REACTIONS OF OXAZOLES (REVIEW)

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The reactions of oxazoles involving 1,2- and 1,4-cycloaddition, aromatic substitution, and nucleophilic addition leading to cleavage of the heterocyclic ring are examined.

Fifteen years have elapsed since the publication in Russian of Cornforth's review [1] on the chemistry of oxazoles, and many new interesting facts that require correlation have accumulated in this field in recent years.

A new review [2] on the chemistry of oxazoles appeared recently, but this publication is rather inaccessible to a large number of Soviet readers, the literature cited in it is incomplete, and the correlations themselves were made from different assumptions. However, we felt that it was not necessary to consider the diene properties of oxazoles in the present review, inasmuch as this problem was the subject of a special examination in other papers [3-5].

BASICITIES

Despite the fact that calculations show considerable excess electron density on the nitrogen atom in the oxazole molecule [6], which is almost comparable to the density calculated for pyridine [7], oxazoles are weak bases. They are less basic by a factor of 10^6 than imidazoles and less basic by a factor of 10^4 than thiazoles (see [8] for the isolation of oxazoles by means of a cation-exchange resin). The pK_a value of unsubstituted oxazole is 0.8[9] as compared with 5.17 for pyridine. The introduction of methyl groups increases the basicity: the pK_a value of 2,45-trimethyloxazole is 3.56. In this case the 2-CH_3 group gives rise to an anomalously high pK_a value ($\sim$1.6 units), whereas the 4-CH_3 group (which is also adjacent to the site of protonation) gives rise to a smaller effect (0.6), which is comparable to that for 5-CH_3.

Oxazoles that contain an electron-acceptor substituent in the 4 position have pK_a values that are close to the value for the corresponding 5-isomer, and this is evidently explained by stabilization of the cation by a hydrogen bond [9]. For oxazolecarboxylic acids the zwitterion form is not the preferred form, in contrast to, for example, imidazole derivatives; this also is explained by the low basicity of the heteroring [10]. The basicities of aminooxazoles are close to the basicities of aromatic amines, and the basicities of the 2-isomers are close to the basicities of compounds that contain an —O—C(=N—)N< grouping [11].

Inasmuch as oxazoles are weak bases they usually do not form stable salts [1]. However, an oxazole picrate [12] and picrates, hydrochlorides, andy hydrobromides of 2,5-diaryloxazoles [13-15] have been described . In addition to complexes with mercuric chloride, which are ordinarily used for the purification of liquid oxazoles [11], analogous complexes with copper halides are also known [16].

Despite the low basicity of the nitrogen atom of the oxazole ring, oxazole N-oxides are known; however, they are obtained by reaction of aromatic aldehydes with oximes [17-20] or by cyclization of N-nitrones [14] rather than by direct oxidation. The hydrochlorides of

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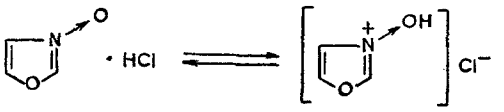
the N-oxides, which apparently exist in two forms or preferably in an oxygen-protonated form [17], are more stable:



We note that N-oxide I, with oxygen attached only to the nitrogen atom of the pyridyl fragment, is formed by treatment of 2-(4-pyridyl)oxazoles with peracetic acid [21].

I

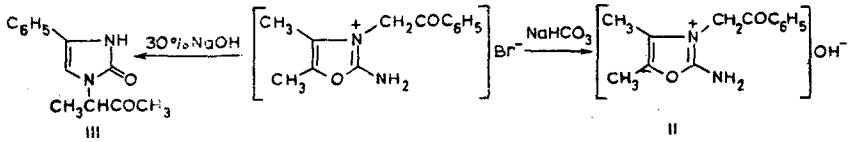
The hydrochlorides of aminooxazoles are more stable [22-31]. In the case of 2- and 5-aminooxazoles, primarily the ring nitrogen atom is protonated [22,32,33] and alkylated [34, 35]. A complex of two molecules of 5-aminooxazole with zinc chloride, in which complexing at the ring nitrogen atom is also assumed [36], has also been isolated. However, protonation in chlorosulfonic acid, in contrast to trifluoroacetic acid and hydrochloric acids, proceeds at the amino group [37,38]. Acylation with anhydrides and acid chlorides also takes place at the exocyclic nitrogen atom to give mono- and diacylaminooxazoles [25,36,39,40].

Despite their low basicities, oxazoles that do not contain an amino group nevertheless can be converted to quaternary salts [34,41,42]. In a number of cases cyclization of N-aryl (alkyl)-N-acylamino ketones or amino acid derivatives [38,43-46] rather than direct alkylation, is used for the synthesis of such salts.

CLEAVAGE OF THE OXAZOLE RING

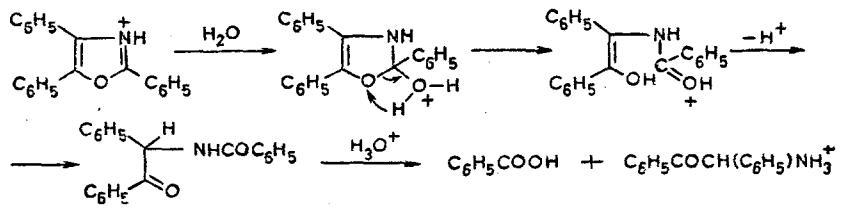
Hydrolysis and Some Reaction with Nucleopholic Agents

The oxazole ring of quaternary salts of oxazoles is opened in alkaline media and even under the influence of traces of water to give N-substituted N-acylamino ketones [38-44]. Closing to an imidazole ring occurs in the presence of ammonia or in the case of 2-amino derivatives [43,47], but careful treatment of these salts with sodium bicarbonate solution makes it possible to isolate the corresponding hydroxides (II), which are converted to imidazolones III on recrystallization from aqueous alcohol [35]:



III II

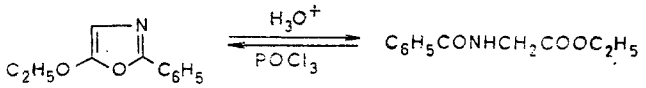
This conversion is a special case of solvolysis of the oxazole ring, which proceeds readily during attack by a nucleophilic particle on the C_2 atom because of the larger deficit of electron density on this atom and the increased adjacency to the charged nitrogen atom. The acid hydrolysis of the free bases proceeds similarly. Thus heating 2,4,5-triphenyloxazole with hydrobromic acid gives ω-phenyl-ω-aminoacetophenone hydrobromide and benzoic acid [48].



