OXO- AND THIOXO-1,3-THIAZINES (REVIEW)

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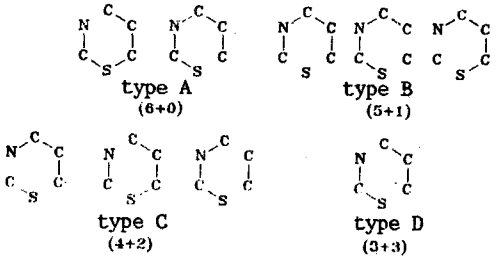
Literature reports on the methods of synthesis, chemical properties, and tautomerism of oxo- and thioxo-1,3-thiazines have been summarized.

1,3-Thiazines, interest in which has increased steadily over the last decade, remain relatively little-known compounds in comparison with pyrimidines and 1,3-oxazines. It has nevertheless been established that a number of oxo- and thioxo-1,3-thiazines possess useful properties, in particular high biological activity. The object of the present review is to summarize the available information on the synthesis, chemical properties, and tautomerism of 2-, 4-, and 6-oxo-1,3-thiazines, their sulfur analogs, and other derivatives.

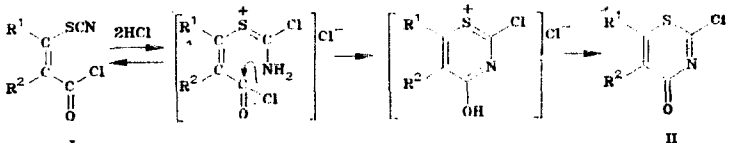
It is preferable to divide the methods of preparation of these compounds into the four general methods of synthesis of six-membered heterocycles, depending on the number of atoms present in the fragments destined to form the ring [1]. Methods of synthesis which involve modifications of compounds already containing the 1,3-tiazine ring will be considered in the section devoted to the chemical properties of these compounds.



(6 + 0) CONDENSATION

Reactions of this type have been relatively little used for the synthesis of 2-, 4-, and 6-oxo-1,3-thiazines. However, many reactions of types B–D occur via intermediates similar to those formed in type A reactions. The closure of six-membered fragments to form the ring usually occurs by nucleophilic addition of nitrogen or sulfur to the carbonyl carbon atom or the more reactive carbon of the protonated carbonyl group.

There have been no reports in the literature on the use of reactions of this type for the synthesis of 2-oxo-1,3-thiazines, but there are a few examples of their use for the preparation of 4- and 6-oxo-1,3-thiazines [2-5]. Condensation of the 2-thiocyanatocarbonyl chlorides (I) in the presence of dry hydrogen chloride gives substituted 4-oxo-1,3-thiazines (II) [2, 3]. The reaction must be carried out at 0°C as a result of the high reactivity of the carbonyl carbon. The reaction is assumed to proceed as follows [4]:



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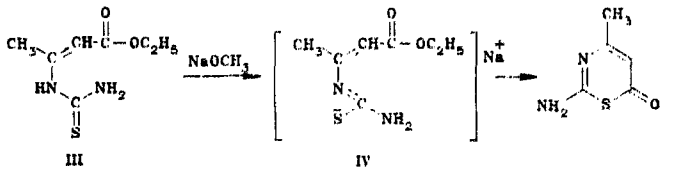
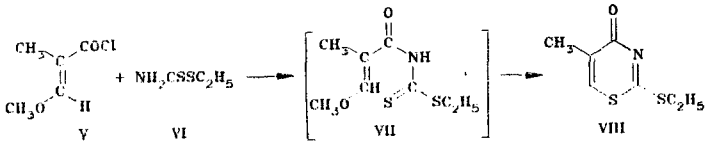
The condensation of the 3-thioureidobutyrate (III) in methanolic sodium methoxide at 80°C has been used to obtain 6-oxo-1,3-thiazines [5]. The unusual nucleophilic attack on the carbonyl carbon by sulfur is explained by the authors [5] as being due to the formation of the anion (IV) in an alkaline medium. In this case, the electron density at the sulfur atom must be increased to a greater extent than that at the amino-group, while simultaneously the positive charge on the carbonyl carbon is reduced by conjugation. These factors result in the preferential formation of the C—S bond.



III IV

A general method for the synthesis of 2,4-dioxo-1,3-thiazines and their thio-analogs, which permits the introduction of substituents into the 5- and 6-positions, is based on intramolecular nucleophilic attack on the carbonyl group or the more reactive corresponding enol ether by the sulfur atom in acyldithiourethanes [1, 6]. For example, acetoacetyldithiourethane slowly cyclizes to2-ethylthio-4-oxo-6-methyl-1,3-thiazine on treatment with cold concentrated sulfuric acid [6]. Reaction of the acyl chloride (V) with the S-ethyldithiocarbamate (VI) affords the unstable acryloyldithiourethane (VII), which on cyclization gives 2-ethylthio-4-oxo-5-methyl-1,3-thiazine (VIII) [6].

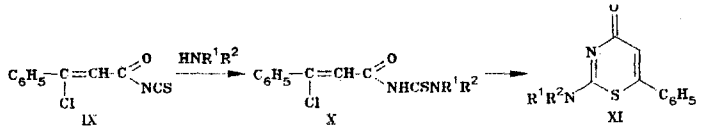


V VI VII VIII

The isomerization of 2-thio-4-oxo-6-methyl-1,3-oxazine to the more stable 2,4-dioxo-1,3-thiazine on treatment with concentrated sulfuric acid [7] may be regarded as a reaction of this type.

(5 + 1) CONDENSATION

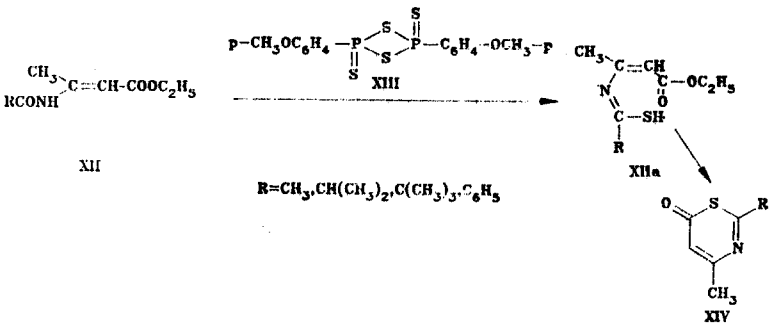
Type B reactions comprize the condensation of five- and one-membered fragments, in the course of which bonds are formed between the heteroatoms and a carbon atom, or between two carbon atoms. The five-membered fragment is frequently an acyl isothiocyanate [8, 9], an unsaturated acid [10-13], or an acyldithiourethane, which condense readily with amines, thiols [8], aromatic carboxylic acid derivatives [11-13], or orthoesters [1, 14]. The reaction is normally carried out in aprotic nonpolar solvents in the presence of acetic anhydride [14] or polyphosphate ester [11-13]. This type of condensation is not used for the preparation of 2-oxo-1,3-thiazines. An example of its use for the synthesis of 4-oxo-1,3-thiazines is the reaction of 3-chloro-3-phenylpropenoyl isothiocyanate (IX) with amines to give the substituted thioureas (X), which then cyclize to 2-alkylamino-4-oxo-1,3-thiazines (XI) [8].



