THE SYNTHESIS AND RING—CHAIN TAUTOMERISM OF 1,2,4-TRIAZOLIDINE-3-THIONES, 2-AMINO-1,3,4-THIADIAZOLINES, AND HEXAHYDRO-1,2,4,5-TETRAZINE-3-THIONES* (REVIEW)

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This review concerns the cyclization of thiosemicarbazones and thiocarbhydrazones of carbonyl compounds leading to the title heterocycles. We examine the irreversible cyclization by the action of oxidizing agents or as the result of acylation or alkylation as well as the ring—chain tautomerism. The effect of the substitution and solvent on the equilibrium of the thiosemicarbazones with some of the possible heterocyclic tautomeric forms was examined. The usefulness of these data for predicting the results of their irreversible cyclization was discussed.

1. REVERSIBLE AND IRREVERSIBLE CYCLIZATION OF THIOSEMICARBAZONES OF CARBONYL COMPOUNDS—SYNTHETIC PRECURSORS OF 1,2,4-TRIAZOLINE-5-THIONES AND 2-AMINO-1,3,4-THIADIAZOLINES

The synthesis of organic compounds containing heterocyclic 1,2,4-triazole and 1,3,4-thiadiazole systems holds great practical interest since these compounds display biological activity and are commonly used as drugs [1-3] and pesticides [4, 5].

1-Acylthiosemicarbazides or, correspondingly, substituted thiosemicarbazones of carbonyl compounds are the most common synthetic precursors of these heterocycles. The existence of several nucleophilic sites (the nitrogen and sulfur atoms) permits possible alternative cyclization, whose direction may be changed by alteration of the substituents and reaction conditions. The cyclization of 1-acylthiosemicarbazides leads to aromatic 3-mercapto-1,2,4-triazoles or 2-amino-1,3,4-thiadiazoles and is irreversible [6]. On the other hand, the cyclization of thiosemicarbazones may be either irreversible (upon oxidation) or reversible. In the latter case, ring—chain tautomerism may be encountered. The study of this phenomenon holds undoubted interest not only for its direct relation to the synthesis of heterocyclic structures but also the marked biological activity of thiosemicarbazones [7], which may be a consequence of their existence in some specific heterocyclic form. Unfortunately, the ring—chain tautomerism of thiosemicarbazones has not yet attracted sustained attention and there are no data on the relationship of the structure of these compounds and their biological activity.

1.1 Oxidative Cyclization of Thiosemicarbazones

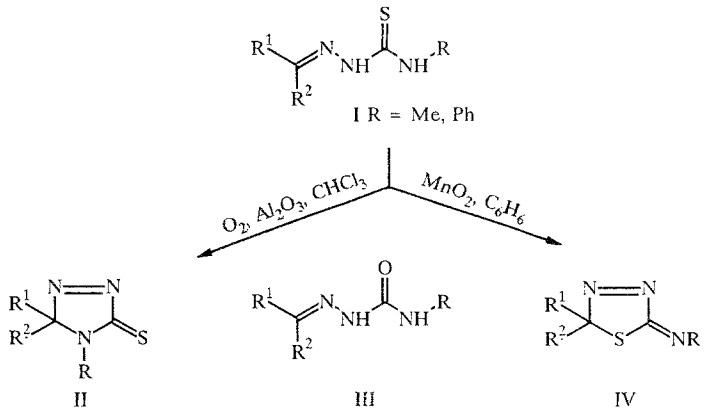
The heterocyclization of thiosemicarbazones by the action of various oxidizing agents has been extensively studied. Depending on the type of oxidizing agent and, as recently demonstrated, the nature of substitution in the thiosemicarbazone molecule, this reaction may lead either to Δ^1-1,2,4-triazoline-3-thiones or 2-imino-Δ^3-1,3,4-thiadiazolines. As early as 1970,

*Dedicated to Professor A. R. Katritzky on the occasion of his sixty-fifth birthday.

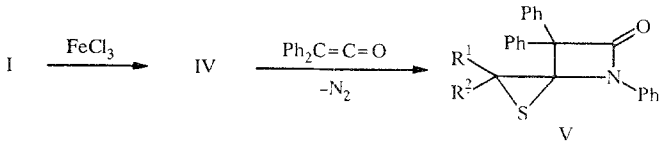
M. V. Lomonosov Moscow State University, Moscow 119899. Translated from Khimiya Geterotsiklicheskikh Soedinenii, No. 7, pp. 991-1005, July, 1993. Original article submitted May 15, 1993.

 0009-3122/93/2907-0844$12.50

Landquist [8] found that upon the chromatography of 4-phenyl- and 4-methylthiosemicarbazones of ketones on alumina with chloroform, these compounds undergo oxidation by atmospheric oxygen to give the corresponding Δ^1-1,2,4-triazoline-3-thiones II. Chromatography on other adsorbents also led to triazolines. On the other hand, only thiadiazolines IV were isolated upon the action of MnO_2. Since only ketone derivatives were studied, the position of the double bond in the ring was determined unequivocally.

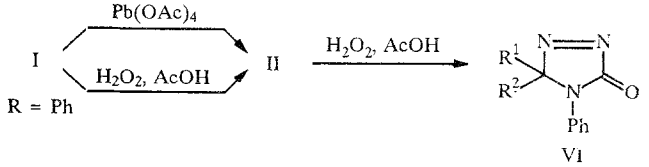


The same position of the double bond in 1,3,4-thiadiazolines IV obtained by the oxidation of 4-phenylthiosemicarbazones of acetone and cyclohexanone [9] by the action of $FeCl_3$ was indicated by the finding of peaks for $[M - N_2]^{+\cdot}$ ions in their mass spectra. The type of the heterocycle formed follows from the structure of the products of [2+2]-cycloaddition with diphenylketene.



