OPENING OF AZOLE RINGS BY REAGENTS THAT CONTAIN AMINO GROUPS

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Data on the opening of oxazole, isoxazole, thiazole, isothiazole, pyrazolidine, and imidazolidine rings (particularly the rings of oxo derivatives) by amines, amino acids and their derivatives, hydrazines, and hydroxylamine are correlated.
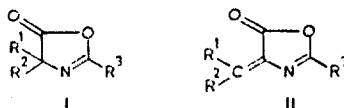
The opening of azole rings under the influence of reagents that contain amino groups, viz., amines, hydrazines, hydroxylamine, and amino acids and their derivatives, makes it possible to synthesize amides and hydrazides of α-substituted carboxylic acids, peptides [1-5], carbamates, dithiocarbamates, aminoamidines, amidrazones, and other compounds. Some of them are intermediates in the recyclization of heterocycles.

The decyclization of azoles is a nucleophilic reaction that commences with attack by the amino group of the reagent on an electron-deficient carbon atom of the heteroring (most often the carbon atom of the carbonyl group of the oxo derivatives of azoles).

In the present review we examine primarily cases involving the decyclization of azoles to give products that are stable under the reaction conditions. The review encompasses the literature up to 1977, in addition to research by D. Simov and co-workers on the aminolysis of benzazoles, which will be correlated separately.

5-Oxazolones

5(4H)-Oxazolones (Azlactones) (I) [1] can react with nucleophilic reagents at two electron-deficient centers, viz., C_2 and C_5. The ring of 4-alkylidene-5-oxazolones (II) is more stable than the ring of their saturated analogs [1, 2], since the electrophilicity of C_5 is reduced here because of conjugation with the double bond.
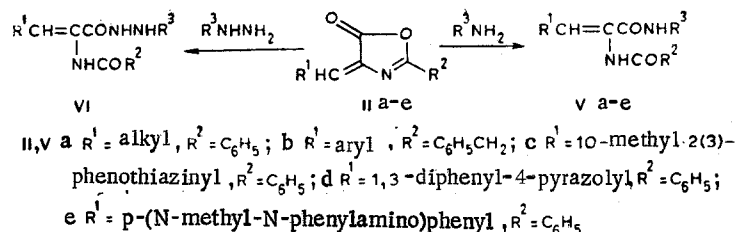

Reaction with Amines. 2-Phenyl-5(4H)-oxazolone (III) undergoes ring opening under the influence of heterocyclic primary amines with cleavage of the O—C_5 bond to give N-(betarylcarbamoyl)methylbenzamides (IV, in 5-91% yields) [6], which are used in the synthesis of 5-hetarylamino-2-phenyloxazoles.
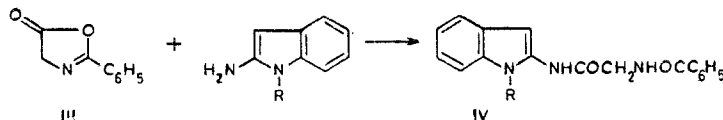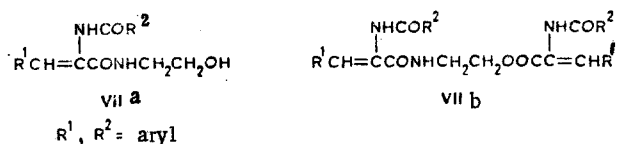

When 2-phenyl-4-alkylidene- [7] and 2-benzyl-4-arylidene-5-oxazolones [8] (IIa,b) are heated with ammonia [8, 9], ethylamine [8], and aromatic amines [7, 8], they also undergo decyclization to give α-acylaminoacrylamides Va, b in 75-95% yields.

This reaction is the first step in the conversion of oxazolones to the corresponding imidazolones [8].

$$R^1CH=CCONHNHR^3 \xleftarrow{R^3NHNH_2} \underset{R^1HC \diagdown N \diagup R^2}{\overset{O}{\big|}} \xrightarrow{R^3NH_2} R^1CH=CCONHR^3$$

