OXO DERIVATIVES OF 1,3-OXAZINES (REVIEW)

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Data on the chemistry of monocyclic oxo-1,3-oxazines with ring multiple bonds for the period 1976 to 1985, inclusively, are correlated.

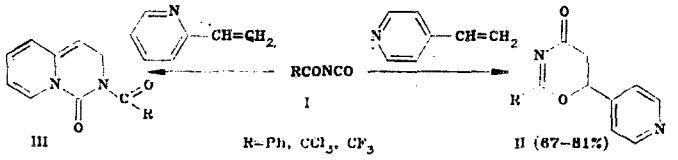
The chemistry of monocyclic 1,3-oxazines, the first representatives of which were known from the end of the last century, has undergone its greatest development only in the last 25 yr. Among these compounds one should particularly single out the oxo derivatives, which are of interest both per se and for the synthesis of other classes of substances.

The aim of the present communication was to correlate data published after 1975 that deal with the chemistry of oxo derivatives of monocyclic 1,3-oxazines with ring multiple bonds. Earlier studies were presented in [1-5]. A recently published review [6] was devoted primarily to saturated rings, and the chemistry of oxo derivatives was virtually ignored. In our paper the material is classified with respect to the number and position of ring multiple bonds, and the thioxo and imino analogs are examined in sections devoted to the corresponding oxo derivatives. It should be especially noted that, to our knowledge, the oxo derivatives of 5,6-dihydro-2H-1,3-oxazines have not yet been obtained.

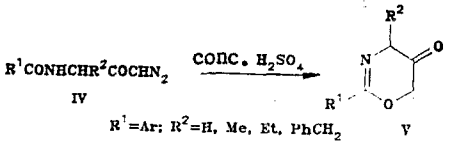
METHODS OF PREPARATION

1. Oxo Derivatives of 5,6-Dihydro-4H-1,3-oxazines

A convenient method for obtaining 5,6-dihydro-4H-1,3-oxazin-4-ones is the addition of acyl isocyanates to unsaturated compounds [3]. Thus acyl isocyanates I react with 4-vinylpyridine to give 2,6-disubstituted oxazines II [7, 8], while 2-vinylpyridine reacts as a diene under these conditions to give pyrido[1,2-c]pyrimidin-1-ones III [8].



A number of 5-oxo derivatives V were obtained in high yields by intramolecular cyclization of 1-diazo-3-aroylamino-2-propanones IV [9-11]. The previously described cyclization of hippuric acid chloride under the influence of diazomethane [12] probably also proceeds with the formation of intermediate diazo ketone IV [9].



5,6-Dihydro-4H-1,3-oxazin-6-ones VII are often obtained by cyclization of 3-acylaminopropionic acids VI in the presence of acetic anhydride [13, 14]. Thionyl chloride and isobutyl chloroformate in the presence of triethylamine [14], as well as dicyclohexylcarbodiimide in pyridine [15], also have been used as the cyclizing agents. In addition to an oxazine, the formation of azetidinone VIII as a result of alternative ring closing at the nitrogen atom is possible; one cannot always distinguish the isomers by means of spectral methods.

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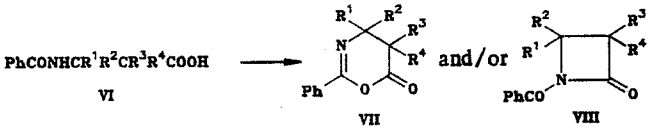
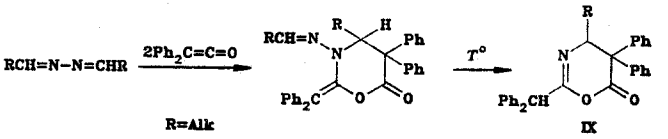
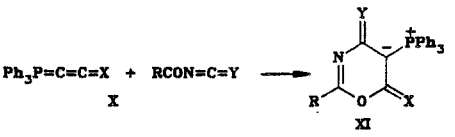
Mass spectrometry [13, 14] or chemical methods [16, 17] may be useful for their identification.



Another method for the synthesis of 6-oxo-1,3-oxazines consists of the use of ketenes and their heteroanalogs as a fragment of the future ring. Thus two molecules of diphenylketene add to aliphatic aldazines in refluxing ether to give oxazinones IX. An intermediate adduct can be isolated at 20°C. Aromatic aldazines react with diphenylketene in a ratio of 1:1 with the formation of 2-azetidinones, whereas ketazines do not undergo the reaction at all [18].

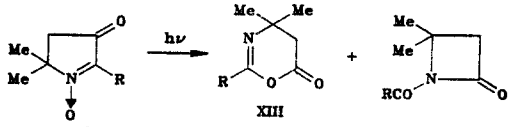


Phosphacumulenes X add to acyl isocyanates and acyl isothiocyanites to give XI [19]



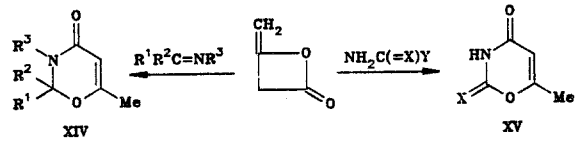
Y=O; X=NPh, fluorenyl, Y=S; X=O, S; R=Me, Ph, *p*-MeC_6H_4

Upon irradiation with UV light, 3-oxo-1-pyrroline 1-oxides XII undergo rearrangement to oxazines XIII together with isomeric azetidines. Only an oxazinone is obtained when R = tert-Bu [15]. Compound XIII (R = Ph) was also obtained by oxidation of the corresponding 1-pyrrolin-3-one with m-chloroperbenzoic acid [20].



2. Oxo Derivatives of 3,4-Dihydro-2H-1,3-oxazines

Cyclization of the (4 + 2) type, in which diketene is used as the four-membered component, is often used to obtain this group of oxo derivatives. Compounds that contain C=N bonds [21-24] and urea derivatives [25, 26] serve as the two-membered fragment. In a number of cases diketene can be replaced by acetaoacetyl chloride [27], acetyl chloride in the presence of triethylamine [23], or acetoacetic ester [25].