I R = Ph; IV, V $R^1 = R^2 = Me$, $R^1 = R^2 = -(CH_2)_5-$

Katritzky and his colleagues [10] studied the effect of the oxidizing in greater detail. They not only confirmed the results of Landquist [8], but also showed that the oxidation of thiosemicarbazones by $Pb(OAc)_4$ or H_2O_2 in acetic acid leads exclusively to Δ^1-1,2,4-triazolines. The structure of the products and the position of the double bond in the ring were indicated by spectral data and x—ray diffraction structural analysis. Thus, the IR spectra of triazolinethiones show bands for the thiocarbonyl group at 1150-1158 cm^{-1} and for the N=N group at 1592-1595 cm^{-1}. We should note that in addition to ketone derivatives, the behavior of the acetaldehyde derivative I (R^1 = Me, R^2 = H) was also studied in this work. The triazolinethione formed upon its oxidation also has a double bond between the nitrogen atoms, as indicated by an x—ray diffraction structural analysis (the N—N bond length is 1.24 Å), although 1,5-dehydrogenation is possible in this case.

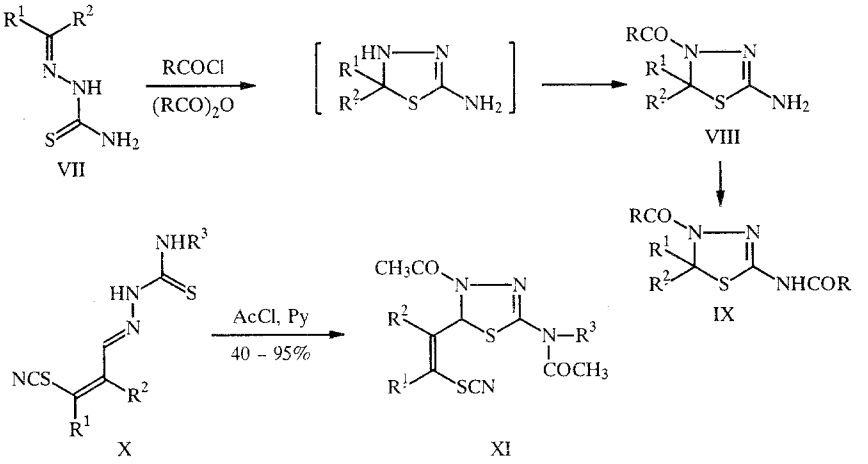


The effect of the substituent at the nitrogen atoms on the type of product of the cyclization of the thiosemicarbazones of aldehydes by the action of $FeCl_3$ was studied in the case of acetaldehyde and benzaldehyde [11]. The thiosemicarbazones of benzaldehyde, which are unsubstituted at N-2, give only thiadiazolines upon oxidation, while the 2,4-diphenylthiosemicarbazones of both aldehydes give only triazolines. On the other hand, the oxidation of 2,4-dimethythiosemicarbazones leads to a mixture of both heterocycles. The replacement of benzaldehyde by 4-nitrobenzaldehyde leads to a decrease in the triazoline content in the product mixture from 80 to 50%. The monosubstituted 2-methylthiosemicarbazone of acetaldehyde gave a 5:3 mixture of thiadiazoline and triazoline.

These results indicate that the cyclization reactions of thiosemicarbazones at sulfur and nitrogen are competitive. The nature of the products depends not only on the oxidizing agent used but also the substitution pattern in the starting molecule. Thus, the type of heterocycle formed upon oxidative cyclization is difficult to predict.

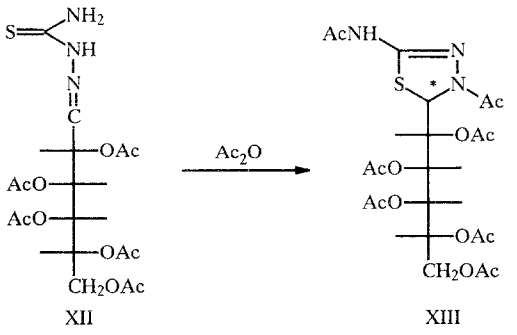
1.2. Cyclization of Thiosemicarbazones by the Action of Alkylating and Acylating Agents

The acylation of the thiosemicarbazones of anhydrides or acid halides leads to Δ^2-1,3,4-thiadiazoline-2-amines. A possible explanation for this result is fixation of the intermediate tautomeric heterocyclic structure by acylation at the nitrogen atom. The excess acylating agent reacts with the amino group of the heterocycle formed [12, 13].



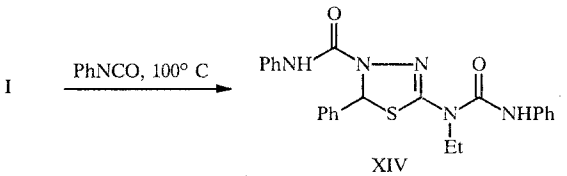
VII–IX R^1 = H, Alk, Ar; R^2 = H, Me [12]; X, XI R^1, R^2 = Alk, R^1R^2 = $-(CH_2)_4-$, R^3 = H, Alk

A similar cyclization occurs upon the acylation of the thiosemicarbazone of pentaacetylgalactose XII [14].