at left with NHCOR² substituent, center II a–e, right V a–e with NHCOR²

VI   II a–e   V a–e

II,V **a** R^1 = alkyl, $R^2 = C_6H_5$; **b** R^1 = aryl, $R^2 = C_6H_5CH_2$; **c** R^1 = 10-methyl-2(3)-
phenothiazinyl, $R^2 = C_6H_5$; **d** R^1 = 1,3-diphenyl-4-pyrazolyl, $R^2 = C_6H_5$;
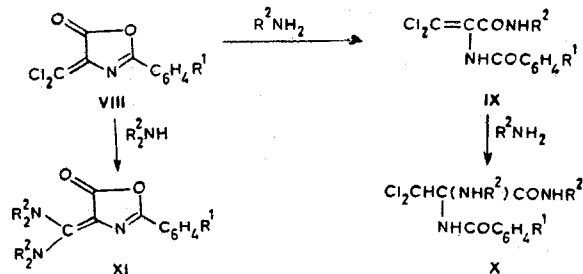**e** R^1 = p-(N-methyl-N-phenylamino)phenyl, $R^2 = C_6H_5$

The reactions of azlactones that contain phenothiazinyl (IIc) [10] and pyrazolyl (IId) [11] groups in an arylidene substituent in the 4 position have been investigated; amides (Vc) [10] and hydrazides (VI) [10, 12] of α-benzamidoacrylic acids are formed in these reactions. The results of kinetic studies of the aminolysis of azlactone IIc by benzylamine in a mixture of chloroform and dimethylformamide (DMF) show that the rate constant of the reaction, which is first-order in azlactone, is increased by a factor of 10 when the ratio of the components in the solvent is changed from 7:1 to 3:1. The constant of the rate of decyclization of substrate IIe is several times smaller, since the presence of a sulfur atom weakens the electron-donor properties of the phenothiazinyl substituent in IIc as compared with the diphenylamino substituent in IIe.

The structures of the products of aminolysis of 2-aryl-4-arylidene oxazolones by ethanolamine depend on the molar ratio of the reagents (VIIa in the case of a ratio of 1:1, and VIIb in the case of a ratio of 2:1) [13]. In both cases the aminolysis products are formed as a result of cleavage of the O–C₅ bond of the oxazolone ring, i.e., as a result of nucleophilic attack on the carbonyl carbon atom.

$$\underset{R^1CH=\overset{|}{C}CONHCH_2CH_2OH}{\overset{NHCOR^2}{\big|}}$$

VII **a**

$$\underset{R^1CH=\overset{|}{C}CONHCH_2CH_2OO\overset{|}{C}C=CHR^1}{\overset{NHCOR^2 \quad\quad\quad NHCOR^2}{\big|\quad\quad\quad\quad\quad\big|}}$$

VII **b**

R^1, R^2 = aryl

The reaction with amines is a more complex process when the 4-ylidene substituent contains reactive groups. 4-Hydroxymethylene- and 4-alkoxymethylene-5-oxazolones react at room temperature with ammonia and primary and secondary amines at the exocyclic carbon atom to give 4-aminomethylene oxazolones; under more severe conditions (100°C) amines attack C₅ to give ultimately acrylic acid derivatives V [1]. 4-Ethylthiomethyleneoxazolones give the corresponding 4-aminomethyleneoxazolones or amides V, depending on the character of the substituent in the 2 position and the reacting amine [1, 14]. 4-Arylidineoxazolones react with hydrazine hydrate under mild conditions to give hydrazides VI; when the latter are refluxed in alcohol solution, they are converted to pyrazolidones [1, 15], whereas when they are refluxed in aqueous NaOH solution, they are converted to 1,2,4-triazines [12].

When equimolar amounts of 2-aryl-4-dichloromethyleneoxazolones (VIII) react with primary amines, they undergo ring opening to give α-acylaminoacrylic acid amides IX in 70–95% yields [16]. These amides, which have a reactive enamide grouping, are converted to propionic acid alkylamides X as a result of the addition of another molecule of the amine. Alkylamides X are also formed directly from the oxazolones if the reaction is carried out in excess amine for a longer time [16, 17]. Secondary amines undergo the reaction, during which primarily the chlorine atom is replaced to give aminomethyleneoxazolones XI. The authors assume that the difference in the reactivities of the amines is probably associated with steric factors. It must be noted that, despite the large volume of the tert-butylamine molecule, the oxazolone nevertheless undergoes decyclization with it.

$$\underset{Cl_2C \diagdown N \diagup C_6H_4R^1}{\overset{O}{\big|}} \xrightarrow{R^2NH_2} \underset{NHCOC_6H_4R^1}{\overset{Cl_2C=\overset{|}{C}CONHR^2}{\big|}}$$