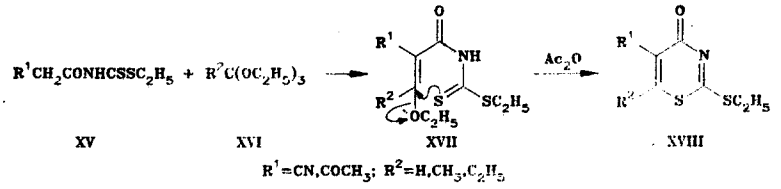
IX X XI

R^1=H,Alk,Ar; R^2=Alk,Ar

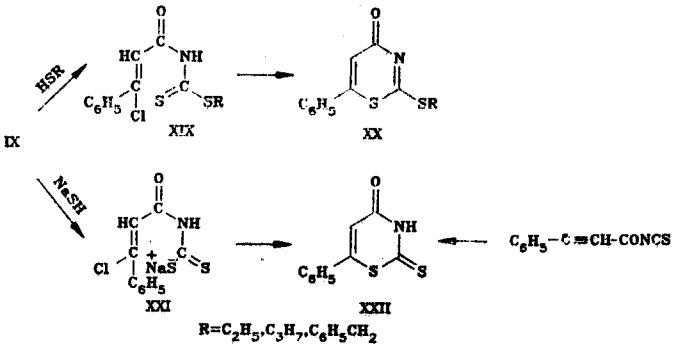
The condensation of the 3-acylamino-2-butenoate (XII) with 2,4-bis(4-methoxyphenyl)-1,3,2,4-dithiaphosphetane 2,4-disulfide (XIII) has been used to prepare the 2-substituted 6-thio-4-methyl-1,3-thiazines (XIV) [10]. In the first step, the 3-(2-thioacylamino)-2-butenoate (XIIa) is formed, and on boiling in xylene this cyclizes by nucleophilic addition of the sulfur to the carbonyl carbon. Simultaneously, the oxygen atom at $C_{(6)}$ is replaced by sulfur.



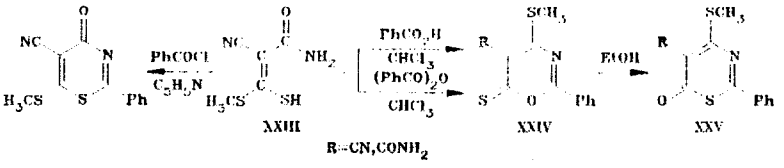
This type of condensation is used rather more extensively for the synthesis of 2,4-dioxo-1,3-thiazines and their sulfur analogs. Condensation of the acyldithiourethanes (XV), which contain a reactive methylene group, with the orthoesters (XVI) gives the intermediate N-β-ethoxyacryloyldithiourethanes (SVII), which cyclize in the presence of acetic anhydride to the corresponding 1,3-thiazines (SVIII) [1, 14]. Triethyl orthoformate is the most reactive in the reaction. It appears that the use of triethyl orthoacetate or orthopropionate increases the electron density at the electrophilic site, thus hindering the formation of the C—S bond.



The acyldithiourethanes (XIX), obtained by reacting the isothiocyanate (IX) with thiols, cyclize to 2-alkylthio-4-oxo-6-phenyl-1,3-thiazines (XX) by intramolecular nucleophilic replacement of halogen by sulfur [8]. Reaction of the isothiocyanate (IX) with sodium hydrosulfide occurs via the unstable dithiocarbamate (XXI) to give 2-thio-4-oxo-6-phenyl-1,3-thiazine (XXII) [8]. This compound (XXII) has previously been obtained from sodium hydrosulfide and 3-phenylpropionyl isocyanate [9].

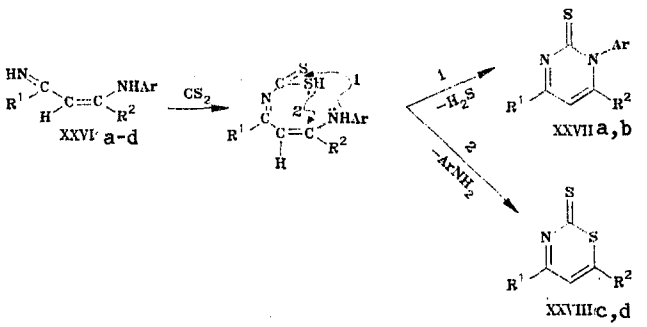


The condensation of substituted acrylamides (XXIII) with aromatic carboxylic acids has been the subject of several studies [11-13]. Varying the reaction conditions and the reactants affords differing reaction products. When benzoic acid or its anhydride is used, the principal cyclization products are 6-thioxo-1,3-oxazines (XXIV), which isomerize quantitatively on heating in protic solvents to give the 6-oxo-1,3-thiazines (XXV) [12. The driving force in this reaction is the greater stability of the 1,3-thiazine ring in comparison with the 1,3-oxazine ring [7, 12]. It is noteworthy that condensation only occurs in the presence of polyphosphate ester.



(4 + 2) CONDENSATION

Type C reactions, which comprize the condensation of a four-membered unit (β-diimines, β-iminopropionitriles, isothiocyanates, or thioacylketenes) with a two-membered unit containing a multiple bond, are quite widely used for the synthesis of oxo- and thioxo-1,3-thiazines.

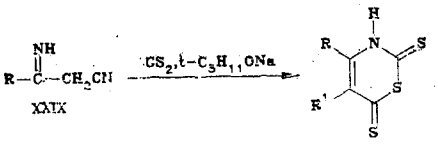


XXVI a-d → XXVII a,b; XXVIII c,d

XXVI—XXVIII a Ar=*p*-$OCH_3C_6H_4$, b, c Ar=C_6H_5, d Ar=*p*-$CH_3C_6H_4$; a-d $R^1=C_6H_5$; a,c,d $R^2=C_6H_5$, b $R^2=CH_3$

The condensation of β-diimines [15] or β-iminonitriles [16] with carbon disulfide has been employed to obtain 2-thioxo-1,3-thiazines. In the case of the diimine (XXVI), nucleophilic addition of the diimine to the CS_2 carbon first takes place. The subsequent course of the reaction depends on the electronic effects of the substituents in (XXVI). Electron-donating substituents R_2 at the electrophilic center hinder the formation of the C—S bond, and in this case the reaction products are the pyrimidines (XXVII). The absence of a substituent with a +M effect in the benzene ring attached to nitrogen results in a decrease in the yields of pyrimidines (XXVII), the thiazines (XXVIII) being formed in yields which are largely independent of the type of substituent present [15].

