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## Synthesis of Aliphatic Bis(Thioureas)

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# Synthesis of Aliphatic Bis(Thioureas)

Donald G. McEwen, IV

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Honors Research  
and  
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at  
Illinois Wesleyan University  
1991

Approval Page

Research Honors

**SYNTHESIS OF ALIPHATIC BIS(THIOUREAS)**

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## Abstract

The synthesis of aliphatic bifunctional thioureas have been attempted using several nucleophilic displacement reactions. The first method involved treatment of an aliphatic diamine with ammonium thiocyanate, under two different sets of reaction conditions. The first set of reaction conditions utilized water as the solvent, while second employed acetone as the solvent. Both of the reactions utilizing 1,2-ethylenediamine and ammonium thiocyanate did not afford the desired bis(thioureas). In particular, the crystalline solid obtained from the reaction carried out in water was  $57.8 \pm 0.05$  % thiocyanate by mass.

The second nucleophilic addition method involved the treatment of both 1,2-ethylenediamine and 1,6-hexanediamine diamine with silicon tetraisothiocyanate in anhydrous benzene. The product from the reaction of 1,6-hexanediamine with silicon tetraisothiocyanate in anhydrous benzene was found to be  $40.3 \pm 2.07$  % thiocyanate by mass.

The third set of reaction conditions involved treatment of 1,6-hexanediamine with silver thiocyanate in concentrated ammonium hydroxide. As a result of the presence characteristic thiocyanate IR absorbance peak at  $2100\text{ cm}^{-1}$  in the product, it was found to contain thiocyanate ions. It was concluded that the product was composed of mainly the 1,6-hexanediamine thiocyanate salts.

The final set of reaction conditions involved treatment of 1,6-hexanediamine with silver thiocyanate and thiourea, in concentrated ammonium hydroxide. Upon analysis of the resulting reaction mixtures, it was determined that each fraction contained no thiocyanate anion or starting thiourea. Further work needs to be carried out in order to determine the products.

## Rationale

The oxidation of monofunctional thioureas to the corresponding thiourea-S,S,S-trioxides has been previously studied. It is known that these thiourea-S,S,S-trioxides are susceptible to nucleophilic attack, and in the presence of nucleophilic amino acid side chains, readily yield guanidino acids and  $\text{SO}_3^{2-}$ . The successful oxidation of the monofunctional thioureas to the corresponding thiourea-S,S,S-trioxides suggests that oxidation of a N,N'-substituted bis(thiourea) to the corresponding bifunctional S,S,S-trioxide should also be feasible. Consequently these homobifunctional molecules may then be vulnerable to nucleophilic attack at two sites, resulting in the formation of a common molecular "bridge" spanning the two nucleophiles. If the two attacking nucleophiles are the side chains of amino acid, such as lysine or cysteine, within a protein, the amino acids would then be crosslinked. Thus, it may be possible to synthesize a new group of variable-length protein crosslinking agents.

# I. Background

## 1.1: Protein Crosslinking Agents

In recent years, the covalent crosslinking agent has been recognized as an indispensable tool for enzymologists, structural biochemists, and biophysicists, as well as chemists. The resulting intra- or intermolecular bridges formed by these reagents can be utilized in a multitude of ways.<sup>1</sup> For example, crosslinking agents have been used to mark immunoglobulins with electron dense ferritin.<sup>2</sup> This marking process has allowed immunologists, with the aid of a transmission electron microscopy, to ascertain the precise location of immunologically-mediated responses. Furthermore, protein crosslinking agents of known lengths have been used to probe intramolecular residue distances, effectively acting as a molecular "meter stick."<sup>3,4</sup> This sort of spatial determination, in conjunction with X-ray crystallography data, has permitted the determination of both the tertiary and quaternary structure of various proteins. Finally, protein crosslinking agents have also been shown to confer increased stability to globular proteins.<sup>5,6</sup> For example, an intermolecular crosslink between the two defective  $\beta$ -chains of sickling hemoglobin has been shown to reduce the extent to which red blood cells sickle under reduced oxygen tension by strengthening the quaternary structure of the globular hemoglobin molecule.

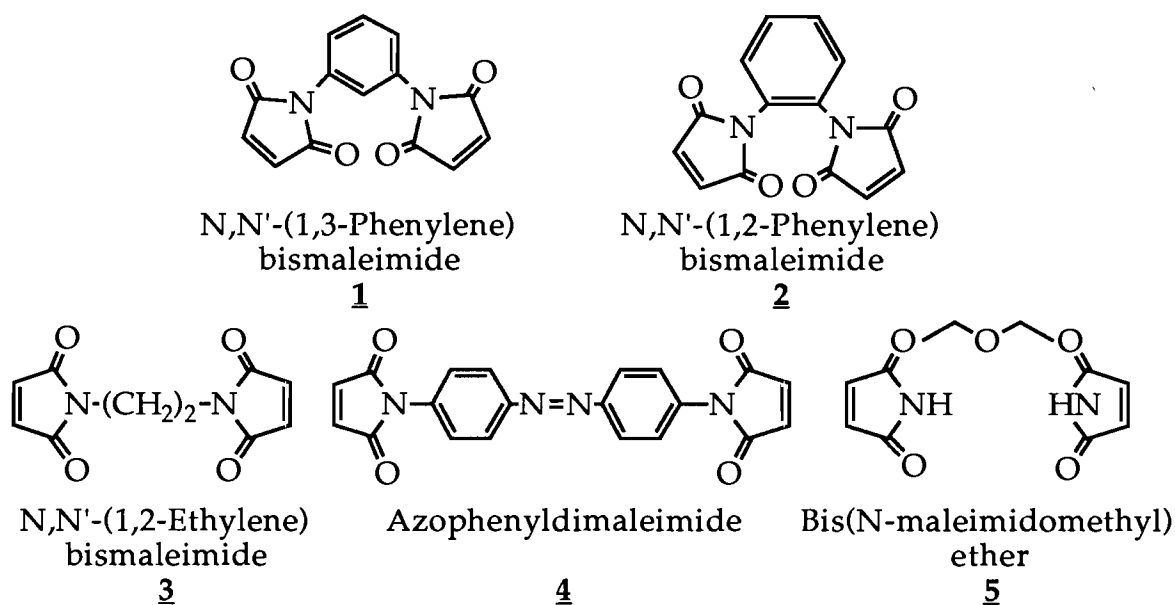
For a crosslinking agent to be of practical use, it must possess several key characteristics. First, the bifunctional agent must be reasonably specific for a distinct group (or groups) within a protein molecule. Second, a reaction of the crosslinking agent with the target molecule must result in a sufficiently stable covalent bond that decomposition is prevented. Third, if

the crosslinking agent is to be used in molecular mapping, it should also be readily identifiable upon sequencing of the polypeptide chain. The reagent should also be readily removeable, so that the protein may also regain its nascent activity. Finally, these crosslinking agents should be readily available in reasonable purity. Without these conditions, a crosslinking agent would be of no practical use, due to its lack of reactivity and specificity.

Although the number of known crosslinking agents is numerous, most of these reagents can be categorized into a smaller group of homobifunctionally substituted compounds.

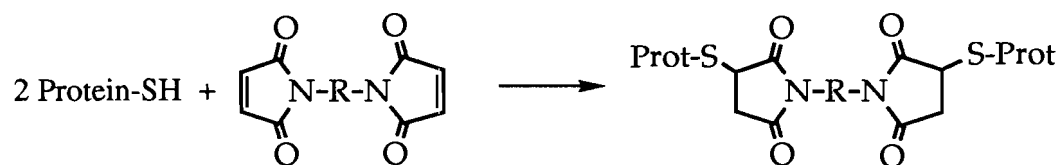
### 1.1.1: Bifunctional Maleimide Derivatives

Many bifunctional N,N'-substituted maleimides are known to possess crosslinking capabilities. Some of these can be seen **Figure 1**.



**Figure 1:** Known Maleimide Crosslinking Agents

These derivatives are valuable crosslinking agents because they react almost exclusively with sulfhydryl groups to form thioether linkages, under mild reaction conditions. (See **Figure 2**.)

