SYNTHESIS AND PROPERTIES OF FUNCTIONAL DERIVATIVES OF 1,3,4-THIADIAZINES AND CONDENSED SYSTEMS BASED ON THESE COMPOUNDS (REVIEW)

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This article is a critical survey of the literature on methods of synthesis, chemical properties, conversions, and applications of 1,3,4-thiadiazines and their hetaryl derivatives.

Advances up to 1969 in the chemistry of 1,3,4-thiadiazines were examined in the review article [1], which was far from complete and which dealt mainly with the work of German and Swedish chemists. That review covered methods for the synthesis of 1,3,4-thiadiazine derivatives from aliphatic and aromatic α-halocarbonyl compounds and from thiohydrazides and dithiocarbohydrazides, as well as the stability of these compounds. A chapter in the review [2] was devoted to the desulfurization of 1,3,4-thiadiazines to pyrazoles.

In recent years, interest in 1,3,4-thiadiazines has increased in connection with the high biological activity and broad-spectrum action of their derivatives. New methods have been developed for the synthesis of 1,3,4-thiadiazines and condensed heterosystems based on these compounds. As new physicochemical methods have become available, data have been obtained on the structure, stability, and conversions of 1,3,4-thiadiazine derivatives, and on the influence of chemical and physical factors on their capabilities for transformation.

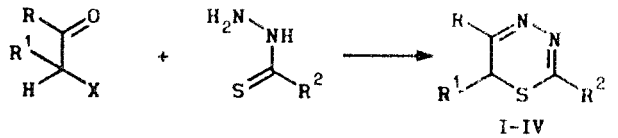
In this review we will examine preparation methods, tautomerism, chemical properties, and transformations of 1,3,4-thiadiazines and their hetaryl derivatives, as well as possible applications.

The review covers the literature of the last 20 years, including 1990.

1. METHODS OF SYNTHESIS

1.1. Synthesis of 1,3,4-Thiadiazines

1,3,4-Thiadiazines were obtained for the first time by Bose in 1925 by the interaction of α-bromoacetophenone with thiosemicarbazide. Condensation of thiosemicarbazide with α=haloketones (R = Me, Ph; R^1 = H, Me, CO_2Et) leads to the formation of 2-amino-1,3,4-thiadiazines I [1, 3]. The yields of the 2-aminothiadiazines are usually high; but, depending on the character of the original reactants, the polarity of the solvent, and the temperature, byproducts may be obtained — 2-hydrazinothiazoles and 3-aminothiazoles [3-5].



I-IV

I $R^2=NH_2$; II $R^2=C_6H_5$; III $R^2=SH$; IV $R^2=SAlk$

High yields of the amines I are obtained in acetonitrile [6] and in hydrochloric or hydrobromic acid [7-9]. In ethanol, byproducts are formed; but when acid is added, higher yields of the amines I are obtained [9-11]. This method has been used to synthesize a series of 2-amino-1,3,4-thiadiazines substituted in positions 3 and 4 and in the amino group [3, 12-17]. The interaction of 16α-, 2α-, and 21α-bromoketosteroids with thiosemicarbazide leads to the formation of the thiadiazinosteroids V-VII [18]:

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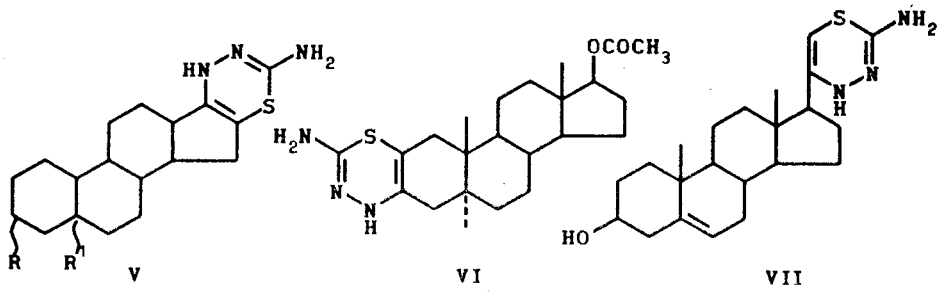
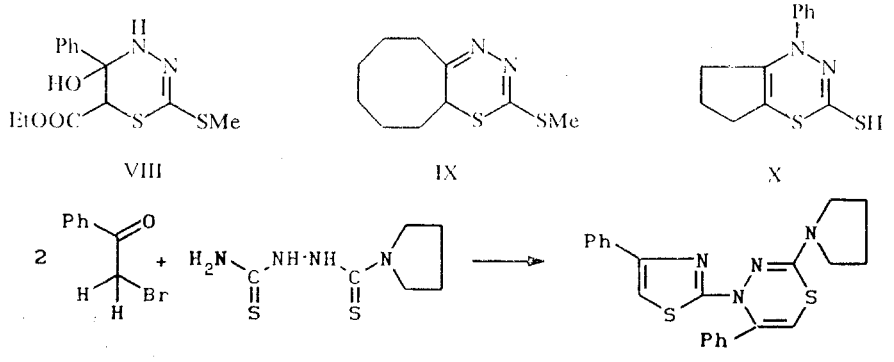


V VI VII

Closure of the thiadiazine ring can be accomplished by using other thiocarbohydrazides as well (phenylthiocarbohydrazides [19], thioarylhydrazides, salts and esters of dithiocarboxylic acid,* dithiourea, etc.). 2-arylamino- and 2-arylhydrazinothiadiazines have been obtained from diazoketones and substituted thiosemicarbazides or thiocarbohydrazide in the presence of copper [20, 21]. Oximes of α=bromoacetophenones with thiourea are also cyclized to thiadiazines I [22].