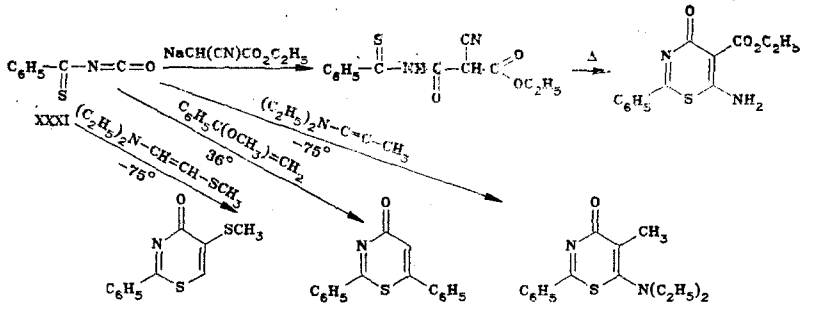
The activating effect of the cyano-group in β-imino-β-arylpropionitriles (XXIX) together with basic catalysis favor the addition of sulfur to the methylene group. When the reaction is carried out in dimethylformamide at 2°C, addition of a further molecule of sulfur occurs with the formation of 5-substituted-2,6-dioxo-4-aryl-1,3-thiazines (XXX) [16].



XXIX → XXX

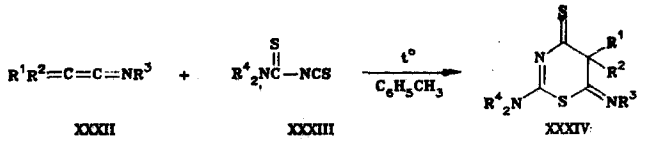
R=Ar,Me; R^1=CN,CO_2CH_3

4-Oxo-1,3-thiazines are most frequently obtained by (4 + 2)-cycloaddition. Usually, thioacyl isocyanates [17, 18] or isocyanates [18-20] are condensed with alkenes [17], alkynes [17], ketenimines [19], or phosphacumulidenes [18]. The reactions are normally carried out in nonpolar aprotic solvents, the temperature used being dependent on the reactivity of the reactants. The condensation of thiobenzoyl isocyanate (XXXI) with nucleophilic alkenes and alkynes [17] has received especially close attention. The rate of this reaction is greater with alkynes than alkenes, and increases as the electron-donor properties of the substituents at the multiple bond of the nucleophile are increased.



XXXI

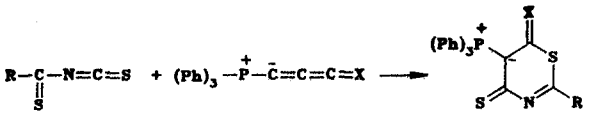
The lower reactivity of the ketenimines (XXXII) in their reactions with isothiocyanates (XXXIII) requires the use of more severe reaction conditions [9]. The condensation is sensitive to the electronic effects of the substituents. The yield of the 1,3-thiazinethione (XXXIV) decreases as the electron density of the isothiocyanate (XXXIII) is increased, and when electron-acceptor substituents are introduced into the keteneimines (XXXII).



XXXII XXXIII XXXIV

XXXIV a,b $R^1=R^2=CH_3$, c $R^1=R^2=C_6H_5$; a,b $R^3=p\text{-}CH_3C_6H_4$, c $R^3=p\text{-}OCH_3C_6H_4$; a $R^4=C_2H_5$, b,c $R^4=i\text{-}C_3H_7$

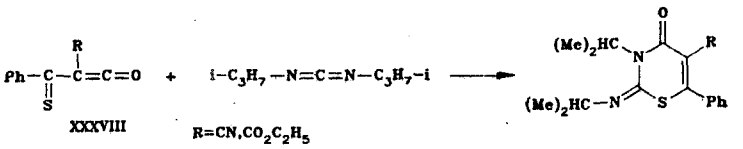
The cycloaddition of the isothiocyanates (XXXV) to the phosphacumylidenes (XXXVI) affords products with a zwitterionic structure (XXXVII) [18] in yields which are highly dependent on steric factors (as the volume of R is increased, the yield of the thiazinethione (XXXVII) decreases).



XXXV XXXVI XXXVII

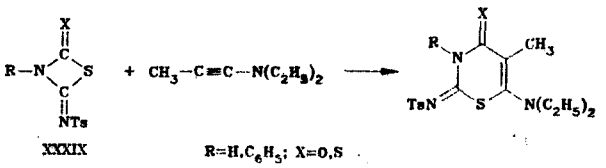
R=N(Alk)$_2$; X=O,S,NPh

The four-membered unit can be thioacylketene (XXXVIII), which reacts with diisopropylcarbodiimide [21].



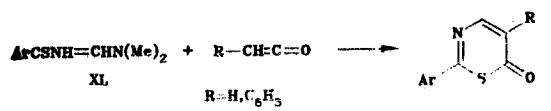
XXXVIII R=CN,$CO_2C_2H_5$

An interesting route to 4-oxo- or 4-thioxo-1,3-thiazines is by the reaction between 3-substituted-2-oxo- or 2-thioxo-4-tosylimino-1,3-thiazetidines (XXXIX) and diethylaminopropyne [22, 23]. Attack on the carbonyl or thiocarbonyl carbon by the ynamine appears to result in recyclization of the four-membered to the six-membered ring.



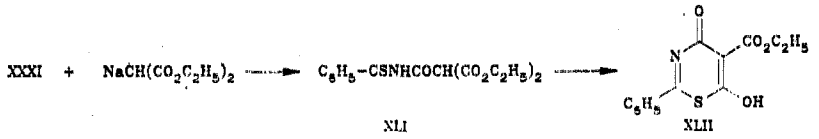
XXXIX R=H,C_6H_5; X=O,S

The (4 + 2)-cycloaddition reaction has rarely been used to obtain 6-oxo-1,3-thiazines. The only example known to the authors is the condensation of N-thioaroyl-N'N'-dimethylformidines (XL) with ketenes [24, 25]. Phenylketene is less reactive than its unsubstituted analog.

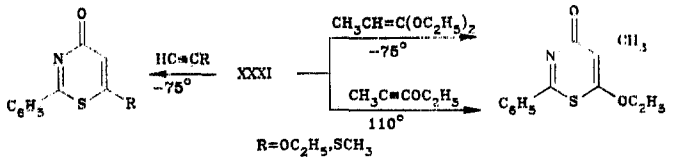


XL R=H,C_6H_5

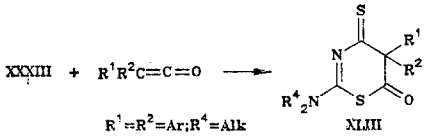
Type C reactions have not been used for the preparation of 1,4-dioxo-1,3-thiazines. They have, however, been used extensively in the synthesis of 4,6-dioxo-1,3-thiazines and their sulfur analogs. The previously-mentioned isothiocyanate (XXXI) reacts with diethyl sodiomalonate to give the straight-chain adduct (XLI), which cyclizes in the presence of α-pyridone to the 1,3-thiazine (XLII) [17].