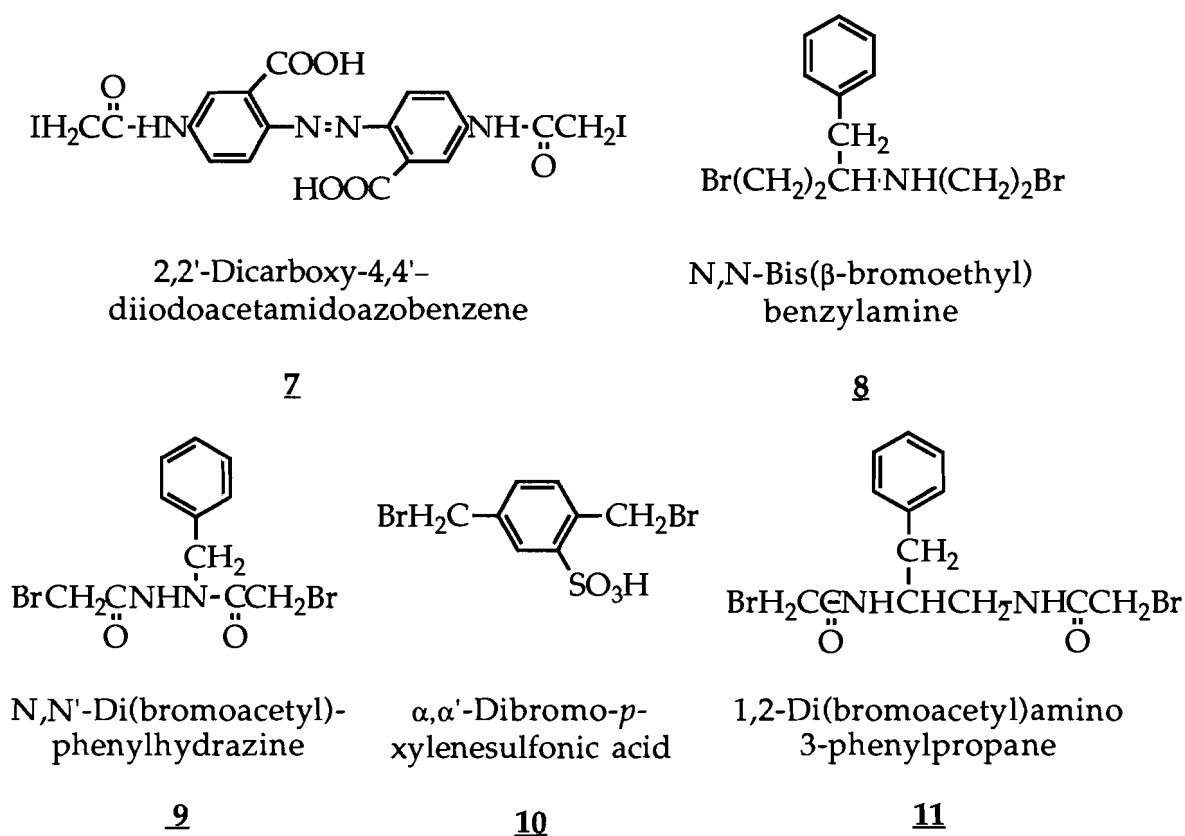


**Figure 2:** Maleimide Crosslinking Reaction

The specificity of these agents has been tested with bovine plasma albumin, which has only one sulfhydryl group per molecule. The albumin was found to dimerize upon reaction with N,N'-(1,2-ethylene)bismaleimide (3).<sup>7</sup> Moore and Ward<sup>7</sup> have also used this reagent to replace the disulfide crosslinkages in wool keratin. They observed a decrease in the rate of alkali, oxidative, and reductive chemical degradation, which they attributed to an increase in molecular stability. Additionally, Bis-(N-maleimidomethyl) ether (5), another known maleimide crosslinking agent, has been used to increase the stability of hemoglobin by crosslinking intermolecular thiol groups.<sup>8</sup>

### 1.1.2: Bifunctional Alkyl Halides

Bifunctional alkyl halides are alkylating agents that can be used to form covalent crosslinks. (See **Figure 3**.)



**Figure 3:** Bifunctional Alkyl Halide Crosslinking Agents

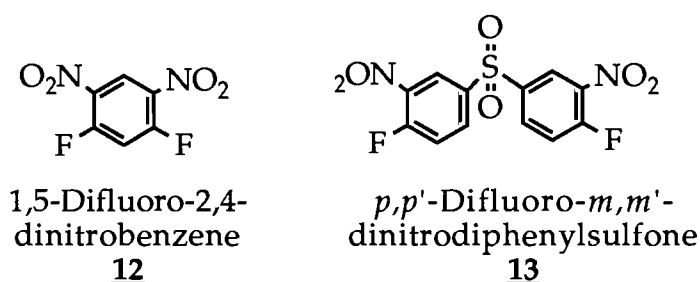
These compounds are capable of reacting with several different polypeptide nucleophiles (thiols, sulfides, imidazole rings, and amino groups), but certain nucleophiles are favored by different reaction conditions. If the reaction is carried out at a neutral to slightly alkaline pH, the thiol nucleophile is favored, while a higher pH favors the free amino groups as the nucleophiles. Thus, by controlling the specific reaction conditions at which the crosslink is formed, the specificity of the attacking nucleophile can be controlled.<sup>9</sup>

Researchers have utilized the specificity of several alkyl halide crosslinking agents in the determination of intermolecular residue distances in protein chains. Hiremath and Day<sup>10</sup> used  $\alpha,\alpha'$ -dibromo-*p*-xylenesulfonic

acid (**10**) to confirm the assigned intramolecular distances between Lys 96 and Lys 97, as well as between Lys 33 and Lys 116, of lysozyme. Furthermore, both *N,N*-bis( $\beta$ -bromoethyl)benzylamine (**8**) and *N,N'*-di(bromoacetyl)phenylhydrazine (**9**), which have known functional group distances of 6.5 Å and 7.3 Å, respectively, have also been used to probe the active site of chymotrypsin.<sup>9</sup>

### 1.1.3: Bifunctional Aryl Halides

Bifunctional aryl halides, which are similar to the alkyl halides, also possess crosslinking capabilities. (See **Figure 4**.)



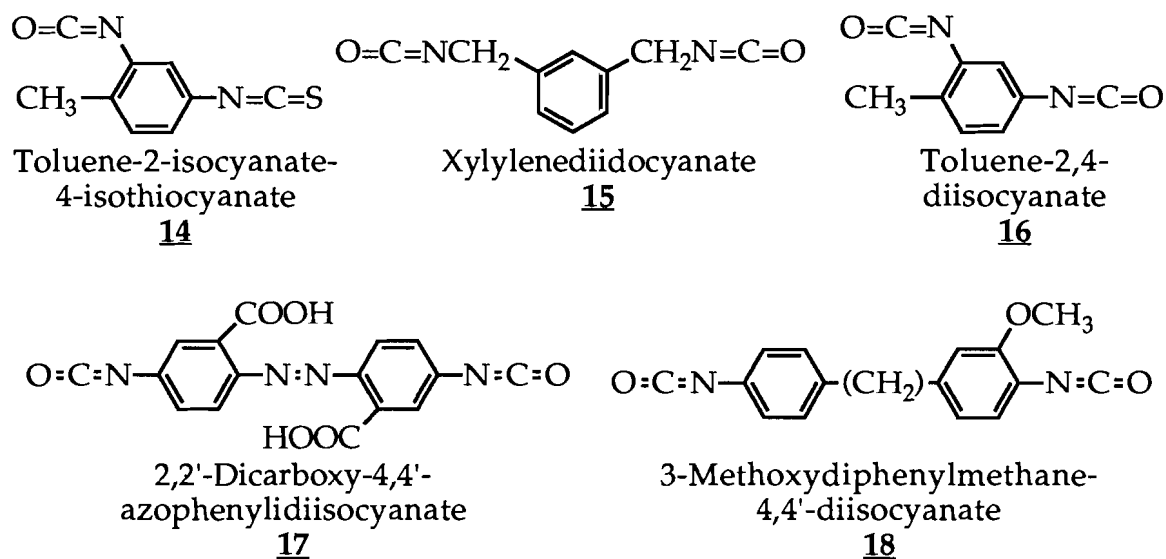
**Figure 4:** Bifunctional Aryl Halide Crosslinking Agents

These reagents react primarily with amino side chains and tyrosine phenolic groups, although they have also been known to react with thiol and imidazole groups. *p,p'*-Difluoro-*m,m'*-dinitrodiphenylsulfone (**13**) has been used to link ferritin to  $\gamma$ -globulins<sup>2</sup>, which allows the sites of immunoglobulin activity to be visualized with transmission electron microscopy. Difluorodinitrobenzene (**12**), having a maximum bridge span of 5-6 Å, has been used in the elucidation of the three-dimensional structure of ribonuclease A.<sup>11</sup> It has also been shown to form dinitrophenylene crosslinks between erythrocyte cell membrane proteins.<sup>5</sup> This particular crosslink has been shown to increase the resistance of red blood cell membranes to lysis.



### 1.1.4: Bifunctional Isocyanates

Diisocyanates are also known to react with amino acids in polypeptide chains.<sup>12</sup> Some of the more general diisocyanate proteins crosslinking agents can be seen in **Figure 5**.



**Figure 5:** Bifunctional Isocyanate Crosslinkers

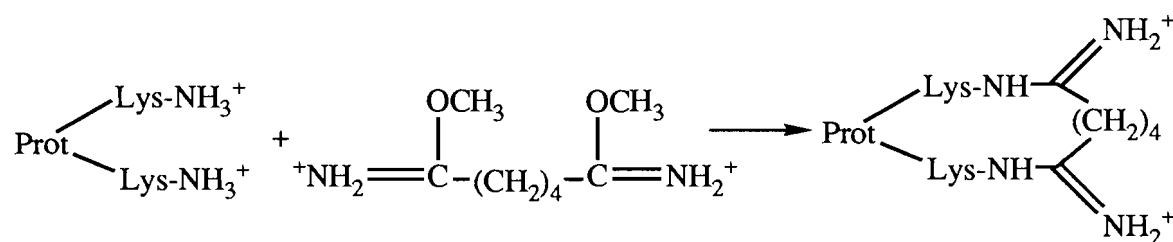
Isocyanates react with amines to form substituted ureas, and with alcohols to form urethanes. In aqueous solutions, they readily hydrolyse to the corresponding amine and carbon dioxide. These reactions have been useful in the elucidation of interresidue distances in myoglobins.<sup>13</sup> The crosslinks established were between Lys 145 and Lys 147, Lys 14 and Lys 34, Lys 56 and Lys 62, and between Lys 34 and Lys 47. These values were found to be consistent with interresidue distances deduced from X-ray crystallography.

### 1.1.5: Aromatic Sulfonyl Chlorides

Aromatic sulfonyl chloride crosslinking agents bridge proteins via acylation. Both phenol-2,4-disulfonyl chloride and  $\alpha$ -naphthol-2,4-disulfonyl chloride form stable sulfonamide linkages. These linkages can be broken with hydrobromic acid in glacial acetic acid, without degrading the parent polypeptide chain.<sup>9</sup>

### 1.1.6: Bifunctional Imidoesters

Many imidoester compounds have been synthesized, and have been observed to react with the  $\epsilon$ -amino group of lysine to form amidines. (See **Figure 6**.)



