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# 4H-1,3-OXAZINES AND N-3-OXOALKYLAMIDES: METHODS OF PRODUCTION AND PROPERTIES (REVIEW)

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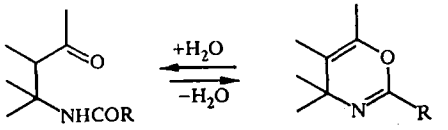
*Data on the methods of synthesis and the properties of N-3-oxoalkylamides and 4H-1,3-oxazines not containing functional groups in the heterocycle are reviewed.*

In the first papers on the chemistry of 4H-1,3-oxazines, which appeared at the end of the last century [1, 2], N-3-oxoalkylamides were used as precursors of 4H-1,3-oxazines. Developments in the chemistry of the monocyclic derivatives of 1,3-oxazine were concerned with the high biological activity discovered in certain functional derivatives of 1,3-oxazines and also their possible use in the synthesis of other practically important compounds. The experimental material that has accumulated during these years has been summarized in several reviews [3-7]. However, existing data on the methods of synthesis, structure, and properties of 4H-1,3-oxazines have not been classified and are sometimes simply contradictory. At the same time it is known that these compounds and their hydrolysis products (N-3-oxoalkylamides) are widely used in the synthesis of heterocycles and biologically active substances. A recent review on this subject [8] was mainly devoted to the oxo derivatives of 4H-1,3-oxazines. Experimental data on the chemistry of N-3-oxoalkylamides that have accumulated since the last century have not been correlated. Information on their synthesis has only been reported in a series of reviews devoted to individual methods of synthesis [9-13].

The aim of the present review was to summarize the data on the chemistry of unsaturated 4H-1,3-oxazines not containing functional groups in the heterocycle and also their hydrolysis products — N-3-oxoalkylamides — published up to 1996. The published data on the two types of compound are treated together in a single paper for the following reasons.

1. For the N-3-oxoalkylamides and 4H-1,3-oxazines there are many common methods of preparation, which can lead to one or the other compound depending on the structure of the reagents or the method of isolation of the reaction products.
2. Since 4H-1,3-oxazines and N-3-oxoalkylamides are used for the synthesis of each other, it is useful to know their specific methods of preparation.
3. Both N-3-oxoalkylamides and 4H-1,3-oxazines can be used in the synthesis of the same compounds.




Classification of the data for the various types of compounds under discussion according to structural features will lead to loss of useful information for each of them.

We divided the methods for the preparation of the compounds under discussion into six types, corresponding to the six formal schemes that follow:

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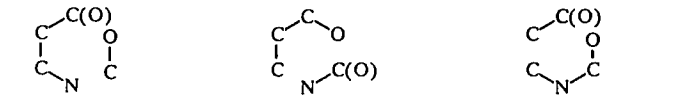
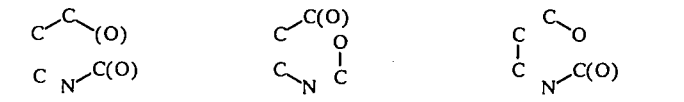


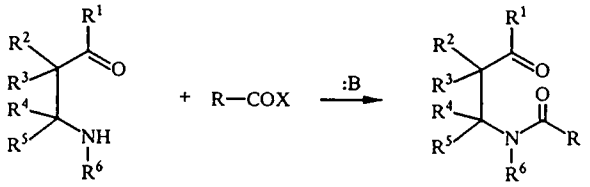




The formal schemes correspond to the numbers and types of atoms in the initial fragments that enter the future chain of the N-3-oxoalkylamide. The oxygen atoms shown in parentheses may be present in the molecule of the initial compound or may appear as a result of the transformation of the intermediates or as a result of hydrolysis of the 4H-1,3-oxazines.

## 1. METHODS OF PREPARATION OF 4H-1,3-OXAZINES AND N-3-OXOALKYLAMIDES

### 1.1. Methods of Preparation of [NCCC(O) + CO]

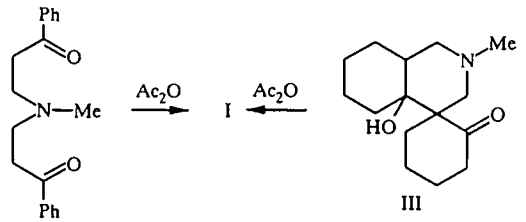
Acylation of 1,3-aminodiketones or their salts in the presence of bases by carboxylic acid anhydrides or halides is one of the methods now used successfully for the synthesis of the N-3-oxoalkylamides (I) [2, 14-17].




I

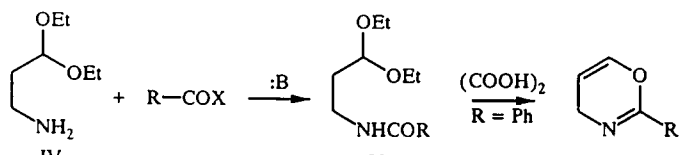
R = Ar. Alk; $R^1$ = Alk, Ar; $R^2$, $R^3$, $R^4$ = H, Alk, Ar;
$R^1 + R^2 = (CH_2)_4$; $R^3 + R^4 = (CH_2)_4$; $R^4 + R^5 = (CH_2)_5$;
$R^5$ = H; $R^6$ = H, Alk

The products (II, III) from the condensation of primary amines under the conditions of the Mannich reaction have been used for the production of N-methyl-substituted N-3-oxoalkylamides [18, 19].




II III

The acylation of the 1,3-amino acetal (IV) gave the amido acetals (V), which can be hydrolyzed to the corresponding N-3-oxoalkylamides [20] or converted by the action of oxalic acid into the oxazines (VI) [1]:



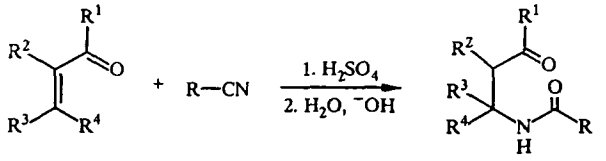

IV V VI

R = Me, X = Ac; R = Ph, X = Cl

In spite of the fact that N-3-oxoalkylamides can be obtained with satisfactory yields by this method, the low stability of many of the initial 1,3-aminocarbonyl compounds substantially limits its possibilities.

### 1.2. Methods of Preparation [CCCO + NC(O)]

The reaction of $\alpha,\beta$-unsaturated ketones with nitriles in the presence of acids was reported in papers by Ritter [21] and in the more recent investigations [22, 23]. It was shown that the action of sulfuric acid on mesityl oxide and phenyl vinyl ketone followed by treatment of the reaction mixture with an aqueous solution of alkali gave the N-3-oxoalkylamides (VII).

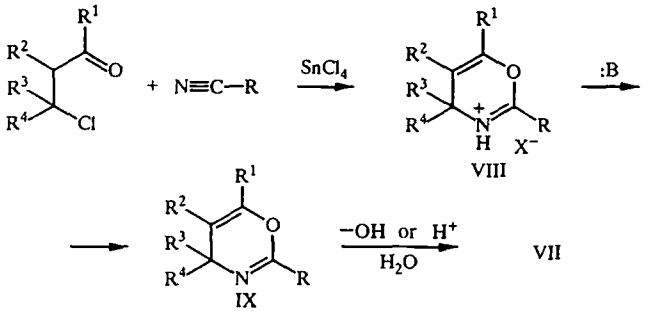



VII

25...55%

R = Alk, Ar; $R^1$ = Me, Ph; $R^2$ = H; $R^3$ = Me, H; $R^4$ = Me, Ph

Higher yields are obtained in the reaction of 1,3-dichloro ketones with nitriles in the presence of tin tetrachloride. In this case, depending on the treatment of the reaction mixture, 4H-1,3-oxazines (IX), their salts (VIII), or N-3-oxoalkylamides (VII) can be isolated [16, 24-27].