VIII   IX

$\downarrow R_2^2NH$ $\downarrow R^2NH_2$

$$\underset{R_2^2N \diagup C \diagdown N \diagup C_6H_4R^1}{\overset{O}{\big|}}$$ with R_2^2N

XI $\underset{NHCOC_6H_4R^1}{\overset{Cl_2CH\overset{|}{C}(NHR^2)CONHR^2}{\big|}}$

X

Little study has been devoted to the reactions of 2-arylidene-4-aryl-5(2H)-oxazolones [pseudooxazolones (XII)] [1, 8] with amines. The decyclization of 2-benzylidene-4-phenyl-5(2H)-oxazolone with aromatic amines in alcohol solution has been carried out by refluxing in the presence of trimethylamine [18]. The authors propose that the amine adds to the endocyclic azomethine bond with attendant ring opening and inclusion of the alcohol in the reaction. As a result, the corresponding methyl or ethyl α-arylamino-α-phenylacetamido-phenylacetates (XIII) are formed in almost quantitative yields.
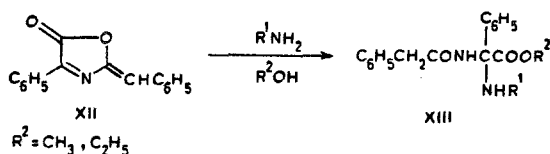
The reaction does not take place with aniline in xylene and 1-butanol even in the presence of triethylamine. Pseudooxazolone XII reacts with equimolar amounts of benzylamine and 4-nitro- and 2,4-dinitrophenylhydrazine when the compounds are refluxed in alcohol solution; decyclization also occurs in this case, but only the corresponding amides or hydrazides of phenylacetic acid are formed.

Reactions with α-Amino Acids and Their Esters. The aminolysis of oxazolones with amino acids and their esters is used in the synthesis of peptides [19] (the Bergmann reaction [1, 20, 21]). Ethanol, ether, acetone, acetic acid, and other polar solvents are used for this reaction.
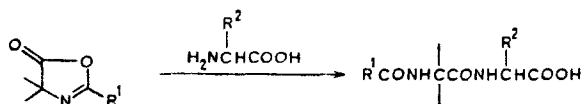

The aminolysis of oxazolones with an unsaturated substituent attached to C₄ proceeds similarly to give the corresponding dipeptide [7, 21].

A substantial inadequacy of the aminolysis of optically active azlactones is the fact that racemization of the azlactone also takes place under the influence of the nucleophilic reagent [22]:
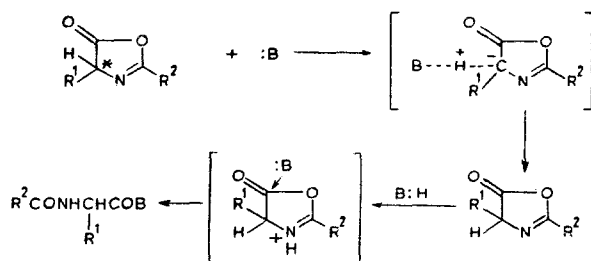

Of the two processes, viz., ring opening or racemization, the one that predominates depends on many factors: the character of the nucleophile, the solvent, the temperature, and other reaction conditions. In connection with the fact that the preparation of optically active peptides is a difficult task but is of practical value, Goodman and co-workers [22-26] have made a series of studies. It was established that the rate of racemization of L-2-phenyl-4-benzyl-5-oxazolone (XIV) decreases in the following order of nucleophilic reagents:

p-nitrophenoxide ion > phenylalanine methyl ester > pyridine. The concentration of nucleophile necessary for decyclization is much higher than the concentration that gives rise to racemization. Pyridine causes racemization but does not open the ring, since for ring opening the reagent must have high nucleophilicity [22]. Kinetic studies made with L-4-benzyloxazolone XV lead to similar conclusions [24].

XIV

XV
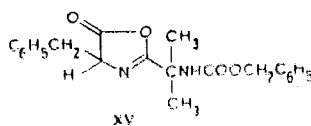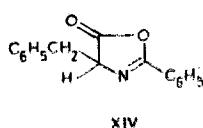
Conclusions have been drawn from a comparison of the reaction of azlactones XIV and XV with DL-phenylalanine in dioxane at 25°C: the racemization of XV is faster by a factor of 11-12 than decyclization, while XIV undergoes racemization faster by a factor of 200. Azlactone XIV is racemized five times faster than XV; in the opinion of the authors, this is due to conjugation between the phenyl substituent in the 2 position and the azomethine bond of the oxazolone ring of XIV. Opening of the ring of azlactone XIV is slower by a factor of three to four than in the case of XV [23]. The more nucleophilic (and less basic) the reagent, the greater the ease of decyclization [25]. Ethyl glycinate proved to be the most suitable of the investigated amino acid esters. An optically active tripeptide is obtained in 75% yield in the reaction of ethyl glycinate with oxazolone XV in toluene. Under the same conditions methyl aminoisobutyrate gives a completely racemized product.