Certain 2-arylamino-5-aryl(hetaryl)-1,3,4-thiadiazines are obtained by oxidative cyclization of 4-substituted thiosemicarbazones of acetophenones with bromine in chloroform [23, 24]. With thiobenzohydrazide, α-bromoacetophenone forms 2,5-diphenyl-1,3,4-thiadiazines II [25].

2-Mercapto- and 2-alkylthio-1,3,4-thiadiazines III and IV are obtained by condensation of salts or esters of dithiocarbazinic acid with α-halocarbonyl compounds [26-28]. The products included, along with 2-mercaptothiadiazine III, a product of a side reaction — 3-amino-4-methyl-2(3H)-thiazolinethione. Interaction of the methyl ester of dithiocarbazinic acid with benzoylchloroacetate at —30°C leads to the formation of the unstable 5-hydroxy derivative of 2-methylthio-5,6-dihydro-1,3,4-thiadiazine VIII [29]. Upon condensation of chloronitroso compounds and salts of dithiocarbazinic acid, 2-mercaptothiadiazines III are likewise formed [30]. 2-Methylthio-5,6-hexamethylene-1,3,4-thiadiazine IX is obtained from 2-nitroso-1-chlorocyclooctanone and methyl dithiocarbazate [30]. 2-Chlorocyclopentanone with potassium N-phenyldithiocarbazate at room temperature forms the 2-mercaptothiadiazine X [31]. With d-glucosamine, methyl dithiocarbazate interacts to form compounds of the ozazone type, which split out ammonia upon crystallization and are cyclized to 6-substituted thiadiazines IV [R^1 = $OHCH_2$—CH(OH)—CH(OH), R^2 = MeSCSNHN=CH] [32]. The methyl dithiocarbazinite of sym-triazine interacts with chloroacetonitrile to form thiadiazines IV containing a triazine ring in position 4 [33]. Interaction of bromoacetophenone with bis(thiourea) in a 2:1 ratio affords the thiadiazine XI with a 4-phenylthiazole radical in position 4 [34].



VIII IX X

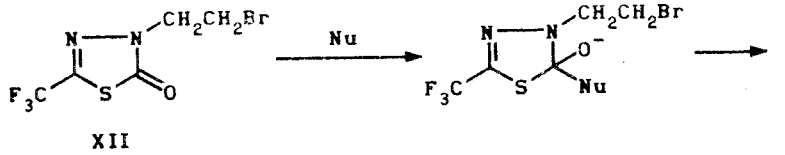
XI

In many cases, transformation of the 1,3,4-thiadiazole ring under the influence of chemical reagents leads to the formation of 1,3,4-thiadiazines. 5,6-Dihydro-4H-1,3,4-thiadiazines are obtained by the action of α-halocarbonyl compounds on 4,5-dihydro-1,3,4-thiadiazole in the presence of a base [35]. By the interaction of α-bromoacetophenones with 3-substituted 1-amino-2-thioxo-4-imidazolidinones, 3,6-dihydro-2H-1,3,4-thiadiazines have been synthesized [36]. Conversion of the thiadiazole ring to a thiadiazine ring also takes place when 1,3,4-thiadiazoline-1-oxide is treated with the anhydrides of acids [37], or when 1,3,4-thiadiazolium salts are treated with

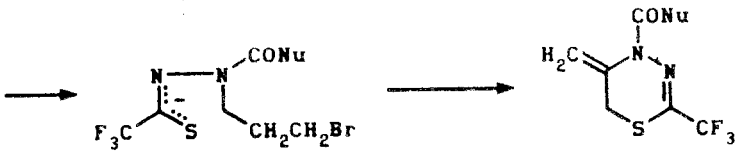
*As in Russian original; possibly should be dithiocarbazinic acid — Translator.

dialkylphosphonates in the presence of a base [38-41]. By the action of nucleophiles (Nu = NH_3, Me_2NH, pyrrolidine, MeSK) on 3-bromoalkyl-5-trifluoromethyl-1,3,4-thiadiazol-2(3H)-one (XII), 2-trifluoromethyl-4H-1,3,4-thiadiazine (XIII) is obtained with a 70-80% yield [42].

Comparative experiments with 5-phenyl- and 5-methyl-substituted analogs of XII have shown that transformation of the thiadiazole ring takes place only when an electronegative CF_3 group is present. 3-Alkyl-6-trifluoromethyl-3,6-dihydro-2H-1,3,4-thiadiazines are obtained by cyclization of $CF_3COCR{=}NNR^1CH_2R^2$ in the presence of Lavesson reagent [43].