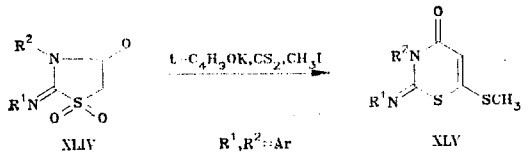
The rate of condensation with nucleophilic alkenes and alkynes increases when gem-electron-donor substituents are present:



The isothiocyanates (XXXIII) condense readily with reactive ketenes to give 5-substituted-2-alkylamino-4-thioxo-6-oxo-1,3-thiazines (XLIII) [19].



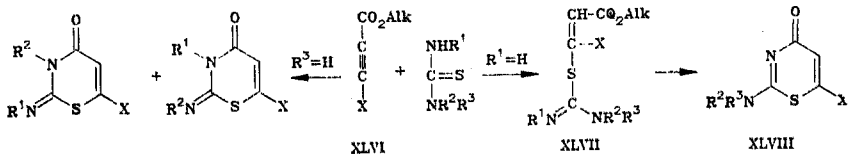
One of the few examples of the condensation of a C_3N fragment with the CS unit is the reaction of 2-imino-4-oxothiazolidine 1,1-dioxide (XLIV) with potassium tert-butoxide, carbon disulfide, and iodomethane in dimethyl-formamide solution [26].



(3 + 3) CONDENSATION

This reaction (type D) is that most frequently used for the preparation of the 1,3-thiazine ring. The most frequently-used method for the synthesis of oxo-1,3-thiazines is the condensation of acetylenecarboxylic acid derivatives with thioureas or dithiocarbamic acid derivatives, and for the preparation of 4,6-dioxo-1,3-thiazines, condensation of the appropriate thioamides with 'malonating' agents. Despite the extensive use of this type of synthesis, there have been no reports of its use to prepare 2-oxo-1,3-thiazines or their thioanalogs.

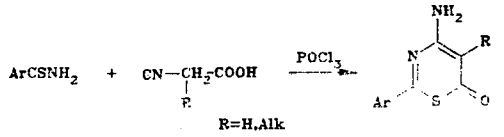
1,3-Thiazines with an oxo-group in the 4-position are formed by the condensation of β-substituted acetylenecarboxylic acids (XLVI) with thiourea or its N-alkyl derivatives [27-36].



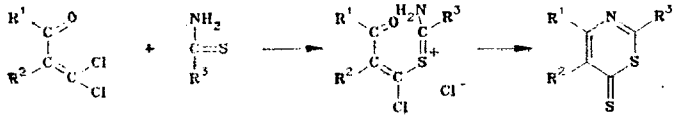
R^1=H, Alk, Ar; R^2=H, Alk, Ar; R^3=H, Alk; X=CO_2CH_3, Ar, 2-furyl

The mechanism of ring closure has unfortunately received little attention, and it is not possible to provide an unambiguous explanation of the effects of substituents on the course of the reaction. The condensation is carried out in both protic and aprotic polar solvents. It appears that initially β-addition of the thiourea sulfur atom to the sp-hybridized carbon takes place preferentially, and in several instances [35] the products of such a reaction (XLVII) have been isolated. The NCS fragment can also be provided by 4-substituted thiosemicarbazides, which condense with acetylenedicarboxylic ester to give 2-imino-3-amino-4-oxo-6-alkoxycarbonyl-1,3-thiazines [37]. The thiazine structure was assigned to the product of the reaction of ethyl propiolate with thiobenzamide [38], but regrettably these authors failed to provide any confirmation of this structure.

1,3-Thiazines with an oxo- or thioxo-group in the 6-position have been obtained by condensing substituted thiobenzamides with cyanoacetic acid in the presence of PCl_3 or $POCl_3$ [39, 40]. The introduction of electron-acceptor substituents into the thioamide, and electron-donor substituents in the α-position of the cyanoacetic acid, reduce the yields of cyclization products.



Reaction of β,β-dichlorovinyl ketones (XLIX) with thioamides or thioureas affords 6-thioxo-1,3-thiazines [41-43]

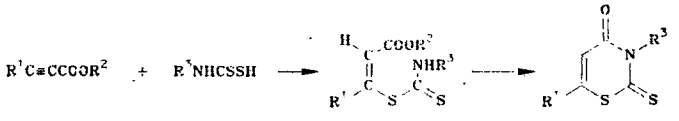


XLIX L

R^1=Ph, Alk; R^2=Cl, H; R^3=NH_2; NHAlk, $NAlk_2$, Alk, Ar

2,4-Dioxo-1,3-thiazines and their sulfur analogs are formed by condensing dithiocarbamic acid [1, 44, 45] or its N-alkyl derivatives [44, 46] with propiolic [1, 44, 46] or γ-hydroxytetrolic acid [45].

The condensation of dithiocarbamic acid derivatives with propiolic acid in the presence of PCl_3 had been studied previously [46]. Subsequently, acetic anhydride with traces of sulfuric acid was used in place of PCl_3 [1, 44], the yields of 1,3-thiazines being considerably increased. The reaction proceeds via the formation of the product of the nucleophilic attack on the β-carbon by sulfur. In several cases these compounds (LI) could be isolated [46].



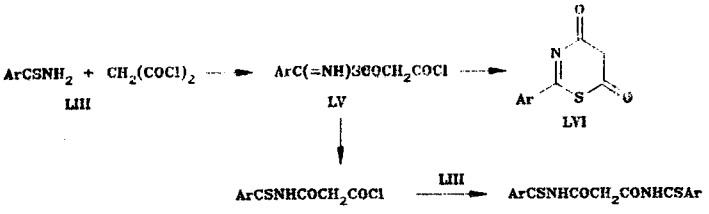
LI LII

R^1=H,CH_2OH; R^2=H; R^3=H,Alk

It is preferable to use the free acetylencarboxylic acids in this reaction, since the use of esters results in the cyclization giving low yields and requiring more severe conditions [1].

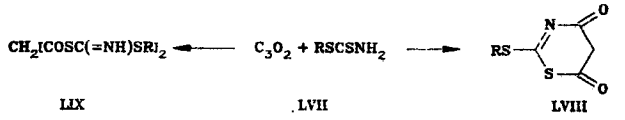
(3 + 3)-Cyclocondensation is most frequently used to obtain 2-substituted 4,6-dioxo-1,3-thiazines. These methods are based on the reaction of thioamides with a variety of 'malonating' agents, namely, malonyl chloride, malonic acid, and carbon suboxide [47-67].

In a study of the condensation of thiobenzamides (LIII) with malonyl chloride, it was suggested that initially the sulfur atom of the thioamide (LIII) was acylated to give the intermediate (LV), which is either converted into the 4,6-dioxothiazine (LVI), and reacts with a second molecule of the thioamide (LIII) [47].



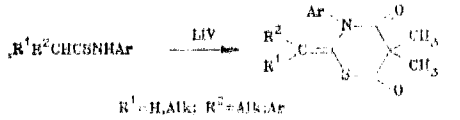
LIII LV LVI

It has been found that the dichloride (LIV) or carbon suboxide react with S-alkyldithiocarbamates (LVII) or thioacetamides to give both cyclic (VLIII) and straight-chain (LIX) products [48-50].