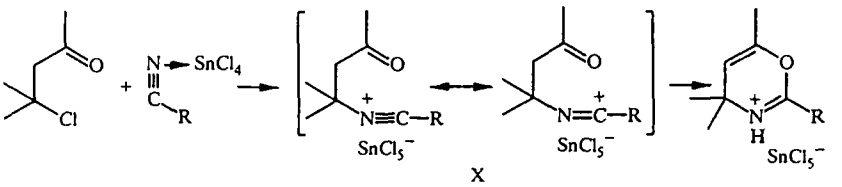



VIII

IX

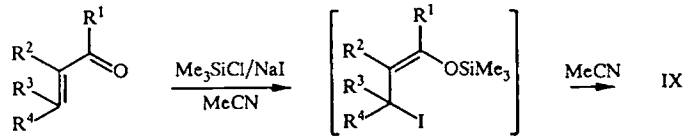
$X^- = SnCl_5^-$; $1/2SnCl_6^{-2}$; $R^1$ = Ar, Alk; $R^2$ = H, Alk;
$R^3$,$R^4$ = Alk or $R^3$ = H, $R^4$ = Ar; R = Alk, Ar, Bn

As in the case of the Ritter reaction, the reaction of nitriles with 1,3-dichloro ketones takes place through the formation of the acyclic intermediate (X) [23, 24]. The possibility of the addition of the nitriles to the 1,3-dichloro ketones, like addition to $\alpha,\beta$-unsaturated ketones, must therefore depend on the ability of the substrate to form a stable carbocation. This agrees well with the fact that the synthetic methods examined in this section give good results only during the preparation of 4H-1,3-oxazines containing two alkyl groups or an aryl substituent at position 4 of the heterocycle.



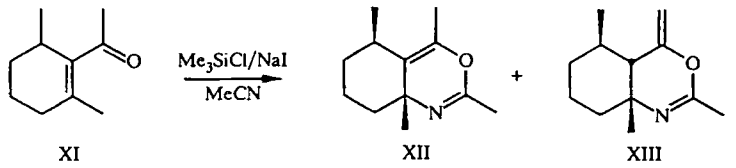

X

4H-1,3-Oxazines readily undergo hydrolysis. During their isolation from the salts N-3-oxoalkylamides are often formed as impurities. The method for the synthesis of 4H-1,3-oxazines from $\alpha,\beta$-unsaturated ketones, nitriles, and trimethyliodosilane [28], generated in the reaction medium from trimethylsilyl chloride and sodium iodide, is free from this shortcoming. As a rule, the method makes it possible to obtain almost pure 4H-1,3-oxazines with yields of 60-90%.



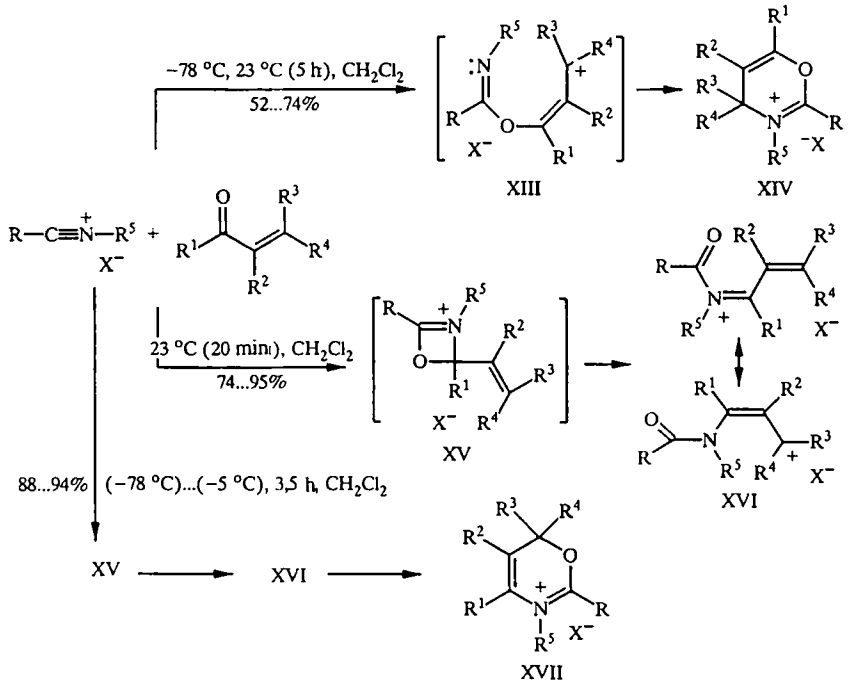

R = Me; $R^1$ = Alk, $R^2$ = H, $R^3$ = Alk, $R^4$ = Alk, $R^1 + R^2$, $R^2 + R^3$ = cycloalkyl

In the case of the α,β-unsaturated ketone (XI), however, a mixture of the isomeric oxazines (XII, XIII) in a ratio of 1:5 was isolated.




XI XII XIII

Nitrilium N-alkylhexachloroantimonates enter into reaction with unsaturated aldehydes and ketones [29, 30]. The reaction of nitrilium salts with chalcones leads to N-alkyl-4H-1,3-oxazinium hexachloroantimonates (XIV), while reaction with crotonaldehyde and (*E*)-2-methyl-2-butenal leads to the 6H-1,3-oxazinium salts (XV). These results are difficult to explain if it is assumed that the reaction takes place by a concerted Diels–Alder mechanism as [4 + $2^+$]-cycloaddition. The authors [29] consider that the formation of the intermediate (XIII) or concerted [2 + $2^+$]-cycloaddition of the carbonyl group and the triple bond of the nitrilium cation to form the intermediate (XV) at the first stage is more likely. The opening of the four-membered ring of compound (XV) can lead to the intermediate compounds (XVI) or (XIII). The cation (XIII) can cyclize to the 4H-1,3-oxazinium salt (XIV), while compound (XVI) can cyclize to the 6H-1,3-oxazinium salt. At the same time the N-acyliminium salts (XVI) are fairly stable and can be isolated in some cases.



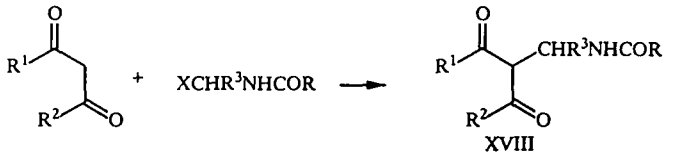

X = $SbCl_6$; R = Alk, Ar; $R^1$ = Ar, H; $R^2$ = Alk, H; $R^3$ = Ar, Alk; $R^4$ = H; $R^5$ = Alk

However, these conclusions are not final, and the authors [29] do not rule out the possibility that the 4H-1,3-oxazinium salts (XIV) are the products from rearrangement of the isomeric compounds (XVII).

## 1.3. Methods of Preparation [CC(O) + CNCO], [CC(O) + C + NC(O)], and [CC(O) + NC + CO]

The type of construction of N-3-oxoalkylamides and 4H-1,3-oxazines under discussion includes amidoalkylation. Carbonyl compounds, enol ethers and esters, silylenol ethers, enamines, and alkynes have been used as substrates in these reactions. Amidoalkylating agents with the general formula $RCON(R^1)CH(R^2)X$ with X = Hal, OH, OAlk, OCOAlk, NHCOAlk, NHCOAr, $NAlk_2$, $NAlk_3^+$, and benzotriazolyl have been used, depending on the activity of the substrate. The substituent $R^1$ can be hydrogen or alkyl, and $R^1 + R^2$ can be linked into a ring. The amidoalkylating reagents can be prepared beforehand or produced directly in the reaction mixture, e.g., from the amide and aldehyde or imine and carboxylic acid halide. Whereas the previous group of methods [CCCO + NC(O)] are used for the construction of 4H-1,3-oxazines containing two alkyl groups or aryl at position 4 of the heterocycle (or at the $\beta$ position from the carbonyl of the N-3-oxoalkylamides), amidoalkylation is as a rule used for the production of 4H-1,3-oxazines and N-3-oxoalkylamides containing hydrogen atoms or one alkyl or aryl substituent at these positions. This is due to the accessibility of the amidoalkylating reagents. A series of reviews by Zaugg were devoted to $\alpha$-amidoalkylation [9-12].