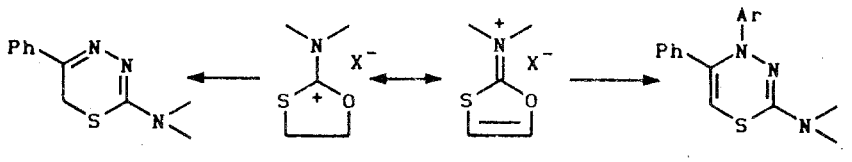


XII



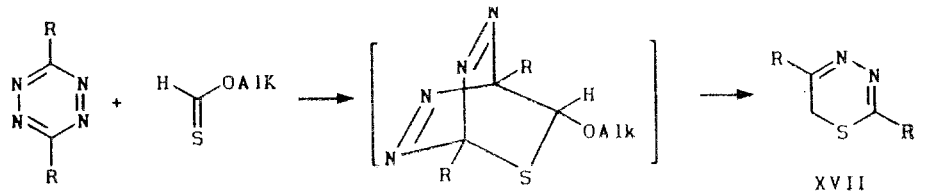
XIII

The reaction of 2-dialkylamino-5-phenyl-1,3-oxothiolium cations with nucleophiles containing an amino group also leads to 1,3,4-thiadiazines. Thus, the 1,3-oxathiole derivative XIV (X = HSO_4), with excess hydrazine hydrate or acrylhydrazine, forms the respective thiadiazines XV and XVI [44, 45]:



XV XIV XIV XVI

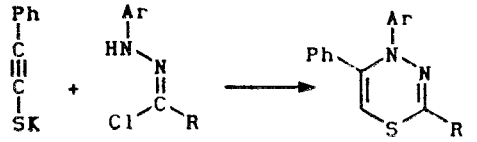
The thiadiazines XVII are obtained from tetrazines by the action of esters of thioformic acid [46]. Here the donor-substituted thiocarbonyl group acts as a heterodienophile in [4 + 2]-cycloaddition. The reaction proceeds through the formation of bicyclic Diels—Alder adducts with subsequent conversion to the thiadiazines XVII:



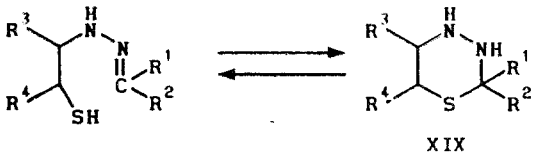
XVII

Cycloaddition of 2-phenylethynylthiolates [47, 48] or phenylethenethiolates [49-51] with chlorohydrazones or nitriles [52] in an inert solvent in the presence of triethylamine also leads to the formation of thiadiazines XVIII, with rather high yields.

Mercaptoalkylhydrazones, formed by the interaction of ketohydrazones with thiranes [53, 54], or from mercaptoalkylhydrazines [55], are cyclized reversibly in the form of hydrazones or in the presence of ketones to



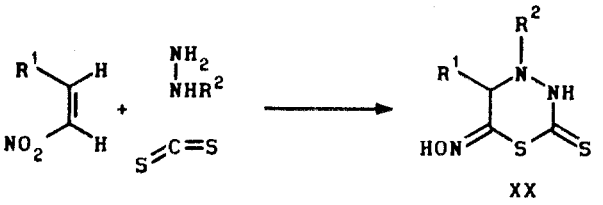
XVIII



XIX

perhydro-1,3,4-thiadiazines XIX. The thermodynamic parameters of the tautomeric equilibrium have been determined [56], and the steric structure of the thiadiazines XIX has been established [57].

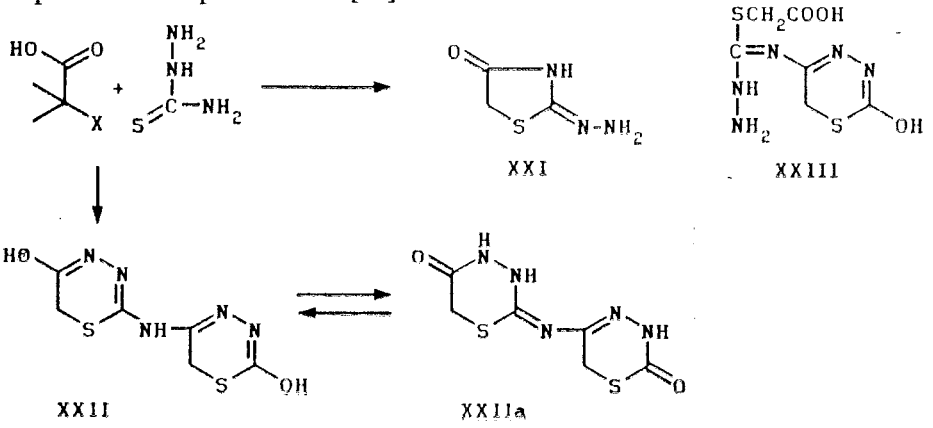
6-Hydroximinothiadiazine-2-thiones XX are obtained by the interaction of substituted hydrazines, carbon disulfide, and nitrostyrene at 50°C in the presence of ammonia [58-60].