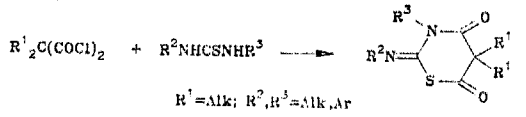


LIX LVII LVIII

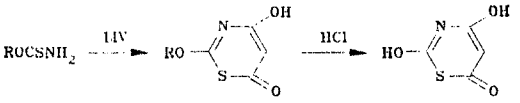
There have been several studies of the reaction of malonyl chloride (LIV) with alkanethiocarboxylic acids or N-substituted thioamides to give 2-arylidene- or 2-alkylidene-4,6-dioxo-1,3-thiazines [51, 52].



Disubstituted malonyl dichlorides react with NN'-disubstituted thioureas to give 3,5,5-substituted 2-alkylimino-4,6-dioxo-1,3-thiazines [53, 54].

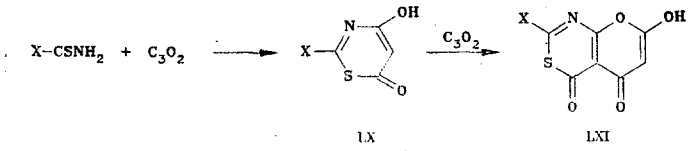


When O-alkylthiocarbamates react with the acid chloride (LIV), in addition to 2-alkoxy-4,6-dioxo-1,3-thiazines there is also formed 2,4,6-trioxo-1,3-thiazine, apparently as a result of the reaction of the former with the hydrogen chloride liberated [55].



Malonic acid and its derivatives react with thiobenzamides in the presence of condensing agents (PCl_3) to give 5-substituted-2-aryl-4,6-dioxo-1,3-thiazines [56]. A drawback of this method is the partial resinification of the cyclization products. This reaction takes place in acetic anhydride with O-ethyldithiocarbamates or N-acetylthiourea [56, 57], but in this case further acylation of the 1,3-thiazines formed takes place to give the 4-acetoxy-compounds [57].

A highly efficient 'malonating' agent is carbon suboxide, which reacts with thioamides to give 2-substituted-4,6-dioxo,1,3-thiazines (LX) [57-60]. The reaction may be complicated by the addition of C_3O_2 to the thiazine (LX) with the formation of bi- (LXI) and polycyclic derivatives [57, 61].



LX LXI

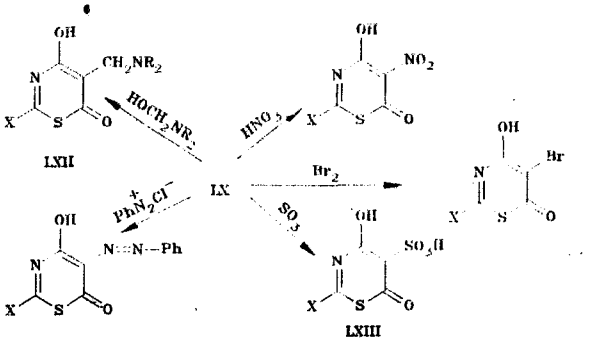
The reaction of carbon suboxide with N-acetylthiourea has received the closest attention. It has been found that acylation reduces the electron density at one of the thiourea nitrogens, facilitating NS-cycloaddition of the carbon suboxide [49, 55, 57]. The use of thiourea or N-arylthioureas results in the formation of 2-thiobarbituric acids [58, 62, 63]. Unsymmetrical NN'-dialkyl(or aryl)thioureas are converted to 2-dialkylamino-4,6-dioxo-1,3-thiazones [63, 64].

CHEMICAL PROPERTIES

The chemical properties of oxo- and thioxo-1,3-thiazines have received much less attention than the condensation reactions used in their preparation. The majority of studies have examined alkylation, acylation, and electrophilic and nucleophilic substitution. It is worthy to note that several reactions have been used to modify compounds already containing the 1,3-thizaine ring. For example, alkoxy-, alkylthio-, and alkylimino-1,3-thiazines are frequently obtained by alkylating the appropriate thiazines with diazomethane [1, 6, 28, 45, 65], dimethyl sulfate [1, 6, 41], or iodomethane [29, 41]. The use of dimethyl sulfate is complicated by the possibility of the opening of the thiazine ring in the presence of caustic alkali. Alkylation takes place both at the ring nitrogen [1, 6, 28] and at the nucleophilic centers of the substituents [1, 29, 41, 45, 65]. Methylation of 2-substituted 4,6-dioxo-1,3-thiazines with diazomethane in ether affords only O-methylation products, which were originally regarded as 6-methoxy-1,3-thiazines [60]. Subsequently, however, quantum-chemical calculations and the ^{13}C NMR spectra of ^{15}N-phenyl-4,6-dioxo-1,3-thiazine and its O-methylation product showed that the latter was 2-phenyl-4-methoxy-6-oxo-1,3-thiazine [68]. Acylation has been closely examined in the case of 2-substituted-4,6-dioxo-1,3, thiazines (LX). The use of acetic anhydride gave the O-acetyl derivatives [69]. Another method of preparation of O-acyl derivatives is by acyl-

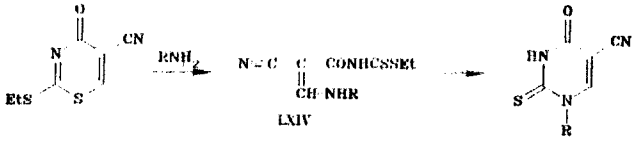
ating the sodium salt of the thiazine (LX) with aromatic carbonyl and sulfonyl halides [70, 71]. In addition to O-acylation, examples are known of the N-acylation of amino-groups in the 2-position of the aminooxothiazines (XLVIII, L) [28, 35, 41].

The 1,3-thiazinediones (LX), which comprize a heteroaromatic system in which $C_{(5)}$ is activated to electrophilic attack, react with great ease with electrophilic reagents. For instance, reaction with phenyldiazonium chloride gives 2-substituted-5-phenylazo-4-hydroxy-6-oxo-1,3-thiazines [56, 65, 72]. Reaction of (LX) with disubstituted aminomethanols affords the Mannich bases (LXII) [73]. Nitration, halogenation, and sulfonation of 2-aryl-4,6-dioxo-1,3-thiazines, even under mild conditions with equimolar proportions of the reactants takes place exclusively at $C_{(5)}$ of the thiazine ring [72]. Nitration has been effected in nitric acid (d 1.42) in acetic acid in the presence of acetic anhydride, and halogenation with bromine in organic solvents (preferably acetic acid). Iodination has been accomplished only with iodine chloride. When sulfonation of the thiazine (LX) was carried out with sulfuric acid of SO_3 in pyridine, no product could be isolated, However, sulfonation takes place readily with SO_3 in dichloroethane.

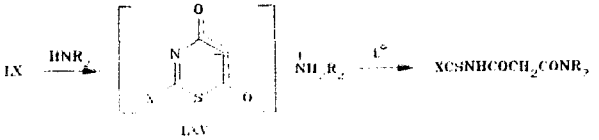


It is interesting that the nitration of 6-(2-furyl)-1,3-thiazines (XLVIII) takes place in the α-position of the furan ring [35].