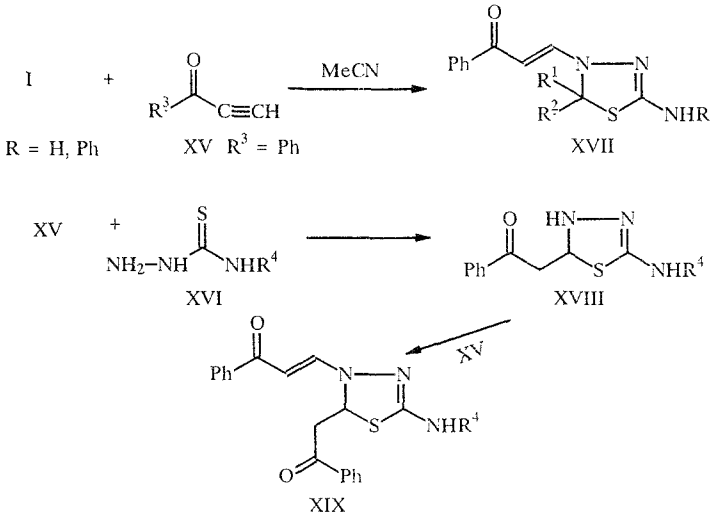
It is interesting that the (−) isomer of thiadiazoline XIII is formed upon acylation in the presence of $ZnCl_2$, while the (+) isomer is formed in the presence of pyridine.

A similar result is found in the addition of phenyl isocyanate to I upon heating [15].



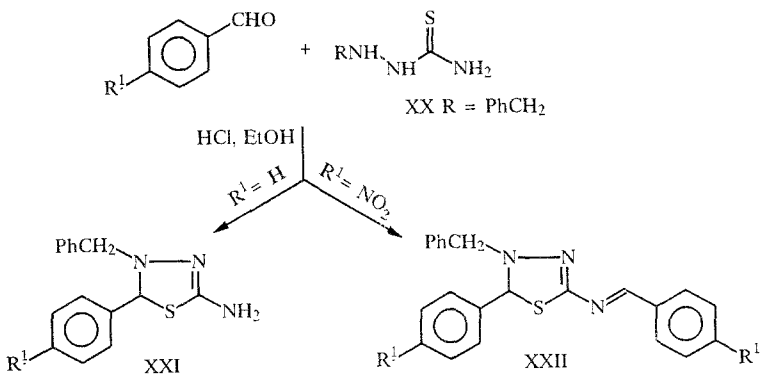
I R = Et, R^1 = Ph, R^2 = H

An analogous heterocycle XVII is formed in the reaction of benzoylacetylene with thiosemicarbazones and 4-phenylthiosemicarbazones of various carbonyl compounds [16]. Furthermore, even the reaction of benzoylacetylene with thiosemicarbazides XVI proceeds not as condensation at the carbonyl group, but rather as addition at the triple bond or N-alkylation and Δ^2-1,3,4-thiadiazoline-2-amines XVIII and XIX [17], which are formally the cyclic forms of the thiosemicarbazones of benzoylacetaldehyde, are isolated instead of the expected thiosemicarbazones.



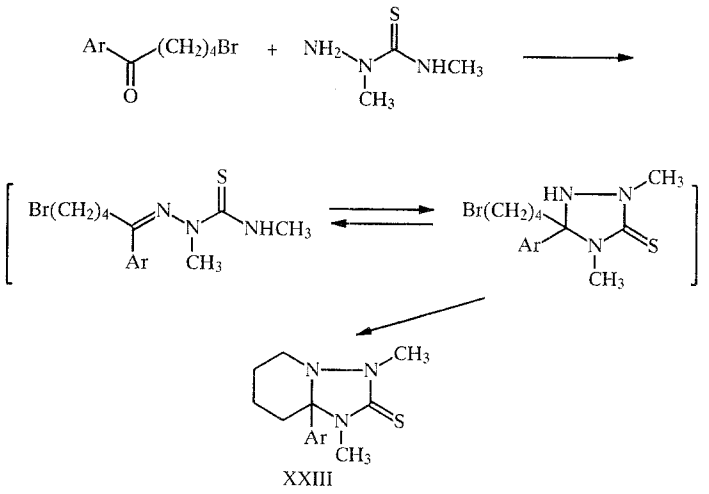
The heterocycles obtained display a broad spectrum of biological activity.

Zoellner et al. [18] have reported that 1-substituted thiosemicarbazides XX also react with benzaldehydes to give the same heterocycles as would be expected from the alkylation of the thiosemicarbazones. In this case, benzaldehyde may then be condensed to give a Schiff base at the amine nitrogen of heterocycle XXI, which is impossible prior to cyclization of the starting thiosemicarbazide.



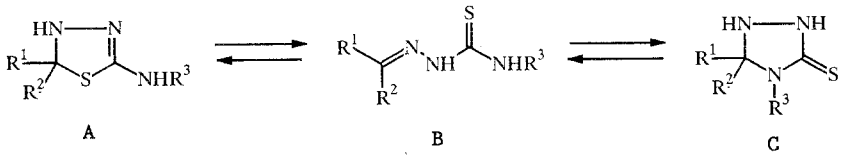
It is quite possible that the formation of 1,2,4-triazolines may actually occur in the case of acylation. In some of the works cited above, the structure of the heterocyclic product was not sufficiently established by spectral methods. Thus, the PMR spectral data given by Glotova et al. [17] may be related to both cyclic structures, while the only evidence for the thiadiazoline structure for the compounds examined in this article is the C—S band in the IR spectral region from 670 to 700 cm^{-1}, which is difficult to interpret.

