CYCLIC THIOUREAS (REVIEW)

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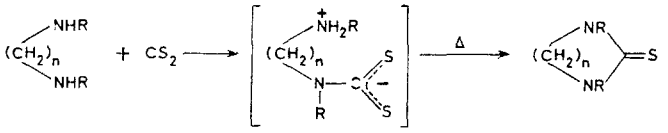
Literature data on methods for the synthesis of cyclic thioureas and their physicochemical properties and transformations are correlated.

Cyclic thioureas and the isothioureas and guanidines obtained from them have a broad spectrum of physiological activity. Respiratory stimulants [1, 2], anticonvulsants [3], analgesics [4], diuretics [3], and hypotensive agents [5, 6] are found in this series of compounds. Cyclic guanidines have high bactericidal activity and are used as disinfectants and antiseptics [4]. Cyclic thioureas and their derivatives also find application as monomers [7] and vulcanization accelerants [8, 9], as well as herbicides and fungicides [10, 11].

In the present review we attempted to correlate data on methods for the synthesis of cyclic thioureas and their structures and properties.

1. Methods of Preparation

1.1. Condensation of Diamines with Carbon Disulfide. The most widely used method for the synthesis of cyclic thioureas is illustrated by the scheme



The set of solvents used in this method is extensive and includes ethanol [8, 12-15], aqueous alcohol [1, 5, 7, 16-18], methanol [19], ether [2, 20], acetone, benzene [21], and methylene chloride [22]. A dithiocarbamate salt, thermolysis of which leads to the formation of the cyclization product, is formed in the first step. In some cases the dithiocarbamate salt is isolated in almost quantitative yield, and its decomposition is realized at 125-180°C without a solvent [2, 12, 14, 19-21] or by refluxing in water [13, 22, 23] or alcohol [14]. A salt is not isolated, as a rule, if the reaction is carried out in ethanol or aqueous alcohol [1, 5, 7, 8, 15-18]. Cessation of hydrogen sulfide evolution serves as an indication of termination of the reaction. The time required for the reaction (up to 2-3 days) is a substantial inadequacy of this method.

The synthesis of the starting diamines is rather laborious. Methods for the synthesis of various 1,2-diamines [2, 19-21], from which a number of substituted imidazolidine-2-thiones have been obtained [1, 2, 5, 8, 16-22], have undergone the greatest development. Considerably fewer six-membered cyclic thioureas have been obtained. In addition to hexahydropyrimidine-2-thione [1, 12, 13], a number of its N,N'-alkyl derivatives have been synthesized [1, 2, 12, 19]. In the seven-membered cyclic thiourea series only hexahydro-1,3-diazepine-2-thione has been obtained [1, 7, 13, 14, 24]. As a rule, the yields of cyclization products are high; however, in the case of 1,4- and, particularly, 1,5-diamine linear-polymeric thiocarbamide side products of the $[-(CH_2)_nNHCSNH-]_x$ type decrease the yields of cyclic thioureas [25, 26]. In order to avoid this, the reaction, commencing with 1,5-diamines, is carried out under high-dilution conditions [15]; in addition to monomeric thioureas, their cyclic oligomers can be obtained in some cases. Only dimeric 18- (I), 20- (II), and 22-membered (III) cyclic thioureas were isolated in the reaction of 1,6-, 1,7-, and 1,8-diamines with carbon disulfide, whereas only monomeric 15-membered ring IV was obtained from 1,12-diaminododecane [15].

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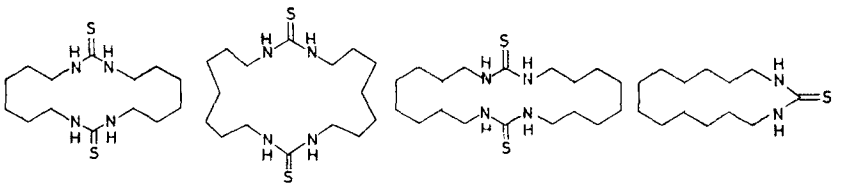
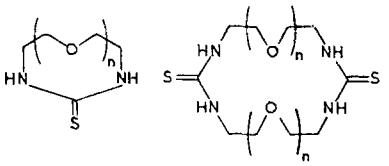


I II III IV

Liquid chromatography makes it possible to isolate, in addition to tetraazacyclodoeicosanedithione III, its cyclic monomer, viz., 1,3-diazacycloundecane-2-thione [27].

The reaction of polyoxyethylenediamines with carbon disulfide in ethanol under high-dilution conditions leads to the formation of cyclic polyoxyethylenethioureas V-X [27, 28], which constitute crown compounds of a new type.