XX

1.2. Synthesis of 1,3,4-Thiadiazinones

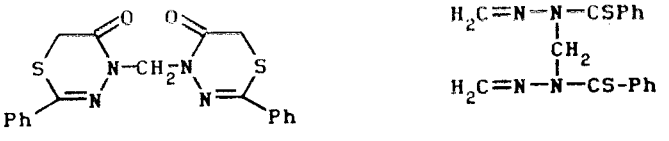
The 2-one, 5-one, and 6-one derivatives of 1,3,4-thiadiazine are known. Of these, the most thoroughly studied is the thiadiazin-5-one, synthesized by the interaction of haloacetic acids with derivatives of thiosemicarbazide, thiocarbohydrazide, or dithiocarbazinic acid. In the condensation of haloacetic acids with a thiosemicarbazide, as already mentioned, important factors in determining the formation of the possible isomers are the character of the substituents and the pH and temperature of the reaction medium; in earlier reports, therefore, information on the structure of the reaction products is contradictory [61]. In the condensation of a thiosemicarbazide with chloroacetic acid in butanol, the formation of two compounds was observed in [62] — the hydrazone of thiazolidine-2,4-dione (XXI) and 2,5′-iminobis(6H-1,3,4-thiadiazine)-5,2-diol (XXII) or its tautomer XXIIa. The structure of compound XXII is confirmed by hydrolytic splitting of one of the thiadiazine rings in concentrated HCl and interaction of the hydrolysis product with aromatic aldehydes to form compound XXIII; further evidence may be found in the IR spectra of compound XXII [63].



XXI XXIII

XXII XXIIa

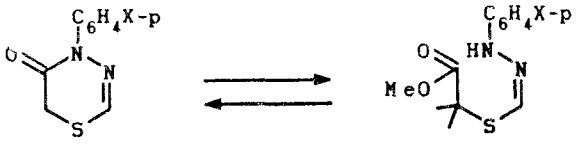
With yields of 60-70%, 4-(1-phthalazinyl)-1,3,4-thiadiazin-5-ones are obtained [64] by boiling 4-substituted 1-(phthalazinyl-1)thiosemicarbazide and ethyl bromoacetate in concentrated HCl; 2,4- and 2,3,4-substituted thiadiazin-5-ones are obtained by the interaction of 1,3- and 1,3,4-substituted thiosemicarbazide with thioesters, anhydrides, and acid chlorides of haloacetic acids [65, 66]. With hydrazides and thiohydrazides in 2 N NaOH, 2-arylthiadiazin-5-ones are formed [67]. From 2-methylenethiobenzhydrazide and bromoacetic acid, 4,4′-methylenebis(5,6-dihydro-2-phenyl-1,3,4-triadiazin-5-one) (XXIV) is obtained, along with methylenebis(methylenethiobenzhydrazide XXV) [68]:



XXIV XXV

A 4-phenyl-4,5-dihydro-1,3,4-thiadiazin-5-one of the type of XXVI, substituted at position 2, has been synthesized from the phenylhydrazone XXVII in methanol in the presence of a weak base [69-71]. The structure of the thiadiazine XXVI has been confirmed by ^{1}H and ^{13}C NMR spectra and by x-ray structure analysis; the structure

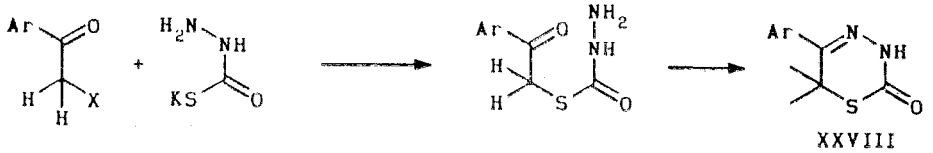
is consistent with what has been reported in other work by these same investigators. The low yield of compound XXVI indicates that the thiadiazinone exists in equilibrium with XXVII.



XXVI XXVII

Higher yields of XXVI are obtained from the phenylhydrazone of methylthioacetic acids and dicyclohexylcarbodiimide [72]. With X = H, the yield of the compound of the type of XXVI is 70-80%; with X = NO_2, the yield drops to 30%. The 5-hydroxy and 5-oxo forms of the thiadiazinone XXVI have been judged on the basis of spectroscopic data and calculations by the Hückel molecular orbital method [73].

The other thiadiazinones have received less attention. For the synthesis of thiadiazin-2-ones, salts or esters of thiocarbazinic acid are alkylated with an arylacyl bromide and then cyclized in dilute HCl to form 5-aryl-6H-1,3,4-thiadiazin-2(3H)-ones XXVIII [74-76]. Also, O-methyl thioformate can be used [74]



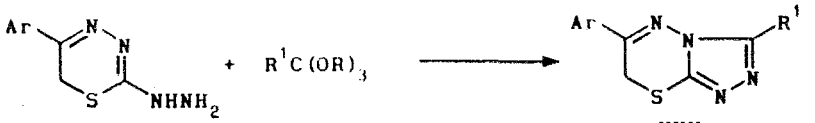
XXVIII

XXIX

Thiadiazin-6-ones XXIX have been obtained by intramolecular cyclocondensation of the thiosemicarbazone of phenylglyoxalic acid, with a 90% yield [77].

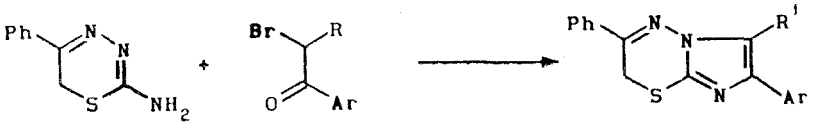
1.3. Synthesis of Condensed 1,3,4-Thiadiazines

The presence of a hydrazino group in position 2 of 1,3,4-thiadiazines increases the local π-excess of the heteroring and facilitates cyclization with π-electrophilic reagents. By the action of esters of orthocarboxylic acids [78] or acid chlorides [79] on 2-hydrazino-5-aryl(alkyl)-6H-1,3,4-thiadiazines, 7H-1,2,4-triazolo[3,4-b]thiadiazines (XXX) are formed. The compounds XXX are also obtained by refluxing 2-benzoylhydrazino-5-phenyl-4H-1,3,4-thiadiazines in ethanol in the presence of HCl [80].