In this regard, we note the work of Kane and Stewart [19], in which intramolecular cyclization led to a bicyclic 1,2,4-triazolidine derivative XXIII [19].



XXIII

Thus, the results of the alkylation and acylation reactions of thiosemicarbazones may be explained assuming the possible formation of heterocyclic tautomeric forms of the starting compounds, which are fixed during the reaction. In this case, the formation of VIII, IX, XI, XIII, XIV, XVII, XVIII, and XXI may proceed through tautomer A, while the formation of XXIII may proceed through tautomer C.



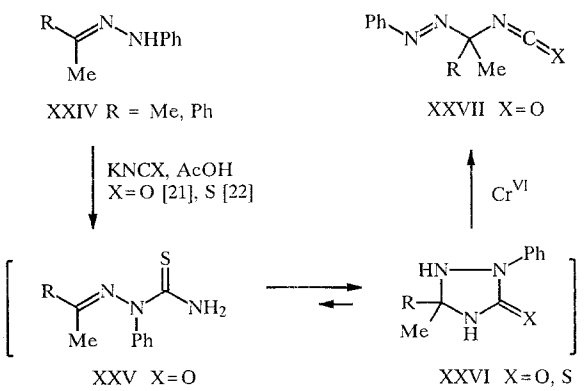
A B C

The conditions for the formation of the corresponding cyclic thiosemicarbazone tautomers and the methods for their identification will be examined below.

1.3 Ring–Chain Tautomerism of Thiosemicarbazones

The possibility of ring—chain tautomerism of thiosemicarbazones was proposed by Karabatsos and coworkers [20] in 1964, who discovered that the doublet for the methyl groups in the PMR spectra of acidified solutions of the thiosemicarbazone of acetone coalesces to a singlet at δ 2.04 ppm. This behavior was attributed to rapid *syn—anti* isomerization of the protonated thiosemicarbazone molecule through an intermediate, corresponding to protonated 1,3,4-thiadiazolidine (structure A).

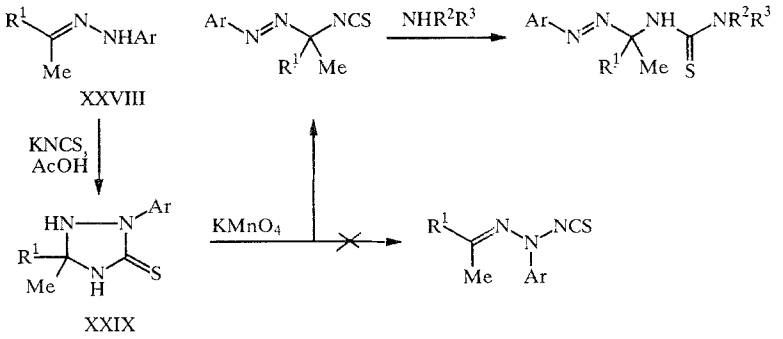
Subsequently, Schildknecht et al. [21] found that reversible isomerization is also characteristic for substituted semicarbazones of ketones. However, in this case, 1,2,4-triazolidin-3-one was formed rather than 1,3,4-oxadiazolidine (the oxygen analog of structure A), that is, the cyclization proceeds as the result of attack of the nitrogen atom [21]. The structure of the heterocyclic product XXVI was supported by its oxidation.



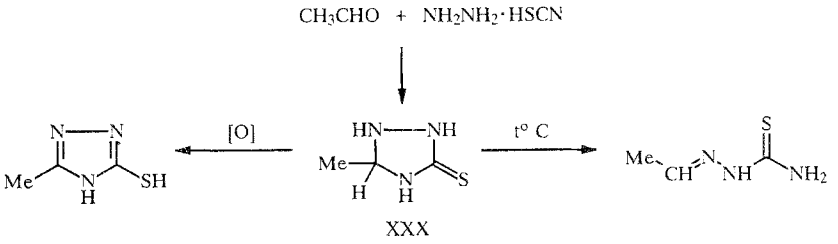
XXIV R = Me, Ph XXVII X=O

XXV X=O XXVI X=O, S

The ring form predominates upon warming or increasing acidity of the solution. These authors established that the reaction of phenylhydrazones with KSCN in glacial acetic acid proceeds analogously and leads to cyclic isomers instead of the expected 2-phenylthiosemicarbazones, specifically to 1,2,4-triazolidine-3-thiones XXVI rather than 1,3,4-thiazolidines; equilibrium with linear XXV is not observed [22]. The cyclic structure of the products was indicated by the IR, UV, and PMR spectral data, which, however, did not permit us to select one of the alternative heterocyclic structures. The selection in favor of the 1,2,4-triazolidine structure with an exocyclic sulfur atom was made on the basis of the following chemical reactions. Treatment of XXVI (X = S) with methyl iodide gave a thiuronium salt, which loses methyl mercaptan with alkali. An approach to establishing the structure of the heterocyclic thiosemicarbazone isomers involving study of the structure of their oxidation products [21, 22], was also used by Schantl et al., who found that the reaction of various ketone arylhydrazones with KSCN gave, as in the case of phenylhydrazones XXIV, 1,2,4-triazolidines XXIX [23, 24], which possess anti-inflammatory and analgesic activity [25]. The formation of a thiadiazoline form under these conditions was not detected.