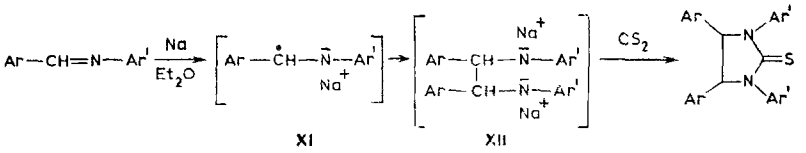


V-VII VIII-X

V,VIII $n=1$; VI,IX $n=2$; VII,X $n=3$

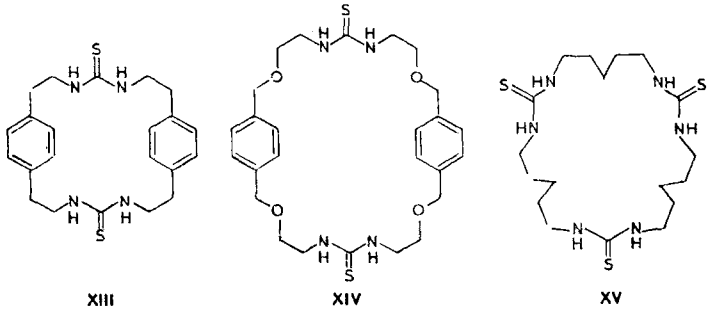
Aryl substituents attached to the nitrogen atoms decrease the reactivities of the diamines significantly. N,N'-Diphenylethylenediamine does not form a dithiocarbamate salt with carbon disulfide even after refluxing for 20 h [19]. However, the use of piperidine as the catalyst makes it possible to obtain N-phenylimidazolidine-2-thione in 86% yield [8]. Arylenediamines also do not react with carbon disulfide [2]. The presence of a stronger organic base such as triethylamine is necessary for carrying out the reaction in this case. It is assumed that the initial product in this case is not the usual inner dithiocarbamate salt but rather a triethylammonium salt [2], which then decomposes to give a cyclic thiourea.

N,N'-Diphenylimidazolidine-2-thiones can be obtained from the corresponding aldimines [29]. The action of sodium metal in ether on them gives anion radical XI, which undergoes dimerization to dianion XII. The reaction of this anion with CS_2 with the simultaneous elimination of Na_2S leads to 1,3,4,5-tetraarylimidazolidine-2-thiones.



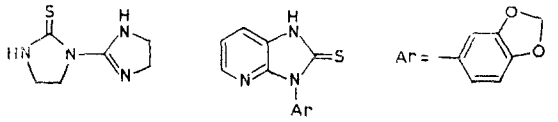
XI XII

1.2. Reaction of Organic Isothiocyanates with Compounds That Contain an Amino Group. This method is not used very often in the synthesis of cyclic thioureas [30, 31]; this is evidently due to the fact that it is necessary to synthesize the starting isothiocyanates. The reaction of diamines with isothiocyanates is a rapid process, and this is convenient for cyclization by the high-dilution method. A number of macrocyclic thioureas (XIII-XV) have been synthesized by this method [31].



XIII XIV XV

1.3. Reaction of Diamines with Sulfur-Containing Reagents. The reaction of ethylenediamine with thiophosgene leads to the formation of a somewhat unusual product, viz., 1-(2-imidazoline-2-yl)imidazolidine-2-thione (XVI) [32]. 1-Aryl-1,3-dihydroimidazo[4,5-b]pyridine-2-thione (XVII) was obtained in the reaction of 3-amino-2-[3,4-(methylenedioxy)phenylamino pyridine with potassium xanthate in aqueous alcohol [33].



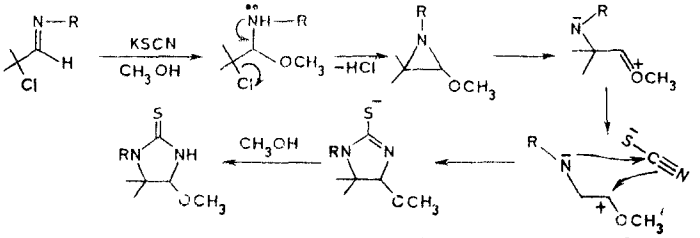
XVI XVII

The reaction of ethylenediamine with exo-5-thiourido- [34] or exo-5-isothiocyano-5,6-dihydro-endo-dicyclopentadiene [35] at 100-250°C and reduced pressure leads to imidazolidine-2-thione in almost quantitative yield.

Cyclic thioureas were also obtained in the reaction of diamines with thiourea [36]. Substituted cyclic thioureas are formed when N,N'-diformyldiamines are heated with sulfur at 130-200°C for 2-3 h or in the reaction of N,N'-diphenylethylenediamine with ammonium thiocyanate in alcohol [19, 37]. N,N'-Diphenylimidazolidine-2-thione can be obtained in good yields (71-76%) by this method.

1.4. Other Methods. Unsubstituted thioureas with from six to twelve links in the rings were obtained from the corresponding cyclic ureas by the action of phosphorus pentasulfide in xylene (the thioureas were obtained in 65-70% yields) [26].

In addition to the methods enumerated above, there are a number of methods that make it possible to synthesize cyclic thioureas of only a certain type. The synthesis of 1-alkyl-4-alkoxy-5,5-dimethylimidazolidine-2-thiones by the reaction of α-chloro aldimines with potassium thiocyanate in alcohols, which, in the opinion of Kimpe and co-workers [18], proceeds via the following scheme, should be classified as a method of this sort:



The reaction proceeds quite readily in ethanol; the use of 2-propanol requires more severe conditions — refluxing for several days. The reduction of the resulting 4-methoxy-imidazolidine-2-thiones with lithium aluminum hydride in ether leads to elimination of the methoxy group.

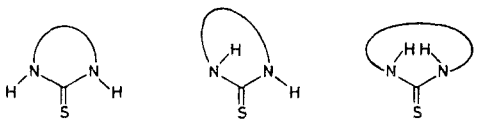
Substituted six-membered cyclic thioureas can be obtained by the reaction of alkali metal thiocyanates or ammonium thiocyanate with amines or unsaturated ketones in water in the presence of a strong mineral acid [38].

A number of 5-hydroxypropylenethioureas were also obtained from substituted thioureas and various aldehydes [39-41].