Only decyclization to give optically pure hydrazide XVI occurs in the reaction of oxazolone XV with excess hydrazine hydrate because of the high nucleophilicity of the latter (the α effect [27]).


XVI
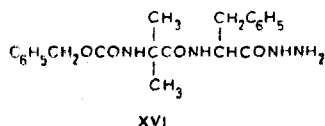
The effect of the temperature, solvent, and reagent concentration on the reaction of nucleophiles of this type (hydroxylamine and hydrazine hydrate and their derivatives) with oxazolone XIV has been studied [26].

The kinetics [28-30] of the decyclization of 2-phenyl-4,4-dimethyl-5-oxazolone (XVII) with DL-alanine ethyl ester [28] and a series of ethyl esters of other α-amino acids [29] in carbon tetrachloride with acetic acid as the catalyst has been investigated. The reaction is a second-order process, and its rate is independent of the initial concentration of the substrate. The excellent correlation between the rate of the catalytic reaction and the Taft σ° constants indicates that the substituents attached to the α-carbon atom of alanine have an effect chiefly owing to the inductive effect.

5-Isoxazolones and Other Oxazole Derivatives

The opening of the ring of 3-unsubstituted 5(2H)-isoxazolones (XVIII) with amines [31] and other nucleophiles [32] proceeds via a different pathway. Diamides XIX are obtained as a result of the reaction of 2,4-disubstituted isoxazolones XVIII with aliphatic amines [31, 33].

XVIII   XX   XXI

XIX

$R^1 = CH_3, C(CH_3)_3, C_6H_5; R^2 = C_6H_5, COOC_2H_5; R^3 = H$, alkyl
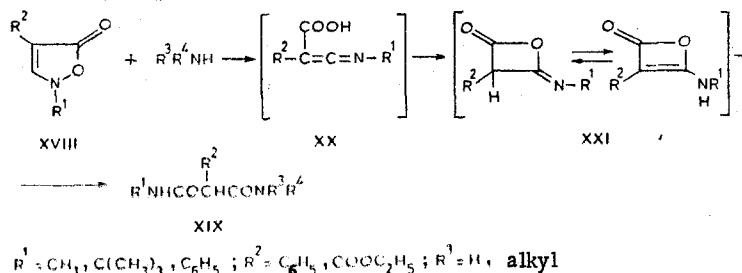
It is assumed [31] that a proton is detached from the C_3 atom by the action of the amine and that the O–N bond of the isoxazolone ring is cleaved to give keteneimine XX. A similar reaction is also known for other azoles [34]. Intermediate XX very readily undergoes cyclization [35] to give lactone XXI, which reacts with the amine to give diamide XIX.

Nucleophilic attack on 5(2H)-isoxazolones probably occurs at C_3. This is confirmed by that fact 2,3,4-trimethyl-5(2H)-isoxazolone reacts with phenylhydrazine at 140°C to give 1-phenyl-3,4-dimethyl-5(2H)-pyrazolone. Attack at C_5 would have led to its isomer — 1-phenyl-4,5-dimethyl-3(2H)-pyrazolone [36].

Uncoordinated data on other instances of opening of the oxazolone ring by amines, hydrazines, and hydroxylamine are also known. For example, an amidoxime was obtained in the reaction of DL-trans-2-phenyl-4,5-dicarbomethoxy-2-oxazoline with hydroxylamine in connection with studies of the synthesis of derivatives and analogs of cycloserine [37], and the corresponding phenylhydrazones of α-acylamino ketones are formed by treatment of 2,4,5-trisubstituted oxoazoles with phenylhydrazine and 2,4-dinitrophenylhydrazine [38, 39].

The decyclization of the oxazole ring has also been accomplished in condensed systems: in halomethyl- [40] and hydroxymethyl-substituted [41] oxazolopurines, in mesoionic pyrido-oxazolone [42], and in 2(3H)-benzoxazolone [43].