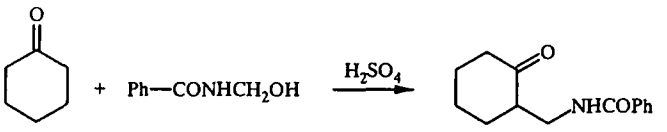
**1.3.1. Amidoalkylation of Carbonyl Compounds.** One of the first papers on the production of N-3-oxoalkylamides by this method was published in 1930. The amidomethylation of 1,3-diketones and cyclic 1,3-diketones by N-hydroxymethylbenzamide in sulfuric acid was described in [31-33]. The amidoalkylation of cyclohexanedione and acetoacetic ester also takes place in acetic anhydride under the action of benzylidenebisbenzamide and benzylidenebisacetamides [33, 34] with the formation of the N-3-oxoalkylamides (XVIII) with low and moderate yields.




XVIII

X = OH, NHCOR;
R = Me, Ar; $R^1$ = Me, Ph; $R^2$ = Ph, $CO_2Et$; $R^1 + R^2 = (CH_2)_2$, $(CH_2)_3$, $R^3$ = H, Ar

With methylolbenzamide in sulfuric acid cyclohexanone forms 2-oxo-1-benzamidomethylcyclohexane (XIX) with yields of 70-80% [35].

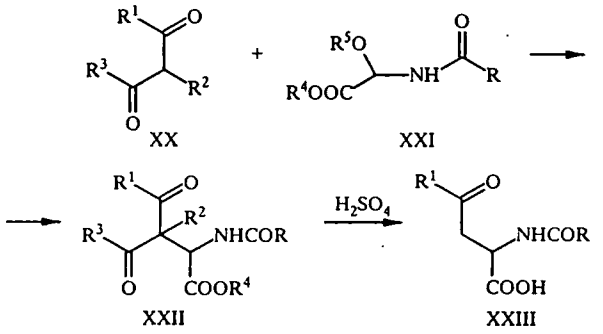



XIX

It is not only $\alpha$-hydroxyalkylamides that can be used as amidoalkylating agents in concentrated sulfuric acid. In this case the reactivity of the amidoalkylating agents is determined by the relative electrophilicity of the carbocations formed from them [9], while the nature of the leaving group is unimportant. The most readily available amidoalkylating agent, usually the $\alpha$-hydroxyalkylamide, is therefore chosen.

Under the influence of strong acids $\alpha$-hydroxyhippuric acid (XXI) enters into reaction with $\beta$-keto esters and $\beta$-diketones (XX) [36, 37]. In concentrated sulfuric acid the initial products of the amidoalkylation of the $\beta$-keto esters (XXII) ($R^2 = R^4 = H$) are converted into the N-3-oxoalkylamides (XXIII). However, in methanesulfonic acid, in a mixture of 10% sulfuric acid and acetic acid, or under the influence of boron trifluoride in methylene chloride, the reaction leads to compound (XXII) with yields of 40-90%. The N-3-oxoalkylamides (XXI) ($R^4$ = Me, $R^2$ = H or Me) were obtained in the same way with yields of 40-80% by the action of methyl methoxyhippurate (XXI) on compounds (XX) in trifluoroacetic acid or in an inert solvent in the presence of boron trifluoride.

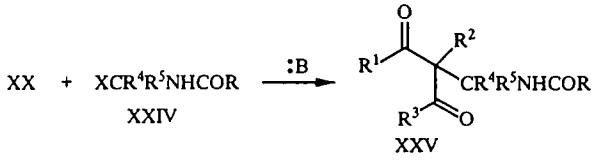
The use of amidoalkylation in sulfuric acid is restricted by side reactions, into which the aliphatic compounds enter in strong acids. It is known that the reaction of N-methylolbenzamide with cyclohexane-1,3-dione gives an aminomethylated diketone with the following yields: 36% in concentrated sulfuric acid; 20% in an alcohol solution of hydrogen chloride; 40% in acetic acid in the presence of zinc chloride; 65% in acetic acid in the presence of boron trifluoride etherate [9, 33].



XX XXI XXII XXIII

R = Ph; $R^1$ = Me, Ph; $R^2$ = H, Me; $R^3$ = Me, Ph, COOEt, COOMe;
$R^5$ = $R^4$ = H, Me

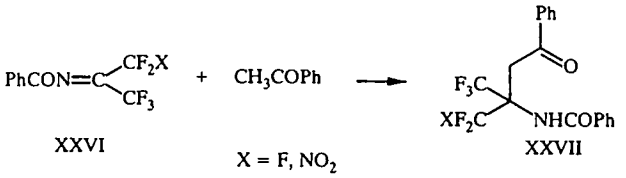
In a number of cases good results were obtained during amidoalkylation in basic media. For example, 1-phenylcarboxamidomethyl-1H-1,2,3-benzotriazole ($PhCONHCH_2Bt$, Bt = benzotriazolyl) in reaction with the lithium enolate of cyclohexanone in a molar ratio of 1:2.1 gave an 85% yield of the N-3-oxoalkylamide (XIX) [38]. Compounds (XXV) were obtained by the amidoalkylation of β-diketones [32], cyclic 1,3-diketones [39, 40], and β-keto esters [32, 41-44] by N-α-chloroalkylamides (XXIV) (X = Cl) [32, 39, 43], N-α-acetoxyalkylamides (XXIV) (X = OCOMe) [42], and N-(dialkylaminomethyl)amides (XXIV) (X = $NEt_2$) [41]. Alkali-metal alkoxides, sodium hydride, triethylamine, and sodium hydroxide were used as bases. The yields of the N-3-oxoalkylamides (XXV) vary within wide limits. The use of equimolar amounts of the enolate in relation to the amidoalkylating reagent leads to the formation of significant amounts of bisamidoalkylation products [38, 44].



XX + $XCR^4R^5NHCOR$ (XXIV) → (:B) → XXV

X = Cl, OCOMe, $NEt_2$; R = H, Alk, Ar; $R^1$ = Alk, Ph; $R^2$ = Alk, Ar, H;
$R^3$ = Alk, OAlk; $R^1 + R^3 = CH_2C(CH_3)_2CH_2$; $R^4$ = H; $R^5$ = H, $CCl_3$, COPh;
$R^4 + R^5 = COC_6H_4CO$

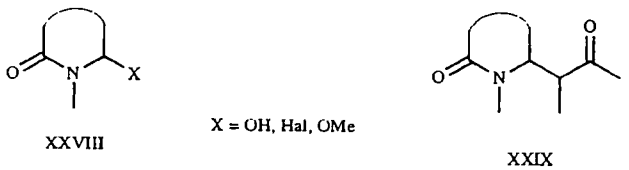
In reaction with bases N-α-chloroalkylamides can be converted into N-acylimides, which are also effective amidoalkylating agents. For instance, when heated with acetophenone without a catalyst the benzoylimines (XXVI) form compounds (XXVII) [45].



XXVI + $CH_3COPh$ → XXVII

X = F, $NO_2$

The amidoalkylation of ketones, acetylacetone, cyclic 1,3-diketones, acetoacetic ester, and its C-alkylated derivatives by heterocyclic reagents having the structure (XXVIII) gave N-3-oxoalkylamides with the general formula (XXIX) [46-49].