The analogous reaction with hydrazinium thiocyanate also gave cyclic structures but heating, on the other hand, led to ring opening [26].



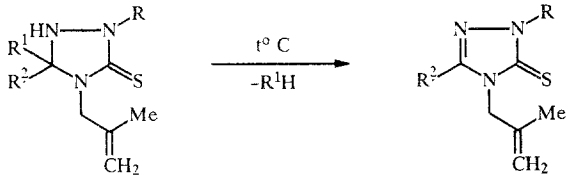
Comparison of the data of Schildknecht [22] and Arai [26] indicates that the substituents in the thiosemicarbazone fragment sterically stabilize the cyclic form of the thiosemicarbazones.

The possibility of forming an alternative heterocyclic form, namely, 1,3,4-thiadiazoline, upon the reversible cyclization of thiosemicarbazones has long been in doubt, while the effect of the reaction conditions and nature of the substitution have been established in the case of the reversible cyclization of 1-acylthiosemicarbazides, leading either to 1,2,4-triazoline-3-thiones or 1,3,4-thiadiazol-2-amines [27].

In 1970, Mayer and Lauerer observed the formation of a heterocyclic form in acid solutions of unsubstituted thiosemicarbazones XXXI of aliphatic and heteroaromatic aldehydes (furfural and picolinaldehyde), which were identified by means of the change in the chemical shift of the methine proton of the CH=N group [28]. A thiadiazoline structure was assigned to the ring form by analogy to previously studied derivatives of hydrazinethiocarboxylic acids XXXII, for which it is the only possible structure.

R^1 = Alk, 2-Py, 2-furyl

Substituted thiosemicarbazones of acetone obtained by the usual method, that is, by condensation of compounds with thiosemicarbazides, display ring—chain tautomerism in CF_3CO_2D solutions involving the thiadiazoline form [29]. Thus, the thiosemicarbazone, 2-methylthiosemicarbazone, and 4-methylthiosemicarbazone of acetone have linear structure in DMSO-d_6 and exist as a mixture of tautomers in CF_3CO_2D. On the other hand, the 2,4-dimethylthiosemicarbazone of acetone exists in a cyclic form in both solvents. Therefore, substitution in the thiosemicarbazone part of the molecule appears to stabilize the cyclic tautomer. However, it has been reported that the nature of the carbonyl compound has the predominant effect on the possibility of cyclization of substituted thiosemicarbazones. Thus, according to Schulze [30], the structure of these compounds was indicated by IR, ^{13}C NMR, and ^{15}N NMR spectral data. The cyclic structure of the ketone condensation products XXXIII was confirmed by studying their thermolysis, in which they eliminate the substituent from C-5 to give triazolinethione XXXIV [31].

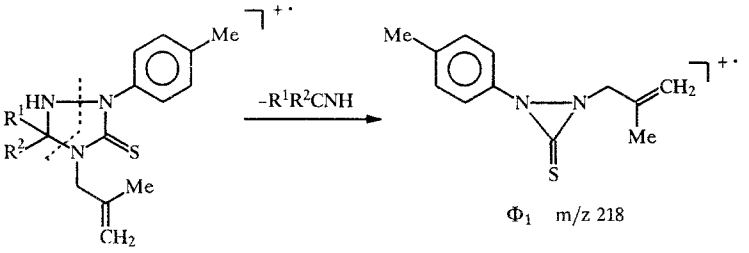


XXXIII XXXIV

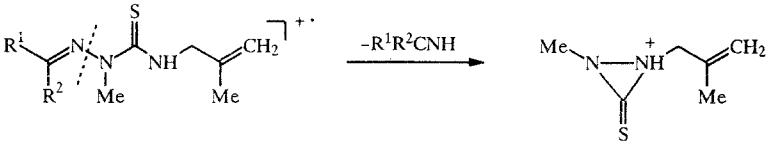
R = Me, 4-MeC_6H_4; R^1, R^2 = Alk; R^1R^2 = $-(CH_2)_n$

Schulze et al. [30, 31] reject the possibility of any cyclic form for the thiosemicarbazones of aldehydes and also did not consider the possibility of the coexistence of linear and cyclic forms in the case of ketone derivatives since the electron impact mass spectral fragmentation for 2-substituted 4-methylallylthiosemicarbazones of a series of ketones [32] was interpreted assuming a known cyclic structure.

However, careful analysis of the mass spectra given by Schulze et al. [32], and our independent mass spectral study of the corresponding aldehyde derivatives showed that the structure of these compounds, at least, in the gas phase, is more likely a function of the type of substituent at position 2 than the nature of the starting carbonyl compound. The strongest peaks in the mass spectra of 2-*p*-tolyl-4-methallyl derivatives of both ketones and aldehydes correspond to fragment Φ_1, formed from the cyclic form, while in the case of 2-methyl-4-methallyl derivatives, the strongest peaks correspond to fragment Φ_2, obtained from the linear isomer. Both fragments are formed in a single step from the corresponding forms of the molecular ion (demonstrated by the existence of metastable transitions).