Reactions with nucleophilic reagents occupy an important place in studies of the chemical properties of oxo- and thioxo-1,3-thiazines. For example, the hydrolysis of 2-alkylimino-[1, 34, 35] or 2-alkylthio-4-oxothiazines [1, 6] is frequently employed for the preparation of 5- and 6-substituted-2,4-dioxo-1,3-thiazines. The reaction is usually carried out with acid catalysis [1]. In alkaline media, cleavage of the thiazine ring often takes place [72]. One of the most interesting of the chemical properties of substituted 2,4-dioxo-13,-thiazines is their reaction with ammonia [6, 44] and primary amines [14, 44] when the thiazines are converted into the corresponding pyrimidines. The first step in this reaction appears to be cleavage of the ring by the nucleophile, and in several cases acyclic reaction products (LXIV) have been isolated [14].

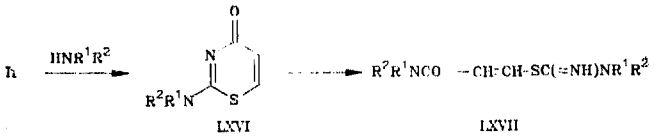


Acyclic products have also been obtained in the reaction of 6-substituted 2-amino-4-oxo-1,3-thiazines or the thiazines (LX) with secondary amines [28, 74-76]. It is interesting that in the case of the thiazines (LX) the intermediate ammonium salts (LXV) have been isolated, these undergoing cleavage on heating in organic solvents.



The reaction between 4,6-dioxo-1,3-thiazines and sodium alkoxides may follow two routes, since 2-aryl-4,6-dioxo-1,3-thiazines form stable salts with sodium ethoxide [71], whereas 2-alkylidiene-4,6-dioxo-1,3-thiazines rearrange to the piperidones [51].

Nucleophilic replacement of the halogen atom in 2-chloro-4-oxo-1,3-thiazines (II) has been examined using amines [3]. Depending on the amine taken and on the reaction conditions either the 2-alkylaminothiazines are obtained, or acyclic compounds, but cleavage always precedes replacement [3].



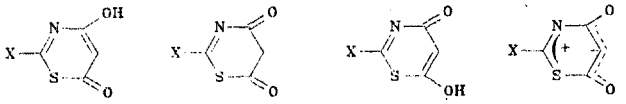
LXVI LXVII

It has been shown to be possible to convert oxo-1,3-thiazines into their thioxo-analogs by treatment with P_4S_{10} [24, 25, 77]. The reverse transformation has been effected with mercuric acetate (II), and in the case of the 6-thioxo-1,3-thizaine (L), the 6-oxo-compound is obtained [41].

The structures of the reduction products of oxo-1,3-thiazines are dependent on the reaction conditions. For example, when sodium borohydride is used only the C=N bond of the thiazine (XXV) is reduced [12], whereas the catalytic hydrogenation of methyl 3-methyl-2-imino-40oxo-1,3-thiazine-6-carboxylate gives N-methylsuccinimide [28].

Less general chemical properties are the conversion of the carboxamide group in (XXV) (R = $CONH_2$) into the nitrile by treatment with trimethylsilyl polyphosphate [78] and the dimerization of 2-alkyl-6-methyl-4-oxo-1,3-thiazines on heating with a catalytic amount of trifluoroacetic acid in dimethylformamide [79].

Oxo-1,3-thiazines are potentially tautomeric. It is unfortunate that up to the present only the tautomerism of 2-substituted-4,6-dioxo-1,3-thiazines (LX) has been studied. These thiazines can exist in at least four tautomeric forms (LXa-d).



LX a LX b LX c LX d

On the basis of the IR, PMR, and UV spectra, Beilin et al., [60, 68] have shown that when the substituent in the 2-position of the thiazine ring is varied, the structure of the β-dicarbonyl fragment also changes, in the opinion of these workers owing to the "differing contributions of the substituent to the conjugation of the thiazine ring." For instance, crystalline 2-(p-chlorophenyl)- and 2-phenyl-4,6-dioxo-1,3-thiazine were assigned a zwitterionic structure (LXd) on the basis of the similarity of the IR spectra to the spectra of their salts, and the absence of absorption above 1600 cm^{-1}. In solution, these compounds already exist in the enol forms (LXa) of (LXc), since their IR spectra correspond to that of 4-methoxy-2-phenyl-6-oxo-1,3-thiazine. The enol form was confirmed by the PMR spectra, since in DMSO solution they showed signals for olefinic (5-H, δ 5.4-5.8 ppm), hydroxylic (12.0-12.6 ppm), and phenyl (7.5-8.3 ppm) protons. The spectra showed no signals for the methylene group with δ ≈ 3.5 ppm, as observed for compounds with structure (LXb) and an olefinic proton for the anionic form with δ ≈ 4.7 ppm such as is present in the spectra of the salts. In order to determine the relative stabilities of the tautomers (LXa) and (LXb), the atomization energies of these forms of 2-phenyl-4-hydroxy-6-oxo-1,3-thiazine were calculated by the PPP method in Dewar's σ, π-parameterization. It was found that the tautomer (LXa) was the more stable. From the IR spectra of crystalline samples and of solutions, 2-alkylthio-4,6-dioxo-1,3-thiazines were assigned the diketonic form (LXb). 2-Methyl- and 2-alkoxy-4,6-dioxo-1,3-thiazines display an interesting structural feature. The IR spectra of crystalline samples of these compounds shown characteristic C=O absorption at 1650-1628 cm^{-1}, showing that they exist in the enol form. However, solutions of these compounds in DMSO solution (from their IR and PMR spectra) contain both the keto- and enol-forms [60]. It is difficult to arrive at any conclusions concerning the structure of 2-amino-4,6-dioxo-1,3-thiazines in the absence of adequate spectral data. In the opinion of Baranova, Dashkevich, et al., [6, 63], the PMR spectra of these compounds in DMSO indicate the presence of two tautomeric forms (enol and diketonic).

SUMMARY

This review has shown that the attention of workers has been concentrated for the most part on the synthesis of 4-oxo-, 2,4-dioxo-, and 4,6-dioxo-1,3-thiazines. These compounds are most commonly obtained by condensing acetylenecarboxylic acids with thioureas or dithiocarbamic acids, or by reacting thioamides with malonic acid derivatives or carbon suboxide. The chemical properties of this interesting group of heterocycles have received relatively little attention, and it is not possible to arrive at any firm conclusions as to the effects of variations in the ring heteroatoms on their chemical properties, and the position of these compounds amongst their hetero-analogs. The available information does enable novel, previously inaccessible compounds to be prepared. It hardly needs to be mentioned that the 1,3-thiazine ring is present in naturally-occurring biologically active compounds such as cephalosporins and antibiotics. Oxo-and thioxo-1,3,-thiazines possess properties which are valuable from the practical point of view, such as antiinflammatory [54], analgetic [80], tranquilizing [81], antipyretic [39], diuretic [39, 70, 71], fungicidal [80], and antimicrobial [43] activity.