2,5-Oxazolidinediones

2,5-Oxazolidinediones XXII (N-carboxy-α-amino acid anhydrides [1] and Leuchs anhydrides [2, 44]) react with nucleophilic reagents to give N-carboxy-α-amino acids and their esters or amides, which are readily decarboxylated. Decarboxylation product XXIII, and α-amino acid amide, is also a nucleophilic reagent and may react with another molecule of the oxazolidinedione to give dipeptide XXIV and in some cases a polypeptide.
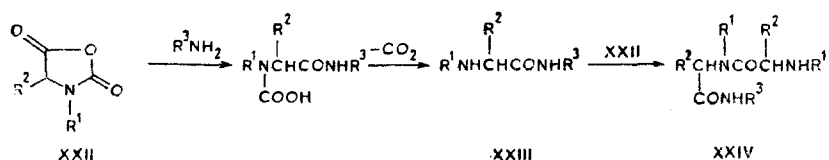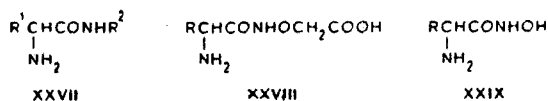

This reaction can be regarded as a polymerization reaction that takes place in each step with subsequent decarboxylation. The number of monomeric units in the peptides obtained will depend on the rates of the successive steps [45]. Favorable conditions for this process are created when the amine is used in the minimal concentrations or when it is a less active nucleophile than the products of the reaction of XXIII. The use of an oxazolidinedione (such as 3-phenyl-2,5-oxazolidinedione) that forms a decyclization product that has an inactive amino group stops the process at the first step. 4-Benzyl-2,5-oxazolidinedione reacts with aliphatic amines to give amides XXIII and with the less active aniline to give peptides [1].

Oxazolidinediones also react with other nucleophiles that contain an amino group. N-Carboxy-N-phenylglycine anhydride reacts with the corresponding amines to give the amide [46], anilide [47], ethylamide, methylanilide, and piperidide of N-phenylglycine, and with glycine and esters of glycine and tyrosine to give peptides [48]. Phenylalanine anilide was obtained from N-carboxy-β-phenylalanine anhydride [49], while N-carboxyglycine anhydride is decyclized by aniline, methylaniline [50], morpholine, and glycine ester [51].

The aminolysis of N-carboxy-α-amino acid anhydrides (XXV) with amino acid esters is used to obtain peptides [52, 53]. The reaction is carried out at low temperatures (from −20 to −30°C) in anhydrous solvents (chloroform, ethyl acetate) in the presence of tertiary amines [21]. Tetrahydrofuran (THF) which is a good solvent for anhydrides at low temperatures [53], is used as the solvent. Intermediate carbamic acids XXVI are also obtained in some cases.
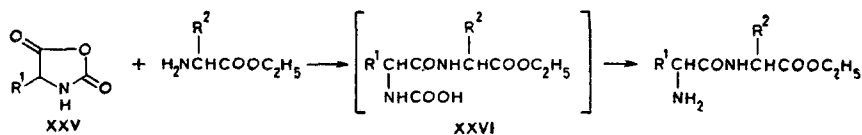
This reaction makes it possible to realize the controlled synthesis of peptides that contain amino acids linked in a definite sequence. To obtain polypeptides with a definite amino acid composition one must know the factors that make it possible to stop the reaction at this stage. Some of these factors have been discovered for the reactions of N-carboxy-α-amino acid anhydrides with the hydrochlorides of aliphatic and aromatic amines, ethyl amino-hydroxyacetate, and hydroxylamine, which lead to the formation of the hydrochlorides of compounds of the XXVII-XXIX type [54, 56].

$$R^1CHCONHR^2 \qquad RCHCONHOCH_2COOH \qquad RCHCONHOH$$
$$\underset{NH_2}{|} \qquad\qquad\quad \underset{NH_2}{|} \qquad\qquad\qquad \underset{NH_2}{|}$$

$$\textbf{XXVII} \qquad\qquad\quad \textbf{XXVIII} \qquad\qquad\qquad \textbf{XXIX}$$

