-104]. The initial rate of formation of the amide depends linearly on the concentration of the substrate and is proportional to the concentration of the initiator to the 0.5 power; this is characteristic for chain unbranched processes with quadratic chain termination. On the basis of these results the following mechanism for the isomerization of oxazolidines was proposed in [100]:



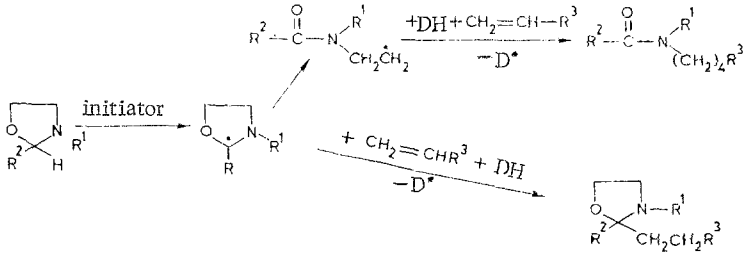
The tert-butoxyl radicals that are generated in the thermal decomposition of tert-butyl peroxide selectively attack the weakest C-H bond in the 2 position of the heteroring, as a result of which tert-butyl alcohol and a 1,3-oxaza-2-cyclopentyl radical ($D^{\bullet}$) are formed [reaction (1)]. Under the reaction conditions (120-150°C) the radical undergoes monomolecular rearrangement to linear amidoalkyl radical $A^{\bullet}$ [Reaction (2)]. Cyclic radical $D^{\bullet}$ is regenerated in the reaction of amidoalkyl radicals $A^{\bullet}$ with the substrate [Reaction (3)], and isomeric amide AH is formed. It follows from the results of kinetic studies that one molecule of the substrate participates in the rate-determining step of the process. Thus the rate-determining step in the isomerization is detachment of a hydrogen atom from the substrate by the rearranged β-amidoalkyl radical. The rate of the process is not determined by the step involving monomolecular rearrangement of cyclic radical $D^{\bullet}$ to linear radical $A^{\bullet}$, and chain termination occurs mainly at the amidoalkyl radicals.

The reactivities of oxazolidines are inferior by a factor of two to three to the reactivities in the isomerization of 1,3-dioxolanes [96, 105]. In a study of the relative activity of oxazolidines in free-radical isomerization by the method of competitive reactions it was established [64, 103] that the nature and size of the substituent attached to the nitrogen atom has only a slight effect on the reactivities of oxazolidines; however, the activity

increases somewhat when the length of the alkyl substituent is increased significantly. The introduction of an alkyl substituent in the 2 position of the heteroring increases (with allowance for the number of active hydrogen atoms) the activity of the oxazolidine. A methyl group introduced in the 5 position of the heteroring decreases its activity, since less active secondary β-amidoalkyl radicals are involved in the rate-determining step. The reactivity decreases on passing from oxazolidines to tetrahydro-1,3-oxazines.

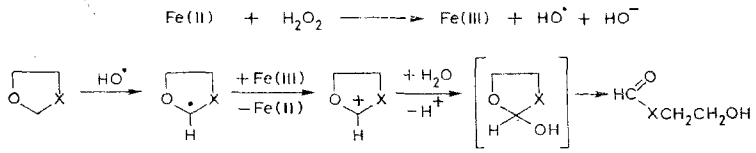
During a study of the effect of high pressure on the homolytic isomerization of oxazolidines it was established that when the pressure is increased to 10,000 atm, the rate of formation of the amides and the length of the chain decrease sharply [106]. This is a consequence of the fact that the monomolecular rearrangement of cyclic D° radicals to linear A° radicals is characterized by an unusually large positive volume effect of activation. As a result, a significant number of D° radicals vanish in reactions involving termination prior to rearrangement to give linear β-amidoalkyl A° radicals, and this is responsible for the sharp decrease in the rate of formation of the amide.