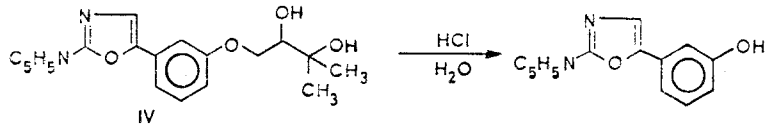
2,4-Diphenyl-5-benzylideneaminooxazole undergoes cleavage on heating with sulfuric acid to give benzaldehyde, ammonia, and α-N-benzamidophenylacetic acid [49] (also see [50]).

Esters of oxazole-4-carboxylic acids are hydrolyzed by hydrochloric acid via the same scheme, i.e., by initial attack of the hydroxyl group in the 2 position and formation of esters of α-amino-β-keto acids [51]. Simultaneous decarboxylation occurs during the acid hydrolysis of (5-oxazolyl) acetic acid derivatives, and hydrochlorides of α-amino ketones are obtained [52,53].

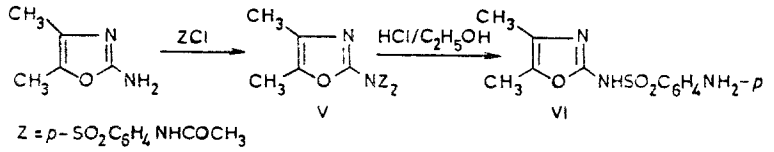
2-Alkoxyoxazoles are also readily hydrolyzed to give 2-oxazolones [54,55], whereas 5-alkoxyoxazoles undergo subsequent cleavage of the oxazolone ring to give esters of acylamino acids [56], which serve as the starting compounds for the synthesis of these oxazoles.



The stability of diaryloxazoles, particularly the 2,5-isomers, with respect to the action of strong acids has also been previously noted [11]. Thus only cleavage of the alkoxy groups occurs when alkaloid IV, isolated from *Halfordia scleroxyla*, is refluxed with concentrated hydrochloridc acid, and the oxazole ring is not involved [57].

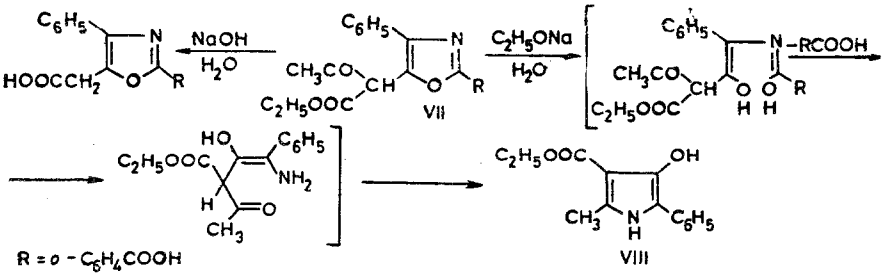


The action of milder agents, for example, a solution of hydrogen chloride in alcohol, does not bring about ring cleavage [58]. This sort of treatment of V leads only to removal of one sulfonyl grouping and the acetyl protective group (VI).



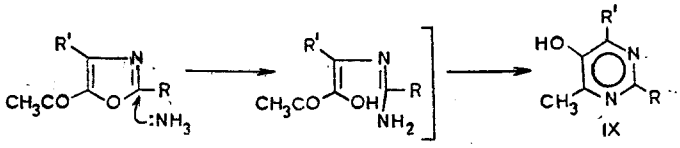
Compounds of this type have been patented as antibacterial agents with prolonged activity. They readily undergo cleavage in the human organism [59].

The nonquaternized oxazole ring is more stable with respect to the action of alkalis, and lower alkyloxazoles are, as a rule, stored and distilled over fused alkalis. For example, treatment of 5-methyl-4-(0-formamidophenyl) oxazole with alkali leads only to hydrolysis of the amide group [60], and only acid cleavage in the acetoacetic ester residue occurs when VII is heated with concentrated sodium hydroxide solution. However, when the same oxazole is heated in the presence of sodium ethoxide, pyrrole VIII is formed via a scheme that evidently included attack by the nucleophilic particle at the 2 position of the oxazole ring [50].



The action of ammonium hydroxide and aqueous solutions of primary amines and hydrazines on oxazoles with electron-acceptor substituents also leads to ring cleavage to give the corresponding dicarbimides or hydrazides or products of their subsequent interaction [53]. Like 2-acylfurans, which give 3-hydroxypyridine derivatives under the influence of ammonia or

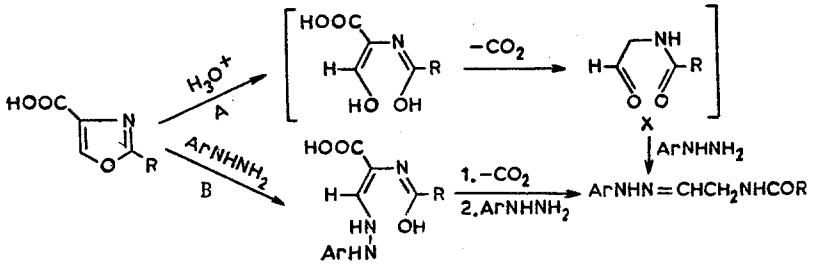
ammonium salts, 5-acetyloxazoles are converted under these conditions to 5-hydroxypyrimidines (IX); in this case also the nucleophile attacks the C_2 atom of the oxazole ring [61].



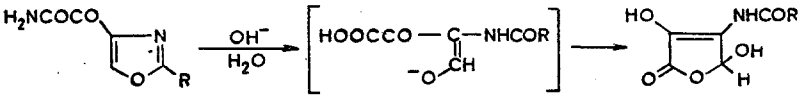
Just as in the case of treatment of 2,5-disubstituted 4-cyanooxazoles with hydrazine hydrate, tetrazine derivatives [62] were isolated instead of the expected amidrazones. However, 2-, 4-, and 5-carbalkoxyoxazoles are more stable and react with hydrazine hydrate [63-67], ammonia, or primary amines [68-70] to give the corresponding hydrazides or amides.

Oxazoles are particularly unstable with respect to the action of 2,4-dinitrophenylhydrazine. In all of the investigated aryl- and alkyloxazoles, the C_2 atom was attacked, and, for example α-hydroxyacetophenone hydrazone, which was oxidized to the corresponding osazone with excess dinitrophenylhydrazine [71], was obtained from 2-methyl-4-phenyloxazole. However, inasmuch as hydrochloric acid solutions of the reagents are used in these reactions, one cannot exclude the possibility that acid hydrolysis via the scheme described above occurs initially in this case with subsequent reaction of the hydrazine with the resulting carbonyl groups of the decomposition products.