**Figure 6:** Reaction of the  $\epsilon$ -Amino Groups of Lysine with Imidoesters

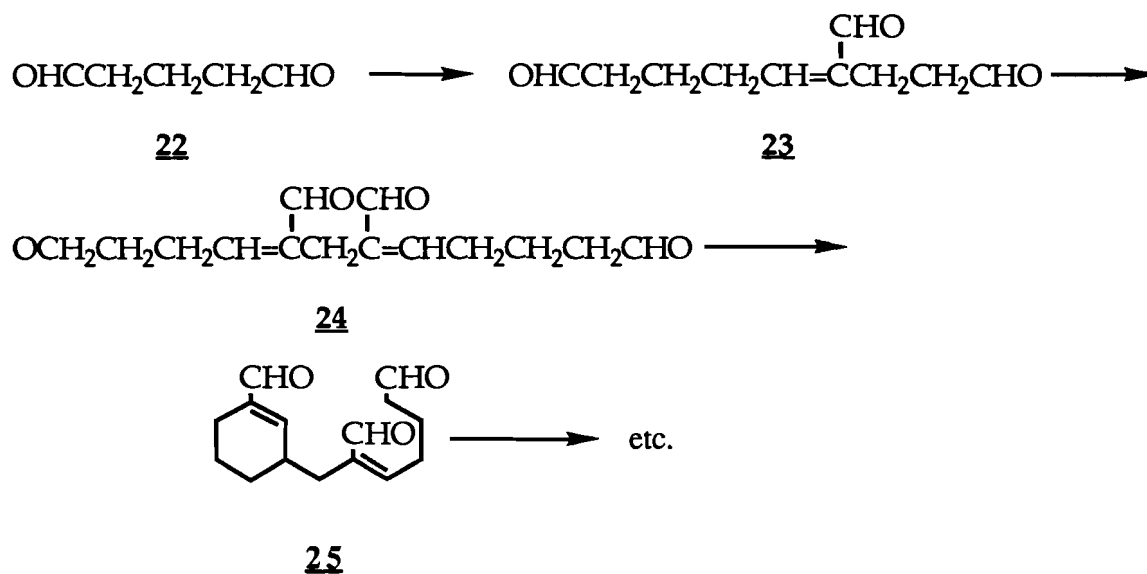
Dimethyl adipimidate (**20**) has been used in the determination of the topology of ribonucleases.<sup>14</sup>

### 1.1.7: Glutaric Dialdehyde

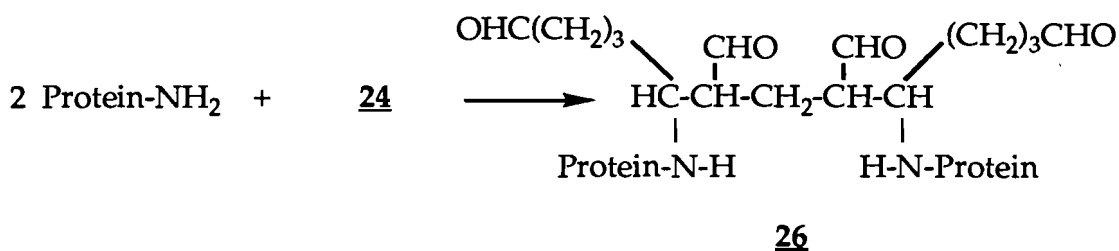
Although the specificity of this crosslinking agent is low, it is believed to readily undergo nucleophilic displacement by both sulfhydryl and amino groups. This molecule (**22**), which is able to form oligomers

(23, 24, 25) (via aldol condensation reactions), can form crosslinks of various lengths within the same protein molecule (26). (See Figure 7.)

1. Polymerization(aldol condensations)



2. Cross-linking reactions



**Figure 7:** Glutaric Dialdehyde Crosslinking Scheme

These polymeric chains are believed to form the covalent crosslinks (26), via a Schiff Base intermediate.<sup>9</sup> This type of reagent has been utilized in the sequencing of carboxypeptidase A.<sup>9</sup>

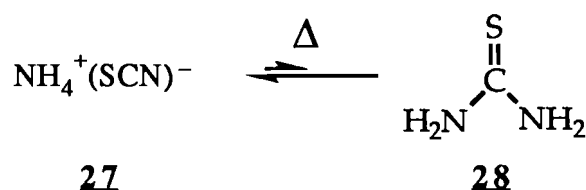
### 1.1.8: Transition Metal Crosslinking Agents

Transition metals, which are able to form multiligated complexes, have been shown to be useful protein crosslinking agents. Platinum, in particular, which forms a number of complexes at acceptable rates, has been used to crosslink proteins. Peerey and Kostic have selectively formed intramolecular crosslinks at thioester bonds in horse cytochrome *c* with  $\text{PtCl}_4^{2-}$ .<sup>1</sup>

## 1.2: Thiourea Synthesis

### 1.2.1: Thiourea Synthesis

Thiourea, the sulfur analog of urea, can be synthesized in a number of ways. First, thiourea itself can be obtained from a thermally induced isomeric shift of ammonium thiocyanate. (See Figure 8.)<sup>15</sup>

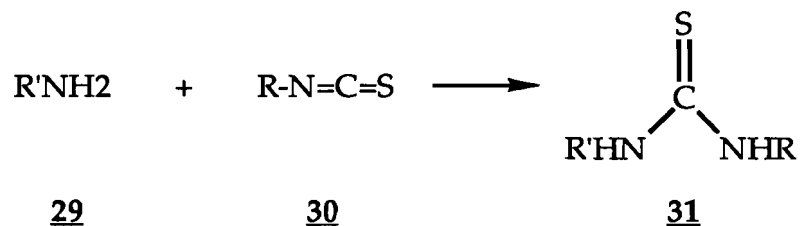


**Figure 8:** Transformation of Ammonium Thiocyanate into Thiourea

When ammonium thiocyanate (**27**) is rapidly heated to 160-170°C, an equilibrium between ammonium thiocyanate (**27**) and thiourea (**28**) is established. After pouring the mixture into cold water, a mixture of both thiourea and ammonium thiocyanate may be collected by evaporating the solvent. Thiourea, which is only slightly soluble in cold water, can then be separated from this reaction mixture.

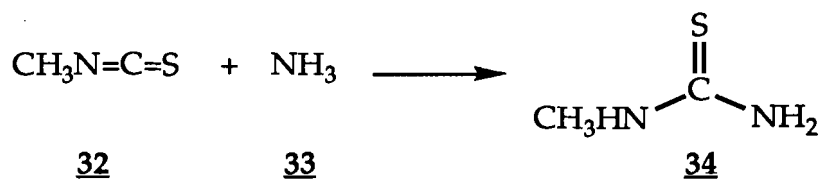
### 1.2.2: Synthesis of Thioureas from Mustard Oils

N-alkylated thioureas (**31**) may be synthesized by the nucleophilic attack of ammonia, primary amines, or secondary amines (**29**) upon mustard oils (**30**) (isothiocyanates).<sup>16</sup> (See **Figure 9**.)



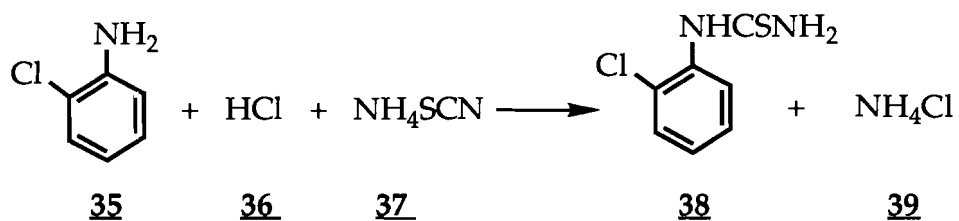
**Figure 9:** Synthesis of Thioureas from Mustard Oils

Moore and Crossley<sup>17</sup> have reported the synthesis of 1-methyl-2-thiourea (**34**) from methyl isothiocyanate (**32**) and ammonia (**33**). (See **Figure 10**.)



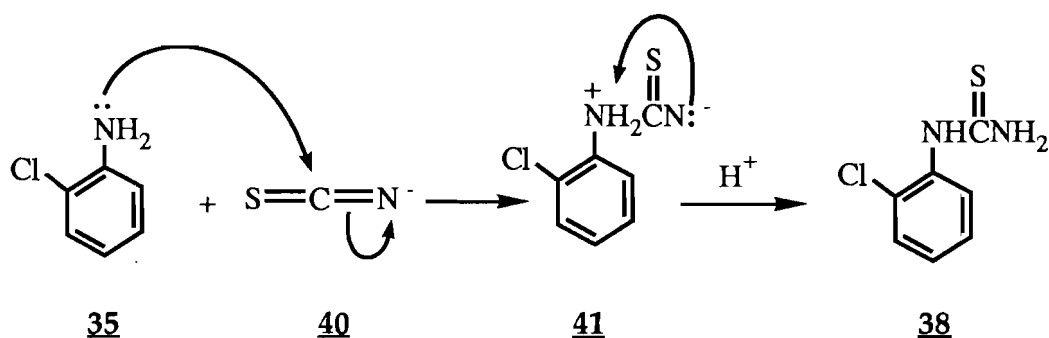
**Figure 10:** Synthesis of 1-Methyl-2-Thiourea

Furthermore, Kurzer has synthesized 1-(*o*-chlorophenyl)-2-thiourea (**38**) from ammonium thiocyanate (**37**) and the corresponding amine (**35**). (See **Figure 11**.)<sup>18</sup>



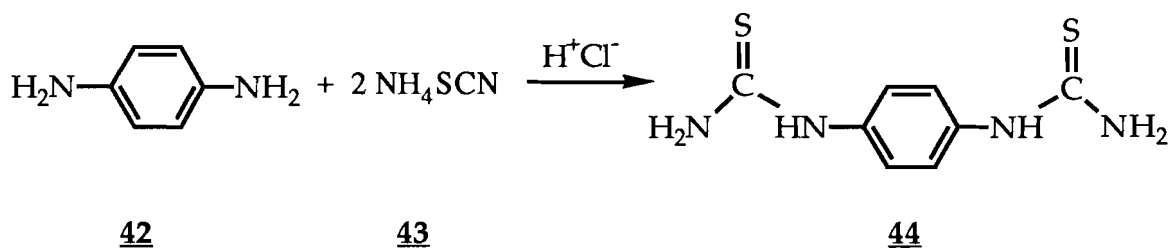
**Figure 11:** Synthesis of 1-(*o*-Chlorophenyl)-2-Thiourea

Both reaction mechanisms are believed to involve nucleophilic attack at the electrophilic carbon of the thiocyanate ion (**40**) by the amine (**35**). A hypothetical mechanism for this reaction can be seen in **Figure 12**.