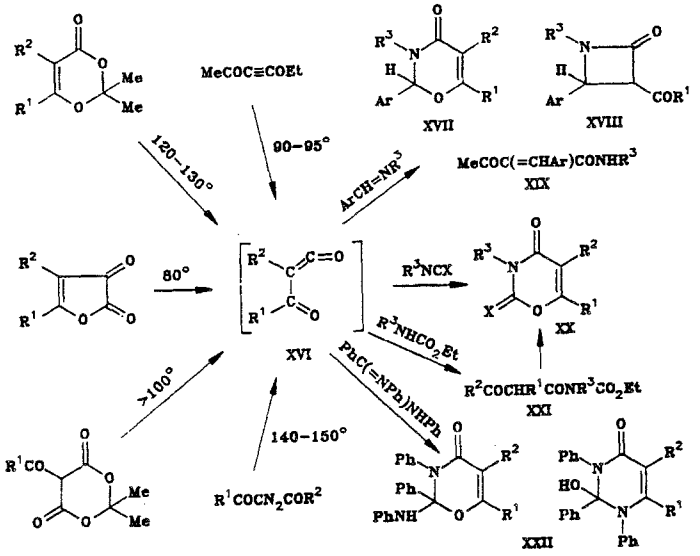


XIV R^1, R^2=H, Alk, Ar; R^3=Alk, Ar, Me_3Si—$N(C_6H_5)CO$, $MeN=C(C_6H_5)$, $PhN=C(C_6H_5)$. $R^1R^2C=CO$; $R^3=SO_2$, Hal; XV X=O, S; Y=NR_2, OEt, $NHNO_2$

Syntheses with the participation of acylketenes XVI generated in situ by various methods have been developed in recent years (Scheme 1). Although, except for perfluoroacylketenes XVIa,b, they were not isolated in the free state, their participation in the reaction is confirmed by the formation of dimers [28-31] and by the IR spectra [27, 32]. Examples of the reactions of acylketenes with isocyanates [31, 33-40], isothiocyanates [31], carbodiimides [31, 36, 39-42], urethanes [43], and Schiff bases [27, 28, 40, 44-48], which lead to oxazi-

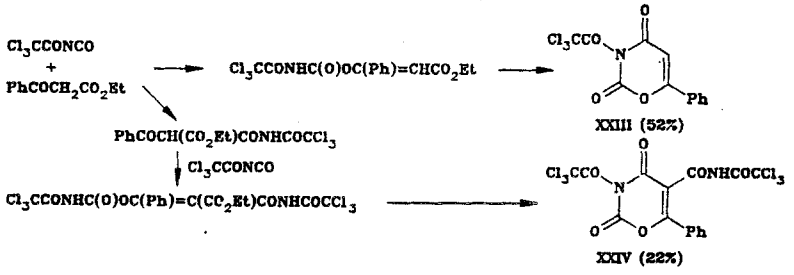
nones XVII and XX, have been described. The reactions are carried out both in inert solvents and without them. As a rule, the yields of products are rather high. In the case of Schiff bases the reaction may be accompanied by the formation of 2-azetidinones XVIII, isomeric oxazines XVII, and 2-arylidene-3-oxobutaneamides XIX; this is probably associated with thermolysis of intermediate oxazinones XVII [27, 40, 44]. The reaction of benzoylphenylketene (XVI, $R^1 = R^2 = Ph$) with urethanes leads to linear adducts XXI, which, under the influence of sulfuric acid, undergo cyclization to oxaziniediones XX in high yields [49]. The structure of the product of the reaction of benzoylphenylketene with N,N'-diphenylbenzamidine (XXII) was not determined unequivocally [49].

Scheme 1

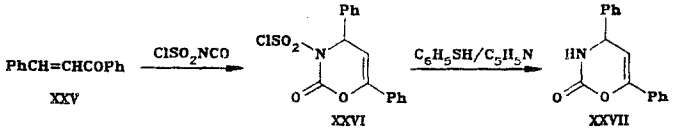


XVI a $R^1=C_2F_5$, $R^2=CF_3$; b $R^1=CF(CF_3)_2$, $R^2=SCF(CF_3)_2$; XVIII, XIX R^1=Me, R^2=H; XX X=O, S, NR^4; XXII $R^1=R^2$=Ph

Acyl isocyanates are also used in the cyclizations of the (4 + 2) type; however, in these syntheses they are donors of a "two-membered" O=C–N–C=O fragment. Thus, in the reaction of trichloroacetyl isocyanate with ethyl benzoylacetate [50], among other reaction products, oxaziniediones XXIII and XXIV were isolated.

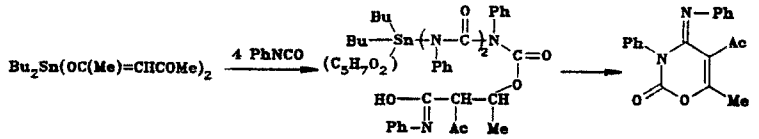


Chlorosulfonyl isocyanate reacts with chalcone XXV to give N-chlorosulfonyloxazine XXVI, which can be converted to oxazinone XXVII [51].



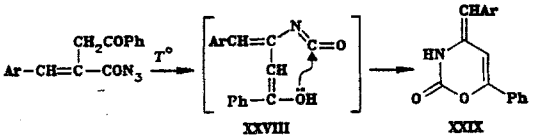
Dibutyldi(O-acetylacetonato)stannane reacts with 4 moles of phenyl isocyanate at 40°C to give 5-acetyl-6-methyl-3-phenyl-4-phenylimino-3,4-dihydro-2H-1,3-oxazin-2-one, probably as a result of incorporation of a Ph–N–C(=O)– fragment into the Sn–O bond with subsequent

cyclization of the intermediate linear adduct. The reaction of phenyl isocyanate with β-dicarbonyl compounds of copper leads to the same compound. [52].

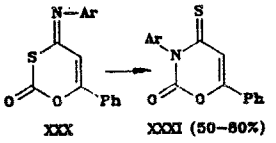


Other preparative methods are used less frequently. Thus the acid-catalyzed cyclization of N-acetoacetyl- and N-(β-methoxymethylacryloyl)-N',N'-disubstituted ureas leads to oxazinedione XV (X = O) [25] and its 5-methyl isomer [53], respectively. Ethyl N-acetoacetylcarbamate undergoes similar cyclization [25].

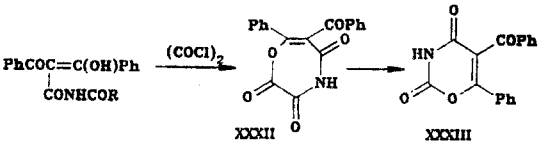
The reaction of 2-arylidene-3-benzoylpropionic acid azides at their melting points proceeds with the formation of intermediate isocyanates XXVIII as a result of the Curtius rearrangement and leads to 2-oxazinones XXIX in high yields [54].



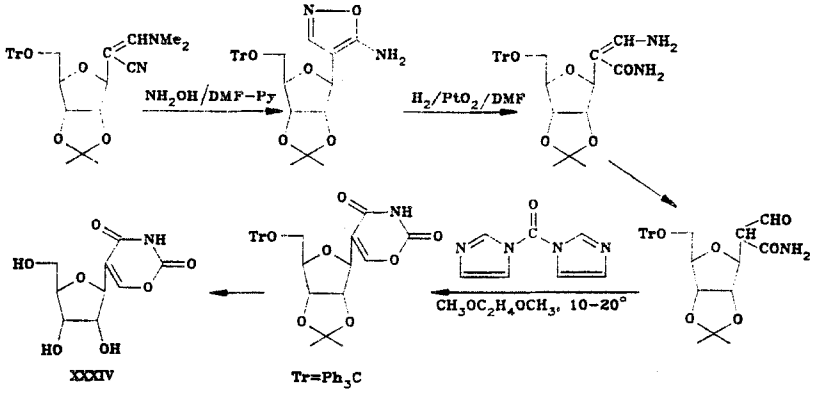
Under the influence of mineral acids in solution in alcohol, 4-arylimino-1,3-oxathiin-2-ones XXX undergo rearrangement to the corresponding 3-aryl-4-thioxo-1,3-oxazin-2-ones XXXI [55].