At the same time, heating 2-benzyloxazole-4-carboxylic acid under these conditions leads to phenylacetamidoacetaldehyde hydrazone, the formation of which can be explained only by nucleophilic attack at the 5 position. The structures of the decomposition products were proved quite rigorously, inasmuch as a hydrazone identical to the hydrazone of methyl penaldate [72] was obtained in the case of the 4-carbomethoxy isomer. This sort of reaction pathway can be explained either by the electron-acceptor properties of the carbomethoxy group, which reduces the electron density on the C_5 atom of the oxazole ring, or by initial acid hydrolysis to give X.

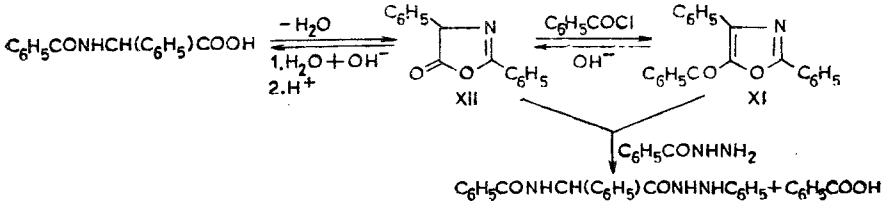


Pathway A is evidently more likely, inasmuch as only hydrolysis of the ester grouping occurs in the reaction of 4-carbethoxyoxazoles with aqueous and even alcoholic alkalis, which are stronger nucleophilic agents [36,73-76], whereas the oxazole ring, in contrast to the situation in acid hydrolysis, is not involved. The isolation of oxazolylacetic acids from their esters is carried out similarly [77-79]. Only-4-oxazolylglyoxylic acid derivatives, which are stable in concentrated hydrochloric acid but unstable when they are allowed to stand with aqueous alkali [80], evidently constitute exceptions to this, but the C_2 atom of the oxazole ring is also attacked in this case.

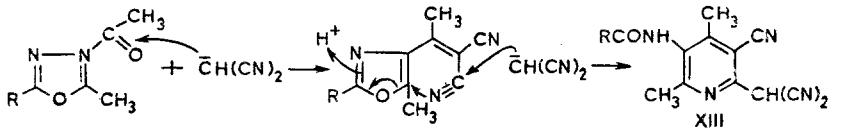


The 5 position is usually the most reactive with respect to nucleophilic agents only if there is an acyloxy group in this position. The reaction then probably proceeds by means of initial hydrolysis of the acyloxy group to give a 5-oxazolone [54,55], which subsequently is readily opened with cleavage of the C_5-O bond [81]. This sort of reaction is observed, for example, when XI is treated with 0.5 M alkali solution, as a result of which N-benzoyl-

α-phenylglycine, i.e., the starting compound for the synthesis of oxazole XI and oxazolone XII [82], is formed (similarly, see [56]).

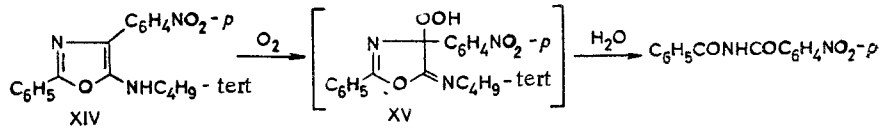


An unusual transformation, which includes nucleophilic attack in the 5 position, was observed in the reaction of 4- and 5-acetyloxazoles with the malononitrile anion. It is assumed [83] that the carbon atom of the acetyl group is attacked initially and that this is followed by reaction with the cyano group or directly with the malononitrile anion through the 5 position of the oxazole ring; in the case of the 4 isomer this leads to the formation of pyridine derivatives XIII, whereas it leads to substituted cyclopentadienes in the case of the 5 isomer



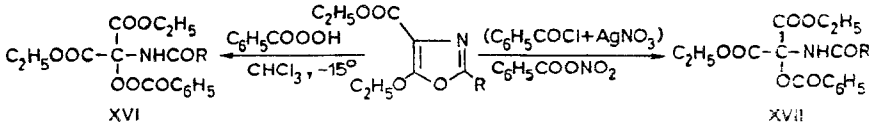
Oxidation

Oxazoles are readily oxidized [11]. The mechanism of the oxidation has not been ascertained, but, judging from the decomposition products, the C_4 atom is attacked first with cleavage of the C—C bond. Thus, for example, 4-nitrodibenzamide was isolated in the oxidation of oxazole XIV with air oxygen [84].



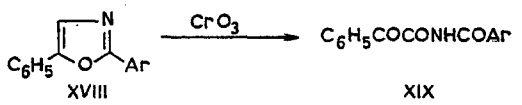
The authors feel that in this case autoxidation occurs under alkaline conditions to give hydroperoxide XV. The analogous formation of hydroperoxides is known [85] when solutions of 2-aminoindole hydrochlorides are made alkaline [86].

An amide of benzoylperoxymalonic acid ester (XVI) was isolated as the chief reaction product when 4-carbethoxy-5-ethoxyoxazole was treated with perbenzoic acid, whereas benzoxymalonic acid ester XVII was the chief product when the same oxazole was treated with benzoyl nitrate [87].



Similarly, benzoin was isolated when 2-(2-quinolyl)-4,5-diphenyloxazole was refluxed with sulfuric acid [88].

As already noted above, the introduction of aryl substituents in the 2 and 5 positions leads to an increase in the stability of the oxazole ring. For example, perbenzoic acid does not react with substances of this type, but chromic anhydride oxidizes them to aroylamides of arylglyoxylic acids (XIX). The introduction of a nitro group in the para position of the 2-phenyl substituent makes it possible to isolate the corresponding acid [89].

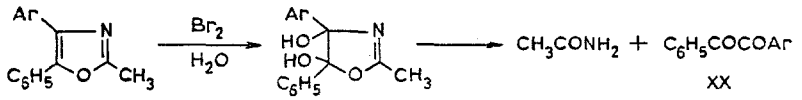


XVIII XIX

Oxidation with potassium permanganate leads to complete cleavage of the oxazole ring even in the case of 2,5-diaryl derivatives [89]. Thus anisic and veratric acids were isolated when the alkaloid annulonine [2-(trans-3,5-dimethoxystyryl)-5-(4-methoxyphenyl)oxazole] was oxidized. Similarly, oxidation of 2- (3-pyridyl)-5-phenyloxazole gave nicotinamide, which was also detected in the products of oxidation of alkaloid IV [57]. Thus the oxazole ring is oxidized much more rapidly and easily than the pyridine or benzene ring. Oxidation of the isomeric 2- (3-pyridyl)- and 2-(4-pyridyl)oxazoles with potassium permanganate in alkaline media gives the corresponding pyridinecarboxylic acids, whereas oxidation with 1% permanganate solution in acidic media gives their amides [91].