XXVIII

X = OH, Hal, OMe

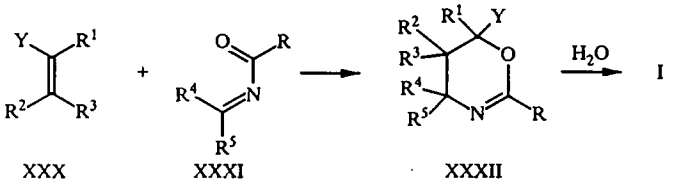
XXIX

Amidoalkylating agents can be produced directly in the reaction medium from aldehydes, amides, or nitriles [11], and amidoalkylation can therefore be realized as three-component condensation. By the condensation of acetoacetic ester or acetylacetone with aromatic or aliphatic aldehydes and acetonitrile in the presence of acetyl chloride and catalytic amounts of

$CoCl_2$ it was possible to obtain good yields of N-3-oxoalkylacetamides (XXV) (R = $R^1$ = Me; $R^2$ = $R^5$ = H; $R^3$ = Me, OMe; $R^4$ = Alk, Ar) [50].

**1.3.2. Amidoalkylation of Enol Ethers and Enamines.** Electronic-excessive olefins, such as enamines, silylenol ethers, and enol ethers and esters, enter readily into amidoalkylation.

The reaction of vinyl ethers [45, 51], 2-methoxybutadiene [52], and enamines [10, 53] (XXX) with electrophilic N-acylimines (XXXI) gave the oxazines (XXXII), while their subsequent hydrolysis led to N-3-oxoalkylamides (I). As a rule the yields of compounds (XXXII) and (I) were fairly high. The acylimines (XXXI) can be prepared in advance or in the reaction medium from the corresponding N-α-halogenoalkylamide and triethylamine. The electronic nature of both the reagent and the substrate have a significant effect on the reaction. In [10] it was noticed that the amidoalkylation of the enamine (XXX) (Y = $NMe_2$, $R^1$ = H, $R^2$ = $R^3$ = Me) by the less electrophilic acetylimine (XXXI) (R = Me, $R^4$ = H, $R^5$ = Ph) and also of the less nucleophilic phenylacetylene and cyclohexanone by compound (XXXI) (R = Me, $R^4$ = H, $R^5$ = $CCl_3$) does not occur. The reaction of the enamine of acetoacetic ester (XXX) (Y = $NMe_2$, $R^1$ = Me, $R^2$ = $CO_2Et$, $R^3$ = H) with N-α-chloromethyltrifluoroacetamide, followed by hydrolysis of the reaction mixture, led to the formation of the N-3-oxoalkylamide (XXV) (R = $CF_3$, $R^1$ = Me, $R^2$ = $R^4$ = $R^5$ = H, $R^3$ = OEt) [54].

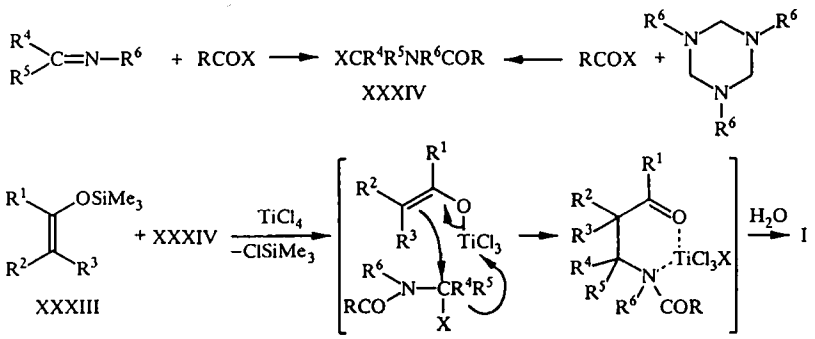


XXX XXXI XXXII

Y = $NAlk_2$, $N(CH_2)_5$, OAlk; R = Alk, Ar, $CF_3$; $R^1$ = H, Me, $CH=CH_2$;
$R^2$ = H, Me, COOEt; $R^3$ = H, Me; $R^1$ + $R^3$ = $(CH_2)_4$; $R^4$ = $CCl_3$, $CF_3$;
$R^5$ = H, $CF_3$

In the presence of Lewis acids vinyl acetate, N-α-alkoxy-, and N-α-halogenoalkylamides (XXIV) (X = OMe, Cl; R = Ph; $R^4$ = H; $R^5$ = H, COOMe) [20, 55] also form the oxazines (XXXII) (Y = OCOMe), R = Ph, $R^1$ = $R^2$ = $R^3$ = $R^4$ = H, $R^5$ = H, COOMe). The yields of compounds (XXXII) amount to 80%.

In contrast to the alkyl vinyl ethers, enamines, and vinyl acetate, the amidoalkylation of the silylenol ethers (XXXIII) leads immediately to the N-3-oxoalkylamides (I). As a rule the N-α-chloroalkylamides (XXXIV), used as amidoalkylating reagents, are produced in the reaction medium [56, 57] from 1,3,5-trialkylhexahydro-1,3,5-triazine or the imine and acyl chloride. N-α-Methoxyalkylamides (R = $CH_3$, $R^4$ = H, $R^5$ + $R^6$ = $(CH_2)_3$, X = OMe) [58]. The reaction is carried out in the presence of Lewis acids [usually titanium(IV) chloride] [12].



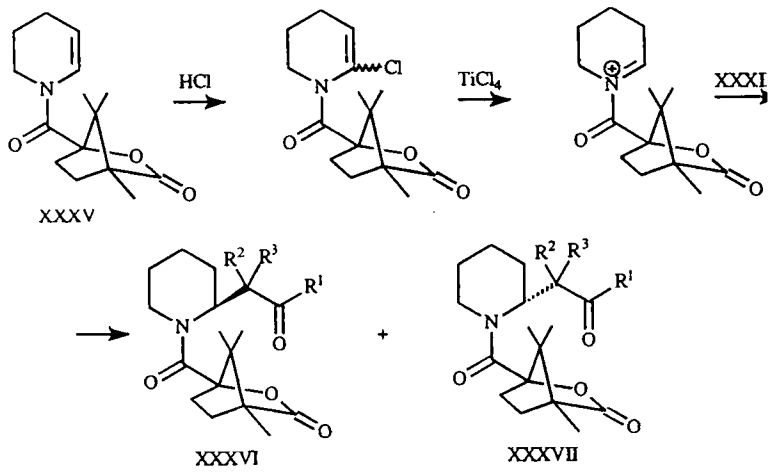
XXXIV

XXXIII

R = Alk, Ar; $R^1$ = H, Alk, Ar; $R^2$= H, Alk; $R^1$ + $R^2$ = cycloalkyl
$R^3$ = H, Alk; $R^4$ = H, Alk; $R^5$ = H; $R^6$ = Alk; $R^5$ + $R^6$ = cycloalkyl

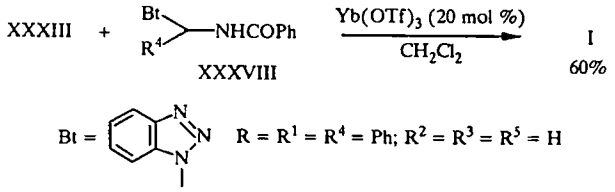
The amidoalkylation of silylenol ethers is a fairly universal method. Not only the alkyl-substituted compounds but also N-3-oxoalkylamides annellated with carbocycles were obtained by this method [56, 58, 59].

By the reaction of the acyleneamide (XXXV) with silylenol ethers (XXXIII) [59] it was possible to realize the enantioselective synthesis of α-substituted piperidines (XXXVI, XXXVII) with high optical purity in the isomer (XXXVI) (87.6%, $R^1$ = $CH_3$, $R^2$ = Ph).