Φ_1 m/z 218

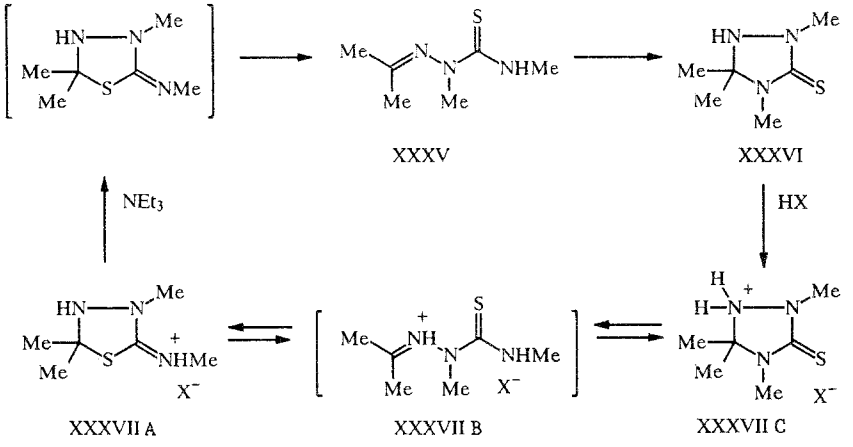


Ketones R^1, R^2 = Alk, $-(CH_2)_n-$
Aldehydes: R^1 = H, R^2 = Ar, PhCH=CH

Φ_2 m/z 143

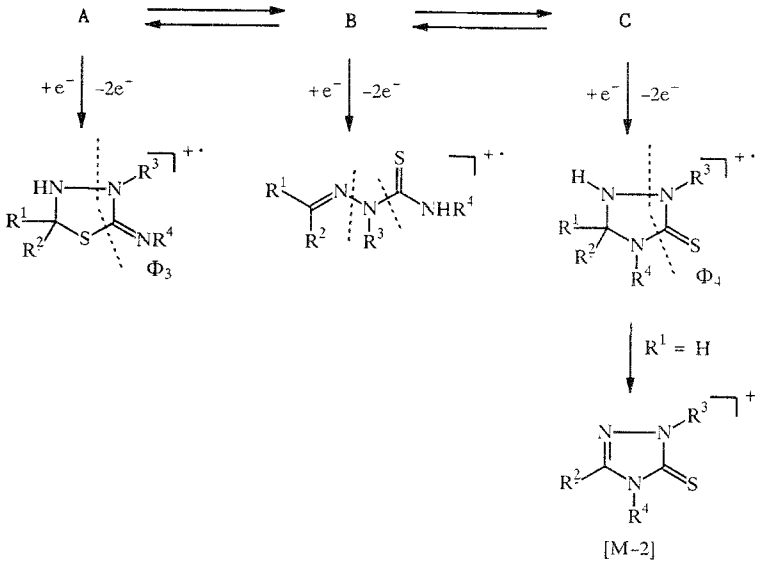
The ring—chain tautomerization processes of N-substituted thiosemicarbazones have recently been studied extensively. Zelenin et al. [3, 34, 37-40] have relied largely on ^1H, ^{13}C, and ^{15}N NMR spectral methods. Thus, the linear thiosemicarbazone XXXV obtained upon the condensation of acetone with 2,4-dimethylthiosemicarbazide was found to convert to 1,2,4-triazolidine-3-thione XXXVI upon storage of its solutions or upon heating to reflux. The hydrogen chloride salt of the latter, XXXVIIC is stable in chloroform but isomerizes in CF_3CO_2H. Both the linear thiosemicarbazone and the

triazolidinethione are converted to thiadiazoline XXXVIIA upon entering solution in CF_3CO_2H. The trifluoroacetate salt of the thiadiazoline form is stable in chloroform but an equilibrium between ring forms A and C is reestablished in DMSO and aqueous CF_3CO_2H. The thiadiazolidine could not be isolated as a free compound by the action of NEt_3 [33]. Tautomerization under these conditions was also observed for other substituted thiosemicarbazones, which indicates that it is a common property for this class of compounds [34].



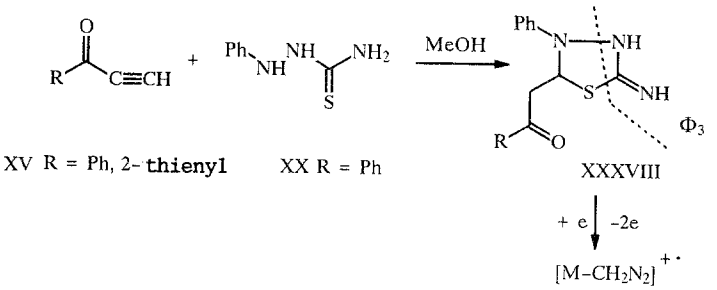
HX = HCl, CF_3COOH

In addition to the application of NMR spectroscopy for the study of the tautomerism of thiosemicarbazones in solution, the mass spectrometric investigation of the fragmentation of these compounds upon electron impact indicated the formation of tautomeric structures in the gas phase. The electron impact mass spectra of substituted thiosemicarbazones of aldehydes showed $[M - 2H]^{+\cdot}$ ion peaks, whose intensity depended on the number and type of substituents in the molecule and may exceed the intensity of the molecular ion in the case of 2,4-disubstituted thiosemicarbazones [34]. We ascribe this effect to thermal dehydrogenation of the molecular ion of the cyclic form of the thiosemicarbazone formed in the gas phase. The facility of the dehydrogenation of 5-monosubstituted 1,2,4-triazolidine-3-thiones to give $\Delta^{1(5)}$-1,2,4-triazolines even upon heating of solutions of these compounds at reflux in the air has been shown by Kazakova et al. [35]. The finding of the $[M - 2]^{+\cdot}$ peak in the mass spectra of XXX was indicated earlier by Arai et al. [26].