**Figure 12:** Nucleophilic Displacement of Thiocyanate

Wolfe, Loo, and Arnold have also reported the synthesis of *p*-phenylene-bis(thiourea) (**44**) from 1,4-phenylenediamine (**42**) and ammonium thiocyanate (**43**).<sup>19</sup>(See **Figure 13**.)



**Figure 13:** Synthesis of *p*-Phenylene-bis(Thiourea)

### 1.2.2.1: Isothiocyanate Synthesis with Thioacyl Chlorides

Isothiocyanates are commonly synthesized from primary or secondary amines and a thioacyl chloride, such as thiophosgene.<sup>20</sup> Ozaka<sup>21</sup> and Twitchell<sup>22</sup> have reported the synthesis of many isocyanates from phosgene, and March<sup>23</sup> has noted that the same type of reaction can be carried out by thiophosgene, to form the corresponding isothiocyanates. Frank and Smith,<sup>24</sup> using a combination of both methods, have reported the synthesis of N-phenylthiourea (**52**) from ammonium thiocyanate (**45**) and benzoyl chloride (**46**). (See Figure 14.)

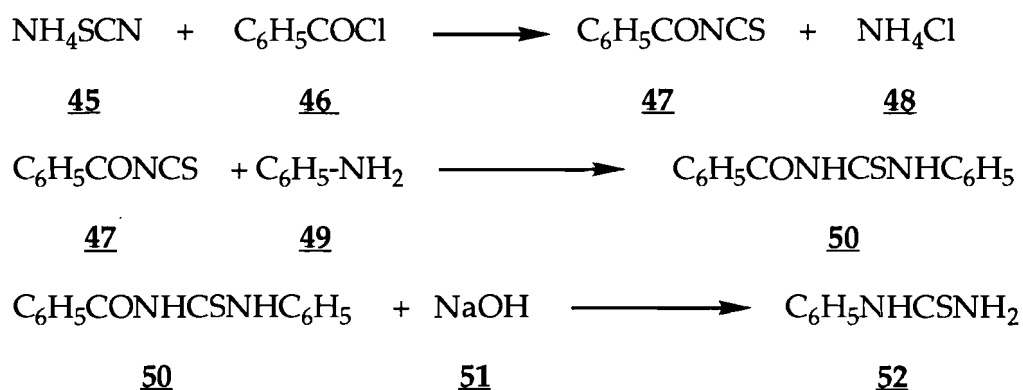


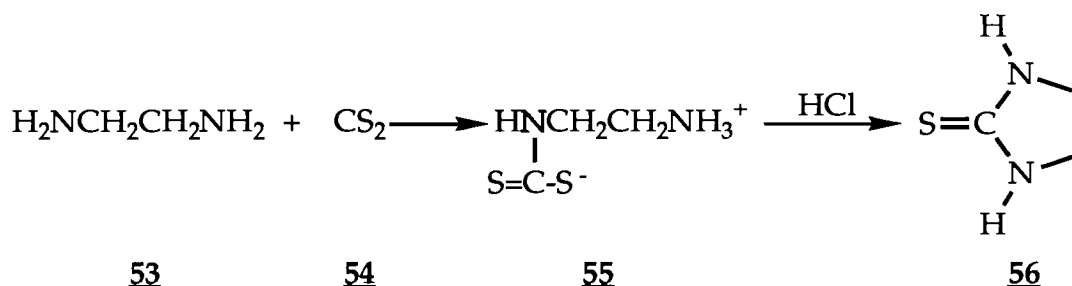
Figure 14: Synthesis of N-Phenylthiourea

Benzoyl chloride (**46**) reacts with ammonium thiocyanate (**45**) to form benzoyl isocyanate (**47**). Upon treatment of the isocyanate with aniline (**37**) N-benzoyl-N'-phenylthiourea is obtained (**50**). This compound can then be hydrolyzed with sodium hydroxide (**51**) to form the final thiourea (**52**).

### 1.2.2.2: Isothiocyanate Synthesis with Carbon Disulfide

Carbon disulfide (**54**) has also been shown to form isothiocyanate compounds.<sup>23</sup> For example, carbon disulfide (**54**) reacts with ethylene

diamine (**53**) to form the alkylammonium salt of the alkyldithiocarbamate (**55**). (See **Figure 15**.)



**Figure 15:** Synthesis of Ethylenethiourea

Under acidic conditions, these salts (**55**) undergo decomposition to yield the corresponding thioureas (**56**) and hydrogen sulfide. Aromatic thioureas have also been synthesized from carbon disulfide and primary aromatic amines.<sup>20</sup>

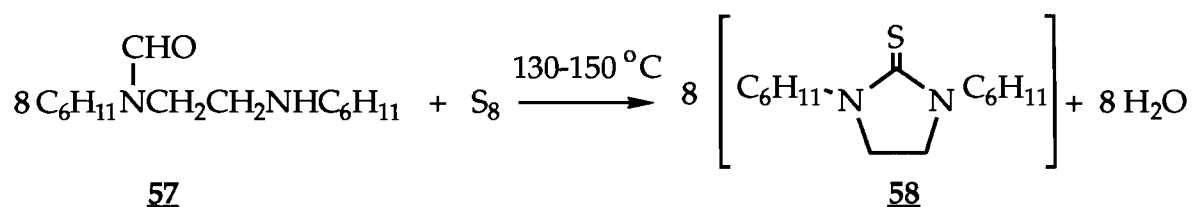
### 1.2.3: Thiourea Synthesis from Silicon(IV) Tetraisothiocyanate

Silicon(IV)tetraisothiocyanate has been reported to react with primary and secondary aliphatic, alicyclic, aralkyl, aromatic, or heterocyclic amines to form the corresponding N-mono- and N,N'-disubstituted thioureas.<sup>25</sup> The synthesis of Si(SCN)<sub>4</sub> from silicon(IV) chloride and ammonium thiocyanate and its subsequent reaction with both mono- and diamines to form mono- and N,N'-disubstituted thioureas has been reported by Neville and McGee<sup>25</sup> in yields of 97 to 100%.

### 1.2.4: Synthesis of Cyclic Thiourea from Elemental Sulfur

Cyclic thioureas have been directly synthesized from diamines and elemental sulfur. Both Zienty<sup>26</sup> and Thielke<sup>27</sup> have reported the synthesis of 1,3-dicyclohexylethylthiourea (**58**) from N-formyl-N,N'-dicyclohexylethylenediamine (**57**) and elemental sulfur. (See **Figure 16**.)

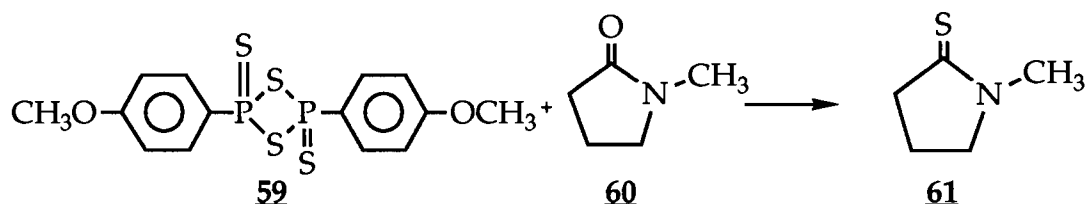




**Figure 16:** Synthesis of 1,3-Dicyclohexylethylthiourea

### 1.3: Thiating Agents

Finally, a number of thiating agents are known to convert the carbonyl groups of ketones, carboxamides, esters, thioesters, lactones, thiolactones, or imides into the corresponding thiocarbonyl groups. Russel, Tanikaya, and Talby<sup>28</sup> have reported that sodium disulfide, in the presence of sulfuric acid, can convert  $\alpha$ -hydroxy ketones into the sulfur analog. Thomsen and coworkers<sup>29</sup> have also reported the use of 2,4-bis-(4-methoxyphenyl)-1,3-dithia-2,4-diphosphetane (**59**), more commonly called Lawessons reagent, as a thiating agent in the conversion of N-methylpyrrolidone (**60**) into N-methylthiopyrrolidone (**61**). (See Figure 17)



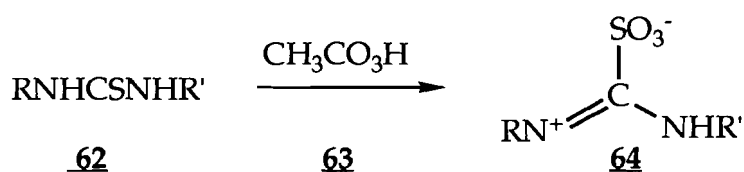
**Figure 17:** Thiation of N-Methylpyrrolidone

Some other common thiating agents are  $\text{PCl}_5/\text{Al}_2\text{S}_3/\text{Na}_2\text{SO}_4$ ,<sup>30</sup>  $\text{Na}_2\text{S}/\text{H}_2\text{SO}_4$ <sup>31</sup>, and  $\text{P}_2\text{S}_5/\text{NaHCO}_3$ <sup>32</sup>.