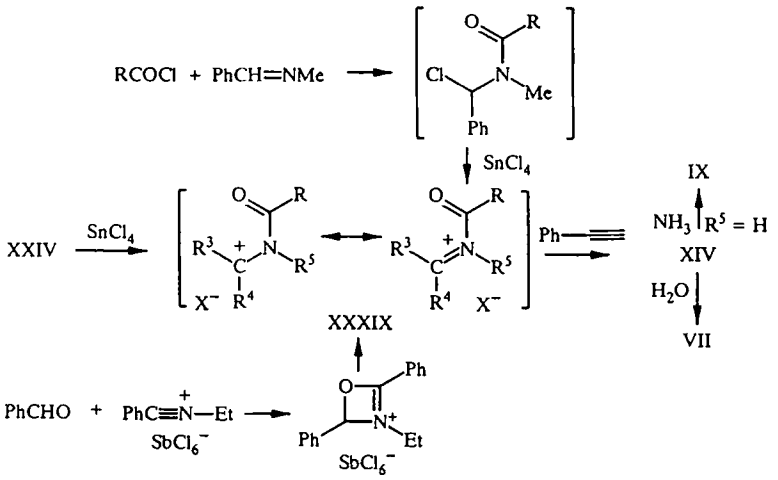



$R^2 = R^3 = H, Me; R^1 = Ph, t\text{-}Bu$

Recently [60] it was shown that N-(α-amidoalkyl)benzotriazoles (XXXVIII) react with silylenol ethers under mild conditions in the presence of ytterbium triflate.



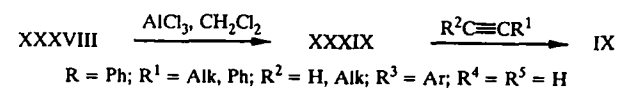

**1.3.3. Amidoalkylation of Acetylenes.** Phenylacetylene enters into reaction with N-α-chloroalkylamides [26] in the presence of tin tetrachloride to form 1,3-oxazinium salts (XIV). The reaction takes place as polar [$4^+ + 2$]-cycloaddition of the cation (XXXIX) to the alkyne [61].




$X = SnCl_5, 1/2SnCl_6$; R = Alk, Ar; $R^1$ = Ph; $R^2 = R^3$ = H, $R^4$ = H, Ar; $R^5$ = H, Me

A mixture of an imine and a carboxylic acid chloride [62] or a nitrilium salt and aldehyde [30] can be used as amidoalkylating agent for the preparation of N-alkyl-substituted 4H-1,3-oxazinium salts (XIII). The treatment of compounds (XIV) with bases leads to 4H-1,3-oxazines (R = H) (IX) [25, 26], and their hydrolysis leads to N-3-oxoalkylamides (VII) [25].

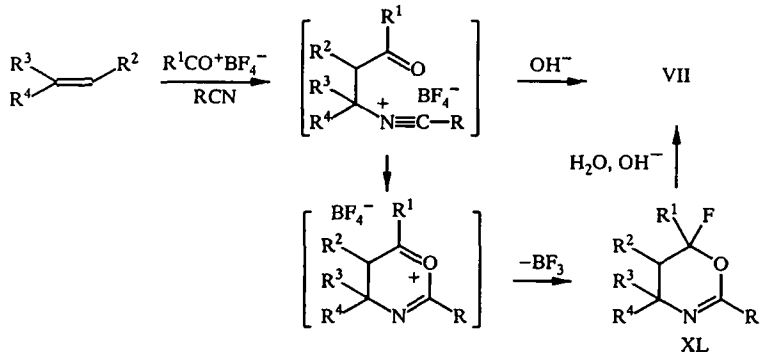
N-(α-Amidoalkyl)benzotriazoles (XXXVIII) react with substituted acetylenes [63] in the presence of anhydrous aluminum chloride in boiling methylene chloride to form 4H-1,3-oxazines (IX) with yields of 76-94%.




R = Ph; $R^1$ = Alk, Ph; $R^2$ = H, Alk; $R^3$ = Ar; $R^4$ = $R^5$ = H

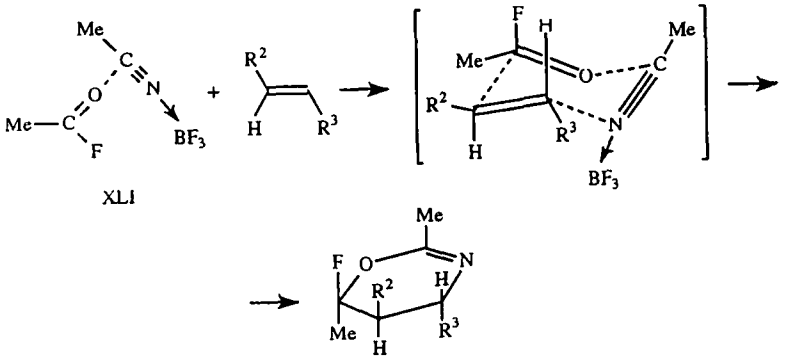
### 1.4. Methods of Preparation [CC + CO + NC(O)]

In 1984 the reaction of alkenes with acetyl fluoroborate in the presence of acetonitrile was investigated [64]. At temperatures between −40 and −20°C in methylene chloride with subsequent treatment of the reaction mixture with aqueous sodium carbonate solution the reaction leads to the products from acetamidation of the alkenes, i.e., N-3-oxoalkylamides (I). If the reaction temperature is increased to 20-40°C, 6-fluoro-5,6-dihydro-4H-1,3-oxazines (XL) are formed as the main reaction products, and they are converted quantitatively into compounds (VII) when heated with an aqueous solution of sodium carbonate. More recently the effect of the nature of the radical of the acylium salt and the nitrile on the nature of the acylamidation reaction was studied [65], and it was shown that acyl fluoroborates containing the radical $R^1$ = Me, Et, Pr enter into reaction in the presence of acetonitrile with the formation of the N-3-oxoalkylamides (VII) at −30°C and the oxazines (XL) at 20°C. If acyl fluoroborates with $R^1$ = *i*-Pr, *t*-Bu, and MeCN are used, the reaction only takes place at 20°C and leads to compounds (XL). It was established that acetonitrile and propionitrile are considerably more active than chloroacetonitrile and benzonitrile in acetamidation.

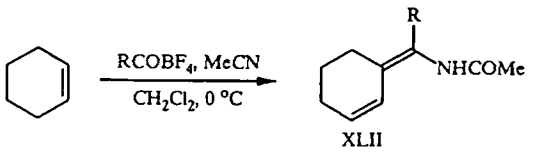



R = Alk, $CH_2Cl$, Ph; $R^1$ = Alk; $R^2$ = H, Alk; $R^3$ = H, Alk; $R^2$ + $R^3$ = $(CH_2)_3$, $(CH_2)_2CH{=}CH$;
$R^4$ = Alk, Ph, $CH_2{=}CH$, cyclo-$C_3H_5$; $R^3$ + $R^4$ = $(CH_2)_3$

Study of the stereochemistry of the acetamidation products showed that the reaction of the alkenes with the MeCOF−MeCN−$BF_3$ system, forming the complex (XLI), results in *syn*-stereospecific addition, leading to 6-fluoro-5,6-dihydro-4H-1,3-oxazines [66, 67]. The structure of the complex (XLI) was confirmed by NMR spectroscopy [67].




Study of the effect of the structure of the unsaturated substrate on the nature of the reaction [64-68] made it possible to establish that cyclohexene, unlike cyclopentene, does not give the products from 1,2-addition during reaction with the MeCOF−MeCN−$BF_3$ system but forms the diene amide (XLII) [68].



