1,3,4-THIADIAZINES: METHODS OF SYNTHESIS AND REACTIVITY (REVIEW)

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The synthetic methods for 1,3,4-thiadiazines and their intramolecular rearrangement reactions are reviewed.

1,3,4-Thiadiazines represent the most widely studied class of compounds among the six theoretically possible thiadiazine isomers; they are of interest in a chemical sense because they are labile compounds which are capable of undergoing intramolecular rearrangements to give thiazole and pyrazole derivatives. In addition, 1,3,4-thiadiazines exhibit a broad spectrum of biological activity.

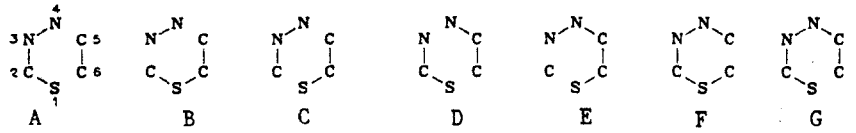
In the early 1970s several reviews by Beyer appeared in the literature [1, 2], dealing with the chemistry of 2-amino-1,3,4-thiadiazines. Little attention had been paid at that time to the synthesis and reactivity of other derivatives of this heterocycle.

Our goal in the present review was to summarize the available literature data concerning synthetic methods for 1,3,4-thiadiazines and their intramolecular rearrangements.

1. SYNTHESIS OF 1,3,4-THIADIAZINES

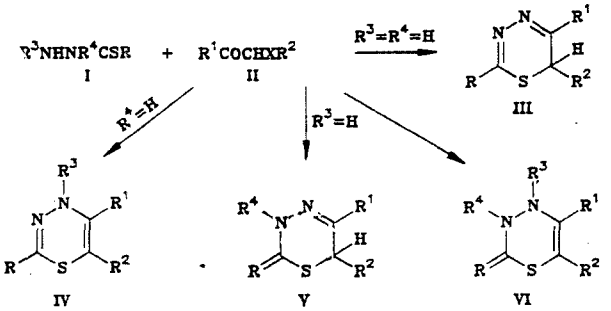
1.1. Preparation of 1,3,4-Thiadiazines via Cyclization Reactions

We can consider the formation of the thiadiazine heterocycle using reagents corresponding to different ring fragments as the basis for a classification scheme for different types or modes of cyclization.



A B C D E F G

Type A. A general feature of this type of synthesis for 1,3,4-thiadiazines is the construction of the $N_{(4)}$—$N_{(3)}$—$C_{(2)}$—S fragment using thiocarbohydrazides. In particular, a synthetic method involving the cyclization of thiocarbohydrazides I with α-halocarbonyl compounds II has found widespread application. Thus, a large number of 6H-1,3,4-thiadiazines (III) [1-56] has been synthesized from compounds I which are unsubstituted at the $N_{(1)}$ and $N_{(2)}$ atoms, while the corresponding 1- and 2-substituted derivatives I have led to the formation of 4-R^3-4H- (IV) [7, 8, 57-61] and 3-R^4-2,3-dihydro-6H-1,3,4-thiadiazines (V) [62-64]. 2,3-Dihydro-4H-thiadiazines VI, containing substituents in the 3- and 4-positions, have been prepared from 1,2-disubstituted thiocarbohyrazides [65].



Varying the thiocarbohydrazide component I has made it possible to prepare compounds with a variety of different substituents in the 2-position: phenyl- [3-5], benzyl- [3, 4], mercapto- [6-11, 16, 58, 61, 66, 67], alkylthio- [4, 12-14, 60], benzylthio- [15, 16], hydroxy- [10, 17-21], amino- [1, 13, 22-47], alkylamino- [1, 27, 28, 35, 36, 50-53, 62, 64, 65], arylamino- [1, 30, 50-52, 63, 64], hydrazino- [1, 13, 37, 48, 49], and dialkylamino derivatives [1, 44-47, 54-56, 59]. Thiadiazines which are unsubstituted in the 2-position can be synthesized from thioformylhydrazine derivatives [57, 68, 69].

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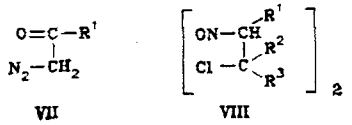
Another advantage of this synthetic method is that it makes it possible to prepare 1,3,4-thiadiazines with a variety of different substituents in the 5- and 6-positions of the ring, due to the ready availability of a variety of α-halocarbonyl compounds II. 5-Methyl- [1, 6, 7, 22-25, 48, 54, 61, 63], 6-methyl- [1, 22, 23], 5-alkyl- [24, 27-29, 49], 5,6-dimethyl- [1, 8, 22, 23], 5-methyl-6-phenyl- [1], 5-ethoxycarbonyl- [30, 70, 71], 5-ethoxycarbonylmethylene- [31, 32], 5-benzyl- [24], 5-methyl-6-ethoxycarbonyl- [1, 8, 9, 12, 26], 5-phenyl- [1, 3, 5-8, 12, 15, 24, 34, 50, 51, 54, 55, 57, 59-63], 5-aryl- [3, 13, 17-19, 24, 35-37, 43-47, 52, 54, 56, 62-64], 5-phenyl-6-methyl- [51], 5-phenyl-6-ethoxycarbonyl [14], 5,6-diphenyl- [1, 3, 4, 12, 51, 53, 62], 5-hetaryl- [10, 11, 20, 21, 38-42, 61], and other thiadiazine derivatives [16, 33, 58, 62, 64] have been synthesized in this manner. In addition, 1,3,4-4H-thiadiazin-5-ones have been prepared using α-haloacetic acids and their derivatives [8, 16, 57, 68, 69, 72-82].

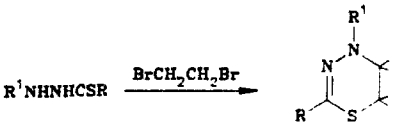
α-Diazoketones VII, in the presence of copper [83, 84], as well as dimeric nitrosochlorides VIII [85, 86], can also be used in these cyclization reactions with thiocarbohyrazides in place of compounds II.



VII VIII

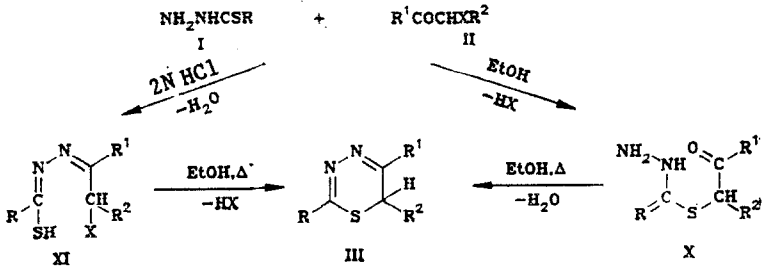
VII R^1=Ph, 4-R′-C_6H_4; VIII R^1=H, Me, Ph; R^2=H, Me; R^3=H, Me; R^1R^2=—$(CH_2)_n$, n=3, 4, 6

Using 1,2-dihaloalkanes as the two-carbon fragment in these reactions leads to the formation of 4,5-dihydro-1,3,4-thiadiazines (IX) [87].



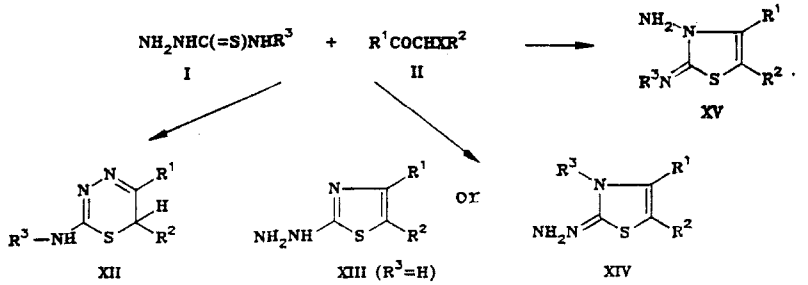
IX

The mechanism of cyclization of thiocarbohydrazides with α-halocarbonyl compounds depends on the acidity of the reaction medium. In neutral media (ethanol) the first step in the reaction process involves alkylation at the sulfur atom to generate an isothiocarbohydrazide X, while in weakly acidic media (2 N HCl) initial formation of an α-halothiosemicarbazone XI takes place. The intermediate products have been isolated and identified in many cases [1, 22-24, 26, 48, 57, 69]. Compounds X and XI can be converted to thiadiazines by heating in ethanol.