Thus a rather large number of different cyclic thioureas (from 5- to 28-membered compounds) have been synthesized thus far. However, only a small number of substituted cyclic thioureas (other than five-membered compounds) have been synthesized. The synthesis of cyclic thioureas that contain aromatic substituents also presents considerable difficulties.

2. Structures and Spectral Properties of Cyclic Thioureas

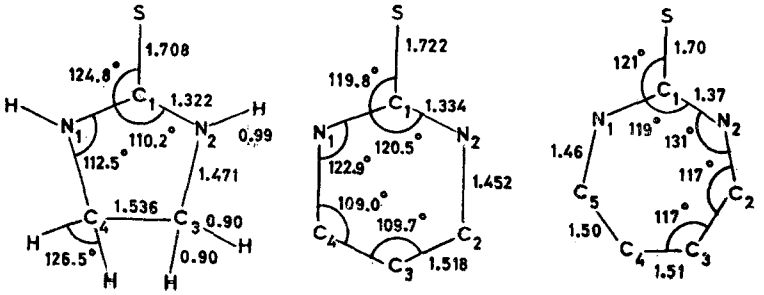
2.1. X-Ray Diffraction Analysis. Three planar configurations, viz., trans,trans (XVIII), cis,trans (XIX), and cis,cis (XX), are possible for the thioamide groups of cyclic thioureas:



XVIII XIX XX

The XVIII configuration is the only possible configuration for five- to nine-membered compounds; this was confirmed by low-temperature NMR experiments [42] and x-ray diffraction analysis [43-50]. The bond lengths and bond angles for ethylene-, trimethylene-, and tetramethylenethioureas are presented below [43, 46, 48].

The ethylenethiourea molecule is virtually planar, and the sulfur atom is located at a distance of 0.030 Å from this plane, which corresponds to an angle of 1° between the S—C



bond and the plane of the molecule. The trimethylene- and tetramethylenethiourea molecules have a chairlike conformation [46, 48].

The realization of the XIX configuration becomes possible as the ring becomes larger. Thus, the S—C(2)—N(3)—C(4) and S—C(2)—N(1)—C(14) torsion angles are 1.08 and 163.38° in 6,9,12-trioxa-1,3-diazacyclotetradecane-2-thione [51]. This conformation is additionally stabilized by a trans-annular N(3)—H...O(12) hydrogen bond [42, 51]. The average geometrical parameters of the ether groups, as well as the C—C and N—C_{sp^3} distances, are similar to the analogous characteristics of other macrocycles [51, 52].

Attempts have been made to solve a number of controversial problems in the establishment of the molecular and crystal structures of cyclic thioureas [43-50]. One such problem is the establishment of the order of the bond between the carbon and sulfur atoms. Two methods, viz., calculation of the bond order by the MO method and calculated by Pauling's resonance method, have been examined. Preference is given to the latter method in [43]. According to the calculations in [43], the degree of double bond character of the C—S bond in the case of ethylene thiourea is only 20%. Partial double bond character of the sulfur atom (∿30-35%) is also proposed for 1-thiocarbamoylimidazolidine-2-thione [44] and tetramethylenethiourea [51]. The C—S bond has a much higher degree of double bond character in the case of 1,3-dimethyl-4-imino-5-oxoimidazolidine-2-thione [45].

The rather high melting points (∿200°C) of cyclic thioureas make it possible to assume the existence of a hydrogen bond between the nitrogen and sulfur atoms. Hydrogen bonds of this sort were established for unsubstituted thiourea [53]. However, x-ray diffraction analysis of ethylenethiourea does not make it possible to draw an unambiguous conclusion regarding the presence of hydrogen bonds of the N—H...S type [43]. The absence of such hydrogen bonds was also noted in tetramethylenethioureas [51]. At the same time, each sulfur atom in trimethylenethiourea is associated with two NH groups [46]. 6,9,12-Trioxa-1,3-diazacyclotetradecane-2-thione crystals are constructed from macrocyclic molecules connected by an N—H...S hydrogen bond (N...S = 3.385, S...H = 2.573, N—H = 0.868 Å, and ∠S—H—N = 156°) in such a way as to give crimped chains directed along the C axis [51]. The contacts between the chains correspond to the van der Waals interactions.

2.2. Dipole Moments. The dipole moments of unsubstituted five- to seven-membered cyclic thioureas in dioxane are quite high (5.36-5.79 D) but somewhat lower for their N,N'-dimethyl derivatives (5.29-5.63 D) [1]. Cyclic thioureas have larger dipole moments than the corresponding ureas, and this difference is much greater than for noncyclic thioureas and ureas [54]. The large dipole moments of thioureas are explained by the large contribution of resonance dipolar forms to the structures of the molecules [55, 56]. The contribution of dipolar forms to the structure of thioureas is 30% [54]. In contrast to this, this contribution, calculated from Pauling's equation with the aid of crystallographic data [46], is 70% for trimethylenethiourea. The dipole moments of cyclic thioureas (in dioxane) correlate well with the chemical shifts of the protons of the NH groups in the PMR spectra [57]:

$$\delta\,(\text{ppm}) = 0{,}877\mu + 1{,}665.$$

2.3. UV and IR Spectra. Two absorption maxima at 210-212 and 234-252 nm are observed in the UV spectra of cyclic thioureas in ethanol [26]. The long-wave maximum is shifted from 238 nm to 252 nm on passing from a five-membered ring to a seven-membered ring. The absorption maximum remains at 234-252 nm on passing further to 28-membered rings [26, 27]. The introduction of alkyl substituents in the 1 and 3 positions causes virtually no shift in the absorption maximum. An aromatic substituent attached to the nitrogen atom leads to a bathochromic shift (30 nm for 1-phenylimidazolidine-2-thione and 10 nm for 1-methyl-3-phenylimidazoline-2-thione [58-60]). A 4.0-11.5-nm bathochromic shift occurs on passing to an aprotic solvent (CH_2Cl_2). On the basis of a calculation of the electronic spectrum of thiourea by

the Pariser–Parr–Pople (PPP) method the short-wave maximum at 195 nm was assigned to local excitation of the C=S group, while the second maximum at 237 nm was assigned to transition of the electrons of the nitrogen atom to the antibonding orbital of the C=S group [61]. The long-wave absorption maximum of cyclic thioureas was also assigned to the $\pi \rightarrow \pi^*$ transition [58-60].

Serious difficulties arise in the interpretation of the IR spectra of cyclic thioureas. This is associated with the fact that the vibrations of the thiocarbonyl group do not have such clearly expressed character as the vibrations of the carbonyl group. In addition, because of the greater single-bond character of the bond in the thiocarbonyl group its vibrations appear at lower frequencies [56] and lie in the "fingerprint" region. Attempts have been made in a number of studies [56, 62-64] to ascertain the vibrations of the thiocarbonyl group by comparison of the spectra of various types of compounds that contain a C=S group with their oxygen analogs. This sort of comparison for cyclic thioureas and ureas leads to a $\nu C{=}O/\nu C{=}S$ value of 1.5 [62, 63]; the 1050-1200 cm^{-1} or 1300-1400 cm^{-1} region [64] is assigned to the vibrations of the C=S group. A more thorough analysis of the IR spectra of 15 pairs of various cyclic (five- to seven-membered) thioureas and ureas leads to the conclusion that the frequencies of the vibrations of the C=S group of unsubstituted thioureas are 100 cm^{-1} lower than in the case of their N,N'-dialkyl derivatives because of the presence of intermolecular hydrogen bonds [1, 65]. In conformity with this, the $\nu C{=}S$ bands appear at 1195-1208 cm^{-1} ($\nu C{=}O/\nu C{=}S = 1.370 \pm 0.023$) for unsubstituted cyclic thioureas and at 1315-1370 cm^{-1} ($\nu C{=}O/\nu C{=}S = 1.240 \pm 0.044$) for the N,N'-dialkyl derivaties. The band at 1238-1342 cm^{-1} is assigned to vibrations of the C(S)–N fragment.

To ascertain the position of the vibrations of the C=S group the IR spectra of cyclic thioureas were compared with the spectra of their selenium analogs [66-70]. On the basis of the fact that the spectra of imidazolidine-2-thione and imidazolidine-2-selenone differ only in the region below 650 cm^{-1}, this region was assigned to the vibrations of the C=S group. The spectral characteristics of noncyclic thioureas, selenoureas, and their deuterated (at the nitrogen atom) derivatives were examined in [71-74]. On the basis of calculations of the frequencies and forms of the normal vibrations with the aid of the Urey–Bradley force field [72, 73] it was concluded that the three bands at 863, 688, and 485 cm^{-1} have approximately equal contributions of the stretching coordinate of the C=S bond. A comparison with the spectrum of isothiourea made it possible to assign the band at 485 cm^{-1} to the vibrations of the C=S group [73]. A similar spectral analysis of imidazolidine-2-thione, its N,N-deuterated analog, and the S-methyl derivative in combination with the calculated data made it possible to assign the band at 516 cm^{-1} to the vibrations of the C=S group [75, 76].

The most nearly complete spectral analysis of series of five- and six-membered cyclic thioureas was given in [77-79]. Mille and co-workers [77-79] note that the assignment of the vibrations of the C=S group is complicated by the fact that they are mixed with other vibrations of the molecules. For substituted imidazolidine-2-thiones the bands at 1270 ± 10 ($\nu C{=}S$), 700 ± 20 ($\nu C{-}S$), and 500 ± 30 cm^{-1} ($\delta C{=}S$) were assigned to the vibrations of the C=S group [79]. Assignment of the bands of the vibrations of the N–H bond was also made for 1-alkylimidazolidine-2-thiones: 320 ± 6 (νNH), 1517 ± 8 (δNH), and 676 ± 6 cm^{-1} (γNH). The stretching vibrations of the NH group of hexahydropyrimidine-2-thiones appear at 3177-3230 cm^{-1} [77], whereas the deformation vibrations show up at 1509-1526 cm^{-1}; the bands at 1515-1555, 1072-1358, and 695-728 cm^{-1} were assigned to the C–N, C=S, and C–S stretching vibrations, respectively. An attempt to isolate the ring vibrations was made for several compounds [78].

Thus, it should be acknowledged that the elucidation of the spectral characteristics of the C=S group is a rather complex problem. It is obvious that there is no band to which one could have assigned the vibrations of a "pure" C=S group. In our opinion, it is most accurate to examine a whole series of bands due to vibrations of the N–C=S fragment, as in the case of noncyclic thioureas [80, 81], cyclic polyoxyethylenethioureas [27, 82], and imidazolidine-2-thione [83]. In the latter case the following four bands were assigned to the vibrations of the H–N–C–S fragment: [$\delta NH + \delta C{-}H + \delta CH_2$] at 1530 and 1505 cm^{-1}, [$\nu C{=}S + \nu C{-}N + \delta NH$] at 1200 cm^{-1}, [$\nu C{-}C + \nu C{-}S + \nu CH_2{-}N$] at 1040 and 919 cm^{-1}, and [$\nu CN + \nu C{=}S + \nu ring$] at 625 cm^{-1}.