Only the side chains are oxidized when milder agents are used. For example, 4-oxazolylglyoxal was isolated in quantitative yield when 4-acetyloxazole was treated with an aqueous dioxane solution of SeO_2 [92]. The oxazole ring also is not oxidized by sodium periodate, and this has been used for the establishment of the structure of an oxazole containing a carbohydrate residue in the 4 position [93].

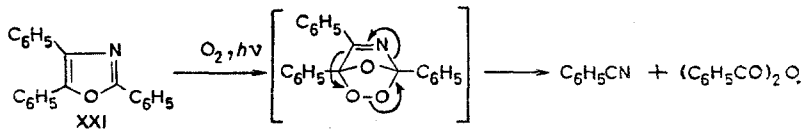
The almost quantitative oxidation with bromine in aqueous acetic acid is of great value for establishment of the structures of di- and triaryloxazoles [94,95]. We note that the 2-CH_3 group is split out in the form of acetamide (but it is not oxidized), and cleavage of the C—C bond gives benzil XX. The reaction proceeds via the scheme [96]



XX

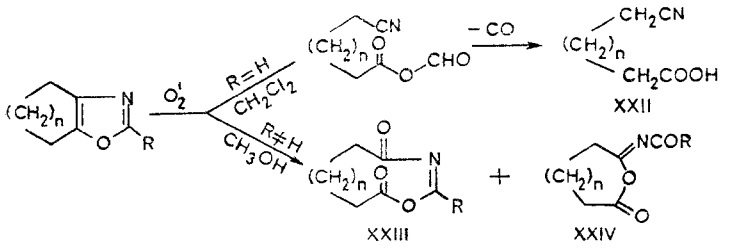
This scheme is confirmed by the fact that the reaction practically does not take place in glacial acetic acid (the oxazole is recovered, and hydrobromic acid is formed, i.e., the oxazole serves as a bromine carrier); the amount of benzil XX increases when water is added to the reaction mixture, and oxidation is retarded by electron-acceptor substituents in the oxazole ring and accelerated by electron-donor substituents. Like bromine, chlorine in concentrated hydrochloric acid, N-bromosuccinimide in acetic acid, tert-butyl hypochloride in water, nitrous acid, iron or copper nitrate, and chloramine-T (all in glacial acetic acid[96]) can serve as oxidizing agents.

Whereas the C_4-C_5 bond undergoes oxidation first in the cases under consideration, photochemical oxidation evidently proceeds via the scheme of the diene synthesis. Thus benzonitrile and benzoic anhydride were isolated in the photolysis of 2,4,5-triphenyloxazole XXI in oxygen [97].

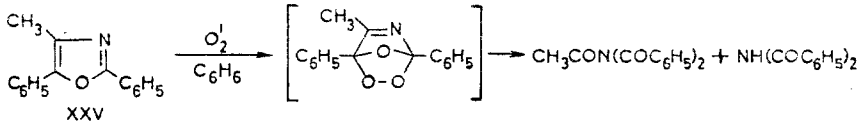


XXI

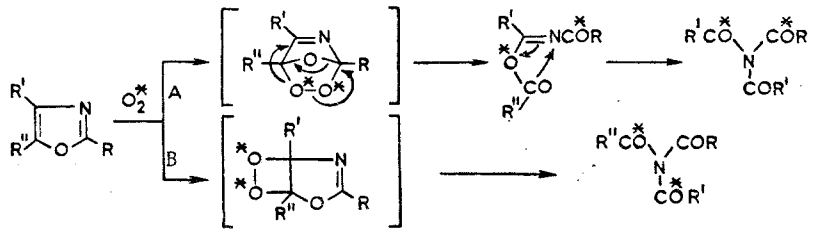
The reaction with singlet oxygen, which is formed during the photodecomposition of peroxides, in methylene chloride probably proceeds in the same way, and 4,5-polymethylene oxazoles give ω-cyanoacids XXII. 2-Substituted oxazoles are oxidized somewhat differently in methanol, so that side products XXIII and XXIV become the major products [98]:



The adduct of oxazole XXV with oxygen forms a triamide in high yield when the reaction is carried out in benzene [99]



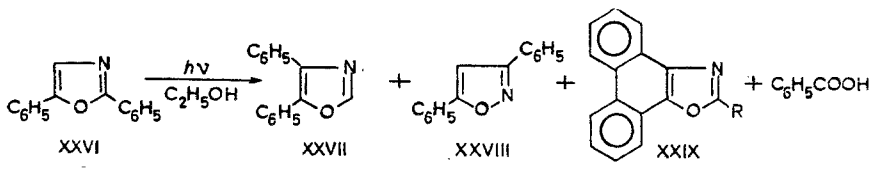
It has been shown by means of an oxygen label (in both the reagent and the oxazole ring) and high-resolution mass spectrometry that the reaction proceeds via scheme A of the diene synthesis in this case also rather than via pathway B with addition at the C_4-C_5 bond [100].



Photolysis and Photochemical Transformations

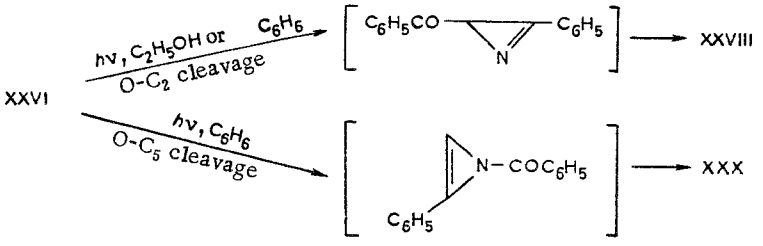
The photolysis processes of oxazoles are accompanied, as a rule, by the formation of their oxidation products. Thus, for example, benzoic acid was detected in the reaction mixture along with 4,5-diphenyloxazole (XXVII), 3,5-diphenyloxazole (XXVIII), and phenanthro-[9,10-d]oxazole (XXIX, R = H) when 2,5-diphenyloxazole (XXVI) was irradiated in ethanol.

Benzoic acid and dibenzimide were formed along with the major products — XXVIII and 2,4-diphenyloxazole (XXX) — when the same compound was irradiated in benzene [101]:

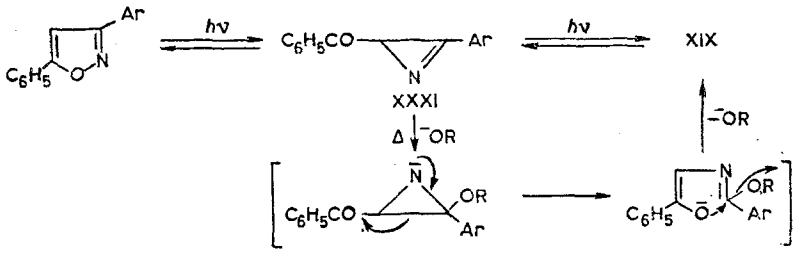


Similarly, the major reaction product in the photolysis of oxazole XXI in the presence of air oxygen is tribenzimide (see above for the mechanism), whereas XXIX (R = C_6H_5) is formed in 46-55% yields in the absence of oxygen [102].