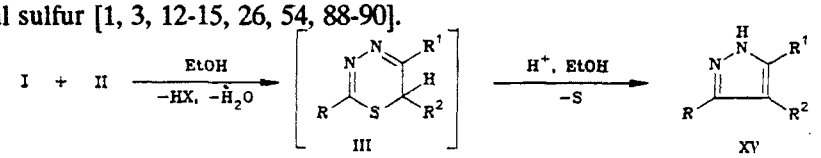
XI III X

In rare cases the synthesis of thiadiazines via method A can be complicated by the formation of side products arising from cyclization at the $N_{(2)}$ atom in the event of thiocarbohydrazides, and at the $N_{(2)}$ and $N_{(4)}$ atoms in the event of thiosemicarbazide. Thus, reaction of dithiocarbohydrazide gave not only 2-mercapto-1,3,4-thiadiazine, but also 3-N-aminothiazoline-2-thione [6]. Reaction of thiosemicarbazide and its 4-R′-substituted derivatives with α-halocarbonyl compounds led to the formation of either 2-R′-aminothiadiazine XII [1, 24, 37, 50, 52, 54], or 2-hydrazinothiazoles XIII and XIV [1, 37], or to mixtures thereof [1, 34, 50, 51, 53]. Unfortunately, no clear relationship or dependence could be discerned between the formation of these various isomers and the structures of the starting materials.



XII XIII (R^3=H) XIV XV

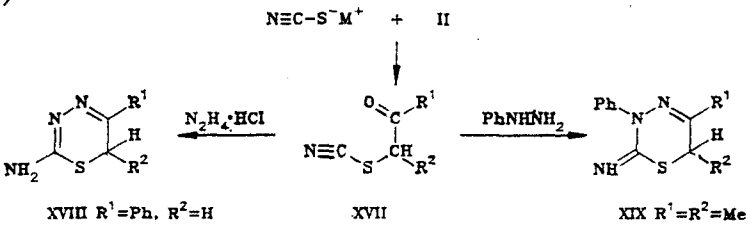
In addition, the thiadiazine isomers III formed via cyclization in alcohol solution are sometimes sufficiently unstable that they are converted, either partially or completely, to pyrazole derivatives XVI, via ring contraction and the elimination of elemental sulfur [1, 3, 12-15, 26, 54, 88-90].



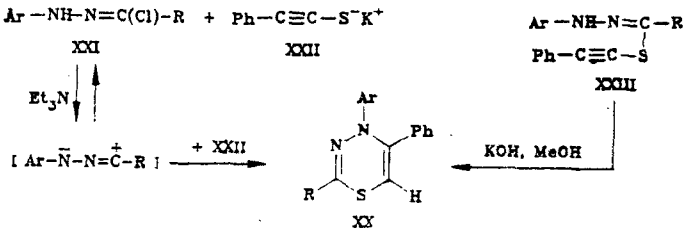
R=Ph, $PhCH_2$, AlkS, NH_2, AlkNH, ArNH, Alk_2N; R^1=Me, Ph; R^2=Ph, COOEt

For the synthesis of 5-phenyl- [1, 37, 91, 92], 5-ethoxycarbonyl- [30, 71], and 5-ethoxycarbonylmethylene [31] derivatives of 2-amino-1,3,4-thiadiazine a solvent such as concentrated HCl has been used. This method is unsuitable, however, for the preparation of 5- (and/or) 6-alkyl-substituted 2-aminothiadiazines; the cyclization products of thiosemicarbazide and its derivatives with α-halocarbonyl compounds in concentrated HCl are 3-N-amino-2-iminothiazolines XV [1, 22, 23, 26, 31, 88, 91].

Type B. Reaction of compounds II with thiocyanate anions leads to the formation of α-thiocyanoketones XVII, which can react further with hydrazine [1, 93] or its derivatives [94] to give 2-amino- and 2-imino-3-substituted thiadiazines (XVIII or XIX).

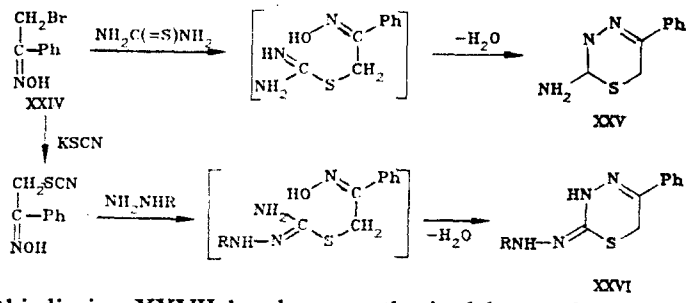


Type C. 4-Aryl-1,3,4-thiadiazines XX have been synthesized by the addition reaction of N-aryl-C-chlorohydrazone aldehydes XXI with unsaturated compounds [95-97]. Thus, potassium 2-phenylethynylthiolate (XXII) reacts with compounds XXI in aprotic solvents in the presence of triethylamine via a [3 + 3] cycloaddition scheme to form 2,4,5-trisubstituted 4H-thiadiazines XX [95, 96]. When these reactions are carried out in the absence of base the products are N-aryl-C-(2-phenylethynylthio)hydrazone derivatives of the aldehydes XXIII; the latter readily undergo intramolecular cyclization upon treatment with strong bases to generate the desired compounds XX [95].



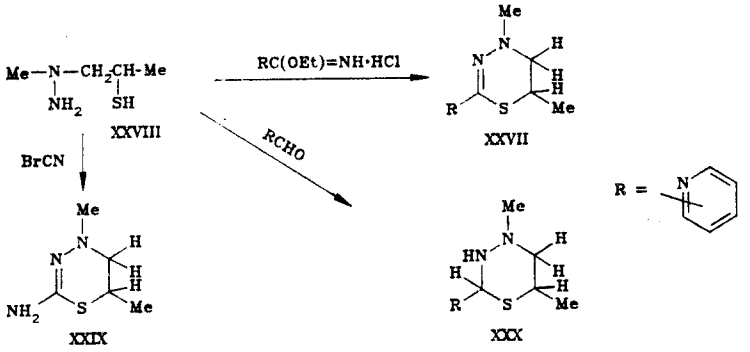
R=Ph, 4-Me−C_6H_4, 4-NO_2−C_6H_4, COMe, COOEt; Ar=Ph, 4-Me−C_6H_4, 4-Br−C_6H_4

Type D. This type of cyclization process for the synthesis of 1,3,4-thiadiazines involves introduction of the $N_{(4)}$—$C_{(5)}$—$C_{(6)}$ fragment using oxime derivatives of α-halocarbonyl compounds. Thus, ω-bromoacetophenone oxime (XXIV) reacts with thiourea to give 2-aminothiadiazine XXV, or with potassium thiocyanate and hydrazine to give the 2-hydrazono derivative XXVI [98].

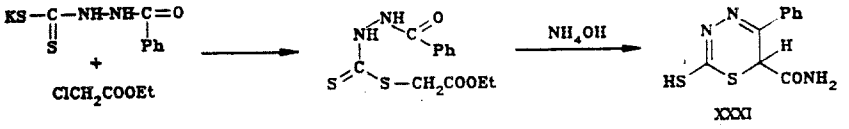


Type E. 5,6-Dihydro-4H-thiadiazine XXVII has been synthesized by condensation of β- hydrazinoalkylthiols XXVIII with iminoesters and nitriles. The 2-amino derivative XXIX can be prepared by this method using cyanogen bromide as the addend. Reaction of β-hydrazinoalkylthiols XXVIII with aldehydes leads to the formation of

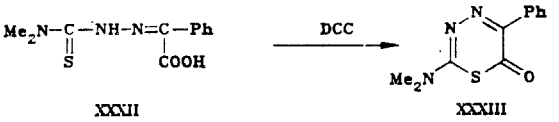
tetrahydro-1,3,4-thiadiazines XXX [99, 100].