The fragmentation patterns of the molecular ions of the two forms differ markedly and are specific for each structure. Thus, the loss of the Φ_3 and Φ_4 fragments may occur only from the corresponding cyclic forms of the molecular ion.

Although we were unable to observe the loss of the Φ_3 fragment in the mass spectra of substituted thiosemicarbazones, this process has been described in the mass spectra of products of the reaction of aroylacetylenes with 1-phenylthiosemicarbazide, which was ascribed 1,3,4-thiadiazoline structure XXXVIII [36].

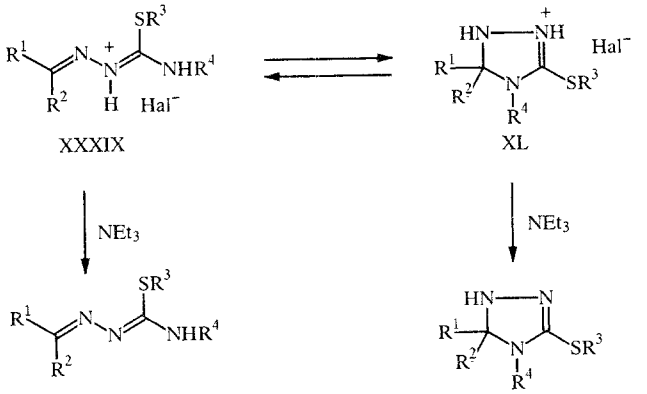


XV R = Ph, 2-thienyl XX R = Ph XXXVIII

In the present case, the fragmentation pattern serves as evidence for the thiadiazoline structure. However, only the triazolidine structure probably obtains for 2,4-disubstituted thiosemicarbazones in the gas phase, while the thiadiazoline structure exists only in solutions in the protonated form.

Zelenin et al. [37, 41] have shown that even in the case of unsubstituted thiosemicarbazones of aliphatic aldehydes or thiosemicarbazones of aliphatic aldehydes monosubstituted at position 4, an equilibrium is established between three tautomeric forms upon dissolution in CF_3CO_2H. Thiadiazolidine form A is predominant in acid media and its content may reach 90%.

S-Alkylisothiosemicarbazonium salts XXXIX, obtained by the action of alkyl halides on thiosemicarbazones, also display ring—chain tautomerism in DMSO solution involving the only possible cyclic form, 1,2,4-triazolidinium salt XL. Upon going from the salt to free base by the action of NEt_3, the structure of the corresponding predominant tautomer is retained [38].

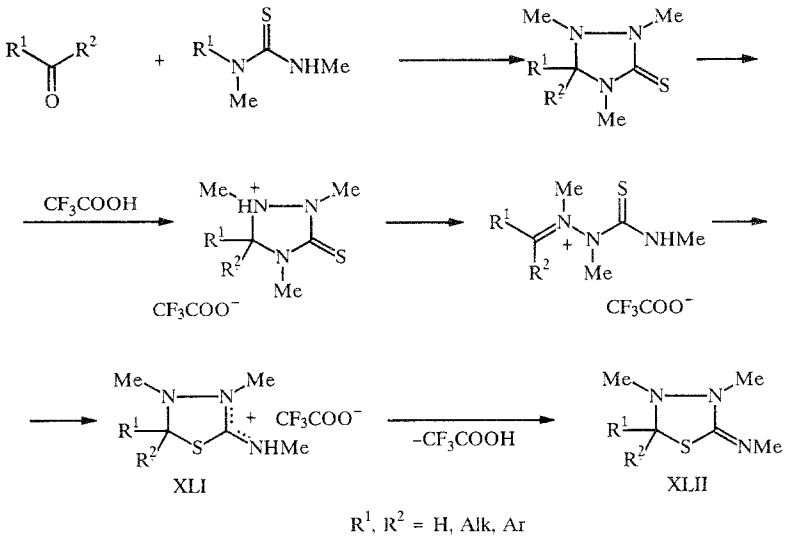


XXXIX XL

The transition from acetone to acetaldehyde and benzaldehyde stabilizes the linear form (compare with the work of Schulze [30]), while an increase in the substitution at the nitrogen atoms, especially at N-2, shifts the equilibrium toward the cyclic form. Thus, 2,4-disubstituted derivatives of aliphatic carbonyl compounds (but not benzaldehyde) exist entirely as 1,2,4-triazolidinium salts XL.

In the general case, derivatives of substituted benzaldehydes and acetophenones exist predominantly in neutral solutions in the linear form. This behavior is attributed to a conjugation effect. In the case of unsubstituted thiosemicarbazones, a ring—chain tautomeric equilibrium in DMSO-d_6 involving the triazolidine form was found only for 2-chloro-6-nitrobenzaldehyde and this is still the only example of the tautomerism of thiosemicarbazones in neutral media [39].

Finally, a study of the reaction of carbonyl compounds with 1,2,4-trimethylthiosemicarbazide in CF_3CO_2H [40] showed that ring-chain tautomerism of the trifluoroacetate of the initially formed permethylated 1,2,4-triazolidinium salt, similar to the recyclization described by Zelenin [33], is not observed but rather we find a quantitative and irreversible transformation to thiadiazolidine XLI, which, in contrast to the incompletely substituted species studied by Zelenin [33], may be isolated as the free base XLII. It is interesting that the triazolidine formed from 1,2-dimethylthiosemicarbazide and benzaldehyde recyclized in acid media to give a thiadiazolinium salt but decomposed to the starting compounds upon an attempt to isolate the free base [33].