Oxalyl chloride reacts with N-acyl-2-benzoyl-3-hydroxy-3-phenylacrylamides to give trioxooxazepine XXXII, which is converted to oxazinedione XXXIII in high yield at 170-180°C [32].



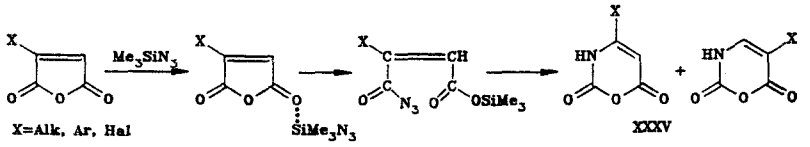
The reaction of substituted 1,2-thiazole-5-thiones with diphenyl- and methylphenylcyclopropenones leads to products that, judging from the IR and PMR spectral data, have substituted 3,4-dihydro-2H-1,3-oxazin-4-one or 2,3-dihydro-6H-1,3-oxazin-6-one structures [56]. A method for obtaining the antibiotic oxazinomycin (minimycin) XXXIV starting from 3-dimethylamino-2-ribofuranosyl-acrylonitrile has been proposed [57].



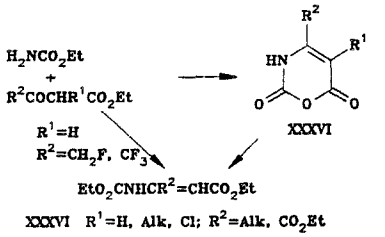
The biosynthesis of XXXIV by several microorganisms has also been investigated [58-61].

3. Oxo Derivatives of 2,3-Dihydro-6H-1,3-oxazines

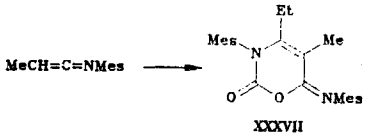
2,6-Dioxo derivatives have the greatest value among compounds of this group. After it had been established that the "3-oxauracil" (XXXV, X = H) that was first obtained in 1927 has valuable biological properties [63], interest in it increased. The reaction of trimethylsilyl azide with substituted maleic anhydrides is a general method for obtaining derivatives of XXXV [64, 65]. It was later shown [66] that this reaction leads to mixtures of 4- and 5-substituted isomers XXXV. 4-Substituted oxazinediones predominate in all cases; Washburne and Lee [67] explain this by primary complexing of the azide at the most accessible carbonyl [67].



A number of oxazinediones XXXVI that contain various substituents in the 4 and 5 positions of the ring were obtained by condensation of β-keto esters with ethyl carbamate by heating in phosphorus oxychloride. In the case of mono- and trifluoroacetyl derivatives (R^1 = H, R^2 = CH_2F, CF_3) one must isolate the intermediate acrylate with subsequent treatment with polyphosphoric acid (PPA) [68].



Methyl-N-mesitylketeneimine at −30°C in the presence of $AlCl_3$ or Et_2AlCl forms a dimer, which, upon treatment with an aqueous solution of sodium hydrocarbonate, adds carbon dioxide to give 6-mesitylimino-2-oxazinone XXXVII together with products of polymerization of the starting keteneimine. The yield of the oxazine increases if the reaction is carried out in a CO_2 atmosphere [69]. In all likelihood, this reaction is similar to the above-examined reactions of acylketenes, but carbon dioxide acts as the dienophile.

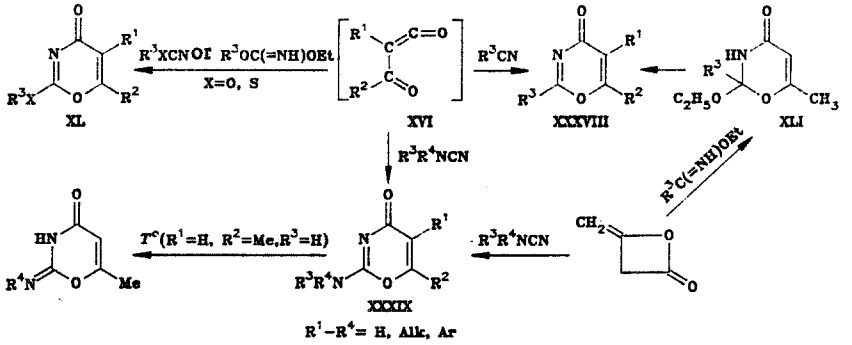


4. Oxo Derivatives of 4H-1,3-Oxazines

Reactions of the (4 + 2) type, in which the already mentioned diketene and acylketenes XVI are used as the starting substances, have been used extensively for the synthesis of 4H-1,3-oxazin-4-ones (Scheme 2). Compounds with triple nitrogen–carbon bonds, viz., nitriles [30, 49, 70-72], cyanamides [29, 36, 72-76], cyanates [29, 36, 77], thiocyanates [37, 38], as well as imidates [49, 78], are used as the "two-membered" component; this makes it possible to obtain 4H-1,3-oxazin-4-ones with various substituents attached to the heteroring $C_{(2)}$ atom (XXXVIII-XL). In the latter case, in the first step 2-ethoxy-3,4-dihydro-2H-1,3-oxazin-4-one (XLI) upon heating splits out a molecule of alcohol [78]. The recently observed recyclization of 3-(o-chlorophenyl)-5-aroylmethylene-2-iminooxazolidin-4-ones upon heating in xylene leads to oxazines XXXIX (R^1 = R^3 = H, R^2 = Ar, R^4 = o-ClC_6H_4), evidently also with the participation of intermediate acylketenes [76, 79, 80].

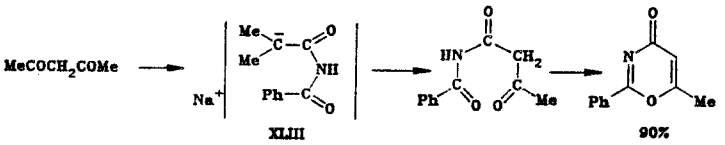
A number of 2-amino-6-aryl-4H-1,3-oxazin-4-ones were obtained by treatment of methylthiopseudourea sulfate with ethyl benzoylacetate in aqueous KOH solution [81, 82].

Scheme 2



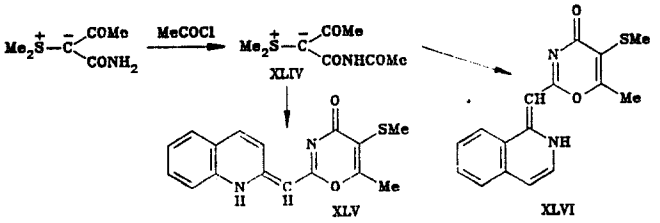
Acyl isocyanates and their analogs are frequently used as the "four-membered" fragment in syntheses of the (4 + 2) type [83]. Thus trichloroacetyl isocyanate adds to N-alkyltrichloro-vinylketeneimines in absolute ether at 18-25°C with the formation of 2-trichloromethyl-5-trichlorovinyl-6-alkylamino-4H-1,3-oxazin-4-ones in greater than 90% yields [84]. The condensation of acyl isothiocyanates with β-diketones gives 5-acyl-4-thioxooxazines XLII in good yields [85].