## 1.4: Synthesis of Thiourea-S,S,S-Trioxides

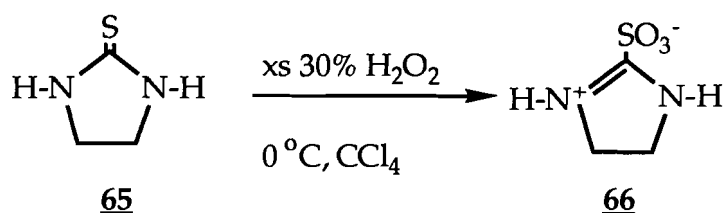
Thiourea-S,S,S-trioxides can be synthesized in a number of ways. It is possible to oxidize thiourea-S,S-dioxides to the sulfonic derivatives, but mixtures of the trioxide and trisubstituted formamidines are often obtained.<sup>33</sup> Spontaneous oxidation of N-substituted aminoiminomethanesulfinic acid to the corresponding sulfonic acid, at 37 °C, has also been reported by Walter.<sup>34</sup>

Thiourea-S,S,S-trioxides can also be readily obtained by the direct oxidation of the parent thioureas. Walter<sup>34</sup> reported the synthesis of the S,S,S-trioxides from the corresponding thioureas and 4-5 molar equivalents of peracetic acid at a temperature near -10 °C. (See **Figure 18**.)



**Figure 18:** Thiourea Oxidation Reaction

Marshall and Singh<sup>35</sup> have reported the oxidation of ethylene thiourea (**65**), with excess hydrogen peroxide in carbon tetrachloride, to the corresponding thiourea-S,S,S-trioxide (**66**) at 0 °C. (See **Figure 19**.)



**Figure 19:** Oxidation of Ethylene Thiourea

Both Miller<sup>36</sup> and Bischoff<sup>37</sup> reported a procedure for the synthesis of thiourea-S,S,S-trioxides, which involves the treatment of the starting thiourea with a freshly prepared peracetic acid solution. They have reported that specific reaction conditions are important for optimum yields of the desired products. For example, methanol could be used as the solvent in the synthesis of aminoiminomethanesulfonic acid, but it was found that when N,N'-diphenylaminoiminomethanesulfonic acid (**67**) is synthesized using methanol as the solvent, decomposition to the bisanilinium salt occurs (**68**). (See Figure 20.)

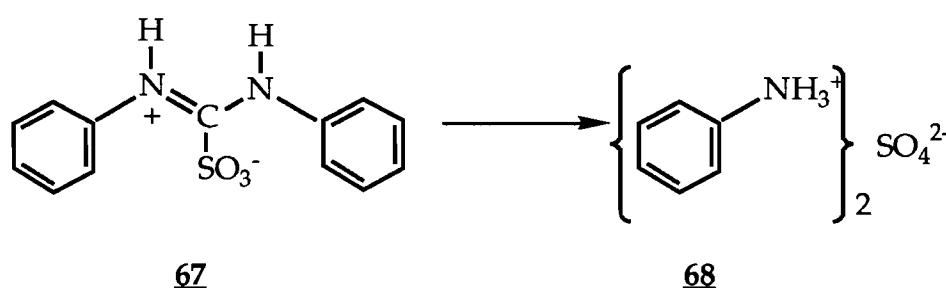
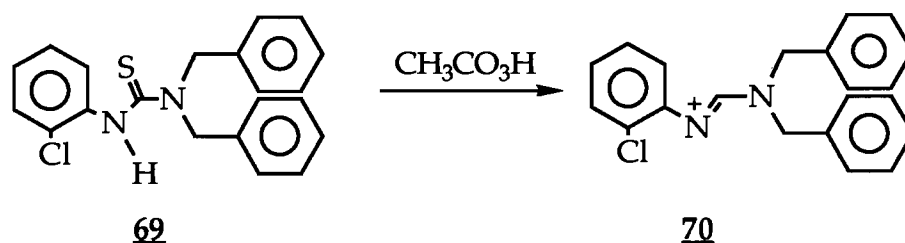


Figure 20: Bisanilinium Salt Formation

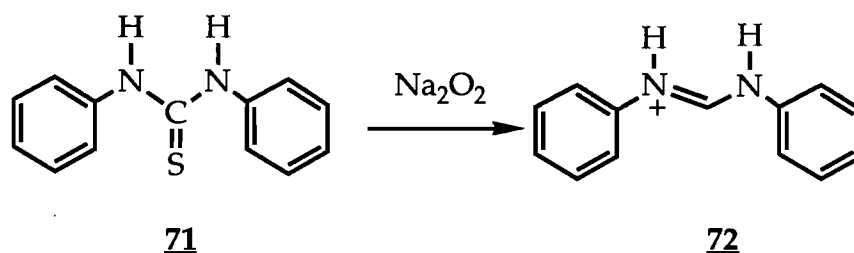
In addition to the solvent, thiourea-S,S,S-trioxides synthesis was also found to depend upon the temperature, the amount of oxidant, and rate of addition of the thiourea. Thus, to maximize yields, reactions condition must be carefully controlled, otherwise formamidines may be obtained.

In an attempt to oxidize 3,3-dibenzyl-1-(2-chlorophenyl)thiourea (**69**) with peracetic acid at a temperature below 10 ° C, Walter and Reuss<sup>38</sup> obtained only the trisubstituted formamidine (**70**). (See Figure 21.)



**Figure 21:** Trisubstituted Formamidine Formation

Shibasaki, Koizumi, and Matsumura<sup>39</sup>, upon attempting to oxidize N,N'-diphenylthiourea (**71**) with  $\text{Na}_2\text{O}_2$  at room temperature, obtained only the N,N'-diphenylformamidine (**72**). (See **Figure 22**.)

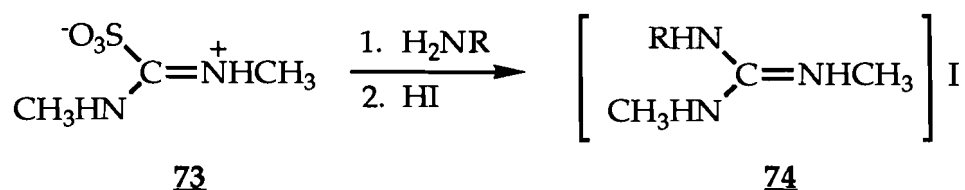


**Figure 22:** N,N'-Diphenylformamidine Formation

## 1.5: Synthesis of Guanidines and Guanidino Acids

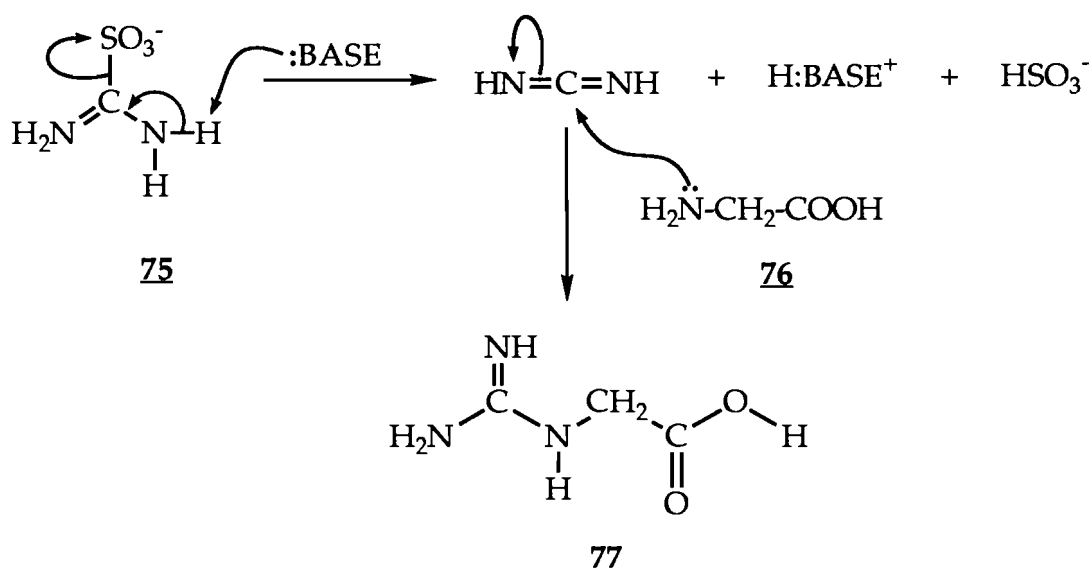
The reaction of amines with S-alkylisothiuronium salt is a common method used to synthesize guanidines.<sup>40</sup> This reaction also produces methyl mercaptan, a known noxious and toxic gas. This product must be transformed into an environmentally safe product. Rasmussen has patented a method of guanidine synthesis from carbodiimides,<sup>41</sup> while Bedereck and Bedereck have reported the synthesis of guanidines from chloroformamidines.<sup>42</sup> Both methods utilize starting materials that are corrosive and toxic and these methods have limited practical use for small

scale syntheses. Alhede and Gelting have patented the synthesis of guanidinium iodides (**74**) from N,N'-dimethylaminoiminomethane-sulfonic acids (**73**).<sup>43</sup> This can be seen in **Figure 23**.