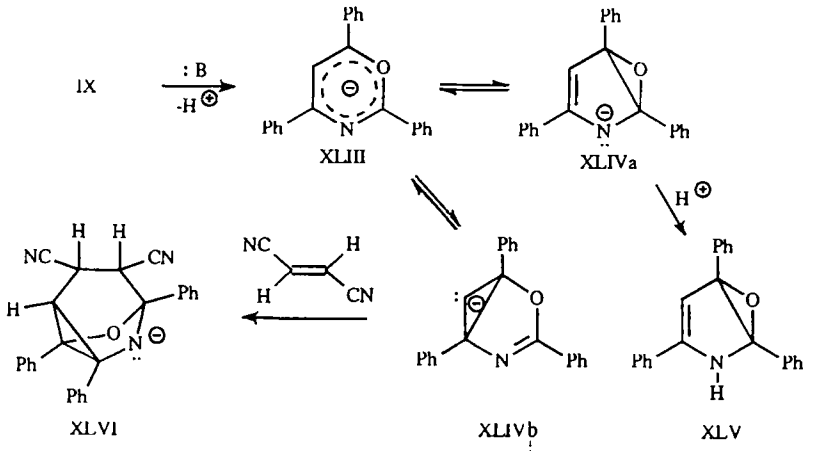

XLII

## 2. CHEMICAL PROPERTIES

In spite of the abundance of familiar methods for the preparation of 4H-1,3-oxazines and N-3-oxoalkylamides, their chemical properties have been insufficiently investigated. Published data on the reactivity of these compounds are fragmentary, and the synthetic possibilities have clearly not been fully realized. Reviews devoted to the reactivity and application of 1,3-oxazines in organic synthesis refer mainly to the hydrated derivatives of oxazine and to azopyrylium salts [5, 6, 69].

### 2.1. Reaction of 4H-1,3-Oxazines and N-3-Oxoalkylamides with Acids and Bases and Electrophilic and Nucleophilic Reagents

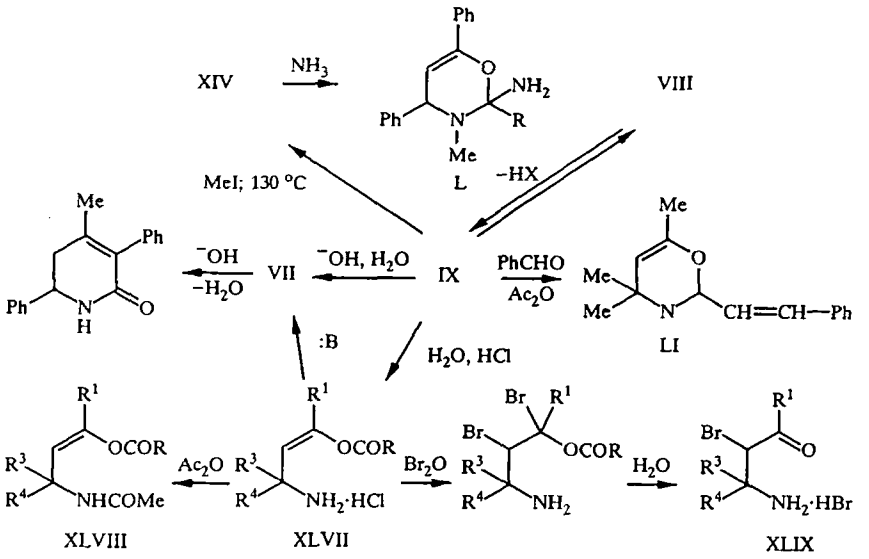
In reaction with strong bases 2,4,6-triphenyl-4H-1,3-oxazine (IX) is deprotonated with the formation of the anion (XLIII). Removal of a proton from the heterocycle (IX) leads to the formation of an extremely unstable conjugated eight-electron $\pi$ system. The dark-blue anion (XLIII) rearranges at temperatures above $-120°C$ to the yellow valence tautomers (XLIVa, b), and compound (XLV) can be isolated from the reaction mixture. The transformation of the anion (XLIVa) into compound (XLV) can be interpreted as $6\pi$-electron electrocyclic ring closure. The anion (XLIVb) can react with fumaronitrile by a mechanism of the [4⁻ + 2]-cycloaddition type, being transformed into the tricyclic system (XLVI) [70-72].




Being weak bases, the 4H-1,3-oxazines (IX) are capable of forming salts (VIII) with strong acids. Treatment of such salts with an aqueous solution of ammonia or sodium bicarbonate leads to regeneration of the 4H-1,3-oxazines [18, 29]. As already noted earlier, the 4H-1,3-oxazines (IX) are hydrolyzed to N-3-oxoalkylamides (VII) by aqueous solutions of bases and acids [15, 16, 24, 25, 30]. Some oxazines are hydrolyzed when stored in air. Their stability depends on the nature of the substituent at position 2 of the heterocycle [15]. The most stable are the 2-aryl-substituted 4H-1,3-oxazines. The products from alkaline hydrolysis of 4H-1,3-oxazines do not make it possible to determine the preferred direction of attack by the hydroxyl unambiguously. It can, however, be said with some certainty that the reaction centers for nucleophilic attack in the oxazine ring are the $C_{(2)}$ and $C_{(6)}$ atoms.

In an acidic medium the oxazines (IX) being hydrolyzed are converted initially into the salts (XLVII), which rearrange under the influence of bases into compounds (VII) [2]. To obtain evidence for the structure of the products from acid hydrolysis the salts (XLVII) were subjected to acylation and bromination, and compounds (XLVIII) and (XLIX) were isolated. This indicates that attack by the nucleophile in an acidic medium is directed at position 2 of the oxazinium salt. Addition of ammonia to the N-methyl-4H-1,3-oxazinium salt (XIV) ($X^- = 1/2SnCl_6^{-2}$) also takes place at position 2 and leads to the dihydrooxazine

(L) [62]. The oxazines (IX) (R = Pr, Ph, *p*-$CH_3C_6H_4$, $R^1 = R^3 = R^4 = Me$, $R^2 = H$) are alkylated with difficulty. For 2-(*p*-tolyl)-4,4,6-trimethyl-4H-1,3-oxazine in reaction with methyl iodide it was only possible to isolate the N-methylation product (XIV) (X = $I^-$) with a yield of 31% [15]. In the presence of acetic anhydride 2,4,4,6-tetramethyl-4H-1,3-oxazine enters into condensation with aromatic aldehydes at the methyl group of the carbon atom at $C_{(2)}$ [15], forming 2-styryloxazine (LI). This is probably due to the strong electron-accepting character of the heterocycle. In an alcohol solution of alkali bis(2-benzyl-6-methyl-4-phenyl-4H-1,3-oxazinium) hexachlorostannate (VIII) is converted into 4-methyl-3,6-diphenyl-5,6-dihydropyridin-2(1H)-one [16].