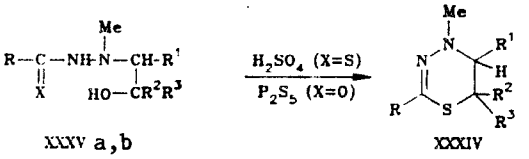
Type F. An example of this type of synthesis is the preparation of 2-mercapto-5-phenyl-1,3,4-6H-thiadiazine-6-carboxamide (XXXI) from the potassium salt of benzoyldithiocarbohydrazide and ethyl chloroacetate [101].



Type G. This reaction type or variation involves construction of the $S-C_{(6)}$ bond via an intramolecular cyclodehydration sequence. For example, oxophenylacetic acid thiosemicarbazone (XXXII) reacted in the presence of dicyclohexylcarbodiimide to give the thiadiazin-6-one XXXIII [102].

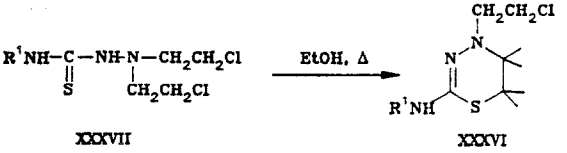


5,6-Dihydro-4H-thiadiazine XXXIV has been synthesized via cyclodehydration of 1-thioacyl-2-(β-hydroxyalkyl)hydrazide (XXXVa) in the presence of concentrated HCl, as well as by treatment of the 1-acyl analog (XXXVb) with phosphorus pentasulfide [103, 104].



XXXIV, XXXV R=Ph, Ar, $PhCH_2$; $R^1=R^2=H$, Me; $R^3=H$, Me, Ph; XXV [a] X=S, [b] X=O

A method has also been reported for the preparation of the 4-substituted thiadiazine XXXVI via intramolecular alkylation of 4-R'-1,1-bis(β-chloroethyl)thiosemicarbazide (XXXVII).

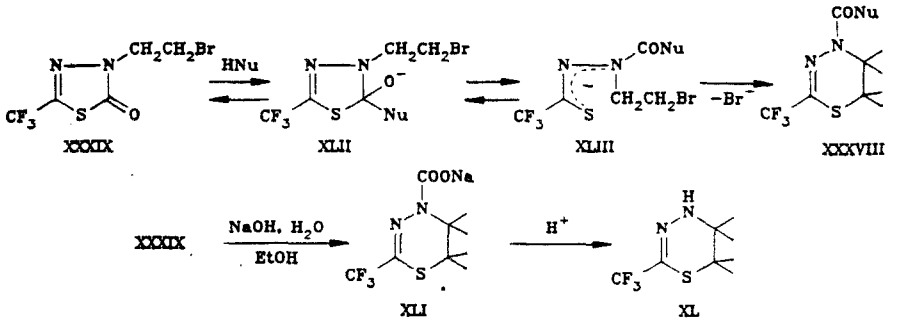


R^1=Me, allyl, Ph, α-$C_{10}H_7$

1.2. Synthesis of 1,3,4-Thiadiazines from Other Heterocycles

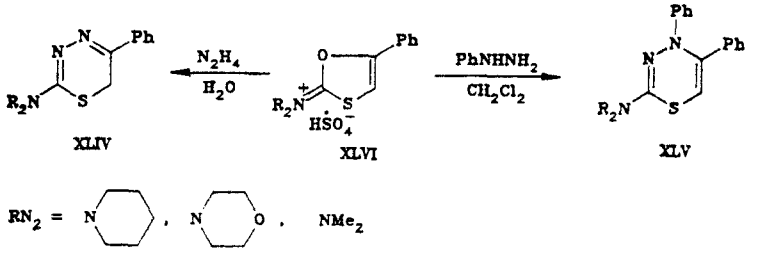
1. 4-Acyl-2-trifluoromethyl-5,6-dihydro-4H-thiadiazines XXXVIII have been prepared by treatment of 3-bromoethyl-5-trifluoromethyl-1,3,4-thiadiazol-2(3H)-one (XXXIX) with various nucleophiles. Compound XL, which is unsubstituted at the $N_{(4)}$ atom, is obtained upon hydrolysis of the sodium salt of 5,6-dihydro-4H-thiadiazine-4-

carboxylic acid (XLI), which in turn is prepared by the reaction of thiadiazolone XXXIX with sodium hydroxide [106].

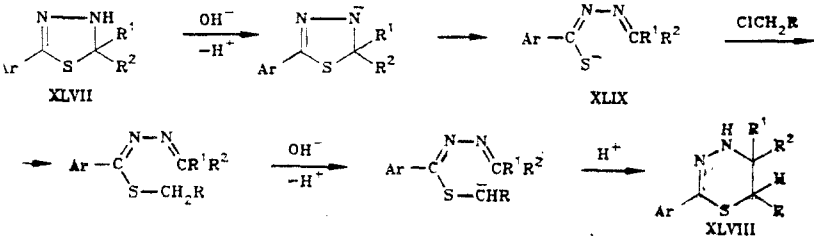


The lability of thiadiazolones XXXIX with respect to reaction with nucleophiles stems from the strong electron withdrawing effect of the trifluoromethyl group. The reaction mechanism probably involves addition of the nucleophile to the C atom in the polarized carbonyl group in the thiadiazolone ring. The resulting carbinol is converted from its deprotonated form XLII via ring opening to thiohydrazide XLIII, which undergoes subsequent intramolecular S_N2 reaction to form the thiadiazine XXXVIII [106]. 3-Propargyl-5-trifluoromethyl-1,3,4-thiadiazol-2(3H)-one reacts in an analogous manner with nucleophiles to generate compounds with an exocyclic methylene group in the 6-position [106].

2. Thiadiazines XLIV and XLV have been prepared by reaction of the quaternary iminium N-(5-aryl-1,3-oxathiol-2-ylidene) salt (XLVI) with hydrazine or its derivatives [107, 108]. These reactions involve formation of a hydrazine adduct with oxathiol XLVI at the $C_{(2)}$ atom, accompanied by cleavage of the C—O bond. Intramolecular cyclization of the intermediate iminoketone and subsequent dehydrogenation result in the formation of thiadiazines XLIV and XLV [107].

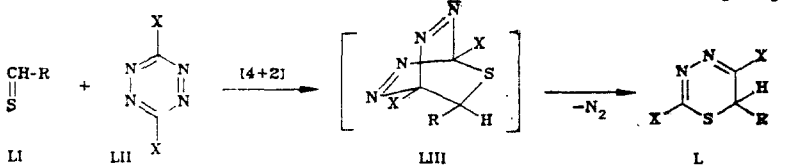


3. Reaction of 4,5-dihydro-1,3,4-thiadiazoles XLVII with $ClCh_2R$-type electrophiles in the presence of base gives 5,6-dihydro-4H-thiadiazines XLVIII. The reaction proceeds via cleavage of the thiadiazole ring in XLVII to form a diazabutadienethiolate XLIX, which reacts further with $ClCH_2R$ to give thiadiazine XLVIII [109].