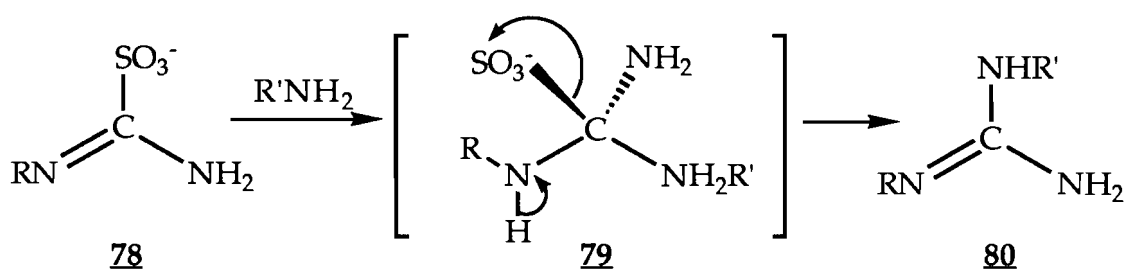
**Figure 23:** Synthesis of Guanidinium Iodides

Brand and Brand<sup>44</sup> have reported a similar synthesis of N-(aminoiminomethyl)glycine (glycocytamine) from thiourea, 1-bromoethane, and glycine, whereas Walter<sup>33</sup> has synthesized glycocytamine (**77**) from the reaction of formamidinesulfinic acid with glycine under basic conditions. Schmidt and Giesselmann<sup>45</sup> proposed a mechanism to account for the formation of this product. The first step of the mechanism involves the oxidation of formamidinesulfinic acid (**75**) to the corresponding sulfonic acid. The sulfonic acid is then attacked by an amine nucleophile (**76**) followed by the loss of the  $\text{SO}_3^{2-}$  moiety, which is a good leaving group. (See **Figure 24**.)



**Figure 24:** Mechanism Proposed For The Formation Guanidines

Furthermore, Maryanoff and co-workers have reported that guanidines can be directly synthesized from substituted amines and thiourea-S,S,S-trioxides.<sup>46</sup> They suggested that an addition/elimination mechanism was favored over mechanism involving a carbodiimide intermediate, and proposed that the amine nucleophile adds to the aminoiminomethanesulfonic acid (**78**) to form a tetrahedral intermediate (**79**), which then collapses to form the guanidine (**80**). (See **Figure 25**)



**Figure 25:** Addition/Elimination Reaction Mechanism

Miller<sup>36</sup> and Bischoff<sup>37</sup> reported the synthesis of guanidino acids from the reaction of thiourea-*S,S,S*-trioxides and amino acids. This reaction is believed to take place via the same type of nucleophilic displacement as that proposed by Maryanoff and coworkers. (See **Figure 25.**)

## 1.6: Objectives

The goals of this research were the synthesis and characterization of bifunctional thioureas from the corresponding diamines: 1,2-ethylene-diamine and 1,6-hexanediamine.



## II. Results and Discussion

**Tables 1** gives the properties of both the reaction mixtures obtained from 1,2-ethylenediamine and ammonium thiocyanate, using both water and acetone as solvents.

**Table 1:** Properties of Products From Ethylenediamine/ Ammonium Thiocyanate Reactions

| Starting Diamine   | Reaction Conditions                                       | M.P.(°C) | Lit. M.P.(°C)<br>47 | IR Bands                               | Mean % SCN <sup>-</sup> by Mass (± SD) |
|--|---|----------|---------------------|--|--|
| 1,2-Ethylene-diamine   | NH <sub>4</sub> SCN in H <sub>2</sub> O                   | 124-6d   | 202                 | 3000b, 2020s, 1500w, 1400m, 1050m      | 57.75±0.05 (12.8)                      |
| 1,2-Ethylene-diamine   | NH <sub>4</sub> SCN in (CH <sub>3</sub> ) <sub>2</sub> CO | 130-1    | 202                 | 2980b, 2020s, 1480m, 1050m, 790w, 470w | -----                                  |
| <b>Note:</b> d indicated decomposition, whereas s denotes sublimation. |   |          |                     |  |  |

No conclusions can be made about the presence of ethylene-1,2-bis(thiourea) (EBT) in any of the reaction mixtures. In the first attempted synthesized of EBT, water was employed as the solvent. This procedure involved refluxing 1,2-ethylenediamine and ammonium thiocyanate for three hours, followed by concentration of the reaction mixture to a residual volume one half of the initial volume. A yellow crystalline solid, which had a melting point of 110-5 °C, was obtained from this procedure. Recrystallization using methanol/ether afforded a purified product that melted between 124-6d °C. Examination of this product via infrared

spectroscopy revealed a characteristic N-H stretching band ( $\sim 3000\text{ cm}^{-1}$ ), a strong thiocyanate absorbance band ( $2020\text{ cm}^{-1}$ ), and a thiocarbonyl absorbance band ( $1050\text{ cm}^{-1}$ ).

Thin layer chromatography (TLC) was performed upon the purified product against 1,2-ethylenediamine and ammonium thiocyanate standards. (See Table 2.)

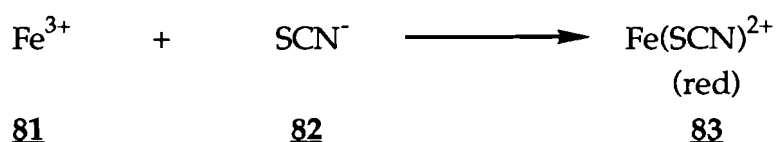
**Table 2:** TLC Separation of Reaction Mixtures

| Compound                       | R <sub>f</sub> Values            |                                 |
|--------------------------------|----------------------------------|---------------------------------|
|                                | Ethyl Acetate:<br>Methanol (1:1) | Ethyl Acetate:<br>Ethanol (1:1) |
| 1,2-ethylenediamine            | 0.1                              | 0.14                            |
| ammonium thiocyanate           | 0.60                             | 0.76                            |
| 1,2-Ethylene-<br>bis(thiourea) | 2 spots: a. 0.15<br>b. 0.58      | 2 spots: a. 0.17<br>b. 0.79     |

Separation was not accomplished with petroleum ether, toluene or ethyl acetate, but the unknown was separated into two separate spots with an ethyl acetate/methanol developing solution, as well as with a ethyl acetate/ethanol eluant. Upon visualization with FCNP reagent and/or UV light, the R<sub>f</sub> factors of the two spots were 0.15 and 0.58, respectively, in a 1:1 ratio of ethyl acetate and methanol ([EA:M]), and 0.17 and 0.79, respectively, in a 1:1 mixture of ethyl acetate and ethanol ([EA:E]). The R<sub>f</sub> factors for 1,2-ethylenediamine and ammonium thiocyanate standards were 0.1 and 0.60, respectively, in the [EA:M] developing solution. When the TLC was run in the [EA:M] developing solution, the diamine and ammonium salt had R<sub>f</sub> values of 0.1 and 0.6, respectively. As a result of the similarity between R<sub>f</sub> values of the unknown and known standards, it was concluded that the

desired bis(thiourea) was either not present, or present in such minute quantities, that its detection was impossible.

Upon testing the sample for the presence of the thiocyanate anion with aqueous ferric chloride, the solution developed a blood-red color. This color is characteristic of the  $\text{Fe}(\text{SCN})^{2+}$  complex;<sup>48</sup> thus, verifying the presence of the thiocyanate anion in the reaction mixture. (**Figure 26.**)



**Figure 26:** Ferric Complexing Reaction

When a sample was purified by recrystallization from methanol/ether, it was found to 12.8% thiocyanate by mass.

The Vollhard<sup>49</sup> titration method was used to quantitate the amount of thiocyanate ion in the crude sample. After several titrations, it was determined that thiocyanate ion constituted  $57.75 \pm 0.05$  % of the product from the reaction of 1,2-ethylenediamine with ammonium thiocyanate. This value is close to the theoretical value of 69.9 % expected for the bis(isothiocyanate) salt of 1,2-ethylenediamine. Assuming that the remainder of the crude sample was the bis(thiourea), this reaction afforded only a 4.4 % yield of the desired product. Further purification by recrystallization afforded a product whose composition was only 12.8 % thiocyanate by mass. It was concluded that the modified method of Wolfe, Loo, and Arnold did not favor the formation of the bis(thiourea). Thus, yields of EBT are likely to be insignificant, making this method not useful as a practical synthesis for bis(thioureas).

When acetone was used as the solvent for the reaction, similar results were obtained. The pink crystalline solid, obtained after recrystallization of the product from acetone, had a melting point of 130-1 °C, and IR absorbance bands (2980b, 2020s, 1050m) comparable to the product obtained previously from the reaction carried out in water. As a result of the similarities in melting points and IR absorbances, this product was thought to also be a mixture of the starting materials, 1,2-ethylenediamine and ammonium thiocyanate.

The synthesis of EBT was also attempted using a modification of the method proposed by Neville and McGee,<sup>25</sup> and the results can be found in Table 3.

**Table 3:** Properties of Products from Modified Neville and McGee Procedure

| Starting Diamine     | Reaction Conditions                 | M.P. (°C) | Lit. M.P. (°C) | IR Bands                               | Mean % SCN <sup>-</sup> by Mass(± SD) |
|----------------------|-------------------------------------|-----------|----------------|--|---------------------------------------|
| 1,2-Ethylene-diamine | Si(NCS) <sub>4</sub> in dry benzene | 200-2     | 202            | 3000b, 2010s, 1400s, 1020s, 700m, 490m | 65.2 <sup>50</sup>                    |
| 1,6-Hexane-diamine   | Si(NCS) <sub>4</sub> in dry benzene | dec.      | -----          | 3000b, 2010s, 1600m, 1450, 1100b       | 40.3 ± 2.1                            |

The reaction of silicon tetrachloride with ammonium thiocyanate was carried out in sodium dried benzene to avoid hydrolysis of the product. Silicon tetraisothiocyanate was prepared but was never isolated and characterized. This reaction mixture, when treated with 1,2-ethylenediamine in anhydrous benzene, resulted in the formation of a yellow solid, which had a melting point range of 200-2 °C. This melting point range corresponds exactly to the

melting point range reported by Neville and McGee for the ethylene-1,2-bis(thiourea).<sup>25</sup> This product was not appreciably soluble in acetone, petroleum ether, methanol, ethanol, water, chloroform, or hexanes, and it showed peaks in its infrared spectrum at 3000b, 2010s 1400s, 1020s, 700m, and 490m  $\text{cm}^{-1}$ . As a result of the strong thiocyanate peak at 2010  $\text{cm}^{-1}$ , it was concluded that this product was not the desired bis(thiourea).