Under the influence of HI, the adduct (XLIII) of sodium acetylacetonate and benzoyl isocyanate gives N-benzoylacetoacetamide, which undergoes cyclization in trifluoroacetic anhydride [86].



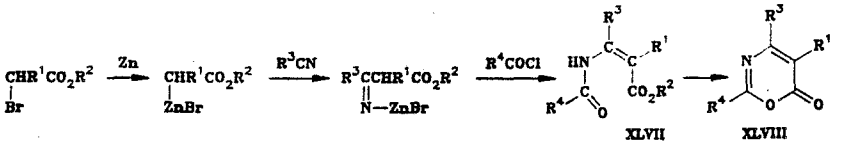
The reaction of benzonitrile oxide with 4,5-disubstituted 3-isoxazolones in refluxing benzene, which leads to the corresponding 5,6-disubstituted 2-phenyl-4H-1,3-oxazin-4-ones in 28-53% yields, was recently described [87].

The reaction of dimethylsulfonium acetylcarbamoylmethylid with quinoline 1-oxide and acetyl chloride in DMF to give XLV is a new method for obtaining 4-oxooxazine derivatives [88]. The intermediate is ylid XLIV, through the methyl carbon atom of the N-acetyl group of which a bond with the quinoline $C_{(2)}$ atom is also formed. Under these conditions isoquinoline 2-oxide gives similar product XLVI [89].



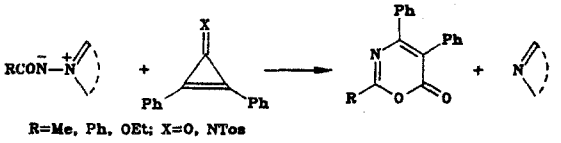
5. Oxo Derivatives of 6H-1,3-Oxazines

The traditional method for obtaining 6H-1,3-oxazin-6-ones is cyclization of β-N-acylamino-α,β-unsaturated acid esters by heating in high-boiling solvents [90]. The method proposed by Lapkin and co-workers [91] makes it possible to obtain oxazines XLVIII under mild conditions (heating in benzene) without isolation of the intermediate acrylates XLVII.



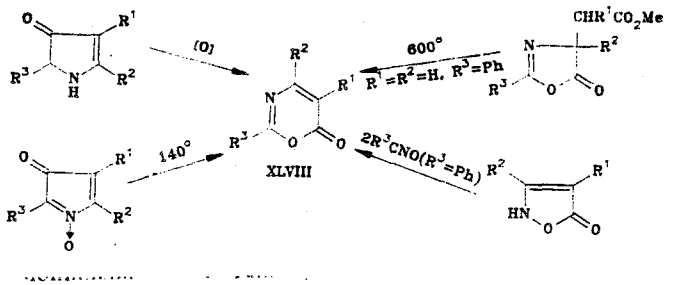
XLVII XLVIII

Another method is based on the reaction of diphenylcyclopropenone and its heteroanalogs with N-acylimino derivatives of N-aminopyridinium, pyridazinium, cinnolinium, and benzocinnolinium ions in hot benzene or DMF [92, 93].



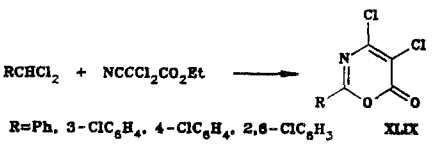
R=Me, Ph, OEt; X=O, NTos

Reactions that proceed with ring expansion of oxo derivatives of five-membered nitrogen heterocycles are often used for the synthesis of 6-oxo-1,3-oxazines. Thus the oxidation of 2-pyrrolin-4-ones [94], the thermal rearrangement of 3H-pyrrol-3-one 1-oxides [95, 96], the pyrolysis of 4-(1-alkoxycarbonylalkyl)-2-oxazolin-5-ones [97, 98], the reaction of benzonitrile oxide and 2H-isoxazol-5-ones [99-103], or the oxidation of the latter [104] lead to oxazines XLVIII in various yields.



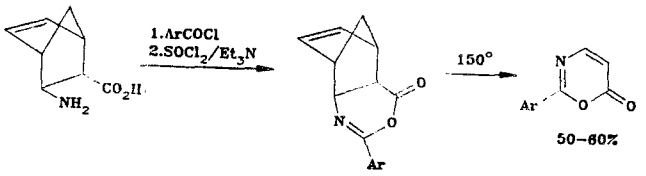
XLVIII

2-Aryl-4,5-dichloro-6H-1,3-oxazin-6-ones XLIX were obtained in up to 50% yields by heating arylidene chlorides and ethyl dichlorocyanoacetate at 150-160°C in the presence of $FeCl_3$ [105].



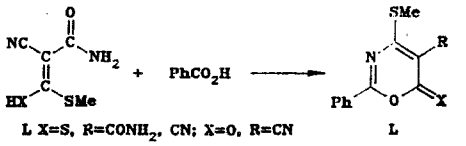
R=Ph, 3-ClC_6H_4, 4-ClC_6H_4, 2,6-$Cl_2C_6H_3$ XLIX

A new method for obtaining 6-oxazinones from norbornene derivatives as a result of a Diels–Alder retroreaction was described in [106, 107]. However, only 2-aryl-substituted compounds could be obtained by this method.



50–60%

6-Thioxo- and 6-oxooxazines L, respectively, were obtained in the reaction of 3-mercapto- or 3-hydroxy-3-(methylthio)-2-cyanoacrylamide with benzoic acid (or its anhydride) in

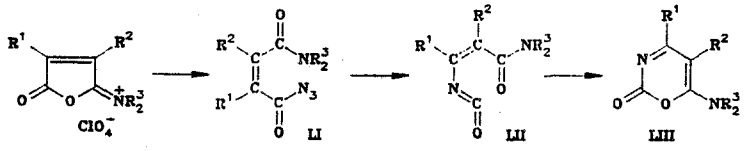


L X=S, R=CONH$_2$, CN; X=O, R=CN

the presence of polyphosphoric ester [108-110]. The formation of an oxazine ring occurs through the cyano group of the starting acrylamide, the carbon atom of which goes into the 4 position of the oxazine ring [109] (see top of following page).

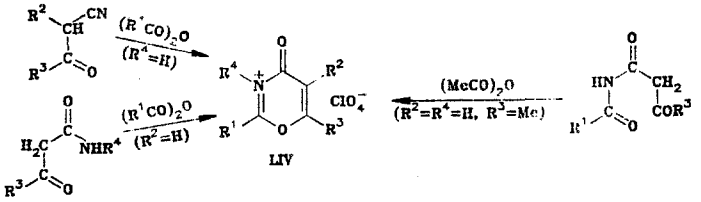
6. Oxo Derivatives of 2H-1,3-Oxazines

Up until recently, 2H-1,3-oxazin-2-ones were unknown. Acyl azides LI, which are formed by treatment of maleinisoimidium perchlorates with sodium azide, in refluxing toluene undergo the Curtius rearrangement to isocyanates LII, which undergo spontaneous cyclization to 6-dialkylaminooxazin-2-ones LIII in up to 80% yields [111, 112]. However, compounds without substituents attached to $C_{(4)}$ and $C_{(5)}$ atoms cannot be obtained by this method [112].