Cooper and Wasserman [103] explain the formation of isoxazole and isomeric diphenyloxazoles by photochemical isomerization of the oxazole ring to the corresponding benzoylazirine and subsequent recyclization of it.



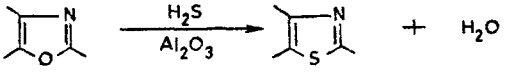
Thermal rearrangements of this type are known for oxazoles [104-108], and 4,5-dimethyl-2-methoxyoxazole is formed in 12% yield in equilibrium fashion on irradiation of N-carbomethoxydimethylazirine [109. In addition, intermediate acylazirine XXXI is also isomerized quantitatively when it is refluxed in methanol [110].



The similar rearrangement of 2-phenyloxazole gives 4-phenyloxazole and 3-phenylisoxazole [111]. There are few example rearrangments of 1,3-heterocycles to 1,2-heterocycles, inasmuch as reversible processes generally occur during irradiation. Photochemical transformations of the isoxazole ring to the oxazole ring are also known [104,110,112].

Replacement of the Heteroatom

The instability of the oxazole molecule is also indicated by its facile conversion to other-five-membered heterocycles; the oxygen atom is usually replaced first in this case. In 1958, Yur'ev and co-workers [113] showed that the oxazole ring is converted to a thiazole ring when alkyloxazole vapors are passed over aluminum oxide in a stream of hydrogen sulfide. However, because of the lower accessibility of oxazoles and their thermal instability, this reaction is not of practical value.



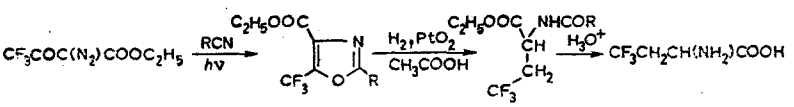
Similar reactions are observed in the 4-(benzimidazolyl)oxazole series, and the imidazole ring remains unchanged under the reaction conditions [114]. Under more severe conditions the oxazole ring is cleaved completely, and, for example, only decomposition products — acetamide and acetanilide — rather than the imidazole or thiazole were detected among the reaction products when 2-methyloxazole was heated in an autoclave with sulfur and aniline (or other amines) at 160-165° [115].

The conversion of oxazoles to the corresponding imidazoles by heating with formamide or ammonium acetate proceeds very readily and gives high yields of the products [116,117]. Quaternary oxazolium salts are converted even more readily. For example, N-phenylimidazoles are formed smoothly when N-phenyloxazolium perchlorates are heated with ammonium acetate [43]. This process is a side reaction in the synthesis of oxazoles from α-halo ketones and acid amides [117]. In the case of the more stable aryloxazoles this reaction under normal conditions proceeds at a lower rate, and, for example, heating with ammonia and formamide in an autoclave is necessary for the conversion of oxazole XXI to an imidazole [118].

In contrast to the side reactions observed, for example, for furan, the reverse conversion of an imidazole or thiazole to an oxazole has never been observed.

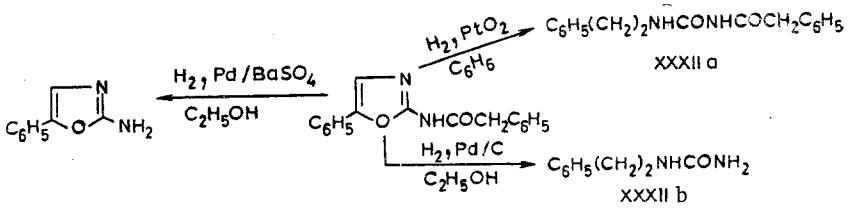
Reduction

The available data on the hydrogenolysis of oxazoles indicate that the oxazole ring is destroyed in the presence of platinum catalysts. In this case the O—C_2 bond undergoes hydrogenolysis and the C—C bond is reduced to give the corresponding amide.



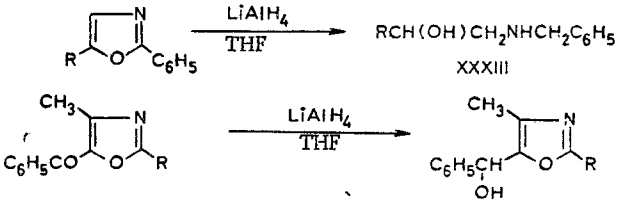
Thus the hydrogenolysis of 4-carbethoxy-5-trifluoromethyloxazole over platinum oxide in acetic acid is a method for the preparation of β-trifluoromethylalanine [119].

The reduction of 2-pyridyl-5-phenyloxazoles in the presence of platinum metal in perchloric acid proceeds similarly, and the pyridine and benzene rings are simultaneously reduced (but are not decomposed) [57,120]. The hydrogenolysis of 2-aminooxazole derivatives over platinum oxide in benzene, petroleum ether, or acetic acid, or when Raney nickel in sodium hydroxide solutions is used leads to the corresponding ureas (XXXIIa,b) [121-123]. Although the oxazole ring is not, as a rule, involved in the presence of palladium catalysts, 2-aminooxazole derivatives are more sensitive to Pd/C [122,123].



In the case of more stable compounds hydrogenolysis does not occur, and, for example, hydrogenation of benzyl 5-acyloxy-4-oxazolylacetate over Pd/C in ethyl acetate leads only to removal of the benzyl group [124]. Similar treatment of 2-(p-nitrophenyl)oxazoles leads to the corresponding p-aminophenyl compound [125], and the meta isomer was reduced with tin in hydrochloric acid, whereas the action of hydrogen iodide on 2-(3-anisyl)-5-phenyloxazole led only to cleavage of the ether without involvement of the oxazole ring [126]. The nitro group in 2-(p-nitrophenyl)oxazoles can also be reduced by Raney nickel in ethanol [127].

In a number of cases the oxazole rings is decomposed by lithium aluminum hydride [128], and, for example, 2-phenyloxazoles undergo reduction in tetrahydrofuran (THF) to give β-benzylaminoethanols XXXIII [60,129]; however, the latter are not reduced when functional groups are present, and the oxazole ring is not involved [130-132].