R = Me, Ph; $R^1$ = Me, Ph; $R^2$ = H; $R^3$ = H, Me; $R^4$ = H, Me

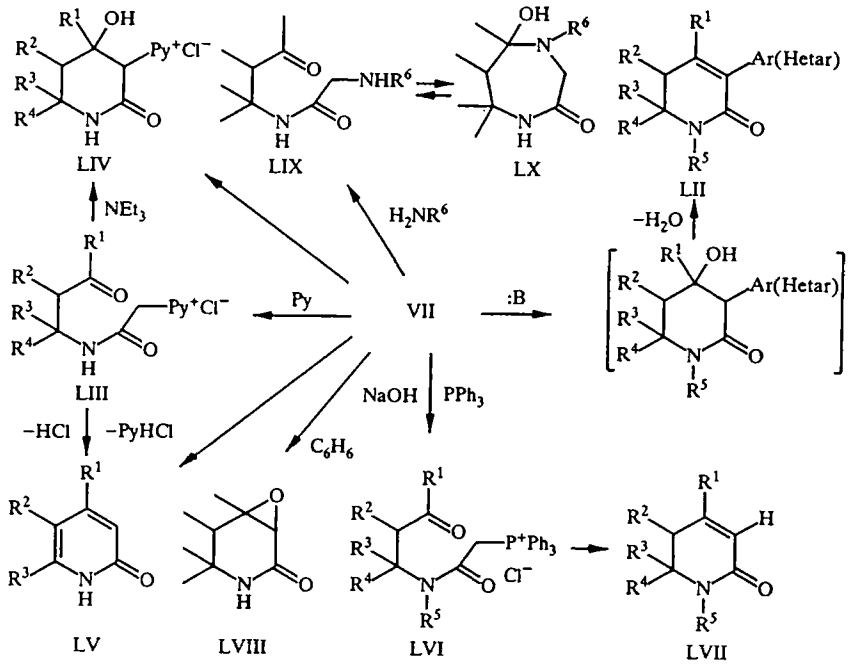
During the recyclization of the salt (IX) to 4-methyl-3,6-diphenyl-5,6-dihydropyridin-2(1H)-one the oxazine ring is hydrolyzed with the formation of the corresponding N-3-oxoalkylamide (VII). The cyclization of N-3-oxoalkylamides having a mobile hydrogen atom at the α position to the carbamoyl group (R = $CH_2Ar$, $CH_2Hetar$) to 5,6-dihydropyridin-2(1H)-ones (LII) by the action of bases is well known [16, 17, 27, 73-76]. In [16, 27] the effect of electronic and structural factors on the rate of this reaction was studied, and it was shown that it depends on the effective volume of the substituents in the N-3-oxoalkyl chain and on the acidity of the α-carbamoyl position of compound (VII). The cyclization of the N-3-oxoalkylamides (VII) is facilitated by increase in the acidity of the α position in relation to the carbamoyl group, by increase in the effective volume of the substituents $R^3$ and $R^4$, and conversely by its decrease in the case of the substituents $R^1$ and $R^2$. The cyclization of compounds (VII) having R = Ph, $R^1 + R^2 = (CH_2)_4$ leads to isomeric derivatives of hexahydroisoquinolin-3(2H)-one, differing in the position of the double bond in the ring [17].

The reaction of N-3-oxoalkylchloroacetamides (VII) (R = $CH_2Cl$) with pyridine at room temperature leads to 1-(3-oxoalkylcarbamoylmethyl)pyridinium chlorides (LIII). 1-(4-Hydroxy-2-oxo-3-piperidyl)pyridinium chlorides (LIV) were obtained by the action of triethylamine at room temperature in DMFA as a result of intramolecular cyclization of the pyridinium ylides generated in the reaction medium from compounds (LIII). When heated, compounds (LIII) [$R^1 = R^4$ = Ph, $R^2 = R^3$ = H; $R^1 + R^2 = (CH_2)_4$, $R^3$ = H, $R^4$ = Ph] in methanol in the presence of triethylamine and also the corresponding N-3-oxoalkylchloroacetamides (VII) in a mixture of pyridine and DMFA give the 2-pyridones (LV) [77].

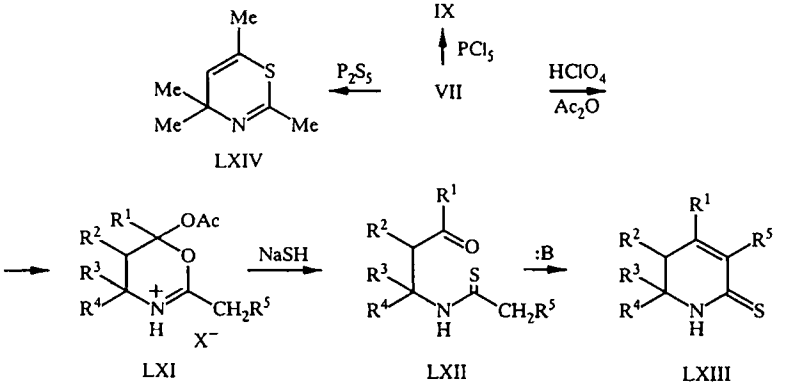
The method for the synthesis of 5,6-dihydropyridin-2(1H)-ones based on the cyclization of N-3-oxoalkylamides is not free from limitations. Their cyclization only becomes possible in the case where the acidity of the α position in relation to the carbamoyl group is higher than the acidity of the α-carbonyl position. This makes it impossible to produce the 5,6-dihydropyridin-2(1H)-ones from the N-3-oxoalkylamides of aliphatic acids. A synthesis of 5,6-dihydropyridin-2(H)-ones by an intramolecular Wittig reaction that makes it possible to remove these limitations was recently developed. The triphenylphosphonium salt (LVI), obtained from compound (VII) (R = $CH_2Cl$) and triphenylphosphine by the action of sodium ethoxide, was converted with a high yield into 5,6-dihydropyridin-2(1H)-one (LVII) [78].

When heated in benzene with a suspension of sodium hydroxide compounds (VII) (R = $CH_2Cl$) cyclize to a mixture of the *cis* and *trans* isomers of 3,4-epoxy-2-piperidinones (LVIII). Substitution of the halogen in the N-3-oxoalkylamides (VII)

(R = $CH_2Cl$) by an amino group leads to the formation of the N-3-oxoalkylamides of α-aminoacetic acids (LIX), which are in ring–chain equilibrium with the corresponding 5-hydroxy-1,4-diazepan-2-ones (LX) [79]

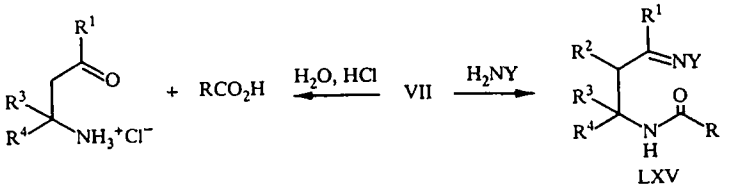


The cyclization of the N-3-oxoalkylamides (VII) to the 4H-1,3-oxazines (IX) by the action of phosphorus pentachloride was realized by Gabriel [2] and was used in the more recent investigations [15]. In the perchloric–acetic anhydride system compounds (VII) ($R^5$ = H, Me, Ph; $R^1$ = Me; $R^2$ = H; $R^3$ = H, Me; $R^4$ = Me, Ph) are converted into 6-acetoxy-5,6-dihydrooxazinium perchlorates (LXI). In reaction with sodium hydrosulfide in methanol or DMFA, compounds (LXI) form the thioamides (LXII) [80, 81] used in the synthesis of 5,6-dihydropyridin-2(1H)-thiones (LXIII) [80, 82, 83]. Direct transformation of the N-3-oxoalkylamides (VII) into the thioamides (LXII) by the action of phosphorus pentasulfide is impossible, since the reaction leads to 4H-1,3-thiazines (LXIV) [84].

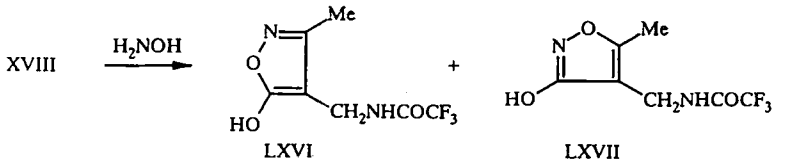


The salts of 1,3-aminoketones and carboxylic acids can be obtained by heating N-3-oxoalkylamides (VII) with aqueous solutions of acids [22].

N-3-Oxoalkylamides react with N-nucleophiles at the carbonyl group. The reaction of compounds (VII) with substituted hydrazines, thiosemicarbazide, and hydroxylamine [22, 35, 37, 51, 54] gave the respective nitrogen derivatives (LXV).