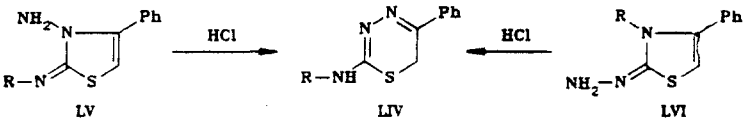
R^1=H, R^2=Ar; R^1=R^2=Me; R=CN, COPh, COOEt

4. Compounds L have been synthesized via reaction of thiocarbonyl compounds LI with tetrazine LII. The first step in this type of reaction involves [4 + 2] cycloaddition of the thiocarbonyl functional group to an acceptor (electron-withdrawing)-substituted diazidine system LII, which results in the formation of a bicyclic intermediate LIII. Elimination of nitrogen from this adduct LIII leads to the formation of a thiadiazine L [110].



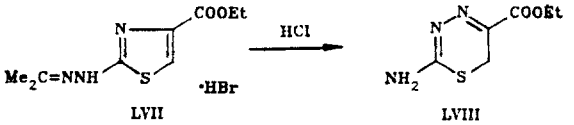
R=OEt, OPr, $N(Me)_2$, piperidino, morpholino, Ph, X=CF_3, COOMe

5. 2-Alkylamino-5-phenylthiadiazines LIV have been prepared as a result of intramolecular rearrangement of isomeric 3-N-amino-2-alkylamino- and 3-N-alkyl-2-hydrazono-4-phenylthiazolines (LV and LVI) upon heating in concentrated HCl [1].



LV LIV LVI

The rearrangement of 2-isopropylidenehydrazino-4-ethoxycarbonylthiazole hydrobromide (LVII) upon treatment with concentrated HCl has also been reported; ring expansion occurs to give 2-amino-5-ethoxycarbonylthiadiazine LVIII [70].

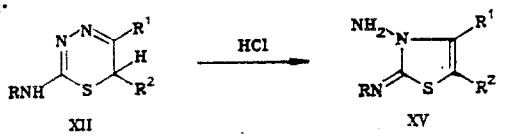


LVII LVIII

In concluding this section of the review, we should note that the only approach which has found widespread practical application involves the synthesis of 1,3,4-thiadiazines via cyclization of thiocarbohydrazides with α-halocarbonyl compounds. All of the other methods which have been outlined above have been described only for individual compounds and are not of preparative interest due either to their low yields or difficulties inherent in the preparation of the required starting materials.

2. REARRANGEMENT OF 1,3,4-THIADIAZINES TO THIAZOLE DERIVATIVES

The intramolecular arrangement of thiadiazines upon treatment with concentrated HCl has been studied in detail by Beyer and co-workers [1, 2]. 2-Aminothiadiazines XII containing alkyl substituents in the ring have been shown to be unstable in acidic media, where they are readily transformed upon treatment with concentrated HCl via intramolecular rearrangement to 3-N-aminothiazolines XV [1, 22-24, 26, 41, 42, 48]. The rate of rearrangement decreases slowly in the series 5-methyl-, 5-ethyl-, 5-isopropylthiadiazines. 5-tert-Butyl-2-amino-1,3,4-thiadiazine is stable with respect to concentrated HCl [24].



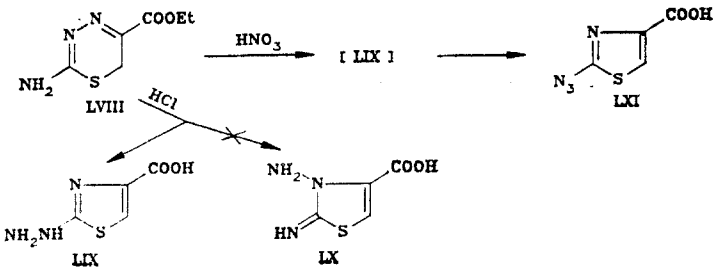
XII XV

XII, XV R=H, Alk, NH_2

5-Ethoxycarbonylmethylene- and 5-benzyl-2-aminothiadiazines also recyclize readily upon heating in HCl to give the corresponding thiazolinimines [24, 31].

An analogous transformation is observed for 2-mercapto-5-methylthiadiazine, which converted to 3-N-amino-4-methyl-2(2H)-thiazolethione upon treatment with concentrated HCl [6, 7].

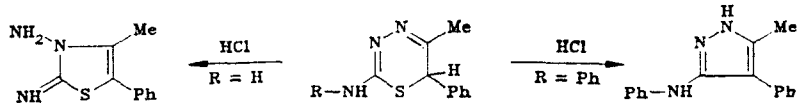
Significant differences are observed, however, in the reactivity or behavior of thiadiazines containing ethoxycarbonyl groups in the 5- or 6-positions of the ring. Thus, 2-amino- [1, 26] and 2-mercapto-5-methyl-6-ethoxycarbonylthiadiazines [9] are converted to thiazolines even in cold concentrated HCl. In contrast to other thiadiazines with aliphatic substituents in the 5-position, 2-amino-5-ethoxycarbonylthiadiazine (LVIII) rearranges upon prolonged heating in concentrated HCl to 2-hydrazino-4-carboxythiazole (LIX), and not to the iminothiazoline LX [70, 71, 111]. Another noteworthy and interesting fact is the conversion of compound LVIII to 2-azido-4-carboxythiazole (LXI) upon treatment with dilute nitric acid. Hydrazinothiazole LIX appears to be an intermediate in this reaction [111].



LVIII LIX LX LXI

The presence of an aromatic substituent in the 5-position of the thiadiazine ring substantially enhances the stability of these compounds with respect to reaction with acids, relative to their alkyl-substituted derivatives. For example, 2-amino- (XXV) [1, 24, 30] and 2-alkylamino-5-phenylthiadiazine (LIV) [1, 54, 112, 113] do not rearrange to their isomeric thiazolinimines even upon refluxing in concentrated HCl. The high stability of these compounds is also evident in the recyclization reaction of thiazolines LV and LVI to thiadiazine LIV upon treatment with concentrated HCl [1].

Introduction of a phenyl group in the 6-position of the thiadiazine ring system, on the other hand, reduces the stability of the compound with respect to acid. Thus, in concentrated HCl 2-amino-5-methyl-6-methylthiadiazine (LXIIa) is converted to thiazoline LXIII, while the 2-phenylamino derivative LXIIb is converted to 3-phenylamino-4-phenyl-5-methylpyrazole (LXIV) [1].

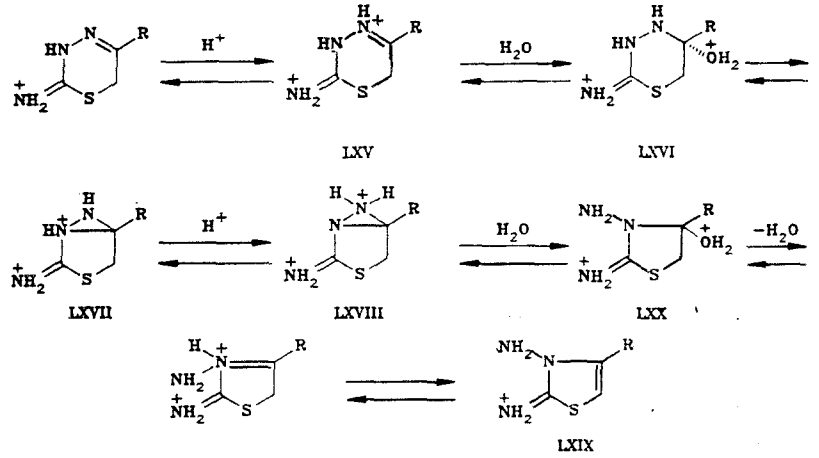


LXIII LXII a R=H; b R=Ph LXIV

In summary, therefore, a phenyl or ethoxycarbonyl group in the 5-position increases the stability of a thiadiazine, while alkyl groups in the 5-position and substituents in the 6-position reduce the stability of thiadiazines. The stabilizing effect of a 5-aryl or 5-carbonyl group has been rationalized in terms of their conjugation with the double bonds in the thiadiazine ring, but can also be attributed to steric factors arising from steric hindrance with respect to attack by a water molecule at the $C_{(5)}$ position [1, 24]. When a phenyl or ethoxycarbonyl group is separated from the thiadiazine ring by a methylene bridge it no longer exerts a stabilizing influence on the ring system.