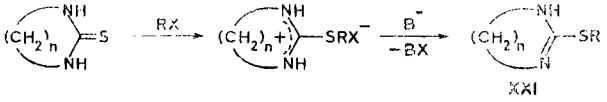
Despite the rather large number of papers devoted to the study of the IR spectra of cyclic thioureas, virtually no data on the IR spectra of solutions of these compounds are available. Verylittle study has been devoted to the hydrogen bonds. Only three papers [84-86], in which the band at 3450 cm^{-1} was assigned to the stretching vibrations of the free NH

group of 1-methyltetrahydropyrimidine-2-thione and the band at 3225 cm^{-1} was assigned to an associated NH group, are known.

2.4. Tautomerism. The problem of the possible tautomeric transformations of the thione–thiol type of thioureas is interesting. On the basis of the IR, Raman, and UV spectra it was concluded that in the crystalline state and in solutions in water, pyridine, and acetone thioureas exist only in the thione form [84, 85]. In other papers [15, 86-89] the thiol form is assigned to thioureas, including cyclic thioureas, without special proof. The tautomeric transformations of cyclic polyoxyethylenethioureas were studied in [27, 28]. On the basis of the fact that the IR spectra of solid samples of these compounds do not contain absorption bands of C=N and SH groups it was concluded that these substances exist in the thione form. Bands of stretching vibrations of a C=N group at 1600-1670 cm^{-1} and a weak band of an SH group at 2450 cm^{-1} appear in the IR spectra of solutions in tetrachloroethane. The intensities of these bands increase slowly with time and upon heating and increase sharply when the investigated solutions are acidified with hydrogen chloride. The presence in the PMR spectra of solutions in $CDCl_3$ of a signal of an SH group at 1.73-1.95 ppm is a distinct spectral characteristic of the thiol form of these substances. The percentage of the thiol form ranges from 11 to 24%.

3. Reactions of Cyclic Thioureas

3.1. Alkylation. S-Alkylisothioureas XXI are formed by the action of alkyl halides, halo acids, and other halo derivatives on thioureas [3, 5, 10, 12, 13, 15, 17, 18, 22, 87-98].

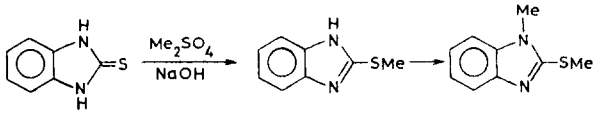


XXI

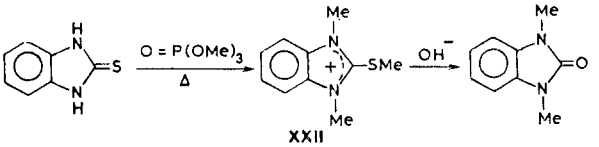
The reaction is carried out at room temperature or at elevated temperatures in alcohols [3, 12, 13, 22, 77, 90, 92, 95, 97, 98] or acetone [17, 18, 91, 93, 94]. An equimolar amount or a small excess of the alkyl halide is generally used.

The resulting salts are easily crystallized compounds with distinct melting points and are isolated in almost quantitative yields. The corresponding bases are hygroscopic and unstable and are crystallized with difficulty [92, 97]. Aqueous solutions of alkalis or alkali metal carbonates with subsequent extraction by organic solvents are most often used for the isolation of the bases from the salts [3, 10, 18, 22, 90, 92, 96]. This method is extremely simple, takes little time, and gives good results when substituents are present in the ring. Unsubstituted thioureas are more difficult to extract, and in this case extraction is carried out from saturated salt solutions [22]. Of the other methods, one should note treatment of **thiuronium** salts with a solution of sodium methoxide in methanol [5, 90] and with concentrated ammonium hydroxide [93] and refluxing in chloroform in the presence of solid alkali [17], or in ether over sodium metal [91]. The yields of the resulting bases are not always satisfactory [90].

The alkylation of cyclic thioureas in alkaline media takes place in two steps: The sulfur atom is alkylated initially, after which the nitrogen atom is alkylated [99]:



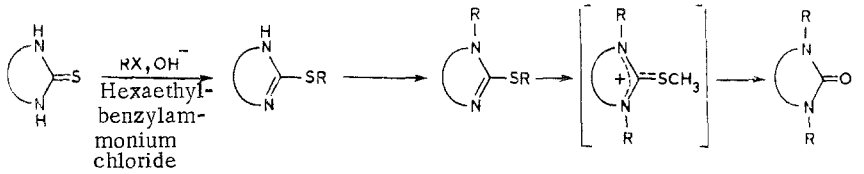
Interesting, although somewhat contradictory, results were obtained when esters of phosphoric and phosphorous acids were used [99, 100]. Thus, trialkylation product XXII is obtained when benzimidazolidine-2-thione is refluxed in the presence of trimethyl phosphate [99]. The authors feel that this method is extremely promising for the transition to N,N'-disubstituted cyclic ureas.