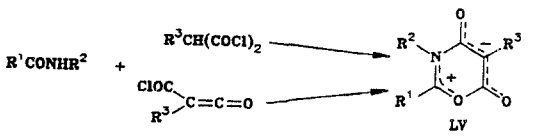


7. Oxooxazinium Salts and Mesoionic Compounds

4-Oxo-4H-1,3-oxazinium perchlorates LIV were synthesized for the first time by acylation of β-keto nitriles by aliphatic acid anhydrides in the presence of equimolar amounts of 70% $HClO_4$ [113]. N-Acylacetoacetamides [114, 115] and β-keto acid amides in acetic anhydride [116] are also used as starting compounds. The use of perchloric acid gives the best yields as compared with other acids [114].



The only representatives of mesoionic oxazinones that have been obtained thus far are betaines — derivatives of 4,6-dioxo-1,3-oxazines (see also a previous review [117]). They are formed in high yields by heating secondary amides with monosubstituted malonyl dichlorides [118] or benzylchlorocarbonylketene [119] in aprotic solvents. In the case of benzanilides (R^1 = R^2 = Ph) at 110°C one observes a side reaction involving recyclization with the participation of the ortho position of the N-phenyl group with the formation of quinoline derivatives [119].



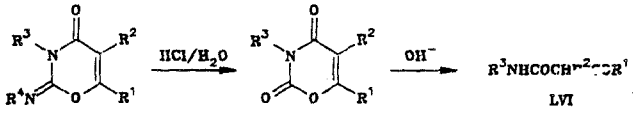
The information stated above provides evidence that the chief attention of researchers has been devoted to the synthesis of 4-oxo derivatives of 1,3-oxazines. To obtain them [4 + 2]-cycloaddition of diketene and related acylketenes to compounds with multiple bonds between nitrogen and carbon atoms, as well as reactions of acyl isocyanates and their analogs with

various unsaturated compounds, are most often used. The intramolecular cyclization of derivatives of β-N-acylamino acids is a convenient method for the synthesis of 6-oxo-1,3-oxazines. Reactions that proceed with ring expansion of five-membered oxaaza- and azaheterocycles are used extensively for their preparation. The reaction of amides with malonic acid derivatives is of general significance for the synthesis of 4,6-dioxooxazines. As a rule, 1,3-oxazines with an oxo group in the 2 position are obtained by cyclization of γ-keto isocyanates, which are formed in the Curtius rearrangement. Other methods have more or less special character.

CHEMICAL PROPERTIES

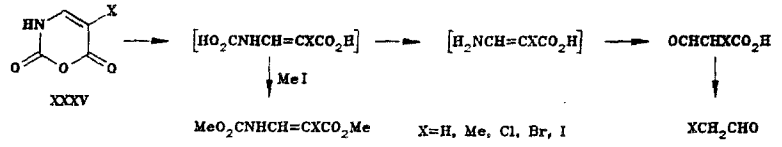
1. Reactions with Oxygen-containing Nucleophiles (Hydrolysis and Alcoholysis)

Oxo derivatives of 1,3-oxazines with ring $C_{(2)}$=N bond, which can formally be regarded as cyclic imido esters, are most sensitive to hydrolytic cleavage reactions. In a number of cases even contact with atmospheric moisture is sufficient for ring opening [7, 15, 113, 114, 118]. The structures of the hydrolysis products depend on the number and sites of the ring oxo groups. Thus the hydrolysis of 4H-1,3-oxazin-4-ones XXXVIII [31, 71, 83] and their salts LIV [113, 114] leads, under mild conditions, to N-acylamides of β-keto acids, whereas 6-oxo compounds, depending on the degree of saturation of the ring, give β-acylamino derivatives [15, 20] or β-acylaminoacrylic acids [94, 104]. The presence of acids and alkalis promotes the cleavage, whereas under severe conditions the reaction is accompanied by decarboxylation [99, 120, 121] and hydrolysis of the acylamino group [99, 101, 118, 120]. The reaction with water makes it impossible to unequivocally determine the primary direction of attack by the nucleophile; however, proceeding from data on methanolysis, it may be assumed that attack at the $C_{(2)}$ atom is preferable for the 4-oxo derivatives [84], while the 6-oxo compounds give methanolysis products corresponding to attack at $C_{(6)}$ atom [99, 101].



The resistance of the ring to hydrolysis increases with saturation of the $C_{(2)}$=N bond. Thus 2,4-dioxooxazines XX (X = O) do not react with dilute acids; this makes it possible to convert 2-imino-4-oxazinones XX (X = NR^3) to dioxo derivatives [31, 36, 82]; alkaline hydrolysis of the latter leads to β-keto acid amides LVI as a result of decarboxylation of the initially formed N-(β-oxoacyl) carbamic acid [31, 36, 53].

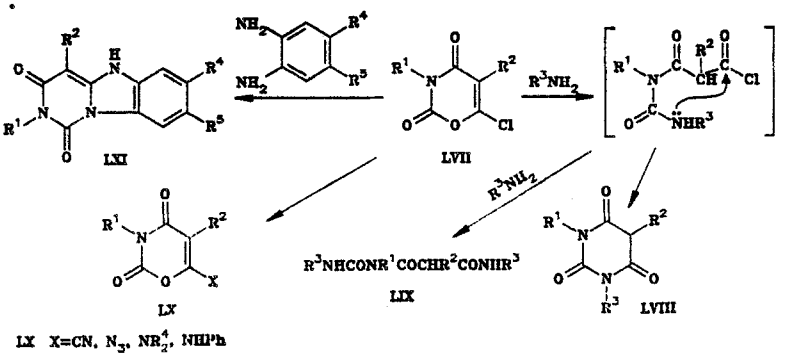
4-Oxazinones XVII, which are resistant to the action of dilute solutions of alkalis, also give amides LVI with splitting out of benzaldehydes under acid-hydrolysis conditions [28, 45, 46]. In slightly alkaline solutions (0.01 M NaOH, 25°C) 2,6-dioxooxazines XXXV form β-carboxyaminoacrylic acids (identified from the dimethyl esters), which then undergo further decomposition to carbonyl compounds. The rate of hydrolysis increases with intensification of the electron-acceptor properties of the substituent attached to $C_{(5)}$ atom [122].



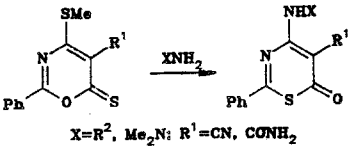
2. Reactions with Nitrogen-containing Nucleophiles

The reaction with aqueous or alcohol solutions of ammonia and primary amines, which leads to the formation of oxo derivatives of pyrimidine, is one of the most widely used reactions of 1,3-oxazinones. The $C_{(2)}$ or $C_{(6)}$ atoms of the oxazine ring undergo nucleophilic attack with subsequent intramolecular cyclization of the linear intermediate, which usually is not isolated. 2,4-Dioxooxazines XX are converted to substituted uracils [25, 49, 53, 123-125], whereas 4H-1,3-oxazin-4-ones XXXVIII [73, 78] and 6H-1,3-oxazin-6-ones XLVIII [91, 99, 125, 126] form 4-hydroxypyrimidine derivatives. Oxazin-4-onium perchlorates LIV react similarly upon refluxing with ammonium acetate in glacial acetic acid [116].