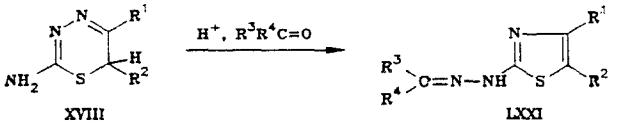
Two mechanisms have been discussed in the literature for the recyclization reaction of thiadiazines to thiazolines. According to [1], rearrangement takes place as a result of hydrolytic cleavage of the $C_{(5)}$—$N_{(4)}$ bond and subsequent cyclization of the acyclic intermediate to give a thiazoline.

An alternative recyclization pathway would involve rapid attack by a water molecule at a diprotonated thiadiazine intermediate LXV, in which the $C_{(5)}$ carbon atom is now saturated and therefore susceptible to nucleophilic attack (compound LXVI). The limiting step in this mechanism is nucleophilic attack of the $N_{(3)}$ nitrogen atom at the sp^3-hybridized carbon atom in the 5-position, leading to the formation of an aziridine intermediate LXVII; subsequent proton migration to the $N_{(4)}$ atom would give aziridine LXVIII. Formation of a monoprotonated thiazolinimine LXIX may be due to rapid S_N2 attack by water to give an imine LXX, which is followed by loss of a water molecule and culminates in loss of another proton [24].



LXV LXVI LXVII LXVIII LXX LXIX

A second pathway for the intramolecular rearrangement of thiadiazines to give thiazole derivatives is illustrated by the recyclization of 2-aminothiadiazine XVIII to 2-hydrazonothiazoles LXXI upon treatment with aldehydes and ketones in acidic alcohol solution [1, 22, 23, 26, 30, 31, 48, 111].



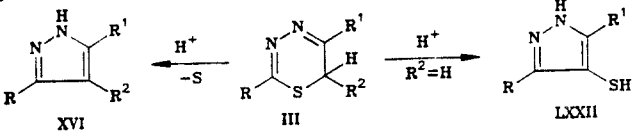
XVIII LXXI

R^1=H, Me, COOEt, CH_2COOEt; R^2=H, Me, COOEt, Ph; R^3=Ph, 4-NO_2—C_6H_4, Me; R^4=H, Me

The proposed mechanism for this reaction involves hydrolytic cleavage of compound XVIII at the $N_{(4)}$-$C_{(5)}$ bond, blocking of the $N_{(1)}$ atom in the resulting isothiosemicarbazide intermediate via condensation with a carbonyl compound, and final ring closure to give a 2-hydrazonothiazole LXXI [1].

3. REARRANGEMENT OF 1,3,4-THIADIAZINES TO PYRAZOLES

Ring contraction to form pyrazole derivatives XVI and LXXII represents another characteristic reaction of thiadiazines. This rearrangement results from the elimination of sulfur from the ring; depending on the nature of the substituents present, sulfur can be removed from the ring either in the form of elemental sulfur (in the case of compound XVI), or in the form of a mercapto group attached to the pyrazole ring (compound LXII) [1, 2]. Elimination of sulfur from the ring takes place upon heating with HCl in ethanol [1, 3, 13, 14, 26, 54], and even more readily in refluxing acetic acid [1, 3, 12, 51, 112, 113].

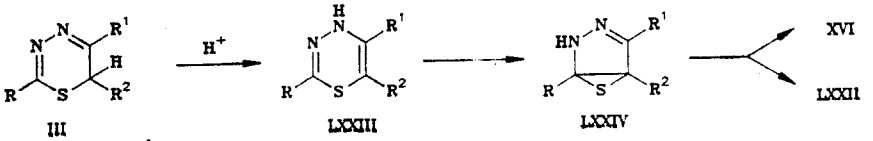


XVI III LXXII

The stability of thiadiazines with respect to ring contraction is determined primarily by the nature of their substituents [1]. The most stable derivatives in acidic media are 5-arylthiadiazines which are unsubstituted in the 6-position [1-3]. Replacement of a 5-phenyl group by an alkyl group, or introduction of a substituent in the 6-position, decreases the stability of a thiadiazine. Pyrazole formation is especially facile in compounds containing an ethoxycarbonyl [1, 3, 14, 15, 54, 88, 90] or phenyl group [1, 3] in the 6-position.

In the series of 2-substituted thiadiazines the most stable derivatives are 2-amino compounds. Replacement of the hydrogen atoms in the 2-amino group by alkyl, aryl, or NH_2 groups [1, 114], or substitution of the amino group by an aryl, benzyl [112], mercapto, or alkylthio group [1, 12, 115], reduces their stability.

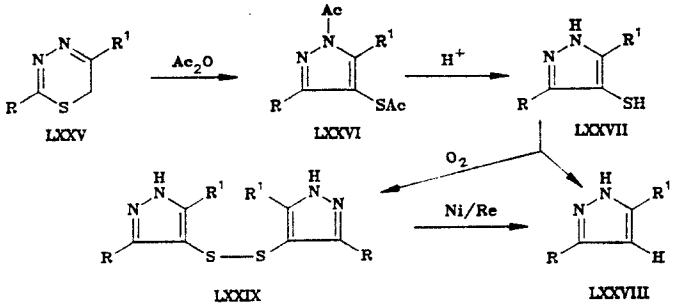
One proposed pathway for the acid-catalyzed rearrangement of thiadiazines to pyrazoles involves the formation, upon proton addition, of an energetically less stable 4H-derivative LXXIII in equilibrium with the 6H-thiadiazine III, which then isomerizes to a bicyclic system LXXIV; subsequent elimination of sulfur gives pyrazoles XVI and LXXII [110, 116].



III LXXIII LXXIV

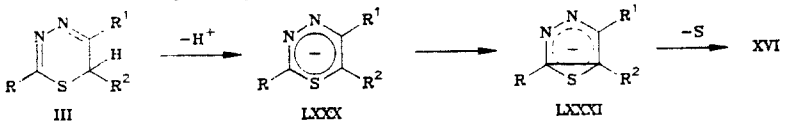
Beyer [1, 2] has proposed that recyclization of thiadiazines to pyrazoles occurs via $C_{(2)}$—S bond cleavage.

Ring contraction of a thiadiazine to a pyrazole ring can be effected by interaction with a variety of agents. One effective method for their conversion to pyrazoles involves treatment with acetic anhydride [1, 54, 112]; using this method it is possible to prepare pyrazoles from 2-alkylamino-5-phenylthiadiazines, which are stable in acidic media. Treatment of compound LXXV, which is unsubstituted in the 6-position, with acetic anhydride, results in ring contraction to give a pyrazole and simultaneous acetylation, with the sulfur group remaining in the product in the form of a mercapto group. Hydrolysis of the acetyl derivative LXXVI gives the 4-mercaptopyrazole LXXVII, which can be converted to pyrazole LXXVIII and disulfide LXXIX upon oxidation with oxygen in air.



LXXV LXXVI LXXVII LXXIX LXXVIII

Thiadiazines III are also readily converted to pyrazoles XVI upon treatment with butyllithium in absolute THF at room temperature [116, 117]. The mechanism of recyclization in this case involves, according to the authors [116], formation of anionic 8π-electron heterocyclic system (LXXX). Formation of anion LXXX is a rate-limiting step,



III LXXX LXXXI

which is followed by rapid valence isomerization to a bicyclic system LXXXI, and sulfur abstraction to generate a pyrazole XVI.

A simple and preparatively useful method for pyrazole formation from thiadiazines involves heating the latter in sodium ethoxide solution; sulfur is removed in the form of sodium thiosulfate under these conditions [118].

Rearrangement of thiadiazines to pyrazoles upon treatment with basic reagents occurs under milder conditions than the corresponding acid-catalyzed transformation, and thus may be used in the case of thiadiazine derivatives which are stable in acidic media [116, 118].