The oxazole ring is stable with respect to sodium borohydride; treatment of 4-oxazolylcarbonyl chloride with sodium borohydride gives the corresponding oxazolylcarbinol [130,133]. The ring also remains unaffected in the reaction with sodium hydride in xylene [134].

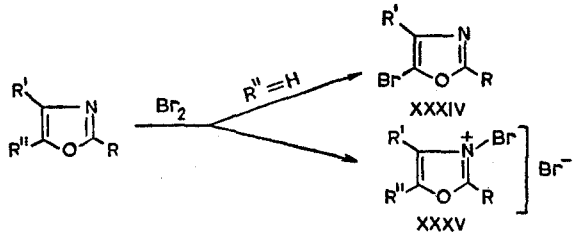
Oxazole N-oxides are reduced by triphenylphosphine [19], zinc in glacial acetic acid [17], and Raney nickel in methanol [18], and the N-oxide group is removed under these conditions without involvement of the heteroring, whereas simultaneous chlorination of the methyl group occurs in the reaction with phosphorus trichloride [18].

The polarographic reduction of oxazoles has been studied in a number of papers [135-138], but, in view of the recently published review devoted to the polarography of heterocyclic compounds [139], we will not present their detailed analysis here. We note only that, on the basis of the results obtained in these studies, it was concluded that the oxazole ring has electron-acceptor character as a substituent with respect to the alkyl chain or the aromatic ring [138].

SUBSTITUTION REACTIONS IN OXAZOLES

Electrophilic Substitution

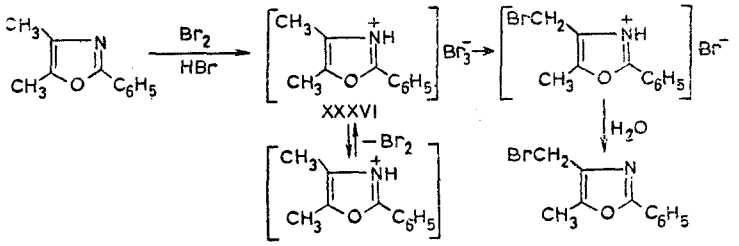
Of the reactions involving substitution of a hydrogen atom in the oxazole ring, bromination has been studied most nearly completely, and the following order of reactivities of the various positions of the oxazole ring was derived: $C_5 > C_4 >> C_2$. Thus 5-bromo derivative XXXIV is formed in yields up to 90% when 2-phenyl-4-methyl-and 4-phenyl-2-methyloxazoles are heated with bromine or N-bromosuccinimide (NBS) in chloroform or benzene [140,141].



The nucleophilic character of the 5 position of the oxazole ring is so great that the reactions with both 2-(nitrophenyl)oxazoles [141-143] and with 2-(p-acetamidophenyl)oxazoles [127,144] proceed similarly. The latter example indicates that the 5 position of oxazole is more reactive than benzene ring containing a strong electron-donor group.

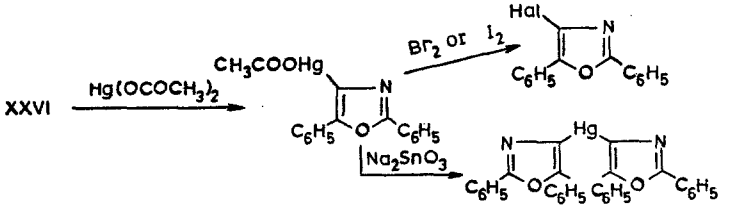
Although the reaction with 2-methyl-5-phenyloxazole does occur, the yield of bromination product (in the 4 position) is half the yield obtained in the case of the 2,4-isomer. However, bromination in the 2 position has never been observed, and either complexes with bromine (for example, XXXV) are formed in the case of 4,5-di- or tri-substituted oxazoles, or the oxazole ring is oxidized (see above). Complexes of the XXXV type, like the analogous complexes of dioxane, pyridine, etc., have brominating properties. On reaction with water or ammonia solutions they decompose to give the free bases [96,140].

Radical bromination of the methyl group to give 2-phenyl-5-(p-bromomethylphenyl)oxazole [145], which is used for the synthesis of styryloxazoles [145-147], occurs in the reaction of NBS in CCl_4 with 2-phenyl-5(p-tolyl)oxazole in the presence of benzoyl peroxide.



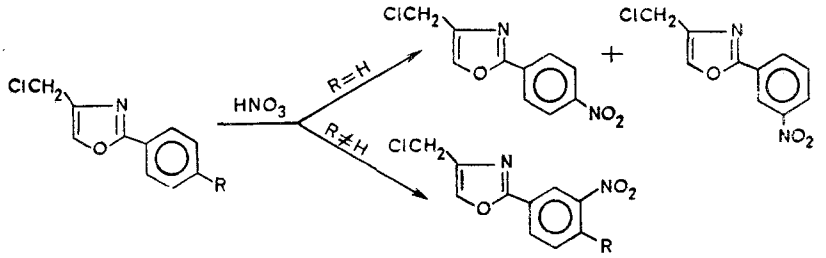
An adduct of the XXXVI type is evidently formed initially. Only the methyl group in the 4 position is brominated in the case of 4,5-dimethyloxazoles [140]. The reaction of oxazole with chlorine proceeds with simultaneous oxidation of the oxazole ring (see below). The direct fluorination of oxazoles has not been described, but there is an indication in a patent regarding the formation of 4-fluorooxazole in the reaction of oxazole-4-carboxylic acid with potassium hydroxide and fluorine gas in a helium atmosphere [148].

Iodooxazoles are also apparently difficult to obtain by direct iodination, but iodooxazoles, as well as 2-and 4-bromooxazoles, are readily formed by reaction of halogens with the appropriate mercuri derivatives [149,150]. The latter are obtained by heating oxazoles with mercuric acetate in glacial acetic acid or alcohol, and in the case of aryl- and diaryloxazoles the mercuriacetate group enters only the oxazole ring. Under these conditions relatively facile mercuration of the 4 and 5 positions is observed. More severe conditions — for example, fusion with mercuric acetate in the case of 4,5-diphenyloxazole (XXVI) — are required for oxazoles with a free 2 position. The reaction of mercurated oxazoles with sodium stannite gives symmetrical dioxazolylmercury compounds [151].



Thus in the case of mercuration also the ability of the various positions of the oxazole ring to undergo substitution reactions decreases in the order $C_5 > C_4 > C_2$ [149-151]; the lability of halogen bonded to the oxazole ring increases in the same order [141].