It has been found [54] that the use of a nucleophilic reagent in the hydrochloride form rather than in the free base form promotes the formation of amides XXVII; in this case weakly basic amines form amides XXVII in higher yields. A decrease in the temperature to 0°C slows down the principal reaction significantly but at the same time virtually excludes polymerization processes; in the opinion of the authors, the ratio of the concentrations of the free and associated bases of the reagent and the α-amino acid amide, which changes during the reaction, is of great importance when the temperature is raised to 60-100°C, over which temperature range the rates for both the formation of amides and polymerization increase. A comparision of the reactivities of amines with close and identical basicities indicates the appreciable role of the steric factor: With p-anisidine and aniline (pK_b 9.0 and 9.4) the yields of amides XXVII are ∿ 70%, whereas the yield with o-anisidine (pK_b 9.6) is 26%. The reaction proceeds much more slowly in polar aprotic and in nonpolar solvents (DMF, ethyl acetate, THF, chloroform, dioxane, and carbon tetrachloride) than in amphoteric solvents.

The aminolysis of N-carboxyamino acid anhydrides also takes place in aqueous solutions and this makes it possible to use free amino acids as the reagents and to build up a peptide chain without isolation of the intermediates [21]. A dipeptide is obtained by treatment of N-carboxy-α-phenylalanine anhydride, dissolved in a solvent that is not miscible water, with an aqueous solution [56]. A study of the reaction of some anhydrides with aqueous solutions of amino acids and di- and tripeptides made it possible to conclude that the reaction can be controlled and that it is thus a general method for the synthesis of peptides in water [57, 58]. The opinion that the reaction can be used for carrying out controlled peptide synthesis in water in cases in which the reacting amine is a weaker base than the resulting amine was later expressed [59, 60].

More detailed studies [61, 62] led to the discovery of conditions that make it possible to use the method for the rapid synthesis of optically pure dipeptides in ∿ 90% yields: the crystalline anhydride is mixed rapidly with an aqueous solution of the amino acid at 0-2°C and pH 10.2. After 2 min, the reaction mixture is acidified, during which dianion XXX is readily decarboxylated to give a dipeptide:

$$\textbf{XXV} + R^2CHCOO^- \longrightarrow \left[R^1CHCONHCHCOO^- \right] \xrightarrow{H^+} R^1CHCONHCHCOO^- + CO_2$$

$$\textbf{XXX}$$
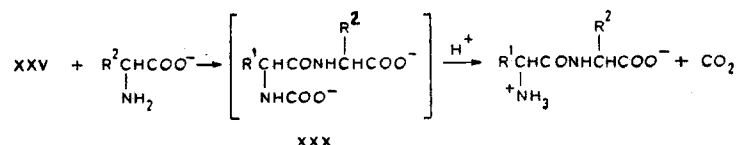
The authors point out that in carrying out this reaction one must take into account the following experimental facts: The stability of the carbamate increases when the pH of the medium is raised, whereas the rate of hydrolysis of the anhydride increases significantly at pH > 10.5; a low temperature favors the principal reaction; rapid mixing of the reagents in the case of relatively slightly soluble anhydrides makes the formation of tripeptides less likely; rapid stirring in the case of more soluble anhydrides makes the processes involving oligomerization of the anhydride less significant [61].
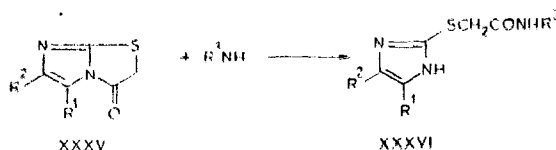
Thiazolones and Isothiazolones

Less study has been devoted to the behavior of the thiazole ring with respect to amines than to the behavior of the oxazole ring. Several communications [63-66] regarding the reaction of 2-thioxo-5-thiazolidones with amines and α-amino acid esters were published in 1950. 2-Thioxo-5-thiazolidone (XXXIa) reacts readily with two equivalents of benzylamine and morpholine to give N-dithiocarboxyglycine amides of the XXXII type (XXXIIa was obtained in 87% yield) [63]. The structure of XXXII was confirmed by chemical transformations and shows that the 5-thiazolidone is cleaved at the S—C$_5$ bond. 2-Thioxo-4-methyl-5-thiazolidone (XXXIb) is decyclized by ammonia and morpholine, but XXXIIb is easily recyclized to XXXIb upon acidification even in an anhydrous medium [64].