XXX

Aryl-substituted 2H-imidazo[2,1-b][1,3,4]thiadiazines XXXI in the form of stable hydrobromides have been obtained by the action of haloketones on 2-amino-5-phenyl-1,3,4-thiadiazines in ethanol in the presence of HBr [81], or by the bromination of 6-bromomethyl-5,6-dihydro-2-methylamino-4H-1,3,4-thiadiazine [82].

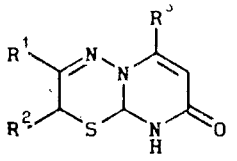


XXXI

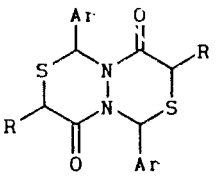
It has been shown in the work of Japanese investigators that by the cyclization of 2-amino-5,6-substituted thiadiazines with acetylenecarboxylates, pyrimido[2,1-b][1,3,4]thiadiazines XXXII are formed [83, 84] (see below).

By the interaction of benzaldazine with excess thioglycolic acid in benzene, 1H,6H-1,3,4-thiadiazino[4,3-c][1,3,4]-thiadiazin-3,8-(2H,7H)-dione [85]. The yield of the final products depends on the nature of the substituents [86]. When the arylaldazine is fused with lactic acid, a mixture of isomers is formed. 1,3,4-Triadiazino[6,5-

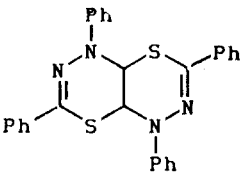
b][1,3,4]thiadiazines XXXIV were obtained along with other products by the interaction of thiobenzhydrazide with orthoformic ester [87].



XXXII



XXXIII

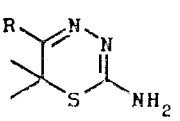


XXXIV

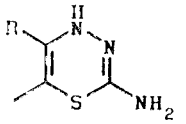
2. CHEMICAL PROPERTIES OF 1,3,4-THIADIAZINES AND 1,3,4-THIADIAZINONES

2.1. Tautomerism of 1,3,4-Thiadiazines

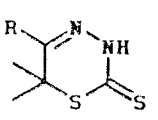
1,3,4-Thiadiazines exist in two tautomeric forms 6H and 4H. According to PMR and IR spectroscopic data, the 6H form dominates in 2-amino-1,3,4-thiadiazines in solution, and the 4H form in the solid state [88, 89]. In the PMR spectra of the 6H, a singlet is observed from the two protons at the $C_{(6)}$ atom of the thiadiazine ring, in the 3.6-3.9 ppm region [4, 7, 8, 45, 88]; for the 4H form, a singlet of one proton is observed in the 5.6 ppm region [89, 45]. In the IR spectra of the 4H form, characteristic bands of ν_{NH} are observed in the 3200-3190 cm^{-1} region, and δ_{NH} in the 1640 cm^{-1} region [45, 89]. 3-Alkyl-2-amino-1,3,4-thiadiazines exist in solution in the 6H form [14, 15].



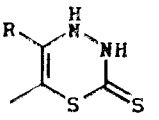
6H



4H



6H



4H

On the basis of studies of NMR, IR, and UV spectra of model compounds, the thione structure has been assigned to 2-mercaptothiadiazines [30]. In the PMR spectra, signals are observed from protons of the $N_{(3)}H$ group in the 10-12 ppm region, and there are no signals of the SH group in the strong field. Always present in the IR spectra is a band higher than 3000 cm^{-1} corresponding to NH vibrations; the weak band at 2500-2600 cm^{-1} is completely absent. In the UV spectra of the thione forms there is a long-wave absorption maximum that is shifted hypsochromically by 25 nm when the system configuration is changed (for the S-alkyl derivatives). The ^{13}C NMR spectra confirm the presence of a C=S structural element. 5,6-Polymethylene-1,3,4-thiadiazines belong to the 6H series [30].

2.2. Chemical Properties of 1,3,4-Thiadiazines

The presence of the sulfur atom in the thiadiazine molecule determines its specific chemical properties — transformation with contraction of the ring under the influence of various factors. The susceptibility of the thiadiazines to conversions depends on the stability of the hetero ring, which is governed in turn by the character of the substituents in positions 2 and 5 and particularly 6, and also by the types of reagents and solvents. Since the thiadiazine ring is not always stable under the conditions existing in many chemical reactions, the possibilities for chemical modification of 1,3,4-thiadiazines are limited.

2.2.1. Reactions in Which the Thiadiazine Ring is Preserved. There are not many reactions in which the thiadiazine ring is preserved. Electrophilic substitution at the carbon atom, which is widely encountered in the aromatic and heterocyclic series, has not been studied adequately in the case of the 1,3,4-thiadiazines. At the same time, 5,6-dihydro-5-hydroxy-4-phenyl-1,3,4-thiadiazine, for which the $C_{(5)}$ atom is in the sp^3 configuration, reacts with electrophiles and enters into nucleophilic substitution reactions with alcohols, thiols, and amines to form the corresponding 5-substituted 1,3,4-thiadiazines with nearly quantitative yields [71, 73]. The reactivity of this compound is explained by resonance stabilization of the intermediate thiadiazinium cation that is formed upon heterolysis of the carbon—oxygen bond [73].