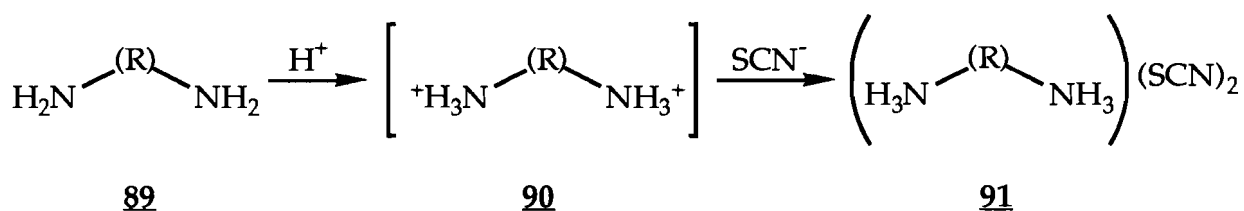
It is likely that the starting diamine, under the given reaction conditions, formed the corresponding thiocyanate salts. Neville and McGee, in characterization of EBT, stated that their product was correctly analyzed for nitrogen, but this evidence would not distinguish the dithiocyanate salt from the thiourea because they are isomeric. Given in Table 4 are the percent compositions for both the EBT and the bithiocyanate salt of the diamine.

**Table 4: Elemental Percent Composition**

| Compound                            | % Carbon | % Hydrogen | % Nitrogen | % Sulfur |
|-------------------------------------|----------|------------|------------|----------|
| Ethylene-1,2-bis(thiourea)          | 27       | 6          | 31         | 36       |
| 1,2-Ethylene-diammonium thiocyanate | 27       | 6          | 31         | 36       |

Thus, Neville and McGee<sup>25</sup> did not rule out the possibility that their product may have been the bis(thiocyanate) salt of 1,2-ethylenediamine.

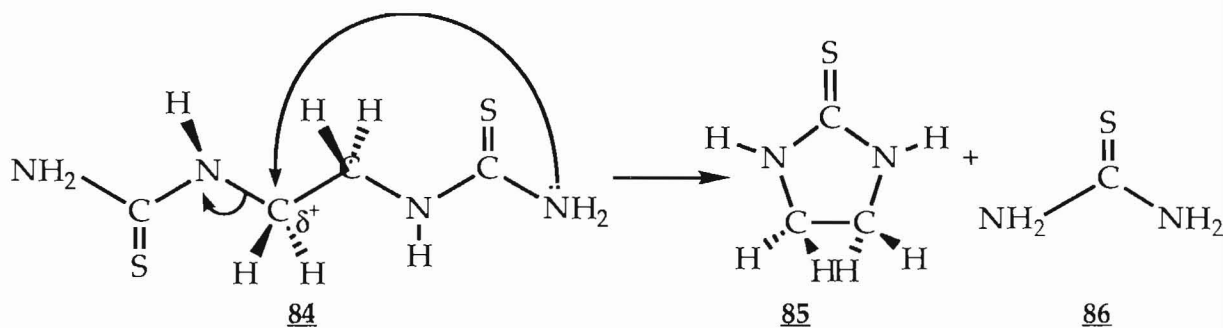
Salt formation would result from the protonation of the primary amino groups of the diamine (**90**), whose positive charge may form an ionic bond with the thiocyanate anion resulting in the formation of the bis(thiocyanate) salt (**91**). (See Figure 27.)



**Figure 27: Bis(thiocyanate) Salt Formation**

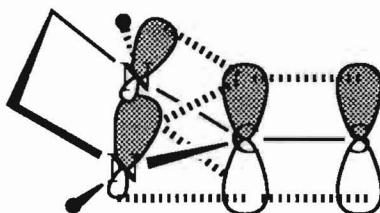
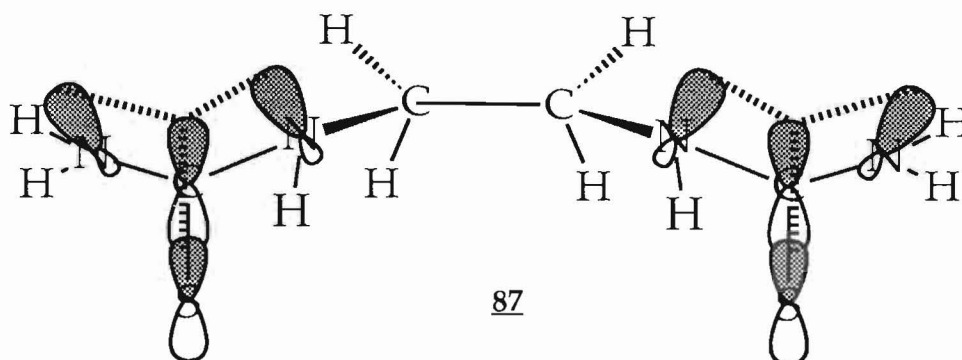
Evidence supporting this hypothesis was provided when Webb<sup>46</sup> attempted syntheses of bis(thioureas) following the method outlined by Neville and McGee. Using the Vollhard titration, Webb determined that the product, which had the same melting point range as that obtained by Neville and McGee, as well as obtained in this study; was 65.2 % thiocyanate by mass. This value, which is close to the expected value of 69.9 % for the bis(thiocyanate) salt, suggests that this methodology favors the formation of the thiocyanate salts, and not the desired thiourea.

Although these results seem to suggest the bis(thiocyanate) salt formation, other side reactions such as polymerization and intramolecular cyclization may have occurred. Nitrogen, having a greater affinity for electrons, can induce a slightly positive charge on the neighboring carbon. The lone pair of electrons of the amino group could then attack the electrophilic carbon center, displacing the thiourea substituent (**86**). (See **Figure 28.**)



**Figure 28:** Cyclization of Ethylenethiourea

This would result in the formation of thiourea and *N,N'*-ethylene-1,2-cyclothiourea [lit.<sup>51</sup> mp 202 °C], which is the same melting point found for the product in the attempted synthesis of EBT. Although no other evidence was found which would support this hypothesis, if one compares the  $\pi$ -electron distribution patterns of EBT (87), and *N,N'*ethylene-1,2-cyclothiourea (88) in Figure 29, one can see that both compounds contain the "Y"-shaped delocalized  $\pi$  orbitals.

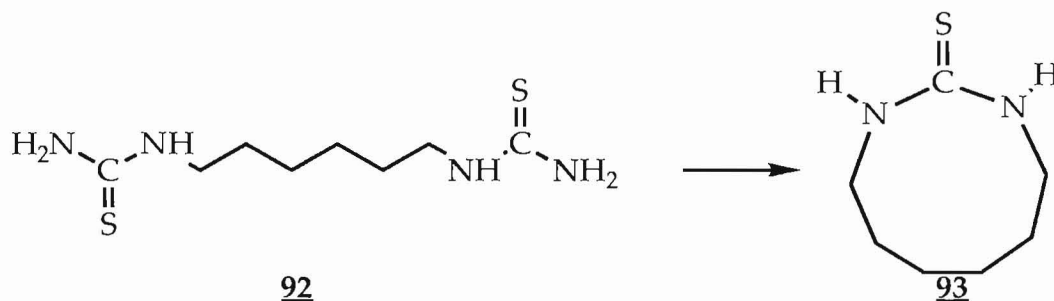


**88**

**Figure 29:**  $\pi$ -Orbital Systems

Additional stabilization of N,N'ethylene-1,2-cyclothiourea may be the result of the formation of the stable five membered ring.

All subsequent experiments, in order to avoid possible intramolecular cyclization, utilized 1,6-hexanediamine. The intramolecular cyclization of hexane-1,6-bis(thiourea) (**92**) would be energetically unfavorable due to the formation of the 9-membered ring (**93**). (See **Figure 30**.)



**Figure 30:** 1,6-Hexanebis(thiourea) Cyclization Reaction

In an attempt to prevent salt formation, different reaction conditions were employed, and the results can be found in **Table 5**.

**Table 5:** Reactions Utilizing Silver Thiocyanate

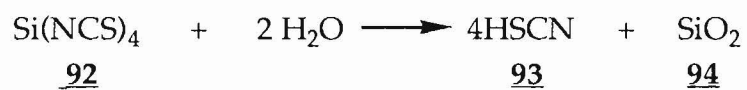
| Starting Diamine  | Reaction Conditions                            | M.P.(°C) | Lit.<br>M.P.(°C)<br>52 | IR Bands  |
|-------------------|--|----------|------------------------|---|
| 1,6-Hexanediamine | AgSCN<br>in<br>NH <sub>4</sub> OH              | 104-9d   | -----                  | 3500b, 2900w<br>2100s, 1400w,<br>1050b, 750m    |
| 1,6-Hexanediamine | AgSCN and<br>Thiourea in<br>NH <sub>4</sub> OH | 229s     | -----                  | 3100b, 2840b,<br>2000w, 1700m,<br>1540m, 1400b, |
|                   |  | 230s     | -----                  | 3000b, 2000wb,<br>1700mb, 1400sb,<br>700bw      |



When 1,6-hexanediamine ( $pK_a = 11.105$ ) was refluxed with silver thiocyanate in concentrated ammonium hydroxide ( $pK_a = 9.255$ ), a heterogeneous mixture of black and white solids formed upon cooling of the reaction mixture. This solid had a melting point of 104-9d °C, an IR spectrum with peaks at 3500b, 2900w, 2100s, 1400, 1050, and 750  $\text{cm}^{-1}$ , which smelled strongly of starting diamine. When treated with aqueous ferric chloride, the solution developed the characteristic deep blood-red color of the iron(III) thiocyanate complex. Based on the presence of thiocyanate, the peculiar diamine odor, and the characteristic thiocyanate peaks near 2100 and 1400  $\text{cm}^{-1}$ , it was concluded that no significant reaction had taken place, except the deposition of silver, which was probably the result of photoreduction of  $\text{Ag}^+$ .<sup>51</sup>

When the reaction was repeated, but this time with the addition of thiourea to the reaction mixture, and two compounds were isolated. One compound sublimed at 229 °C, and had the following IR peaks: 3100b, 2840b, 2000w, 1700m, 1540m, and 1400b  $\text{cm}^{-1}$ . The second product also sublimed, at 230 °C, and had corresponding IR peaks of 3000b, 2000wb, 1700mb, 1400sb, and 700bw  $\text{cm}^{-1}$ . From the IR and TLC data, it was determined that neither product contained thiocyanate or thiourea. No conclusions as to the nature of these products has been made at this time.