LITERATURE CITED

1. E. N. Cain and R. N. Warrener, Austral. J. Chem., 23, 51 (1970).
2. G. Simchen and G. Entenmann, East German Pat. No. 2 010 558; Chem. Abstr., 76, 3181 (1972).
3. G. Simchem and G. Entenmann, Liebigs Ann., 8, 1249 (1977).
4. G. Simchem and J. Wenzelburger, Chem. Ber., 103, 413 (1970).
5. J. Kaválek, S. El-Bahaie, V. Machacek, and V. Sterba, Coll., 45, 732 (1980).
6. R. N. Warrener and E. N. Cain, Tetrah. Lett., 28, 3225 (1966).
7. R. N. Warrener and E. N. Cain, Tetrah. Lett., 28, 3231 (1966).
8. J. Imrich and P. Kristain, Coll, 47, 3268 (1962).
9. M. Dzurilla and P. Kristian, Coll., 41, 1388 (1976).
10. R. Shabana, J. B. Rasmussen, and S.-O. Lawesson, Bull. Soc. Chim. Belges, 90, 75 (1981).
11. M. Yukoyama, Y. Sawachi, and T. Isso, J. Org. Chem., 38, 802 (1973).
12. M. Yokoyama, M. Nakamura, H. Otheki, T. Imamoto, and K. Yamagushi, J. Org. Chem., 47, 1090 (1982).
13. M. Yukoyama, M. Nakamura, T. Imamoto, and K. Yamagushi, Chem. Commun., No. 11, 560 (1981).
14. M. R. Atkinson, G. Shaw, K. Schaffner, and R. N. Warrener, J. Chem. Soc., No. 10, 3847 (1956).
15. T. Nishio and Y. Omote, J. Chem. Soc., Perkin I, No. 9, 2149 (1982).
16. M. Muraoke, T. Yamamoto, S. Yamagushi, F. Tonosaki, T. Takeshima, and N. Fukada, J. Chem. Soc., Perkin I, No. 11, 1273 (1977).
17. J. Goerdeler, M.-L. Tiedt, and K. Nandi, Chem. Ber., 114, 2713 (1981).
18. H. J. Bestmann and I. Schmidt, Tetrah. Lett., No. 21, 2401 (1980).
19. J. Goerdeler and H. Luedke, Chem. Ber., 103, 3393 (1970).
20. K. Seifert, S. Johne, and A. Shaks, East German Pat. No. 149 807; Chem. Abstr., 96, 52326 (1982).
21. I. Goerdeler and K. H. Koehler, Tetrah. Lett., No. 34, 2961 (1976).
22. G. L'Abbe, J.-P. Dekerk, and M. De Ketele, Bull. Soc. Chim. Belges, 91, 243 (1982).
23. G. L'Abbe, P. Vangheluwe, and S. Toppet, Bull. Soc. Chim. Belges, 92, 61 (1983).
24. J. S. Meslin and H. Quiniou, Synthesis, No. 4, 298 (1974).
25. J. C. Meslin and H. Quiniou, Tetrahedron, 31, 3055 (1975).
26. E. Fisher, I. Hartmann, and H. Priebs, Z. Chem., 15, 480 (1975).
27. J. W. Lown and J. C. N. Ma, Canad. J. Chem., 45, 939 (1967).
28. E. Winterfeldt and J. M. Nelke, Chem. Ber., 100, 3671 (1967).
29. L. I. Giannola, S. Palazzo, P. Agozzino, L. Lamartina, and L. Cerualo, J. Chem. Soc., Perkin I, No. 11, 1428 (1978).
30. U. Voegeli, W. Von Philipsborn, K. Nagarajan, and M. D. Nair, Helv. Chim. Acta, 61, 607 (1978).
31. G. Dallas, J. W. Lown, and J. C. N. Ma, J. Chem. Soc., C, No. 20, 2510 (1968).
32. H. Tanaka and A. Yikoyama, Chem. Pharm. Bull, 10, 13 (1962).
33. A. Yokoyama and H. Tanaka, Chem. Pharm. Bull., 12, 683 (1964).
34. Y. Kishida and T. Atsusuke, Chem. Pharm. Bull., 16, 1351 (1968).
35. E. Akerblom, Chem. Ser., 6, 35 (1974).
36. E. G. Kataev, L. K. Konovalova, and E. G. Yarkova, Zh. Org. Khim., 5, 621 (1969).