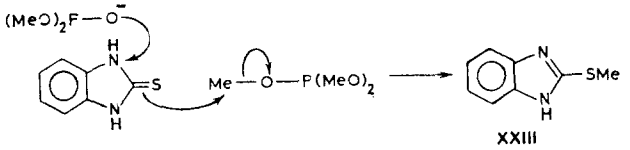
XXII

The alkylation of cyclic thioureas with alkyl halides under interphase-catalysis conditions is, in our opinion, a more convenient method for the synthesis of cyclic N,N'-dialkyl-

ureas [101]. A number of cyclic N,N'-dialkylureas with 5- and 22-membered rings were obtained by this method [101].

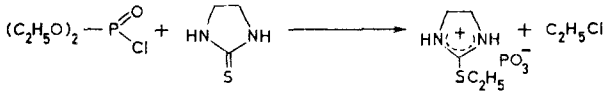


Alkylation with trimethyl phosphite takes place in a few minutes and gives S-methylation product XXIII. However, the reaction does not take place at all if freshly distilled phosphite is used. The addition of a drop of water makes it again possible to rapidly obtain an alkylation product. On the basis of this it has been assumed that dimethyl phosphite, which also promotes the reaction, is formed as a result of hydrolysis of the trimethyl phosphite.

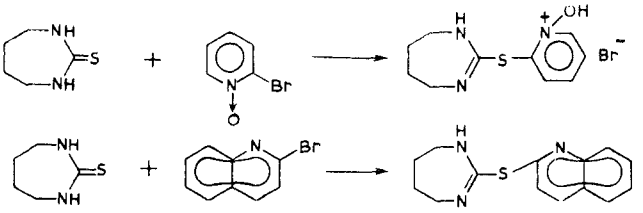


XXIII

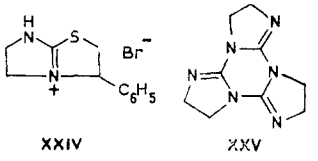
In contrast to this, it has been reported [100] that an attempt to carry out the alkylation of ethyleneurea with diethyl phosphite and triethyl phosphate both in the fused state and in solution was unsuccessful. It was found that it was possible to carry out this reaction when diethyl chlorophosphate was used as the alkylating agent.



The arylation of cyclic thioureas takes place only with activated aryl halides [102].



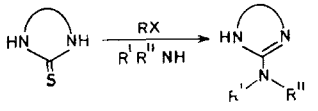
The accessibility of cyclic isothioureas is responsible for their extensive use for the preparation of other classes of organic compounds: various two-ring systems of the XXIV type [15, 93, 94, 103], s-triazines XXV (104], and particularly cyclic guanidines [5, 12, 13, 97, 105-108].



XXIV XXV

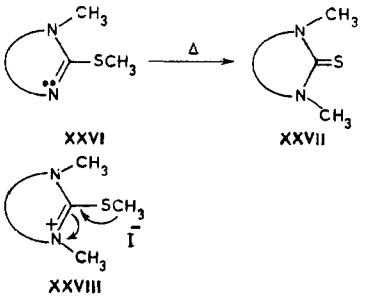
The reaction of ethylenethioureas with phenacyl bromide in acetone does not give the usual S-alkylation product. When this same reaction is carried out in refluxing ethanol, it leads to 3-phenyl-2,3,5,6-tetrahydroimidazo[2,1-b]thiazolium bromide (XXIV), which is formed as a result of dehydration of the isothiuronium salt and subsequent ring closing [93, 94]. The use of acetic acid or dimethoxyethane as the solvent accelerates the formation of salt XXIV [94, 104].

The reaction of isothiourea with amines is the most general method for the preparation of cyclic guanidines. The reaction is carried out in water [12, 97], alcohols [5, 97, 105-108], and acetone [97]; the reaction product is usually isolated in good yield:



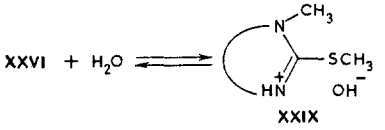
Secondary diamines are usually used to prepare N,N'-dialkyl derivatives of cyclic thioureas. The selective alkylation of the nitrogen atoms in cyclic thioureas is difficult. An example of the alkylation of the disodium salt of tetramethylenethioureas with methyl iodide in dioxane has been described [1]. However, in the opinion of Hornyak and co-workers [109], the formation of an N,S-dimethyl derivative is more likely under these conditions. The N-alkylation of imidazolidine-2-thione by heating with propylene oxide in the presence of pyridine [88] and its reductive alkylation with a mixture of decahydroquinoline and formaldehyde have been described [110].

3.2. SR⇄NR Rearrangement. Among the extremely interesting properties of cyclic thioureas, one should include a rearrangement of the SR⇄NR type [99, 111, 112], which has been studied in detail in a series of papers [17, 58-60, 77-79, 91, 113, 114] in the case of five- and six-membered thioureas at various temperatures and with the aid of various catalysts. The best catalyst is quaternary salt XXVIII:



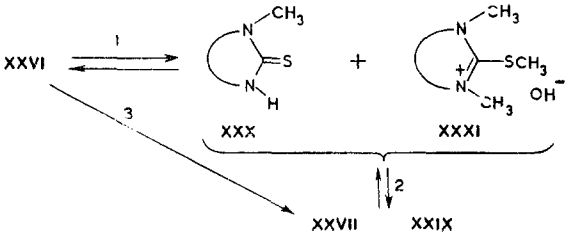
XXVI XXVII XXVIII

The reaction also takes place in the absence of a quaternary salt; salt XXIX, which catalyzes the subsequent process, is formed as a result of hydrolysis of isothiourea XXVI by traces of water:



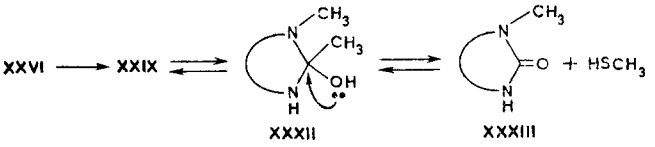
XXIX

The first step leads to the formation of thione XXX and quaternary salt XXXI. Thione XXX suppresses the subsequent catalysis by salt XXXI to give normal rearrangement product XXVII (Step 2). The mechanism of the reaction via pathway 3 corresponds to the classical rearrangement.