Alkylated thiadiazines are usually obtained by a directed synthesis in which alkylthiocarbohydrazides are condensed with α-halocarbonyl compounds. 2-Mercapto-5-phenyl-4H-1,3,4-thiadiazine is methylated at the sulfur by methyl iodide in the presence of KOH [80].

Tetrahydro-6-hydroximino-3-methyl-5-phenyl-4H-1,3,4-thiadiazine-2-thion, when subjected to the action of $NaNO_2$ in acetic acid, is converted smoothly to the $N_{(4)}$-nitroso derivative [58]. By oxidation of 5,6-diphenyl-2-phenylhydrazino-6H-1,3,4-thiadiazine by atmospheric oxygen in acetic acid or hydrogen peroxide in ethanol, the 2-phenylazo derivative is obtained [19].

2.2.2. Transformation of Thiodiazines with Ring-Opening. As mentioned above, the stability of the thiadiazine ring is determined by many factors. Thermal cleavage of the ring to give pyrazoles with extrusion of sulfur or to form dipyrazolyl-4,4′-disulfides takes place when substituted thiadiazines are heated above their melting point [90], or at 180°C [91]. Transformation of the thiadiazine ring takes place upon heating in nonpolar organic solvents [92-94] or under the action of nucleophiles, certain acylating agents, or acids. For thiodiazines with electron-acceptor substituents in position 6, extrusion of sulfur sets in when they are exposed to ultrasound [95, 96]. Such 6-substituted thiadiazines are so unstable that, even in the course of their synthesis, they are converted to pyrazoles while sulfur is extruded, so that they are often intermediates rather than final reaction products [2, 92, 97]. Certain triazolothiadiazines are resistant to the action of triphenylphosphine and acetic acid [78]. In a number of cases, condensed thiadiazines are transformed to the corresponding pyrazoles with extrusion of sulfur [2, 98].

2.2.2.1. Catalysis by mineral and organic acids. Transformation of thiadiazines into 4-mercaptopyrazoles or to pyrazoles with the extrusion of sulfur, depending on the substituents in the hetero ring, will take place as a result of the catalytic action of mineral acids or glacial acetic acid. In concentrated mineral acids, the 2-aminothiadiazines XXXVa, b, which are mainly 5-alkyl-substituted, are rearranged to the isomeric 2-imino-3-amino-Δ^4-thiazolines XXXVIa, b [1, 99-102]

XXXVa,b XXXVIa,b

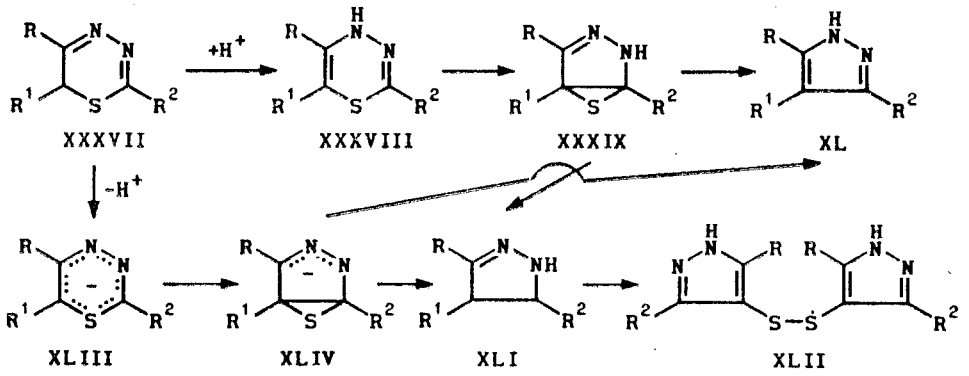
a) R=Alk, $PhCH_2$, Ar; $R^1=R^2=H$, b) R^1=Me, R^2=Pr or *i*-Pr, R=Ph

The rate of intramolecular rearrangement XXXVa → XXXVIa in HCl or H_2SO_4 at 30-50°C decreases in the series 5-alkyl > 5-benzyl > 5-aryl derivatives, and the rate increases with increasing acid concentration and reaction temperature [100, 102]. For the 5-aryl-substituted 2-aminothiadiazines, rearrangement to Δ^4-thiazolines either does not take place at all or is very slow [1, 93, 102, 103]. In the case of 2-amino-5-phenylthiadiazine, prolonged boiling in concentrated HCl is required to form small quantities of 2-hydrazino-4-phenylthiazole and 3-amino-2-imino-4-phenyl-Δ^4-thiazoline [100]. It can be seen from kinetic studies reported in [102] that the isomerization of 5-arylthiadiazines to thiazolines in mineral acids is reversible and that the equilibrium of the reaction is shifted toward the formation of thiadiazines; this is in accord with the data of [1].

The mechanism of rearrangement of 5-alkyl-2-amino-6H-1,3,4-thiadiazines to Δ^4-thiazolines includes transannular attack, of the S_N2 type, by the $N_{(3)}$ atom on the sp^3-hybridized $C_{(5)}$ atom of the thiadiazine, with the formation of a bridge bond between them. Subsequent formation of a diaziridine ring, followed by its opening, leads to the Δ^4-thiazolines [100]. An alternative mechanism of the rearrangement [1, 102] assumes hydrolytic cleavage of the thiadiazine ring at position 4—5 and recyclization to form the Δ^4-thiazoline. Other studies of the rearrangement of 2-aminothiadiazines to Δ^4-thiazolines have been reported in [104].