37. J. W. Lown and J. C. N. Ma, Canad. J. Chem., 45, 953 (1967).
38. A. K. Mushkalo and G. Ya. Yangol', Ukr. Khim. Zh., 21, 732 (1955).
39. E. Ziegler, US Pat. No. 3,062,816; Chem. Abstr., 58, 6841 (1963).
40. E. Steiner and E. Ziegler, Monatsh. Chem., 95, 1550 (1964).
41. W. Schroth, G. Dill, Nguyen Thi Kim Dung, Nguyen Thi Mai Khoi, Phan Thi Binh, H. J. Waskiewicz, and A. Z. Hildebrandt, Z. Chem., 14, 52 (1974).
42. W. Schroth, G. Dill, and A. Hildebrandt, East German Pat. No. 106 650; Chem. Abstr., 82, 73011 (1975).
43. A. N. Mirskova, A. S. Atavin, G. G. Levkovskaya, and P. V. Lidina, in: Abstr. Reports, 13th Scientific Session on the Chemistry and Technology of Organic Sulfur Compounds and Sulfur-Containing Petroleum [in Russian], Zinatne, Riga (1974), p. 196.
44. R. N. Warrener and E. N. Cain, Chem. Ind., 48, 1989 (1964).
45. R. N. Warrener and E. N. Cain, Austral. J. Chem., 21, 785 (1971).
46. J. L. Garraway, J. Chem. Soc., No. 10, 4077 (1962).
47. G. Goerdeler and H. Horstmann, Chem. Ber., 93, 663 (1960).
48. L. B. Dashkevich, V. G. Beilin, N. A. Baranova, E. N. Kirillova, S. P. Saenchuk, and G. G. Verga, in: The Chemistry of Dicarbonyl Compounds. Abstr. Reports, 3rd All-Union Conference on the Occasion of the 80th Birthday of Academician of the Academy of Sciences of the Latvian SSR Gustav Vanag [in Russian], Riga (1971), p. 54.
49. V. G. Beilin, L. B. Dashkevich, and E. N. Kirillova, Zh. Org. Khim., 6, 2609 (1970).
50. L. B. Dashkevich, V. G. Beilin, and E. N. Kirillova, Inventor's Cert. (USSR) No. 291,920; Publ. in Byull. Izobret., No. 4, 70 (1971).
51. J. C. Martin, K. C. Bronnock, and R. C. Menn, J. Org. Chem., 31, 2966 (1966).
52. W. Zankowska-Jasinka and J. Eilmes, Roczn. Chem., 50, 1059 (1976).
53. T. Zawisza, E. Wagner, J. Matczakova, and T. Jacobiec, Arch. Immunol. Ther. Exp., 26, 943 (1978).
54. T. Zawisza, J. Matczak, S. H. Kowalczyk-Bronisz, and T. Jacobiec, Arch. Immunol. Ther. Exp., 29, 235 (1981).
55. L. I. Khirul'kova, V. G. Beilin, and L. B. Dashkevich, in: Results and Prospects in the Search for New Drugs at the Leningrad Institute for Pharmeceutical Chemistry. Abstr. Reports [in Russian], Leningrad (1979), p. 27.
56. E. Ziegler and E. Steiner, Monatsh. Chem., 95, 495 (1964).
57. E. Ziegler and E. Steiner, Monatsh. Chem., 96, 548 (1962).
58. E. Ziegler and H. Biemann, Monatsh. Chem., 93, 34 (1962).
59. E. Ziegler and R. Wolf, Monatsh. Chem., 95, 1061 (1964).
60. V. G. Beilin, V. A. Gindin, E. N. Kirillova, and L. B. Dashkevich, Khim. Geterotsikl. Soedin, No. 8, 1042 (1976).
61. N. A. Baranova, V. G. Beilin, L. B. Dashkevich, and L. I. Khitul'kova, in: Results and Prospects in the Search for New Drugs at the Leningrad Institute for Pharmaceutical Chemistry. Abstr. Reports [in Russian], Leningrad (1979), p. 28.
62. T. Kappe, G. Lang, and E. Ziegler, Naturforschung, 29B, 258 (1974).
63. L. B. Dashkevich and V. M. Siraya, Zh. Obshch. Khim., 32, 2330 (1960).
64. V. G. Beilin, V. A. Gindin, L. B. Dashkevich, V. N. Kuklin, and L. I. Khirul'kova, in: Results and Prospects in the Search for New Drugs at the Leningrad Institute for Pharmaceutical Chemistry. Abstr. Reports [in Russian], Leningrad (1979), p. 31.
65. E. Ziegler and E. Steiner, Monatsh. Chem., 95, 495 (1964).
66. J. C. Martin and R. N. Meen, US Pat. No 3 408 348; Chem. Abstr., 70, 11709 (1969).
67. J. C. Martin and K. C. Bronnock, US Pat. No. 3 373 159; Chem. Abstr., 69, 59254 (1968).
68. V. G. Beilin, V. A. Gindin, and B. Ya. Simkin, Khim. Geterotsikl. Soedin., No. 4, 481 (1979).
69. H. C. Scarborough and C. A. Hanning, US Pat, No 3 336 305; Chem. Abstr., 68, 12968 (1968).
70. V. G. Beilin, E. N. Kirillova, L. B. Dashkevich, A. A. Lebdev. and N. S. Malachevskaya, Khim.-farm. Zh., No. 1, 20 (1980).
71. V. G. Beilin, E. N. Kirillova, and L. B. Dashkevich, Inventor's Cert. (USSR) No. 596,583; Publ. in Byull. Izobret., No. 9, 107 (1978).
72. V. G. Beilin, V. A. Gindin, V. N. Kuklin, and L. B. Dashkevich, Khim. Geterotsikl. Soedin., No. 1, 44 (1979).
73. E. Ziegler and E. Kiesewetter, Monatsh. Chem., 96, 659 (1965).
74. L. M. Manoilova, E. N. Kirillova, V. G. Beilin, T. N. Zozulya, and L. B. Dashkevich, Khim.-farm. Zh., No. 10, 89 (1976).
75. V. G. Beilin, E. N. Kirillova, and L. B. Dashkevich, Inventor's Cert. (USSR) No. 412,186; Publ. in Byull Izobret., No. 3, 96 (1974).

76. V. G. Beilin, I. M. Ginzburg, E. N. Kirillova, and L. B. Dashkevich, Zh. Org. Khim., 13, 1333 (1977).
77. R. N. Warrener and E. N. Cain, Chem. Ind., No. 7, 591 (1982).
78. M. Yokoyama, S. Yoshida, and T. Imamoto, Synthesis, No. 7, 591 (1982).
79. Y. Yamamoto, S. Ohnishi, A. Moroi, and A. Yoshida, Chem. Commun., No. 1, 56 (1983).
80. K. Tomito and T. Murakami, Jap. Pat. No. 7 920 504; Chem. Abstr., 91, 157 755 (1979).
81. H. M. Blather and G. Stevens, US Pat. No. 3 098 071; Chem. Abstr., 60, 1766 (1964).

MASS-SPECTROMETRIC STUDY OF THE CYCLIZATION REACTIONS OF DIAZOKETONES.

8.* 1-DIAZO-3,4-EPOXY-4-ARYLBUTAN-2-ONES

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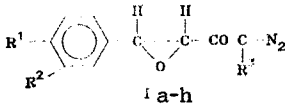
An analysis of the mass spectra of 1-diazo-3,4-epoxy-4-arylbutanones has shown that the molecular ions of these compounds lose a molecule of nitrogen and that the $[M - N_2]^+$ ions formed cyclize to form hydroxyfuran structures, whose further fragmentation determines the whole picture of the dissociative ionization of the compounds investigated under electron impact. The majority of the $[M - N_2]^+$ ions have the form of the cyclic intermediate formed in the first step of the cyclization process. It cannot, however, be ruled out that a certain portion of the $[M - N_2]^+$ ions are stabilized as a result of a Wolff rearrangement and do not cyclize at all.

We previously [2] showed that under electron impact in the gaseous phase diazoketones which contain a heteroatom or a heteroatomic grouping in their chain eliminate a nitrogen molecule and cyclize to form heterocyclic systems owing to the practicable cooperation of the heteroatom, rather than decompose according to a mechanism involving a Wolff rearrangement [3, 4]. Since the action of acids on diazoketones in solutions produces similar products [5, 6], it was concluded that it would be possible to predict the direction of this reaction on the basis of mass-spectrometric data. The results of the treatment of phthaloyldipeptide derivatives of diazomethane with acidic reagents completely correspond to the predictions made on the basis of the mass spectra of these compounds [2, 7].

Continuing this investigation, we studied the mass spectra of a series of arylepoxydiazoketones I, whose conversions in solutions were not previously investigated.



I a-h

I a R^1=H, b R^1=CH_3, c, h R^1=OCH_3, d R^1=NO_2, e R^1=F, f, g R^1=Cl; a–f R^2=R^3=H, g R^2=H, R^3=D; h R^2=OCH_3, R^3=H

The first step of the fragmentation of these compounds under electron impact, as would be expected [1, 2], is the elimination of a nitrogen molecule. This results in the formation of $[M - N_2]^+$ ions, whose structure makes it possible to draw a conclusion regarding the direction of the reactions of diazoketones with acidic reagents, which is the main goal of the present work. The possible structures of the $[M - N_2]^+$ ions (see Scheme 1) can be suggested on the basis of the preceding investigations [1, 2] and the data in [3, 4].

*For report 7 see [1].

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