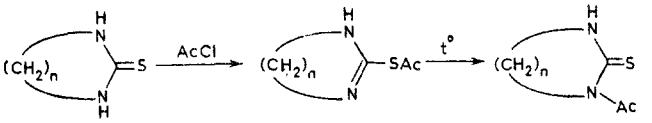
XXX XXXI XXVII XXIX

Catalysis by traces of water promotes various side processes, the principal one of which is the formation of the corresponding cyclic ureas XXXIII:

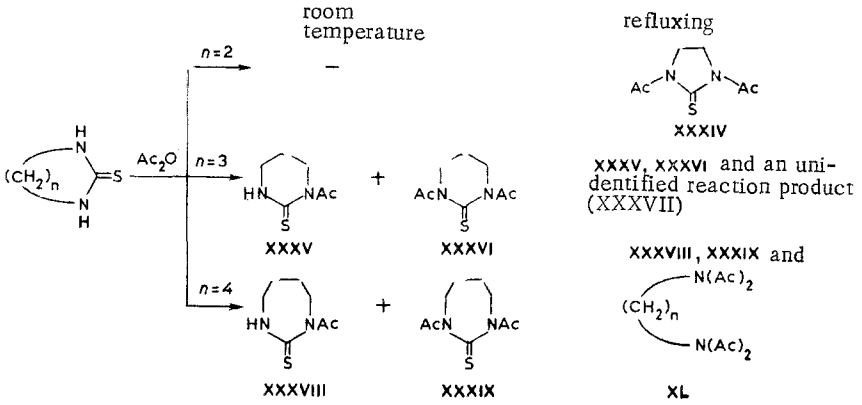


XXXII XXXIII

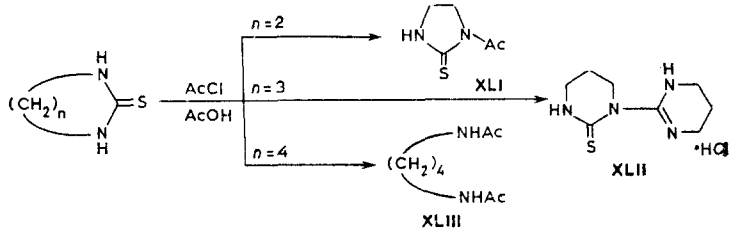
3.3. Acylation. The acylation of cyclic thioureas by means of acid anhydrides and chlorides has been studied quite adequately [49, 89, 90, 94, 115-119]. N-Acyl derivatives of cyclic thioureas are formed as a result of the reaction [116, 117, 119, 120]. Acylation at the sulfur atom is possible only in the cold, since rearrangement to N-acylthioureas occurs when the reagents are heated [90, 121].



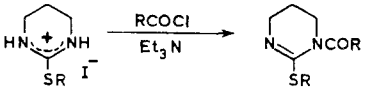
Acylation is extremely sensitive to the ring size and to the acylating reagent [118]. Ethylenethioureas does not react with acetic anhydride at room temperature, and N,N'-diacetyl derivative XXXIV is produced when the reagents are heated. Trimethylenethioureas is acylated even at room temperature to give a mixture of N-acetyl- (XXXV) and N,N'-diacetyltetrahydropyrimidine-2-thiones (XXXVI). In the case of heating, the rapidly formed N,N'-diacetyl derivative vanishes from the reaction mixture, but the resulting XXXVII cannot be identified [116]. At room temperature tetramethylenethiourea gives monoacetyl derivative XXXVIII, whereas upon brief heating it gives diacetylation product XXXIX, which upon prolonged heating is converted to N,N,N',N'-tetraacetyl-1,4-diaminobutane (XL).



Thus, the ability to undergo acylation by means of acetic anhydride increases as the number of atoms in the ring increases. In the case of acylation with acetyl chloride in acetic acid ethylenethiourea gives monoacetyl derivative XLI, while trimethylenethiourea gives symdialkylguanylthiourea hydrochloride (XLII); tetramethylenethiourea gives successively mono- and diacylation products XXXVIII and XXXIX. N,N'-Diacetyl-1,4-diaminobutane (XLIII) is formed upon prolonged heating:

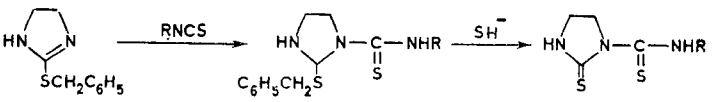


Acylated cyclic thioureas readily undergo S-alkylation by means of alkyl halides [121]. The reaction can be carried out in the presence of triethylamine, which makes it possible to increase the yield of the alkylation product [121]. However, a more convenient method for the preparation of N-acyl derivatives of cyclic isothioureas is acylation of their hydriodides with acid anhydrides in the presence of triethylamine [122].