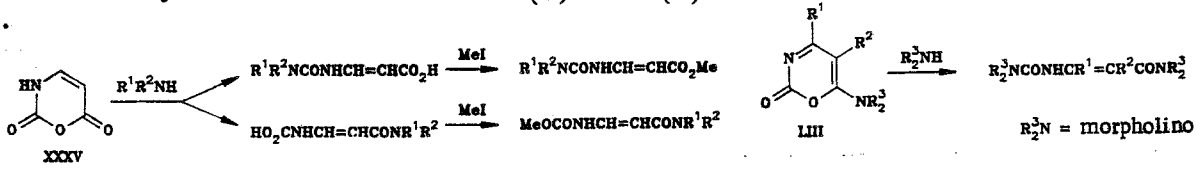
Under the influence of primary amines 6-chloro-2,4-dioxooxazines LVII give barbituric acids LVIII, along with acylureas LIX [127, 128]; ring opening as a result of attack on the $C_{(2)}$ atom by the amine precedes replacement of the halogen [128]. The halogen can be replaced in the cold by cyano, azido, dialkylamino, and anilino groups with retention of the ring [127]. This is actually the only example of nucleophic substitution in the ring of oxazinones. Pyrimidobenzimdazole derivatives LXI are formed in the reaction of dioxooxazines LVII with o-phenylenediamines as a result of ring opening by a second amino group and subsequent recyclization [129].



In the reaction of 6-thioxooxazines L (X = S) with primary amines or 1,2-disubstituted hydrazines replacement of the 4-methylthio group is accompanied by rearrangement to a thiazine ring [121].

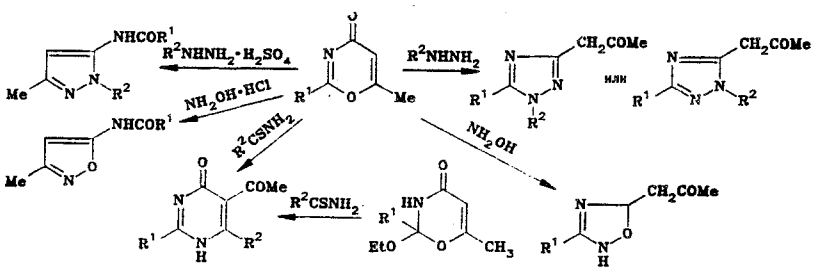


2-Oxooxazines LIII and 2,6-dioxooxazines XXXV give linear aminolysis products; the former react unambiguously at the $C_{(2)}$ atom [112], while the latter form products that correspond to attack by the amine at both the $C_{(2)}$ and $C_{(6)}$ atoms with preponderance of the latter [130].

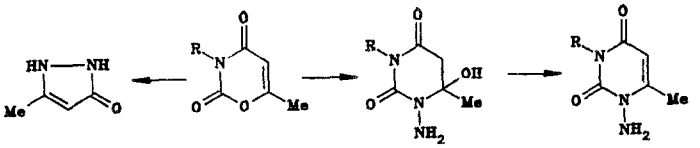


The acid-catalyzed rearrangement of 2-aminooxozinones XXXIX to the corresponding uracils [73] as a result of intramolecular cyclization of the linear intermediate should be ascribed to the same group of reactions. It is noteworthy that the reaction of XXXIX ($R^3 = R^4 = H$) with primary amines proceeds regioselectively and that the nitrogen atom of the amino group in the 2 position is included in the pyrimidine ring. If there is a bulky substituent such as a phenyl group attached to the $C_{(6)}$ atom, to carry out the reaction one must isolate the primary product of ring opening with treatment of the latter with polyphosphoric acid (PPA) [82].

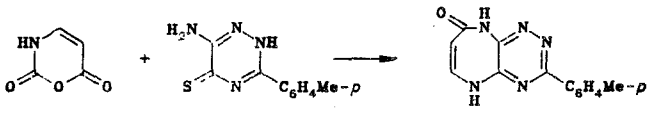
The reactions of oxazinones with bifunctional nitrogen nucleophiles such as derivatives of hydrazine, hydroxylamine, and thioamides are of great interest. By means of these reagents 4-oxazinones XXXVIII can be converted to derivatives of pyrazole [114], 1,2,4-triazole [125, 131, 132], oxazole, 1,2,4-oxadiazole [125, 133], or 4-pyrimidone [131, 134, 135]. The formation of different reaction products is evidently associated with the possibility of nucleophilic attack at both the $C_{(2)}$ and $C_{(6)}$ atoms. Similar transformations under the influence of monosubstituted hydrazines and hydroxylamine to five-membered heterocyclic systems are also known for 6-oxo- [10] and 6-thioxooxazines L [121].



2,4-Dioxooxazines XX react with alcoholic hydrazine hydrate to give 1-aminouracils [26], while refluxing with hydrazine hydrate in the absence of a solvent leads to 5-methyl-3-pyrazolone [26, 136].



Triazino[5,6-b][1,4]diazepinone LXII is formed when "3-oxauracil" and 6-amino-3-(p-tolyl)-1,2,4-triazine-5-thione are heated in DMF [137].

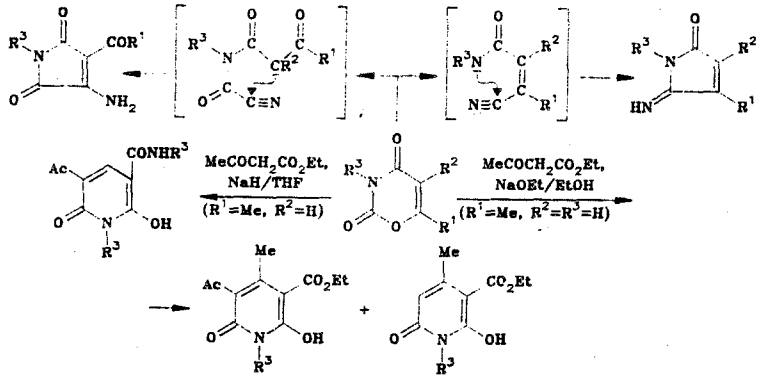


LXII (48%)

The reaction of XLV and XLVI with primary and secondary amines [138] leads to substituted pyrimidoquinolines [89].

3. Reactions with Other Nucleophiles

The reaction of oxazinediones XX with potassium cyanide in aqueous DMFA leads to pyrrole derivatives of two types, depending on which of the ring atoms, $C_{(2)}$ or $C_{(6)}$, of the substrate undergo attack by the nucleophile [139]. Attack on the "soft" 6 position turns out to be preferable, while the other pathway is realized if there is a bulky substituent attached to the $C_{(6)}$ atom. The reaction of oxazinediones XX with sodium ethyl acetoacetate leads to substituted dioxopyridines [136].