When an electron-acceptor phenyl group is introduced into position 6 of the thiadiazines XXXVa, b, formation of Δ^4-thiazolines is accompanied by competitive formation of pyrazoles with extrusion of sulfur [1, 95, 102]. Subsequent dealkylation is possible [95, 105]. In concentrated HCl, for 2-tert-butylamino- and 2-[(2,2,4,4-tetramethylbutyl)amino]thiadiazines, differentiated behavior is observed, depending on the character of the substituent in position 6 [105].

In an acidic medium, the 6H-thiadiazines XXXVII are converted to the equilibrium, energy-rich 4H-thiadiazine XXXVIII. As a consequence of valence isomerization, this cyclic 8π system is transformed to the thia-σ-homopyrazole XXXIX, which, upon elimination of sulfur or cleavage of the episulfide ring, forms the pyrazoles XL or XLI [106].

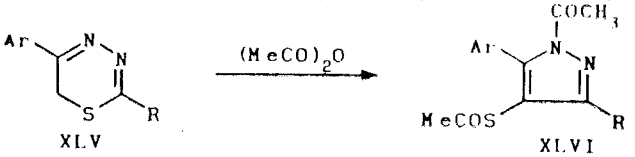


R=Ph; R^1=H, Ph; R^2=NMe, SMe, CH_2Ph, Ph

With such a mechanism for the thiadiazines that are capable of desulfurization, deuterium exchange of protons is accomplished in position 6 [106]. It is also suggested that, upon protonation, the $C_{(2)}$—S bond is split to form a 4-mercaptopyrazole, which in certain cases may be converted to a pyrazole with extrusion of sulfur through the disulfide [1]; or formation of a thiirane is suggested [2]. The mechanism of desulfurization has received very little attention. In dilute mineral acids, desulfurization takes place for 2-cycloalkylimino- [107] and 2-dimethylamino-5-aryl-6H-1,3,4-thiadiazines [97, 106]. The stability of the thiadiazine ring in this case is influenced not only by the character of the cycloalkylamine, but also by the substituent in the phenyl ring [108].

The 6-unsubstituted thiadiazines XXXVII, when heated for an extended period in acetic acid, are transformed to the 4-mercaptopyrazoles XLI [1, 106, 109]. These latter compounds, upon oxidation by I_2 in an alkaline medium or by atmospheric air, are converted under the action of Raney nickel to pyrazoles, with extrusion of sulfur [93]. Desulfurization of 2-methylimino-3-methyl-5-aryl-2,3-dihydrothiadiazines [14] and other 2-substituted 5-arylthiadiazines [1, 3, 92, 97, 110, 111] to pyrazoles proceeds most smoothly when they are heated in acetic acid. This is a preparative method for obtaining pyrazoles [2, 103]. If an aryl, acyl, or alkoxyl group is present in position 6, the transformation to pyrazoles with extrusion of sulfur is accelerated severalfold in comparison with 6-unsubstituted derivatives, and the yields of pyrazoles are higher. For certain 6-substituted 2-alkylamino-5-arylthiadiazines in acetic acid, along with the elimination of sulfur, dealkylation in position 2 takes place, as well as acetylation to form 3-acetyl derivatives of the pyrazole [105].

2.2.2.2. Action of acylating agents. For the acylation of thiodiazines, carboxylic acid anhydrides and acid chlorides are used. Upon heating the thiodiazines XLV with acetic acid, acylation takes place, with opening of the thiadiazine ring and the formation of 3-substituted 1-acetyl-4-acetylmercapto-5-arylpyrazoles (XLVI) [1, 93, 97].



Ar=C_6H_5, C_6H_4Br-4, C_6H_4Cl-4; R=$N(CH_3)_2$, piperidine, morpholine, CH_3, $CH_2C_6H_5$, C_6H_5

Upon boiling triazolothiadiazines with acetic anhydride, N-acetylpyrazolotrazoles are formed [98]. The formation of pyrazoles and the acetylation apparently take place simultaneously. The introduction of an acetyl group into position 4 of thiadiazino[5,6-b]quinoxalines, upon heating in acetic anhydride with the addition of triethylamine, produces the 4-acetyl derivative of the thiadiazine, without recyclization [112].

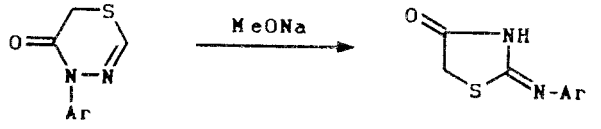
Benzoylation of 5-substituted 2-aminothiadiazines proceeds selectively, depending on the solvent and the ratio of initial reagents, at the amino group of the side chain [101, 113] or at the terminal nitrogen atoms; or it may proceed with the formation of a mixture of several benzoyl derivatives [101]. The acylation of 2-arylamino-5-hetarylthiadiazines by acetic anhydride [24], or the acylation of 5,6-substituted 2-aminothiadiazines by ketene [84], takes place at the exocyclic nitrogen atom.