XLI XLII

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

In summary, it would appear that, in the general case, the reversible cyclization of thiosemicarbazones is an example of ring—ring tautomerism (this interesting phenomenon was reviewed extensively by Zelenin and Alekseev [41]), which degenerates into ring—chain tautomerism, for example, thiosemicarbazone—1,2,4-triazolidine tautomerism. 2,4-Disubstituted thiosemicarbazones of ketones are more likely to have 1,2,4-triazolidine structure than the corresponding aldehyde derivatives. On the other hand, the thiosemicarbazones of virtually all carbonyl compounds in acid media exist as 1,3,4-thiadiazolines. Returning to the problem of the alternative irreversible cyclization of thiosemicarbazones, we should expect that cyclization will proceed at the nitrogen atom in neutral and slightly acidic media and at the sulfur atom in highly acidic media.

It is unnecessary to stress the importance of the ability to predict the direction of a reaction when two comparable nucleophilic sites exist in a molecule. However, the situation may even be more complicated as seen in an examination of the cyclic forms of monothiocarbhydrazones, for which the existence of a fourth form, namely, the hexahydro-1,2,4,5-tetrazine-3-thione form, is possible in addition to one linear and the two abovementioned five-membered heterocyclic forms.

2. RING—CHAIN TAUTOMERISM OF MONOTHIOCARBHYDRAZONES AND HEXAHYDRO-1,2,4,5-TETRAZINE-3-THIONES

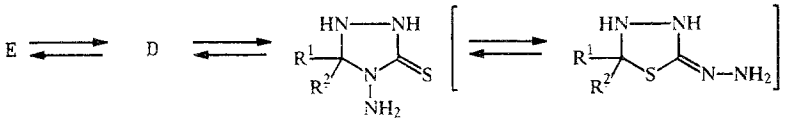
Although a rather efficient method for the preparation of the indicated compounds was developed as early as 1931 [42] and their properties have been described [43], there was no information in the literature on ring—chain tautomeric transformations for this systems until the 1960's. The tautomeric equilibrium of a linear form D and hexahydrotetrazine form E was detected only in 1969 by PMR spectroscopy in DMSO-d_6 solution for monothiocarbhydrazones of aliphatic carbonyl compounds.

XLIII D XLIII E

The ratio of forms D and E depend strongly on the nature of the substituents R^1 and R^2. Thus, for example, the virtually pure linear form D was found in the case of a sterically hindered derivative of 3,3-dimethyl-2-butanone XLIII (R^1 = Me, R^2 = *t*-Bu), while only tetrazine E was formed for a cyclohexanone derivative XLIII (R^1R^2 = —$(CH_2)_5$—). A pure linear form D was found in solution also for benzaldehyde derivative XLIII (R^1 = H, R^2 = Ph).

Later PMR spectral studies showed that the monothiocarbhydrazones of both aliphatic and aromatic carbonyl compounds also failed to show any other tautomers than D and E in solution [45]. Derivatives of formaldehyde XLIII ($R^1 = R^2 = H$) and acetaldehyde XLIII ($R^1 = H$, $R^2 = CH_3$) and also the aromatic aldehydes studied exist only in the linear form. Rajendran and Jain [46] were able to isolate both tautomer forms D and E as pure compounds for the propiophenone derivative and showed that each of these forms gives the same equilibrium tautomer mixture with 60% cyclic form E after about 6 h.

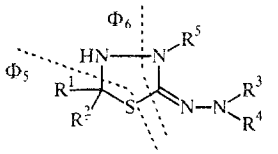
In a more detailed study of the structure of monothiocarbhydrazones of carbonyl compounds, Zelenin et al. [47] used ^1H, ^{13}C, and ^{15}N NMR spectroscopy to show equilibrium in DMSO-d_6 solution involving D, E, and F, i. e., ring—ring tautomerism [41].



XLIV F XLIV G

R^1 = Me, R^2 = Me, $PhCH_2$

In this case, the content of five-membered heterocycle F did not exceed 25%. We stress that, as in the case of other aromatic aldehydes, the anisaldehyde derivative had only linear form D, which the monothiocarbhydrazone of acetophenone is a mixture of only tautomers D and E. We should note that the fourth possible tautomeric form, namely, 2-hydrazino-1,3,4-thiadiazoline G, was not detected in solution of either DMSO-d_6 [44-48] or $CDCl_3$ [48]. On the other hand, form G was detected along with the other three forms in the gas phase upon analyzing the mass spectra of a large series of monothiocarbhydrazones [48].



XLV G

R^1, R^2 = H, Alk, Ar; R^1R^2 = -$(CH_2)_5$-;
R^3 = H, Alk. Ph; R^4, R^5 = H, Me

Thus, the mass spectra of these compounds show ion peaks corresponding to fragments Φ_5 and Φ_6, whose formation is possible only upon decomposition of the molecular ions of tautomer G.

Hence, the formation of both linear and heterocyclic tautomeric forms is found for thiosemicarbazones and monothiocarbhydrazones both in solution and in the gas phase, depending on the nature of the substituents of the carbonyl component. It cannot be excluded that later studies will show a direct correlation between the predominant tautomeric form of these compounds and the nature of their biological activity.

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