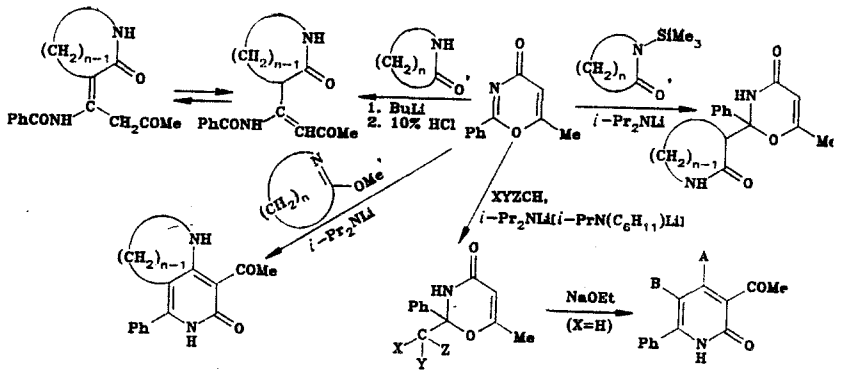


In the reaction of 6-methyl-2-phenyl-4H-1,3-oxazin-4-one with lactams in the presence of butyllithium the nucleophile attacks the heteroring $C_{(4)}$ atom without opening the ring. N-Trimethylsilyllactams in the presence of lithium diisopropylamide react with oxazine to give products of addition to the C=N bond, whereas under the influence of lactim esters oxazine is converted to substituted 2-pyridones as a result of attack at the $C_{(2)}$ atom [140]. The latter are also formed by the action of bases on adducts of oxazine and compounds with an activated methylene group [141].

Replacement of the heteroatom with the formation of the corresponding oxothiazinium salts occurs in the reaction of oxooxazinium salts LIV with hydrogen sulfide in acetic anhydride [114, 115]. 6-Oxothiazines were obtained when 6-thioxooxazines were heated in alcohol [108, 109]. With respect to their mechanism, these reactions are similar to the above-examined transformations of oxazinones to pyrimidones. In a number of cases, under conditions of acidic or alkaline catalysis, ring opening is accompanied by recyclization with involvement of the substituents in the 2 [89, 138] or 5 [121] position (see top of following page).

4. Reactions with Electrophilic Reagents

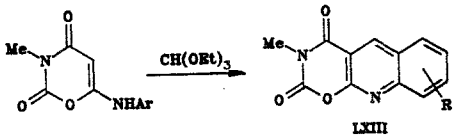
There have been only a few examples of electrophilic substitution reactions in the oxazine ring. Thus "3-oxauracil" readily gives 5-chloro, 5-bromo, and 5-iodo derivatives upon



treatment with, respectively, chlorine in ethyl acetate, bromine in dioxane, and iodine chloride in acetic acid in the presence of potassium acetate [122]. Washburne and Lee [142], on the basis of data on deuterium exchange of 5-H, assume that the ease of halogenation is due to reaction via an addition–cleavage mechanism. The 5-fluoro derivative was obtained by the action of fluoroxytrifluoromethane on XXXV (X = H) [143]. 2,4-Dioxooxazines XX readily add bromine to the multiple bond to give 5,6-dibromo derivatives. Subsequent treatment with triethylamine gives 5-bromooxazinediones [31]. 5-Bromo-6-dibromomethyloxazinedione is formed as a side product under more severe conditions [prolonged refluxing in dichloroethane in the presence of iron (III) chloride] [139]. 2-Amino-6-phenyl-4H-1,3-oxazin-4-one is brominated in the 5 position in the presence of aqueous alkali solution [82].

The hydrogen atom of the NH group of dihydrooxazinones XV and XXXV is readily replaced by alkyl groups by the action of ordinary alkylating agents (dimethyl sulfate, diazomethane, methyl iodide) [25, 66, 68, 136, 144]. Oxa analogs of natural nucleosides – uridine [123] and isouridine [145] – were obtained through trimethylsilyl derivatives.

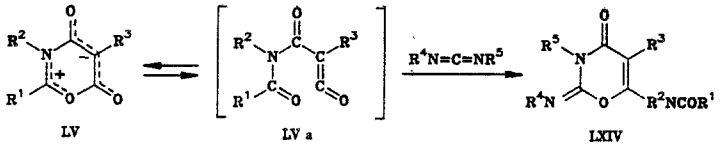
Upon treatment with halo derivatives in the presence of triethylamine 2-thioxo-4-oxo-1, 3-oxazines XV (X = S) give exclusively S-alkylation products [124, 146], while acid chlorides react only at the nitrogen atom [146].



LXIII

The reaction of 6-arylaminooxazinediones LX (X = NHAr) with ethyl orthoformate leads to oxazinoquinolines LXIII [147].

Carbodiimides react with zwitter-ionic compounds LV in refluxing toluene to give 6-acylamino-2-imino-1,3-oxazin-4-ones LXIV. The reaction may be initiated by electrophilic attack by the carbodiimide at the $C_{(5)}$ atom, although the possibility that the reaction proceeds via a cycloaddition mechanism with involvement of acyclic isomer LVa is not excluded [148].

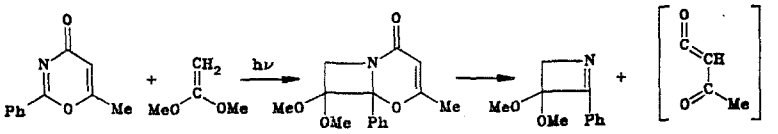


LV LV a LXIV

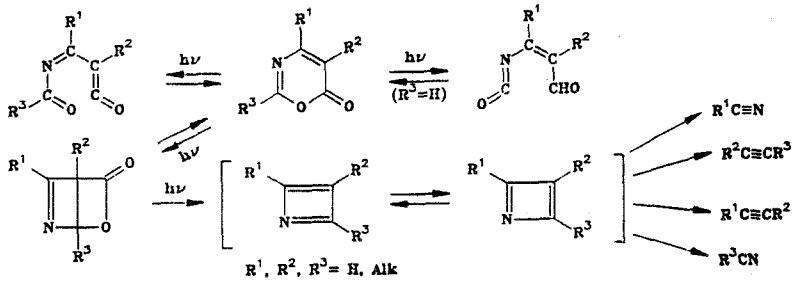
5. Other Reactions

Upon catalytic hydrogenation 6-oxooxazines VII give β-acylaminopropionaldehydes, and a perhydro derivative was isolated only in the case of 4,4-dimethyl-2-phenyl-5,6-dihydro-4H-1, 3-oxazin-6-one [16, 17]. Dehalogenation occurs in the action of zinc in acetic acid on 6-chlorooxazinediones LVII; subsequent catalytic hydrogenation leads to tetrahydro-1,3-oxazine-2,4-diones [127].