6-Hydroximinothiadiazine-2-thiones XX are acylated at the exocyclic nitrogen atom by acyl chlorides and esters of chlorocarbonic acid in acetonitrile in the presence of pyridine [58, 60]. Upon heating 3-methyl-substituted thiadiazines XX in a mixture of acetic anhydride and acetic acid in the presence of sulfuric acid, the 4-acetyl derivative is formed; upon acylation by an ester of chlorocarbonic acid or by benzoyl chloride in pyridine, it is transformed to the 1,3,4-thiadiazoline-2-thione.

2.2.2.3. Transformation under the influence of nucleophiles. The action of nucleophiles, in particular butyllithium, results in recyclization of 6H-thiadiazines with a contraction of the ring to pyrazoles XLII or XLI through the formation of a reactive heterocyclic 8π system — the thiadiazine anion XLIII and thia-σ-homopyrazole XLIV [106]. Desulfurization of the thiadiazines XXXVII to the pyrazoles XL proceeds in benzene at room temperature [106, 114]; this reaction proceeds at —110°C in THF under the influence of lithium diisopropylamine [106]. The 6-substituted thiadiazine XXXVII is converted quantitatively to the pyrazole XL by the action of butyllithium in THF at —80°C. From 6-unsubstituted thiadiazines in absolute THF at —100°C under anaerobic conditions with butyllithium, red solutions of the thiadiazine anions XLIII are obtained [114]. Desulfurization of a number of thiadiazines takes place under the influence of potassium tert-butoxide [114] or sodium ethylate [103], in alcohols in the presence of a twofold excess of caustic [115], or upon heating with triphenylphosphine or triethyl phosphite [93, 109, 116]. It is suggested in [109, 117] that valence isomerization to thiirane derivatives takes place under the influence of thiophilic compounds of phosphorus. 2-(Methylthio)thiadiazines are transformed to dipyrazolyl disulfide under the influence of hydrazine hydrate or aniline [80].

2.3. Chemical Properties of Thiadiazinones

Thiadiazinones interact with nucleophiles and other reagents in ways that are different from the reactions of thiadiazines. The 4-arylthiadiazin-5-ones exhibit high resistance to the action of nucleophiles, electrophiles, and radical reagents [73]. An important role in resonance stabilization of the thiadiazin-5-ones is played by the mesomeric effect of the carbonyl group [71]. Thiadiazin-5-ones are resistant to the action of O,O-dialkylhalophosphates [118] and lithium aluminum hydride [71], and they react with reagents without opening the ring. However, the action of sodium methylate in methanol on the thiadiazin-5-ones XLVII transforms them quantitatively to 2-arylamino-1,3-thiazoidin-4-ones XLVIII, with rupture of the N—N bond [119].

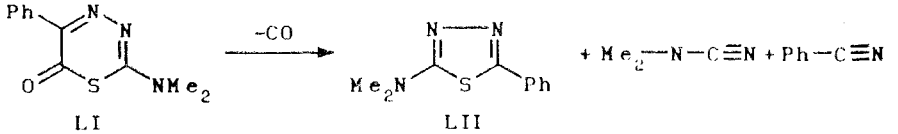


XLVII XLVIII

Oxidation of the thiadiazin-2-one XLIX by tert-butyl hypochlorine in DMFA, by chlorine in chloroform, or by 30% H_2O_2 in formic acid, leads to the formation of 4-aryl-1,2,3-thiadiazoles L with extrusion of CO_2 [74]:

XLIX L

The thiadiazin-6-one LI interacts with 1-diethylaminopropyne to form a mixture of adducts 1H-pyridazin-4-one and 5H-pyridazin-4-one [77]. Flame—vacuum pyrolysis at 550°C results in thermal fragmentation of LI to the thiadiazole LII, dimethylcyanamide, and benzonitrile [77]:



LI LII

3. APPLICATIONS

Interest in the thiadiazines is related to their high biological activity and their broad-spectrum action. A number of thiadiazines have fungicidal [120-122], antimicrobial [59, 60, 120, 123-125], antiinflammatory [12, 38-40, 84, 126], and antiedematic [38, 40] activities. Certain thiadiazines are inhibitors of monoaminooxidase [124], lipoxygenase [127, 128], phosphodiesterase [129], and angiotensin-converting enzyme [130]. The general class of thiadiazines includes compounds with antioxidant [127], analgesic [12, 39, 127], antiviral [12, 131], and radiation-protective [132] properties. Substituted 5,6-dihydro-4H- and 3,4,5,6-tetrahydrothiadiazines can be used as central nervous system depressants [133, 134].

In the last decade, many thiadiazines have been discovered with possible applications in medical practice as sedatives [39, 135], antianxiety agents [136], antiasthmatic agents [137], anticonvulsants [64], myorelaxants [138-140], coronary vasodilators [15, 129, 141], and spasmolytics [15, 136, 142]. Many thiadiazines have cardiovascular activity [16, 67, 75, 137, 143-149]. A number of thiadiazines are effective against viruses [66, 150].

Certain derivatives of thiodiazines that have pesticidal activity [10, 65, 113, 118, 151-154] may find applications in agriculture. Thiadiazines can be used in the manufacture of varnish resins for coatings [155, 156], raw and vulcanized rubber [157, 158], polypropylene [159], in mixtures for impregnating fabrics [160], in the manufacture of dyes [11, 161], in plating technology as brightening agents for copper-plating electrolytes [51, 162], in photography [163, 171], and in analytical chemistry as a reagent for the photometric determination of iron [172].

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