Oxazolidines in the liquid phase in the presence of free-radical initiators add homolytically to terminal olefins to give 2-n-alkyl-1,3-oxazacyclopentanes and N,N-disubstituted amides of carboxylic acids [64, 107, 108].



The former are the principal products at 20-50°C. When the temperature is raised to 150°C, the yields of products with linear structures increase and become commensurable or predominant as compared with the yields of adducts with cyclic structures. As the length of the hydrocarbon chain of the monomer is increased, its activity decreases, as a result of which the yields of adducts with linear and cyclic structures decrease, while the yield of the isomeric amide increases. As the pressure is increased from 1 atm to 10,000 atm in the homolytic addition of 3-propyloxazolidine to 1-hexene, the selectivity of the formation of 3-propyl-2-hexyloxazolidine as compared with N-propyl-N-octylformamide increases by a factor of two; this is evidently associated with a decrease in the rate of monomolecular rearrangement of 3-propyl-1,3-oxaza-2-cyclopentyl radicals as the pressure is increased [64, 107, 109].

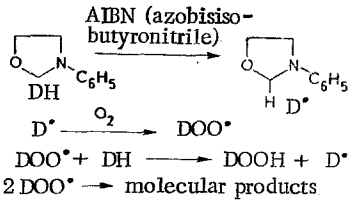
In [110, 111] it was shown that oxazolidines and 1,3-dioxolanes in aqueous media under the influence of the Fe(II) + H_2O_2 + Fe(III) redox system are converted to N(β-hydroxyethyl)-amides and ethylene glycol monoether, respectively. Their formation is represented by the following scheme:



The reaction proceeds through a step involving one-electron oxidation of 1,3-oxaheterocycloalkyl radicals to the corresponding carbonium ions, which react with the medium (H_2O) to give labile 2-hydroxyl-1,3-oxaheterocycloalkanes. The latter undergo monomolecular conversion to the corresponding hydroxyethylamides and ethylene glycol monoethers.

The molecular oxygen-initiated oxidation of 3-phenyloxazolidine proceeds via a radical-chain mechanism with quadratic chain termination [112]: (See top, following page.)

Peroxide radicals primarily attack the C_2—H bond adjacent to the two heteroatoms. The activity of 3-phenyloxazolidine in oxidation with molecular oxygen is higher than the activities of 1,3-dioxanes and 1,3-dioxolanes [113] and is close to the activities of tertiary aliphatic amines [114-116].



5. Practical Application of 1,3-Oxazolidines and Tetrahydro-1,3-oxazines

1,3-Oxazolidines and tetrahydro-1,3-oxazines, as well as their derivatives, display diversified biological and physiological activity and have valuable technical properties.

5-(Indenyl-7-hydroxymethyl)oxazolidines are intermediates for the preparation of medicinals, and some of them can be used for the treatment of arrhythmia, stenocardia, and diseases of the coronary arteries [117]. Both 2- and 3-aralkyltetrahydro-1,3-oxazines have bronchodilating and sympathomimetic activity [30]. A number of 3-alkyl- and 5-alkyl-5-nitrotetrahydro-1,3-oxazines [35] and some substituted oxazolidines [118, 119] display antitumorigenic activity.

Data on the testing of a large number of substituted oxazolidines as herbicides are presented in [120-123].

Some 1,3-oxazolidines that contain polyhydroxymethylene groups attached to the nitrogen atom can be used as biocidal compositions in surface coatings [124-126]. N-Nitroalkyloxazolidines can be used as bactericides [127].

4,5-Disubstituted 3-imidomethyloxazolidines [88], 5-naphthyloxazolidines [128], and 3,4,5-substituted oxazolidines (with C_1—C_{18}-alkyl, hydroxyalkyl, and aminoalkyl substituents) [129] also display a broad spectrum of biological actiivty (antiprotozoal, antibacterial, fungicidal, etc.).

The use of oxazolidines for the extraction of aromatic hydrocarbons from mixtures with nonaromatic hydrocarbons has been reported [130, 131]. Substituted oxazolidines are effective stabilizers of polymers against the action of UV rays [132].

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