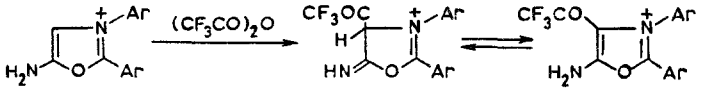
In contrast to halogenation and mercuration, nitration, sulfonation, and chlorosulfonation of aryloxazoles take place in the benzene ring rather than in the oxazole ring, and this is evidently associated with deactivation of the oxazole ring because of its protonation. For example, all three phenyl groups in triphenyloxazole are nitrated successively in the order 5 > 4 > 2 [152]. Sulfonation proceeds more selectively, and, for example, only the benzene ring in the 5 position is sulfonated in the case 2-methyl-4,5-diphenyloxazole, in which both phenyl groups undergo nitration [152]. However, in the case of 4-benzyl-5-phenyloxazole substitution takes place at the benzyl group rather than in the 5 position of the benzene ring [153], and this confirms both the passivity of the oxazole ring itself under these conditions and its electron-acceptor effect on the benzene ring.



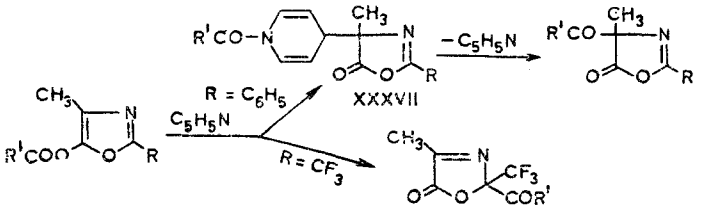
Nitration of the aryl group is also observed even when the 5 position of the oxazole ring is free [69,142,154]. However, whereas only para substitution is observed for 4- and 5-phenyloxazoles, a mixture of m- and p-substituted products was isolated in the nitration of 2-phenyl-4-chloromethyloxazole.

Sodium compounds are readily reduced to the corresponding amines [69], and one nitro group in 2-methyl-4,5-di(p-nitrophenyl)oxazole was selectively reduced with sodium sulfide to give the 5-(p-aminophenyl) derivative [152]. Amines are normally diazotized [60,125], and substituents can be introduced in the phenyl ring in this way. However, the corresponding substituted compounds are most frequently used for the preparation of nitro-, sulfo-, and aminoaryloxazoles [143,154,155], inasmuch as the oxazole ring is unstable in acidic media.

No data on the C-acylation reactions of oxazoles are available in the literature, but in the synthesis of oxazoles by the action of trifluoroacetic anhydride on α-acylaminonitriles [33,38,44], 4-trifluoroacetyl-5-aminooxazole, the formation of which is explained by acylation of the quaternary salt of 5-aminooxazoles, was detected in the reaction products.



In addition, the rearrangement of 5-acyloxyoxazoles under the influence of organic bases to give 2- and 4-acyl-5-oxazolones is formally related to the C-acylation reactions of the oxazole ring [156-159]. Steglich and Höfle assume that the more stable C isomer is formed from the O-acyl isomer on heating, and this was confirmed by isolation of XXXVII.



Thus electrophilic substitution reactions in the heteroring are not characteristic for oxazoles, despite the certain excess electron density in the 4 and 5 positions. Bromination

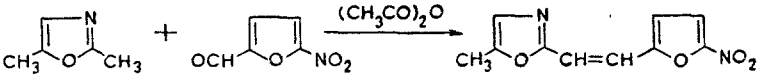
and mercuration apparently have different mechanisms: in the first case the mechanism involves a radical process, whereas in the second case the mechanism involves electrophilic substitution of the multiple bonds, as indicated by the formation of a 2-mercuri derivative.

Reaction that Characterize the Electrophilicity of the 2 Position of the Oxazole Ring

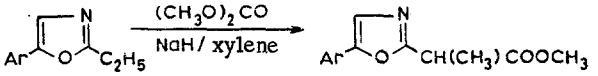
Calculations of the electron density distribution [6] and the electrophilic substitution reactions discussed above show that the 2 position of the oxazole ring has strongly expressed electrophilic character. The location of the signal of the 2-H proton in the PMR spectrum at very weak field and the increased splitting constant [13] of the C_2-H proton indicate that this proton is unusually strongly deshielded, i.e., it has increased acidity [160]. In fact, it is readily replaced by deuterium on reaction with CH_3OD, and the rate of deuterium exchange, as expected, increases on passing from the oxazole bases to the quaternary salts by a factor of ~ 200. The rate of exchange in oxazole is much higher than the rate of exchange at the C_2 atom in imidazole and thiazole [161-162].

In the case of 2-chlorooxazoles, obtained by the action of $POCl_3$ on 2-oxazoles [163, 164], the lability of the chlorine atom is similar to the lability of the chlorine atom in benzyl chloride or an amido chloride, and it is readily replaced by an amino or hydrazino group [163-167]. The 2-hydrazinooxazoles obtained in this way react with aldehydes and ketones to give hydrazones and with keto esters to give pyrazolones [168]. The reaction of 2-chlorooxazoles with metal alkoxides proceeds very rapidly and gives 2-alkoxyoxazoles [163-164], whereas only the acetyl group is removed without involvement of the halogen when 5-bromo-4-methyl-2-(p-acetamidophenyl)oxazole is heated with alkali [144]. Similarly, the reaction of 4-chloromethyl- and 4-dichloromethyl-5-chlorooxazoles with alkoxides in alcohol gives 4-alkoxymethyl- and 4-formyl-5-chlorooxazoles [64]. Thus, in contrast to 2-chlorooxazoles, the chlorine and bromide atoms in the 4 and 5 positions behave like those of ordinary aromatic derivatives. The halogen atoms in the chloromethyl derivatives are, of course, labile [41]; for example, the chlorine atom in 5-chloromethyloxazole is readily replaced by a cyano group [169].

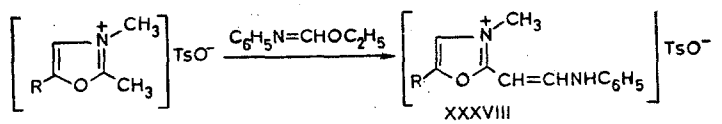
Methyl groups in the 4 and 5 positions of the oxazole ring have reactivities that are similar to the reactivity of the methyl group of toluene (facilitated radical bromination). At the same time, the protons of the $2-CH_3$ group have extremely acidic character because of the large deficit of electron density in the 2 position. Like α-picolines, 2-methyloxazoles are readily condensed with aromatic aldehydes in the presence of sulfuric acid or strong bases (for example, sodium amide) to give 2-styryloxazoles [170-171] or β-(2-oxazolyl)ethanol derivatives [172]. Only the $2-CH_3$ group undergoes condensation in the case of 2,5-dimethyloxazole [102-173].