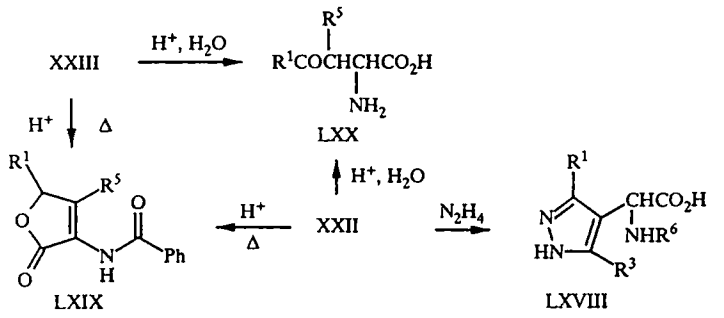


The reaction of the N-3-oxoalkylamide (XVIII) (R = $CF_3$, $R^1$ = Me, $R^2$ = OEt, $R^3$ = H) with hydroxylamine leads to a mixture of the isomeric isoxazoles (LXVI) and (LXVII). The reaction mixture was separated, and the isoxazoles (LXVI) and (LXVII) were isolated in the individual form in a ratio of 7:3 respectively [54].



LXVI LXVII

The pyrazoles (LXVIII) ($R^6$ = COPh) were obtained by the reaction of the N-3-oxoalkylamides (XXII) (R = Ph; $R^1$ = Me, Ph; $R^2$ = $R^4$ = H; $R^3$ = Me, Ph) with hydrazine [37]. Under the action of acids with heat compounds (XXII) and (XXIII) cyclize to 2,5-dihydro-2-furanones (LXIX) ($R^5$ = H, COMe, COPh) [36, 37]. The acid hydrolysis of the benzoylamides (LXVIII, XXII, XXIII) was used for the synthesis of 2-(4-pyrazolyl)-substituted derivatives of glycine (LXVIII) ($R^6$ = H) and α-amino acids (LXX) [37].

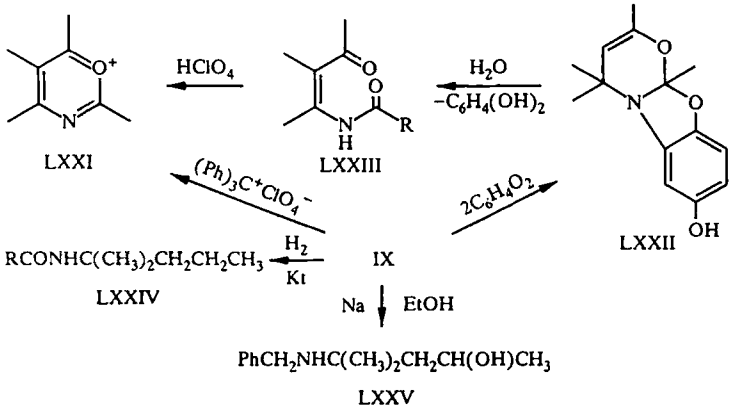



$R^1$ = Me, Ph; $R^3$ = Me, Ph; $R^5$ = H, COMe, COPh; $R^6$ = H, COMe, COPh

## 2.2. Oxidation and Reduction

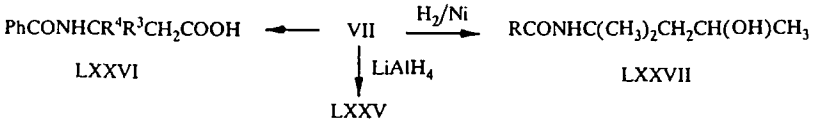
In reaction with trityl perchlorate 4-H-1,3-oxazines (IX) ($R^4$ = H) are converted with quantitative yields into 3-azopyrylium perchlorates (LXXI) [26], which are used in the synthesis of pyrimidine, pyrazole, 1,2-oxazole, and pyridine derivatives [6]. The oxazines (IX) are also oxidized by 1,4-benzoquinone with the intermediate formation of adducts (LXXII), which are transformed in the presence of water into the amides (LXXIII) [85].

The catalytic hydrogenation of the oxazines (IX) (R = Alk, Ph) over Adams catalyst in ethanol leads to cleavage of the ring and the formation of the amides (LXXIV) with yields of 51-81%. The reduction of compound (IX) (R = Ph) with sodium in ethanol leads to 2-benzylamino-2-methyl-4-pentanol (LXXV) [15].

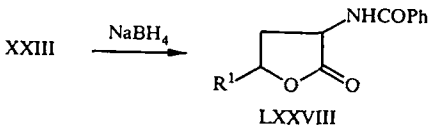


The 3-amidobutyric acids (LXXVI) were synthesized by the haloform cleavage of the N-3-oxoalkylamide (VII) ($R^1$ = Me) [22] and also by oxidation of the aldehyde (VII) ($R^1$ = H) with potassium permanganate [51] and trifluoroacetic acid [59].

The catalytic hydrogenation of N-3-oxoalkylamides (VII) over Raney nickel [14] led to the 1,3-amido alcohols (LXXVII). The reduction of compounds (VII) with 1.2 equivalents of lithium aluminum hydride in ether gave the amino alcohols (LXXV) [15], while reduction with 0.5 equivalent gave compound (LXXVII) [59].




The reaction of N-3-oxoalkylamides (XXIII) with sodium tetrahydroborate took place as reductive cyclization and led to the formation of the γ-lactones (LXXVIII) [36, 37].

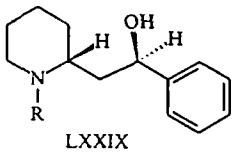


LXXVIII

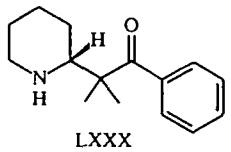
## 3. CONCLUSION

While concluding examination of the methods of preparation and properties of N-3-oxoalkylamides and 4H-1,3-oxazines, we should mention the range of their applications. Unlike their hydrogenated and functionally substituted derivatives [4, 5, 7, 86], the examined 4H-1,3-oxazines have not found wide use as biologically active substances. This can apply to an equal degree to N-3-oxoalkylamides. At the same time the oximes of N-3-oxoalkylamides have found use as herbicides and plant growth regulators [87], while the thiosemicarbazones [35] have antiviral activity.

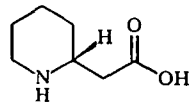
Most important, however, is the use of these compounds as readily available synthons for the production of other heterocyclic and acyclic compounds, including biologically active compounds. For example, it is well known that 1,3-amino alcohols (the products from the reduction of N-3-oxoalkylamides) are used in the synthesis of 5,6-dihydro-4H-1,3-oxazines [88]. N-3-Oxoalkylamides are used for the production of 5,6-dihydropyridin-2(1H)-ones, which are used as herbicides [74, 76] and bacteriostatic substances [75]. Syntheses of a series of α-amino acids [37] and alkaloids of the sedamine group (LXXIX-LXXXI) [59] have been realized on the basis of N-3-oxoalkylamides. In [50] it was reported that 2-methoxycarbonyl-substituted N-3-oxoalkylamides are good precursors of β-lactams.



LXXIX
R = H, Me



LXXX



LXXXI

As already mentioned, 4H-1,3-oxazines and N-3-oxoalkylamides can be easily converted into each other. The position of nucleophilic attack changes in the transition from N-3-oxoalkylamides to 4H-1,3-oxazine derivatives. The condensation of 4H-1,3-oxazines with aldehydes and their reaction with alkylating reagents, followed by opening of the oxazine ring, can be used for the production of N-3-oxoalkylamides with appropriate structures. At the same time the synthesis of azapyrylium salts (LXXI) can be planned on the basis of N-3-oxoalkylamides, which are in a number of cases more readily accessible. An understanding of the individual chemical properties of N-3-oxoalkylamides and 4H-1,3-oxazines in the light of the arsenal of methods that have accumulated for their preparation and of their mutual transformation gives the possibility of seeking new ways of using these compounds in organic synthesis.

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