Thiazolidone XXXIa can be used as a reagent for the introduction of a glycyl group in α-amino acid esters or peptides [65]. The reaction takes place in chloroform in the presence of a tertiary amine or in ethanol. Peptide ester hydrochloride XXXIV is formed in up to 78% yield by subsequent treatment of the resulting dithiocarbamate XXXIII with hydrogen chloride. Thus, a pentaglycine ethyl ester hydrochloride is obtained from the glycine ester with good yields in each step. Thiazolidone XXXIb is used for the preparation of alanylpeptides [66]. When the reaction with α-amino acid esters is carried out as in [65], the yields of peptides are lower; however, one can carry out the process with amino acids in alkaline solution with subsequent slow acidification with weak acids or with amino acids in hot acetic acid.
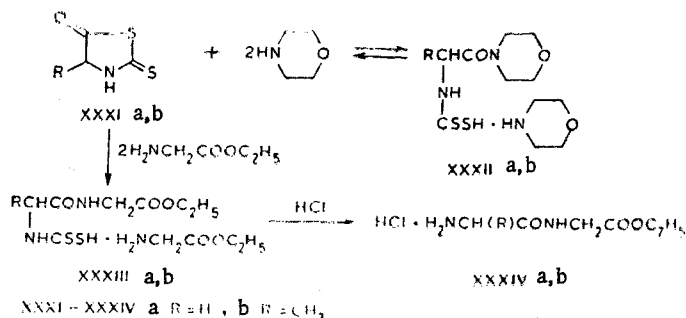
The reaction of imidazothiazolones XXXV with amines, ammonia, and phenylhydrazine in ethanol leads to S-(2-imidazolyl)thioacetamides XXXVI in 72-81% yields [67]. Other thioacetanilides and hydrazides with heterocyclic substituents attached to the sulfur atom are also obtained in this way from thiazoloquinazolinediones [68] and benzimidazothiazolones [69, 70].
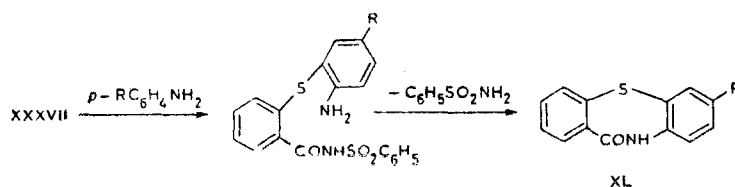

2-Phenylsulfonylbenzisothiazolone (XXXVII) is decyclized under the influence of aromatic amines. Substituted diphenyl sulfides of the XXXVIII type are obtained when it is
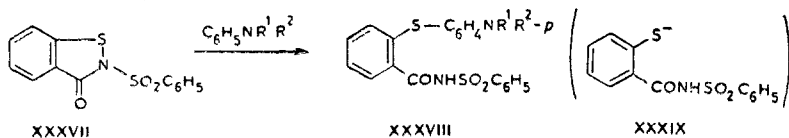
refluxed in alcohol solution with tertiary aromatic amines [71] and aniline [72], as well as with methylaniline and o-toluidine. Disulfide XXXIX is obtained with benzylamine and phenylhydrazine under similar conditions.

The reaction with p-substituted aromatic amines (p-toluidine, p-anisidine, and p-chloroaniline) leads to lactams XL and benzenesulfonamide.

Weakly basic amines (nitroaniline and anthranilic acid) do not react with 2-phenyl-sulfonylbenzothiazolone.
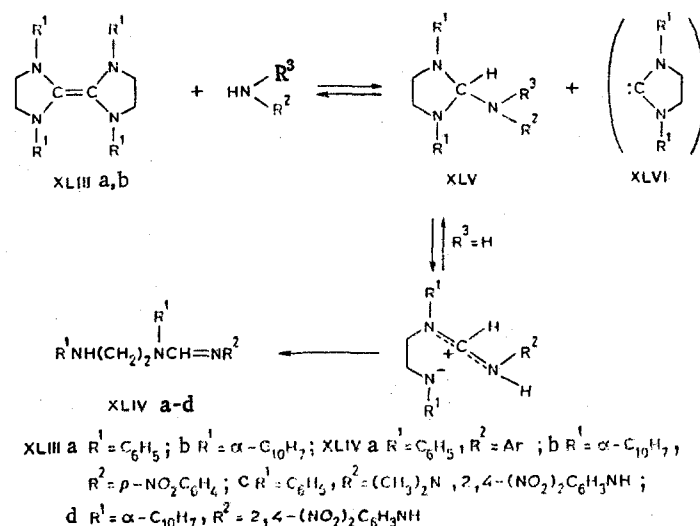
Pyrazolidones and Imidazolidines