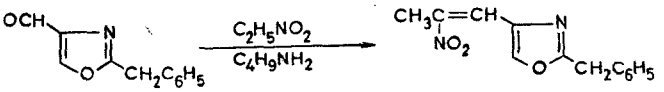
2-Alkyloxazoles may participate as a methylene component in the presence of strong bases; for example, this is observed in the reaction with dimethyl carbonate, which proceeds in the same way as the Claisen condensation [134].



The reactivity of the $2-CH_3$ group may be increased even more by quaternization of the oxazole; salts of this type react even with formamidines [174] or amido esters [175] to give

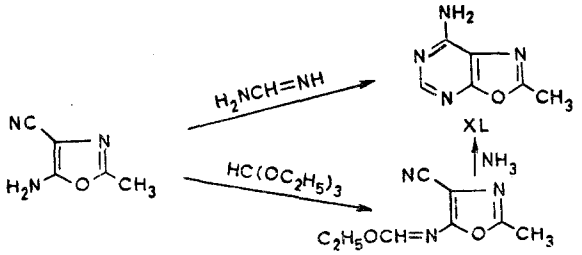


XXXVIII

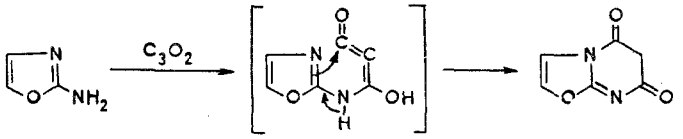


the corresponding 2-(β-aminovinyl)oxazoles (XXXVIII). Vinyloxazoles XXXIX, which contain a vinyl group in the 4 position, are not obtained from 4-methyloxazoles but rather from the formyl derivatives by condensation with, for example, aliphatic nitro compounds [176,177].

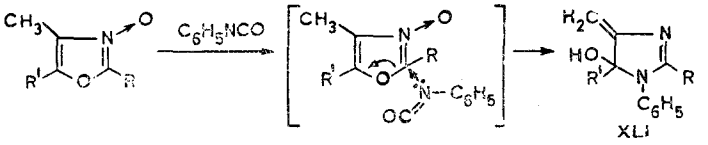
However, when a methyl group and an amino group are present in the oxazole molecule, the amino group primarily undergoes condensation. For example, only oxazolopyrimidine XL is formed in the reaction of formamidine with 2-methyl-4-cyano-5-aminooxazole [178,179]:



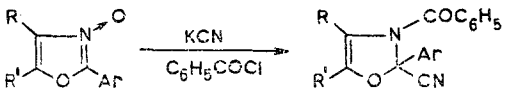
In contrast to 4- and 5-aminooxazoles, which condense readily with aldehydes and weaker quasicarbonyl compounds (see the reactions presented above) to give the corresponding azomethines [50,180], reactions of this sort are unknown for 2-aminooxazoles, the basicities of which are reduced. However, the reaction proceeds almost quantitatively with stronger reagents, for example, with carbon suboxide [181].



The electrophilicity of the 2 position of the oxazole ring can be increased by conversion of the base to the N-oxide, and attack by even such a relatively weak nucleophile as the nitrogen atom of phenyl isocyanate then becomes possible. Rearrangement of the product leads to 5-hydroxy-Δ^2-imidazolines (XLI) [182].

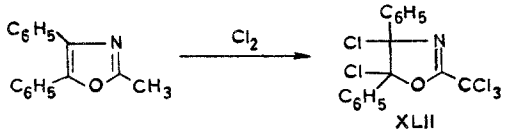


Like Reissert compounds, the N-oxides of 2-aryl-4,5-disubstituted oxazoles react with KCN and benzoyl chloride to give N-benzoyl-2-cyano-Δ^2-oxazolines [183]:

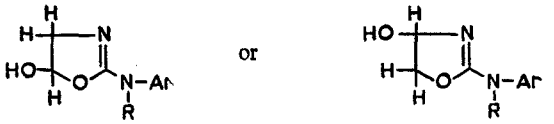


REACTIONS INVOLVING ADDITION TO MULTIPLE BONDS

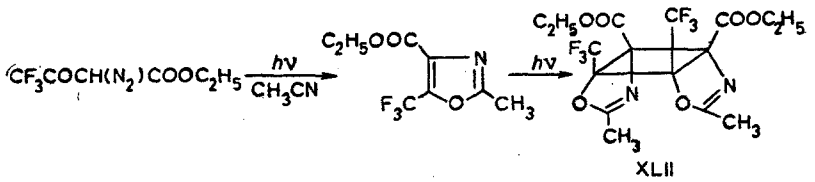
In addition to the properties of oxazoles, including the ability to undergo the Diels—Alder reaction (see reviews [3-5]), already mentioned above, even the oxidation of the oxazole ring may proceed via this mechanism (see above). However, the C—C bond of the oxazole ring also participates in some reaction. For example, in contrast to the bromination of oxazoles, addition product XLII was isolated in reaction with chlorine [141].



Similarly, the hydrate rather than the base was isolated in the synthesis of 2-amino-oxazole derivatives, and Najer and co-workers [184] assert that water is added to the C = C bond



Finally, dimerization product XLIII (1,2-addition) was isolated in the preparation of oxazoles by photochemical 1,3-dipolar addition of diazo compounds to nitriles [185,186], and in this case only the C = C bonds of the oxazole ring participate in the reaction.



XLII

No instances of addition to the C = N bond have been described (if one does not consider the above-cited Reissert reaction to be an addition of this type).

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UNUSUAL MEERWEIN REACTION IN THE FURAN SERIES

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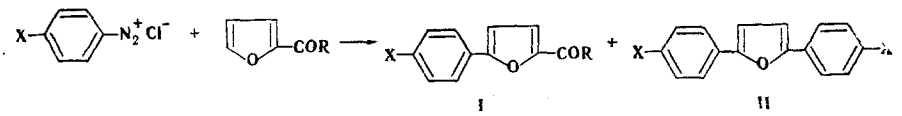
Aldehydes formed as side products in the Meerwein arylation of 2-acylfurans were detected by a polarographic method.

In previous papers [1,2] we showed that a series of side products are formed along with the major products — 5-aryl-2-acylfurans (I) — in the Meerwein arylation of acylfurans. Of these side products, the 2,5-diarylfurans (II) seemed of greatest interest.



I II

X = Cl, Br, NO_2; R = CH_3, C_2H_5, C_3H_7

Up until now, the formation of compounds of the 2,5-diarylfuran type has never been noted in the Meerwein reaction either in the furan series or in the case of unsaturated compounds

Inasmuch as we have established [1] that arylacetylfurans I are not intermediates in the formation of diarylfurans II, it might have been assumed that the 2,5-diarylfurans are formed directly during the arylation of 2-arylfurans.

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