Thiadiazine rearrangement to pyrazoles has also been reported for reactions with triphenylphosphine in absolute ethanol or triethylphosphite in dry argon [112, 119, 120]; other rearrangement conditions include potassium hydroxide in butanol [121], ultraviolet irradiation in ethanol or toluene solution [122, 123], heating above the melting point [124], or heating in an organic solvent [3, 4, 12, 112].

4. APPLICATIONS OF 1,3,4-THIADIAZINES

Thiadiazine derivatives exhibit a broad spectrum of biological activity: antihypertensive and cardiotonic [17-21, 65, 125-129], antimicrobial [38, 39, 61, 66, 67, 104, 130], antiviral [43], antiinflammatory [43, 131-133], analgesic [43, 56, 132], spasmodic or convulsive [35, 36, 44, 46, 47, 55, 64, 76], and sedative [45, 132]. 1,3,4-Thiadiazines may be used in agriculture as herbicides [27-29], fungicides [11, 39, 134], pesticides [135, 136], insecticides [80, 81, 137, 138], and as plant growth regulators [32]. Applications have also been suggested for these compounds as reagents in analytical chemistry [139], as antioxidants [123, 140], in photography [141], and in dye manufacture [49].

LITERATURE CITED

1. H. Beyer, *Z. Chem.*, **9**, 361 (1969).
2. H. Beyer, *Q. Reports on Sulfur Chem.*, **5**, 177 (1970).
3. E. Bulka and W. D. Pfeiffer, *J. Prakt. Chem.*, **318**, 971 (1976).
4. J. Sandström, *Ark. Kemi*, **15**, 195 (1960).
5. B. Holmberg, *Ark. Kemi*, **9**, 65 (1955).
6. J. Sandström, *Ark. Kemi*, **7**, 249 (1954).
7. S. Tadashi and O. Masaki, *Yakugaku Zasshi*, **77**, 771 (1957); *C. A.*, **51**, 17,941 (1957).
8. R. A. Methes, *J. Org. Chem.*, **17**, 877 (1952).
9. J. Sandström, *Ark. Kemi*, **9**, 127 (1955).
10. G. H. Dewey and E. D. Amstutz, *Rec. Trav. Chim.*, **83**, 1047 (1964); *C. A.*, **62**, 1662 (1965).
11. J. Saikawa and S. Takano, Japanese Patent No. 7,041,593; *C. A.*, **75**, 5965 (1971).
12. H. Beyer, E. Bulka, and F. W. Beckhaus, *Chem. Ber.*, **92**, 2593 (1959).
13. I. Ya. Postovskii, A. D. Sinegibskaya, A. P. Novikova, and L. P. Sidorova, in: Abstracts of Proceedings, 14th Scientific Meeting on the Chemistry and Technology of Organic Sulfur Compounds and Sulfur Oils, Riga (1976), p. 207.
14. J. Sandström, *Acta Chem. Scand.*, **16**, 2395 (1962).
15. J. Sandström, *Ark. Kemi*, **8**, 523 (1955).
16. P. K. Bose, *Q. J. Indian Chem. Soc.*, **3**, 148 (1926); *C. A.*, **21**, 383 (1927).
17. D. Brown, R. B. Hargreaves, B. J. McLoughlin, and S. D. Mills, European Patent No. 80,296; *C. A.*, **100**, 22,672 (1984).
18. R. B. Hargreaves, B. J. McLoughlin, and S. D. Mills, European Patent No. 85,227; *C. A.*, **100**, 6561 (1984).
19. D. Brown, R. B. Hargreaves, B. J. McLoughlin, and S. D. Mills, US Patent No. 4,489,074; *C. A.*, **102**, 149,291 (1985).
20. H. Ao, M. Obata, and I. Inui, European Patent No. 180,158; *C A.*, **105**, 97,488 (1986).
21. R. Jonas, J. Piulats, I. Lues, and M. Klockow, European Patent No. 294,647; *C. A.*, **110**, 192,866 (1989).
22. H. Beyer, W. Lassig, and E. Bulka, *Chem. Ber.*, **87**, 1385 (1954).
23. H. Beyer, W. Lassig, E. Bulka, and D. Behrens, *Chem. Ber.*, **87**, 1392 (1954).
24. R. E. Busby and T. W. Dominey, *J. Chem. Soc., Perkin Trans. 2*, No. 6, 890 (1980).
25. S. Avramavici, *Analele Stünt. Univ. "Al. I. Cuza,"* Sec. 1, **1**, 315 (1955); *C. A*, **51**, 10.541 (1957).
26. H. Beyer and C. Wolter, *Chem. Ber.*, **89**, 1652 (1956).
27. W. C. Doyle, US Patent No. 3,862,183; *C. A.*, **82**, 171,094 (1975).
28. W. D. Doyle, US Patent No. 3,854,924; *C. A.*, **82**, 112,114 (1975).
29. T. D. Thiblaut, US Patent No. 4,436,549; *C. A.*, **101**, 23,510 (1984).
30. J. Hildegard, K. Seifert, S. Johne, and E. Bulka, *Pharmazie*, **33**, 259 (1978).