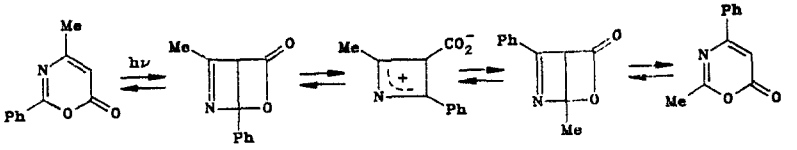
Upon UV irradiation in methylene chloride oxazine XXXVIII (R^1 = H, R^2 = Me, R^3 = Ph) reacts with dimethoxyethene to give a bicycloadduct, which undergoes cleavage to acetylketene and an azetine when it is heated [86, 149].



Attempts to photolytically generate four-membered nitrogen heterocycles with two multiple bonds starting from 6H-1,3-oxazin-6-ones were, in all likelihood, unsuccessful. Although obtaining nitriles and acetylenes with various structures as the final products in the case of prolonged UV irradiation may also constitute evidence for the intermediate formation of azetes, the latter were not detected [150, 151].



De Mayo and coworkers [90, 152] investigated the photochemical isomerization of 4-methyl-2-phenyl-6H-1,3-oxazin-6-one to 2-methyl-4-phenyl-substituted compound. The preponderance of the latter among the photolysis products is probably associated with stabilization of the corresponding bicyclic compound owing to conjugation with the phenyl group.



2-Oxo- and 6-oxooxazines, which have a quasi o-quinoid structure, display a certain degree of diene character and react with dienophiles to form products of addition via the Diels–Alder reaction. The primary bicycloadduct with a bridge —OCO— fragment splits out carbon dioxide to give substituted pyridines [97, 153, 154]. Oxo derivatives of 3,4-dihydro-2H-oxazines upon heating above 100°C undergo Diels–Alder retrodecomposition with splitting out of acylketenes [31, 44, 146]. At 750°C in vacuo (0.005 mm Hg) 2,4,5-triphenyl-6H-1,3-oxazin-6-one gives diphenylacetylene and benzonitrile [155, 156]. 2,4,5-Triphenyloxazole is formed in low yield at 800°C. Vacuum pyrolysis of 2-oxooxazines (650°C, 0.007 mm Hg) gives a mixture of approximately equal amounts of oxazinone LIII and isomeric isocyanate LII; the mixture is stable at temperatures below —5°C, whereas at 18-25°C the isocyanate undergoes complete conversion to the oxazinone after a few hours [153, 155].

Thus the chemical behavior of oxo derivatives of 1,3-oxazines is determined primarily by reactions with nucleophilic reagents; the reactions are undoubtedly of no small interest both for synthetic organic chemistry as a whole and, in particular, for the chemistry of heterocyclic systems. It should also be noted that, despite the presence of three electrophilic centers in the oxazinone molecules, attack by the nucleophile is almost always directed to the $C_{(2)}$ or $C_{(6)}$ atom of the heteroring; the choice between them is determined by the specific nature of the substrate and the nucleophile and the conditions under which the reaction is carried out, and the only example of nucleophilic attack at the $C_{(4)}$ atom does not lead to ring opening. Clearly, the reactions with electrophilic reagents have been studied inadequately and may serve as the subject of future investigations, just like the other properties of oxazinones; in the final analysis, this will make it possible to construct a more nearly complete picture of this interesting class of compounds.

BIOLOGICAL ACTIVITY AND POSSIBLE USE

Most of the research on the biological activity of oxo derivatives of 1,3-oxazines involves "3-oxauracil" (XXXV, X = 5-H) (for greater detail see a previous review [157]). Here it is appropriate to note only that this interesting compound, like some of its derivatives, being a powerful inhibitor of the biosynthesis of nucleic acids in microorganisms [63], has pronounced antitumorigenic [143, 158-163], cancerostatic [164], cytostatic [160], antibacte-

rial [165, 166], immunosuppressive [159], and antivirus [167] activity and inhibits the action of a number of enzymes [168-171] and the degradation of the pyrimidine bases of nucleac acids [172]. The mechanism of the pharmacological activity of "3-oxauracil" is discussed in detail in [145, 173].

Oxazinomycin XXXIV and a number of its derivatives have anticancerogenic properties [174-176]. 2-Amino-4H-1,3-oxazin-4-ones display antiphlogistic, antiarthritic [81], and immunostimulating activity [177], while 2-phenyl-6-(p-methoxyphenyl)-3,4-dihydro-2H-1,3-oxazin-4-one has tranquilizing activity [47].

N-Halosulfonyl-6-methyl-1,3-oxazine-2,4-diones XIV have been claimed as sweetening agents [24], and N-polychlorophenyl-substituted analogs have fungicidal activity [33]. A number of 5,6-disubstituted 2,4-dioxooxazines XX have proved to be useful as toning additives for thermally developable photographic materials [178].

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1,3-DIPOLAR CYCLOADDITION OF 2-BENZYLIDENEINDAN-1,3-DIONE α-OXIDE TO OLEFINS

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A carbonyl ylid, which reacts with maleic anhydride, N-phenylmaleinimide, and β-nitrostyrene to form adducts resulting from 1,3-dipolar cycloaddition, is formed reversibly when 2-benzylideneindan-1,3-dione α-oxide is heated (80°C). The reaction proceeds regio- and stereospecifically.

We have investigated the ability of 2-benzylideneindan-1,3-dione α-oxide (I) to undergo a thermal 1,3-dipolar cycloaddition reaction. We were compelled to do this because of the relatively little study devoted to the thermal transformations of epoxy ketones; at the same time, a significant amount of research has been devoted to their photochemistry [1-3]. Moreover, 1,3-dipolar cycloaddition reactions with the participation of spirooxiranes have not been studied at all. Only the generation of carbonyl ylids from oxopyrazonespirooxiranes has been described [4, 5]. It also seemed of interest to examine the regio- and stereochemical peculiarities of the cycloaddition.

It is well known that the activity of addends in 1,2-dipolar cycloaddition reactions depends mainly on their donor-acceptor properties [6]. We selected β,β-dimethylstyrene, cyclohexene, and 1-heptene as olefins with increased nucleophilicity of the double bond and maleic acid derivatives (the anhydride, N-phenylimide, and dimethyl ester), methyl methacrylate, vinyl acetate, β-nitrostyrene, trans-stilbene, and trans-4,4'-dinitrostilbene as alkenes with increased electrophilicity of the double bond. An analysis of the reactivities of these dipolarophiles enabled us to draw a conclusion regarding the character of the interaction of the boundary orbitals of the reagents. We used benzene or liquid dipolarophiles as the solvents.

The formation of cycloaddition products was not detected from TLC and PMR spectroscopic data in the reactions of α-oxide I with dimethylstyrene, cyclohexene, and 1-heptene (see scheme on following page).

Olefins with reduced electron density of the C=C bond displayed different reactivities. The cycloaddition adducts were obtained only for anhydride II and imide III of maleic acid and nitrostyrene IV. Methyl methacrylate and vinyl acetate underwent polymerization under the reaction conditions. Cycloaddition products were not isolated for the remaining dipolarophiles.

Only one of the possible isomers was isolated in 50-70% yield from the reaction mixture for dipolarophiles II-IV. The residue after isolation of the desired product was a resinous

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