Under the influence of benzylamine, hydrazine hydrate, and phenylhydrazine 3,5-pyra-zolidinediones undergo decyclization at the N—C_5 bond to give hydrazides XLI in high yields [73]. In the absence of a solvent at room temperature hydrazine hydrate also splits out 1 phenyl- and 1,2-diphenyl-4-benzylidene-3,5-pyrazolidinediones to give hydrazides XLII. A bispyrazolidine derivative is obtained in the presence of a solvent (ethanol, pyridine).
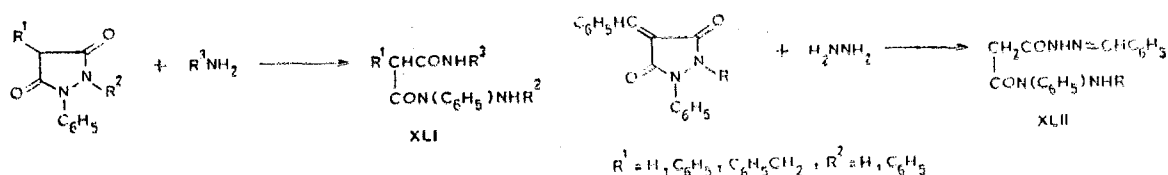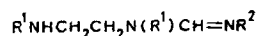

Primary aliphatic and aromatic amines open up the heteroring of bis(1,3-diphenyl-2-imidazolidinylidene) (XLIIIa) in the case of refluxing in an atmosphere of dry nitrogen in an anhydrous solvent. Aminoamidines XLIVa are obtained in quantitative yields [74]. 2-Amino-1,3-diphenylimidazolidines (XLV) are obtained in 78-95% yields (18% yield with methyl-aniline after heating for 10 h) under the same conditions with secondary amines (piperidine, morpholine, benzotriazole, 2-methyl-2H-indole, and methylaniline). The reaction with hydra-zines (1,1-dimethyl- and 2,4-dinitrophenylhydrazine), which leads to aminoamidrazones XLIVc, proceeds in the same way as the reaction with primary amines.

When the phenyl substituent in bis(imidazolidinylidene) XLIII is replaced by an α-naphthyl group, the reactivity of the substrate with respect to some secondary amines de-creases. Compound XLIIIb does not react with piperidine and morpholine in refluxing xylene but forms aminoamidine XLIVb and aminoamidrazone XLIVd in quantitative yields with p-nitro-aniline and 2,4-dinitrophenylhydrazine. The authors propose the following scheme for the mechanism of the reaction:

XLIII a $R^1 = C_6H_5$; b $R^1 = \alpha - C_{10}H_7$; XLIV a $R^1 = C_6H_5$, $R^2 = Ar$; b $R^1 = \alpha - C_{10}H_7$,
$R^2 = p - NO_2C_6H_4$; c $R^1 = C_6H_5$, $R^2 = (CH_3)_2N$, $2,4-(NO_2)_2C_6H_3NH$;
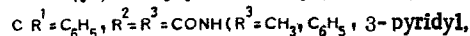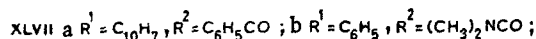d $R^1 = \alpha - C_{10}H_7$, $R^2 = 2,4-(NO_2)_2C_6H_3NH$

The N–H bond in the amine becomes weaker under the influence of the strong π bases XLIII. 2-Aminoimidazolidines XLV are obtained in reactions with secondary amines as a result of the formation of a new C–H bond, addition of the "amine anion," and splitting out of nucleophilic carbene XLVI [75]. The reduced electron density on the C_2 atom facilitates heterocyclic cleavage of the N–C_2 bond. Compounds of the XLIV type are formed in the case of primary amines and hydrazines with the migration of a proton.

The reaction of bis(imidazolidinylidenes) XLII with both amides and hydrazides of carboxylic acids, urethanes, and ureas has been described [76]. 1,1-Dimethylurea and some hydrazides react like primary amines to give decyclization products XLVII in 80-97% yields.

$$R^1NHCH_2CH_2N(R^1)CH=NR^2$$

XLVIIa-c

XLVII a $R^1 = C_{10}H_7$, $R^2 = C_6H_5CO$; b $R^1 = C_6H_5$, $R^2 = (CH_2)_2NCO$;

c $R^1 = C_6H_5$, $R^2 = R^3 = CONH(R^3 = CH_3, C_6H_5$, 3-pyridyl, 4-pyridyl)

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