31. E. Campaigne and T. P. Selby, *J. Heterocycl. Chem.*, **15**, 401 (1978).
32. E. Campaigne and T. P. Selby, US Patent No. 4,254,259; *C. A.*, **95**, 25,150 (1981).
33. H. A. Walter, US Patent No. 2,534,087; *C. A.*, **45**, 2714 (1951).
34. P. K. Bose, *Q. J. Indian Chem. Soc.*, **1**, 51 (1921); *C. A.*, **19**, 831 (1925).
35. W. D. Jones and F. P. Miller, French Patent No. 2,493,844; *C. A.*, **97**, 192,467 (1982).
36. W. D. Jones and F. P. Miller, BRD Patent No. 3,031,703; *C. A.*, **95**, 81,033 (1981).
37. I. Ya. Postovskii, A. P. Novikova, L. A. Chechulina, and L. P. Sidorova, *Khim. Geterotsikl. Soedin.*, No. 8, 1051 (1976).
38. M. Ito, *Yakugaku Zasshi*, **87**, 539 (1967); *C. A.*, **67**, 54,071 (1967).
39. H. Zenno, A. Sugihara, and M. Ito, Japanese Patent No. 8033; *C. A.*, **67**, 54,173 (1967).
40. R. Djudjic, M. Trkovnik, and D. Kitan, *Org. Prep. Proc. Intern.*, **17**, 206 (1985); *C. A.*, **103**, 37,329 (1985).
41. J. Hadacek and J Slotova-Trnkova, *Pharmazie*, **15**, 226 (1960).
42. J. Hadacek and J. Slotova-Trnkova, *Spisy Prirod. Fak. Univ. Brne*, **22**, 39 (1960); *C. A.*, **55**, 25,926 (1961).
43. N. Yoshida, K. Tanaka, Y. Iizuka, K. Wachi, T. Nishimura, and H. Yasuda, Japanese Patent No. 7,488,889; *C. A.*, **82**, 57,744 (1975).
44. W. D. Jones and F. P. Miller, Belgian Patent No. 884,991; *C. A.*, **95**, 115,618 (1981).
45. F. P. Miller and W. D. Jones, Belgian Patent No. 884,990; *C. A.*, **95**, 62,276 (1981).
46. W. D. Jones and F. P. Miller, US Patent No. 4,309,426; *C. A.*, **96**, 181,397 (1982).
47. Netherlands Appl. NL 8,006,206; *C. A.*, **97**, 216,243 (1982).
48. H. Beyer, W. Lassig, and U. Schultz, *Chem. Ber.*, **87**, 1401 (1954).
49. S. Kida, H. Ishikawa, Y. Kawashima, T. Tanaka, and K. Matsuda, Japanese Patent No. 61,260,072; *C. A.*, **106**, 215,514 (1987).
50. P. K. Bose, *Q. J. Indian Chem. Soc.*, **2**, 95 (1925); *C. A.*, **20**, 415 (1926).
51. W. D. Pfeiffer, E. Dilk, and E. Bulka, *Z. Chem.*, **17**, 218 (1977).
52. P. K. Bose and B. K. Nandi, *J. Indian Chem. Soc.*, **7**, 733 (1930); *C. A.*, **25**, 1532 (1931).
53. E. Bulka, W. D. Pfeiffer, C. Troeltsch, E. Dilk, H. Gaertner, and D. Daniel, *Coll.*, **43**, 1227 (1978).
54. H. Beyer, H. Honenck, and L. Reichelt, *Ann.*, **741**, 45 (1970).
55. W. D. Pfeiffer and E. Bulka, East German Patent No. 220,311; *C. A.*, **104**, 68,891 (1986).
56. W. Thorwart, U. Gebert, R. Scheleyerbach, and R. Bartlett, BRD Patent No. 3,792,756; *C. A.*, **109**, 170,466 (1988).
57. S. Tadashi and O. Masaki, *Yakugaku Zasshi*, **74**, 821 (1954); *C. A.*, **49**, 9537 (1955).
58. E. Talger and Z. El-Hewehi, *J. Prakt. Chem.*, **18**, 255 (1962).
59. L. P. Sidorova, A. P. Novikova, and I. Ya. Postovskii, Nucleophilic Reactions of Carbonyl Compounds, Abstracts of Proceedings, 2nd Conference of Schools of Higher Education, Saratov (1982), p. 129.
60. P. K. Bose, *Q. J. Indian Chem. Soc.*, **3**, 197 (1926); *C. A.*, **21**, 391 (1927).
61. L. Giammanco, *Atti Accad. Sci., Lett. Arti Palermo*, Part 1, **23**, 129 (1964); *C. A.*, **62**, 14,680 (1965).
62. W. D. Pfeiffer, E. Dilk, and E. Bulka, *Z. Chem.*, **17**, 173 (1977).
63. P. K. Bose and D. C. Rav-Chaudhury, *Q. J. Indian Chem. Soc.*, **4**, 257 (1927); *C. A.*, **21**, 3200 (1927).
64. W. D. Pfeiffer, E. Bulka, and R. Fermum, East German Patent No. 209,196; *C. A.*, **101**, 191,974 (1984).
65. W. D. Pfeiffer, E. Bilk, and E. Bulka, East German Patent No. 204,092; *C. A.*, **101**, 7216 (1984).
66. U. Petersen and H. Heitzer, BRD Patent No. 2,251,683; *C. A.*, **81**, 13,564 (1974).
67. U. Petersen, H. Heitzer, and K. G. Metzger, BRD Patent No. 2,251,684; *C. A.*, **81**, 25,700 (1974).
68. Y. Matsubara, M. Yoshihara, T. Nakanura, Sh. Yamada, and T. Maeshima, *Phosp. Sulf.*, **16**, 89 (1983); *C. A.*, **100**, 6468 (1984).
69. Y. Matsubara, T. Nakamura, M. Yoshihara, and T. Maeshima, *Kinki Daigaku Rikogakubu Kenkyu Hokoku*, No. 18, 91 (1983); *C. A.*, **100**, 22,627 (1984).
70. G. P. Andronnikova, S. L. Nikolaeva, S. V. Usol'tseva, and V. I. Shishkina, Advances in the Chemistry of Azines, Abstracts of Proceedings, 2nd All-Union Conference, Sverdlovsk (1985), p. 187.
71. S. V. Usol'tseva, G. P. Andronnikova, S. L. Nikolaeva, and V. A. Shevyrin, Nucleophilic Reactions of Carbonyl Compounds, Abstracts of Proceedings, 3rd Conference of Schools of Higher Education, Saratov (1985), p. 69.
72. P. Chabrier and E. Cattelain, *Bull. Soc. Chim. France*, 48 (1950).
73. B. Holmberg, *Ark. Kemi, Mineral. Geol.*, **25A**, 18 (1947); *C. A.*, **42**, 5919 (1948).
74. J. Sandström, *Ark. Kemi*, **4**, 297 (1952).
75. J. Sandström, *Ark. Kemi*, **8**, 487 (1955).

76. R. Soliman, M. Gabr, M. Abouzeit-Har, and E. M. Sharabi, *J. Pharm. Sci.*, **70**, 94 (1981); *C. A.*, **94**, 175,019 (1981).
77. P. K. Bose and B. K. Nandi, *Q. J. Indian Chem. Soc.*, **7**, 961 (1930); *C. A.*, **25**, 3002 (1931).
78. S. Winthrop and G. Gavin, *Canad. J. Chem.*, **36**, 879 (1958).
79. J. Klosa, *Arch. Pharm.*, **287**, 12 (1954); *C. A.*, **50**, 969 (1956).
80. L. H. Edwards, Canadian Patent No. 1,121,349; *C. A.*, **97**, 144,885 (1982).
81. L. H. Edwards and J. D. Cleveland, European Patent No. 42,246.
82. E. Bulka, P. Mittag, G. Berg, and H. Beyer, *Rev. Chem. Akad. PPR*, **7**, 725 (1962).
83. W. Hampel, M. Kapp, and G. Proksch, *Z. Chem.*, **10**, 142 (1970).
84. W. Hampel, *Z. Chem.*, **9**, 61 (1969).
85. S. P. Epshtein, T. I. Orlova, A. F. Rusakov, V. P. Tashchi, and Yu. G. Putsykin, *Khim. Geterotsikl. Soedin.*, No. 4, 554 (1987).
86. J. Beyer, C. Thielemann, and P. D. Thong, *J. Prakt. Chem.*, **321**, 959 (1979).
87. F. A. Neugebauer and H. Fischer, *Chem. Ber.*, **107**, 717 (1965).
88. E. Bulka, H. G. Ronde, and H. Beyer, *Chem. Ber.*, **98**, 259 (1965).
89. H. Beyer and E. Bulka, *Z. Chem.*, **2**, 321 (1962).
90. H. Beyer, G. Wolter, and H. Lemke, *Chem. Ber.*, **89**, 2550 (1956).
91. H. Beyer, G. Henseke, E. Bulka, H. Drews, and E. Muller, *Chem. Ber.*, **92**, 1105 (1959).
92. H. Beyer and E. Bulka, *Chem. Ber.*, **87**, 223 (1956).
93. H. Beyer and G. Ruhling, *Chem. Ber.*, **89**, 107 (1956).
94. J. T. Gregory, US Patent No. 2,871,237; *C. A.*, **53**, 11,419 (1959).
95. Ya. V. Zachinaev, M. L. Petrov, A. N. Frolkov, V. N. Chistokletov, and A. A. Petrov, *Zh. Org. Khim.*, **16**, 938 (1980).
96. M. L. Petrov, V. N. Chistokletov, and A. A. Petrov, USSR Patent No. 537,999; *Byull. Izobret.*, No. 45, 92 (1976).
97. M. L. Petrov, V. V. Bobylev, V. N. Chistokletov, and A. A. Petrov, *Zh. Org. Khim.*, **17**, 1100 (1981).
98. R. M. Mohareb, A. Habashi, E. A. Hafez, and S. M. Sherif, *Arch. Pharm.*, **320**, 776 (1987).
99. D. L. Trepanier, P. E. Krieger, J. H. Mennear, and J. H. Eble, *J. Med. Chem.*, **10**, 1085 (1967).
100. D. L. Trepanier and P. E. Krieger, US Patent No. 3,428,631; *C. A.*, **70**, 106,577 (1969).
101. S. Tadashi and O. Masaki, *Yakugaku Zasshi*, **75**, 1535 (1955); *C. A.*, **50**, 10,727 (1956).
102. A. E. Baydar, G. V. Boyd, and P. F. Lindley, *J. Chem. Soc., Chem. Commun.*, No. 19, 10,030 (1981).
103. D. L. Trepanier, W. Reifschneider, W. Shumaker, and D. S. Tharpl, *J. Org. Chem.*, **30**, 2228 (1965).
104. D. L. Trepanier, US Patent No. 3,290,303; *C. A.*, **68**, 29,729 (1968).
105. W. Schultze, G. Letsch, and H. Fritzsche, *J. Prakt. Chem.*, **36**, 128 (1967).
106. H. Kristinsson, T. Winkler, and M. Mollenkopf, *Helv. Chim. Acta*, **66**, 2714 (1983).
107. K. Hirai and T. Ishiba, *J. Chem. Soc. D*, No. 20, 1318 (1971).
108. K. Hirai and T. Ishiba, *Chem. Pharm. Bull.*, **26**, 3017 (1978); *C. A.*, **90**, 87,338 (1979).
109. D. M. Evans, D. R. Taylor, and M. Myers, *J. Chem. Soc., Chem. Commun.*, No. 21, 1444 (1984).
110. G. Setz, R. Mohr, W. Overheu, R. Allmann, and M. Nagel, *Angew. Chem.*, **96**, 885 (1984).
111. S. V. Usol'tseva, N. V. Volkova, G. P. Andronnikova, T. G. Koksharova, L. N. Dianova, S. L. Nikolaeva, V. A. Shevyrin, and A. L. Suetin, Nitrogen-Containing Heterocycles, Abstracts of Proceedings, 4th All-Union Conference, Novosibirsk (1987), p. 214.
112. W. D. Pfeiffer and E. Bulka, *Z. Chem.*, **16**, 80 (1976).
113. W. D. Pfeiffer, E. Dilk, and E. Bulka, *Z. Chem.*, **18**, 65 (1978).
114. N. Yoshida, K. Eachi, K. Tanaka, and Y. Iizuka, Japanese Patent No. 74,100,080; *C. A.*, **82**, 170,912 (1975).
115. N. Yoshida, H. Mijazawa, K. Tanaka, and Y. Iizuka, Japanese Patent No. 75,130,760; *C. A.*, **85**, 46,637 (1976).
116. R. R. Schmidt and H. Huth, *Tetrahedron Lett.*, No. 1, 33 (1975).
117. W. D. Pfeiffer, K. Geisler, H. Rossberg, and E. Bulka, *Z. Chem.*, **22**, 137 (1982).
118. W. D. Pfeiffer, E. Dilk, and E. Bulka, *Synthesis*, No. 3, 196 (1977).
119. W. D. Pfeiffer and E. Bulka, *Synthesis*, No. 7, 485 (1977).
120. W. D. Pfeiffer, H. Rossberg, and E. Bulka, East German Patent No. 228,248; *C. A.*, **105**, 60,599 (1986).
121. W. D. Pfeiffer and E. Bulka, East German Patent No. 211,343; *C. A.*, **102**, 62,228 (1985).
122. W. D. Pfeiffer, E. Bulka, and R. Mietchen, *Z. Chem.*, **27**, 296 (1987).
123. W. D. Pfeiffer, R. Mietchen, and E. Bulka, East German Patent No. 253,030; *C. A.*, **109**, 93,001 (1988).
124. W. D. Pfeiffer and E. Bulka, East German Patent No. 235,640; *C. A.*, **105**, 226,554 (1986).
125. Japanese Patent No. 6,253,976; *C. A.*, **107**, 115,607 (1987).