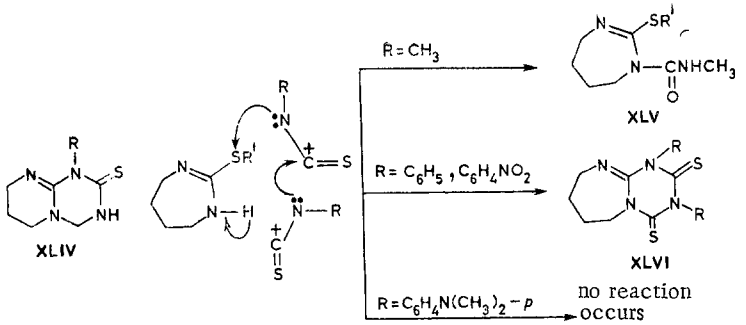


In this case the reaction takes place under milder conditions, proceeds considerably more rapidly, and gives the products in better yields.

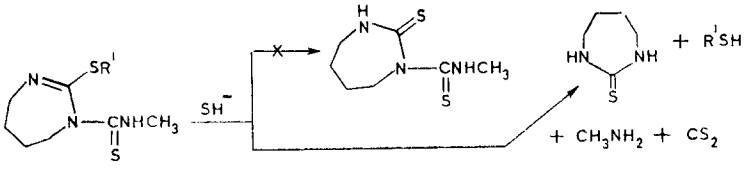
3.4. Reaction with Isothiocyanates. Cyclic thioureas and isothioureas [11, 92, 123-126] react with isothiocyanates to give derivatives involving the nitrogen atom. The character of the reaction products depends on the ring size and the nature of the isothiocyanate [125]. The reaction of 2-benzylthioimidazoline with isothiocyanates leads to N-thiocarbamoyl derivatives. The corresponding imidazolidine-2-thiones are readily formed by the action of an alkali metal hydrosulfide on thiocarbamoylimidazoline; this indicates the weakness of the C-SR' bond in the five-membered ring:



The reaction of 2-benzylthio-3,4,5,6-tetrahydropyrimidine with isothiocyanates leads to pyrimido[1,2-a][1,3,5]triazine XLIV. Depending on the nature of the isothiocyanate, seven-membered isothioureas give different reaction products: N-thiocarbamylation product XLV is formed with methyl isothiocyanate; phenyl isothiocyanate and aromatic isothiocyanates that contain electron-acceptor substituents in the ring give 1,3-diazepino[1,2-a][1,3,5]triazine derivatives XLVI; as in the case of the six-membered ring, p-dimethylaminophenyl isothiocyanate does not undergo the reaction.



The C–SR' bond in the seven-membered ring is much stronger than in the five-membered ring, and N-methylthiocarbamoylperhydrodiazepine-2-thione cannot be obtained by the action of a hydrosulfide [125].



On the basis of his research, D'Angeli [125] concludes that five- and seven-membered rings have similar reactivities.

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SYNTHESIS OF ISOXAZOLINES FROM ARYLCYCLOPROPANES UNDER NITROSATION CONDITIONS

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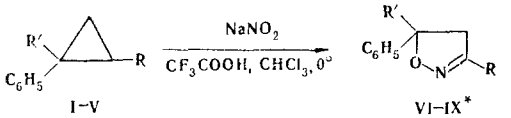
It is shown that the corresponding isoxazolines are formed in high yields when aryl-, diaryl-, and alkylarylcyclopropanes are treated with sodium nitrite in trifluoroacetic or trichloroacetic acid at 0°C. The reaction does not take place in acetic or chloroacetic acid. A possible mechanism for the formation of the isoxazolines is proposed. The latter were subjected to a mass-spectrometric study.

A study of the mutual effect of an aryl group and a small ring in arylcyclopropanes has given new information regarding the properties of the cyclopropane fragment, viz., its ability to enter into conjugation with unsaturated groupings [1, 2], the substantial dependence of the electron-donor properties on the nature of the aryl group [3, 4], its ability to undergo complexing [5], etc. From this point of view, a study of the reactivities of arylcyclopropanes under nitrosation conditions seemed of definite interest.

Previously, in a brief communication [6] we described the synthesis of R-5-phenyl- and 3,5-diphenylisoxazolines from arylcyclopropanes by treatment with sodium nitrite in trifluoroacetic acid. The formation of isoxazoles [7, 8], or isoxazolines [9] from arylcyclopropanes with certain structures was previously observed in the nitration of the latter under various conditions.

Isoxazolines are finding extensive application in organic synthesis [10, 11]. They can be used as starting compounds for the preparation of compounds that are inaccessible by other pathways. In this connection, the development of convenient methods for the preparation of isoxazolines is of undoubted interest.

In the present research we studied the behavior of aryl-, diaryl-, and arylalkylcyclopropanes (I-V) upon treatment with sodium nitrite in trifluoroacetic and trichloroacetic acids. As the subjects of our study we selected phenyl-, 1-methyl-2-phenyl-, cis-1,2-diphenyl-, trans-1,2-diphenyl-, and 1-methyl-1-phenylcyclopropanes (I-V). The reaction of these compounds with sodium nitrite in a mixture of trifluoroacetic acid and chloroform leads to the production of the corresponding isoxazolines in high yields:



I-V VI-IX*

I R=R'=H; II R=CH$_3$, R'=H; cis-III, trans-IV R=C$_6$H$_5$, R'=H; V R=H, R'=CH$_3$

*Compounds III and IV form the same compound, viz., VIII.

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