126. J. Dizon and D. H. Robinson, Great Britain Patent No. 2,179,655; *C. A.*, **108**, 37,839 (1988).
127. R. B. Hargreaves and B. J. McLoughlin, European Patent No. 86,301.
128. K. H. Meyer, S. Schuetz, K. Stoepel, and H. G. Kroneberg, US Patent No. 3,328,387; *C. A.*, **68**, 105,467 (1968).
129. D. Brown, R. Dowell, R. B. Hargreaves, and B. G. Main, European Patent No. 52,442; *C. A.*, **97**, 144,886 (1982).
130. F. B. Cooper, P. Gross, and M. Lewis, *Proc. Soc. Exptl. Biol. Med.*, **47**, 508 (1941); *C. A.*, **35**, 6667 (1941).
131. A. Takamizawa and H. Sato, Japanese Patent No. 6,928,102; *C. A.*, **72**, 79,112 (1970).
132. A. Takamizawa and H. Sato, Japanese Patent No. 6,927,896; *C. A.*, **72**, 55,523 (1970).
133. A. Takamizawa and H. Sato, Japanese Patent No. 6,928,103; *C. A.*, **72**, 43,738 (1970).
134. Y. Usui, *Yakugaki Zasshi*, **89**, 689 (1969); *C. A.*, **71**, 61,352 (1969).
135. K. Ruelfenacht, *Helv. Chim. Acta*, **56**, 2186 (1973).
136. V. V. Dovlatyan and R. A. Gevorkyan, *Arm. Khim. Zh.*, **31**, 851 (1976).
137. L. Edwards, US Patent No. 4,144,335; *C. A.*, **91**, 20,550 (1979).
138. J. D. Cleveland and L. Edwards, US Patent No. 4,158,732; *C. A.*, **91**, 108,013 (1979).
139. L. V. Kholevinskaya, L. N. Emel'yanova, L. P. Sidorova, and A. V. Yuminov, USSR Inventor's Certificate No. 1,189,862; *Byull. Isobret.*, No. 41, 103 (1985).
140. G. Minagawa, M. Akutsu, and M. Goto, Japanese Patent No. 7,537,651; *C. A.*, **84**, 180,229 (1976).
141. L. P. Roosens, Belgian Patent No. 571,917; *C. A.*, **56**, 8217 (1961).

SYNTHESIS AND PROPERTIES OF FURAN DERIVATIVES.

1. SYNTHESIS OF 3,5-DISUBSTITUTED Δ^2-ISOXAZOLINES CONTAINING FURFURYL FRAGMENTS

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3,5-Disubstituted Δ^2-isoxazolines containing furan fragments have been synthesized by 1,3-dipolar cycloaddition reactions.

Substituted Δ^2-isoxazolines are convenient synthons for the synthesis of polyfunctional compounds (α,β-unsaturated ketones, β-hydroxyketones, etc.) [1], 2-substituted furans, bisheteroaromatic compounds, and others [2]. However, until recently only limited reports have appeared in the literature concerning the preparation and properties of Δ^2-isoxazolines containing furan fragment substituents. In this regard the only example which has been published is the synthesis of Δ^2-isoxazolines via 1,3-dipolar cycloaddition reactions involving 2-furancarbonitrile-N-oxide and 5-nitro-2-furancarbonitrile-N-oxide [3, 4].

We now report the synthesis of 3,5-disubstituted Δ^2-isoxazolines containing furfuryl radicals in the 3-position. These compounds are of potential interest as biologically active compounds and as intermediates for the preparation of 2-substituted furans containing a functional group in the β-position of the side chain.

In order to pursue the preparation of these compounds we have studied the 1,3-dipolar cycloaddition reactions of monosubstituted ethylenes with 1,3-dipoles generated in situ from 2-(2-nitroethyl)-5-R-furans Ia, b via treatment with phenylisocyanate in the presence of triethylamine. According to the literature data, the 1,3-dipoles formed from the aci form of primary nitro compounds upon treatment with phenylisocyanate in the presence of catalytic amounts of tertiary amines represent either nitrone esters (A) [5] or their further transformation products, namely nitrile-N-oxides (B) [6].

We have found that the most favorable conditions for carrying out the reactions are in absolute benzene at a mole ratio for nitroalkane Ia, b to dipolarophile to phenylisocyanate equal to 1:5:2, for a period of 6-8 h at room temperature, followed by refluxing the reaction mixture for an additional 2 h. Under these conditions the desired 3,5-disubstituted Δ^2-isoxazolines are obtained in satisfactory yields (Table 1). However, when allyl chloride and

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