Finally, the preparation of hexane-1,6-bis(thiourea) in a one-pot synthesis from silicon tetrathioisocyanate and 1,6-hexanediamine was attempted with inconclusive results. The product, upon exposure to the air, yielded a yellow gel. This is consistent with the report of Neville and McGee,<sup>25</sup> who observed that silicon tetrathioisocyanate (**92**) readily hydrolyzes on contact with moisture to form silica gel (**94**) and thiocyanic acid (**93**). (See Figure 31.)

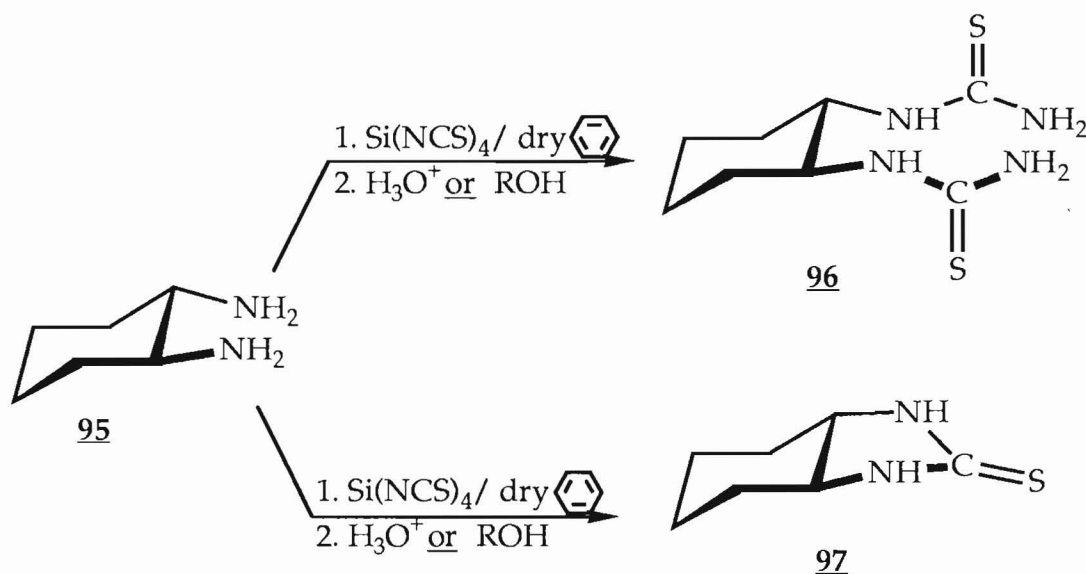


**Figure 31:** Hydrolysis of Silicon Tetraisothiocyanate

The thiocyanic acid (93), which is unstable, forms a yellow solid, which is the polymer of the free acid. It was concluded that the silicon tetraisothiocyanate hydrolyzed readily in the presence of water, and the polymer of the free acid was formed instead of the thiourea.

### III. Suggestions for Future Work

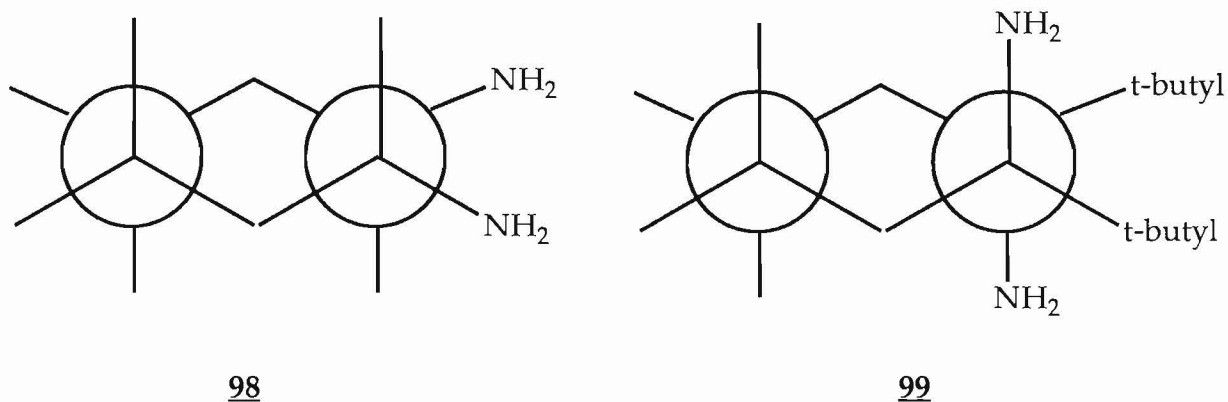
If a method of synthesis of bis(thiourea) can be found, one may further probe the question as to whether intramolecular cyclization of EBT may afford the five membered ring structure. In doing so, one might attempt to synthesize the bis(thiourea) (96) in a strained conformation. For example, *trans*-1,2-cyclohexanediamine could be used as the starting diamine. Although the amino groups would hold the ring in a chair conformation where both amino groups are equatorial (95), the formation of the five-membered ring might be energetically unfavored due to the rigidity of the cyclohexyl ring (97).



**Figure 32:** Strained Conformation Synthesis

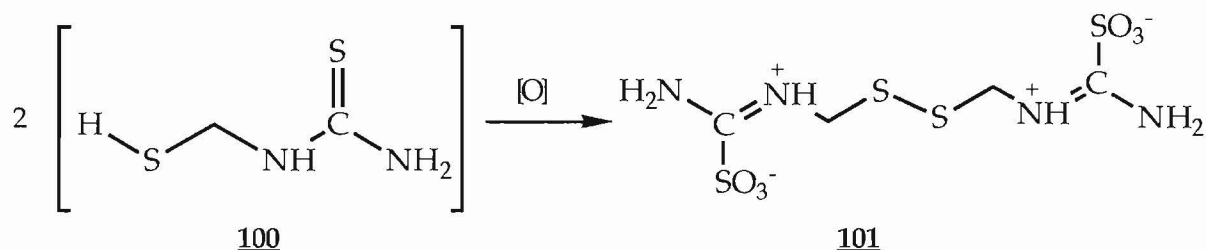
If the ring strain is insufficient (98), bulky substituents could then be added to the cyclohexyl ring structure in such a way that both the amino groups are held in the axial position (99). This in turn would prevent cyclization, while

maintaining the length of the crosslinking agent, just as if it was the *trans*-ethylene-1,2-bis(thiourea). (See **Figure 33**.)



**Figure 33:** Newman Projections of Starting Diamines

Another possible avenue of research could be in the production of monothioureas with sulfhydryl groups at one end (100). These compounds could be oxidized to form the disulfide linkages, as well as oxidizing the new compound to the desire S,S,S-trioxide (101). (See **Figure 34**.)



**Figure 34:** Disulfide-Bis(Thiourea) Crosslinker

This method would also allow for an easy way in which the disulfide crosslink may be reductively cleaved. Furthermore, if the corresponding ureas can be formed, such thiating agents as Lawessons' reagent<sup>29</sup> may be used to convert these ureas to the corresponding thioureas.

## IV. Experimental Procedures

### 4.1: Determination of Physical and Spectroscopic Properties

A "Mel-temp" capillary melting point apparatus was used to determine the uncorrected melting points, while infrared spectra were obtained on a Perkin Elmer 398 infrared spectrophotometer. All solid samples were analyzed in a potassium bromide pellet and liquids were analyzed as a thin film between salt plates. Reported band intensities are abbreviated as s, m, w, and b to specify strong, medium, weak, or broad peak absorbances, respectively.

### 4.2: Analysis of Reaction Mixtures

Thin layer chromatography was used to analyze reaction mixtures. TLC was performed on Whatman Silica Gel Plates (CAT No. 44 20 222), and spots were visualized with FCNP solution [1:1:1:3 ratio of 10% sodium hydroxide, 10% sodium nitroprusside, potassium ferrocyanide, and water] and/or ultraviolet light.<sup>53</sup>

### 4.3: Commercially Available Starting Materials

Ammonium thiocyanate was obtained as Baker's Analyzed reagent from J.T. Baker Chemical Company, and was used without further purification. Silicon tetrachloride was obtained from Aldrich Chemical Company, and was refrigerated prior to use. 1,2-Ethylenediamine was obtained from Aldrich Chemical Company, and was purified by distillation before use. 1,6-Hexanediamine was purchased from both Fisher Scientific and Eastman Kodak. The samples obtained from Fischer Scientific were used

without purification, but the 1,6-hexanediamine obtained from Eastman Kodak was purified by distillation prior to use: bp 198-199 °C [lit.<sup>49</sup> 204 °C]; IR 3200bm, 2900bm, 1570s, 1450m, 1370m, and 900m cm<sup>-1</sup>. Thiourea was obtained from Fisher Scientific, and was utilized without further purification.

Common solvents, such as acetone, ammonium hydroxide, ethyl acetate, hexanes, methanol, methylene chloride, and toluene were obtained from Fisher Scientific, whereas 95% ethanol was obtained from U.S. Industrial Chemicals. Benzene was purchased from Aldrich Chemical Company, and was dried with sodium metal prior to use.

Other chemical that were used included ferric nitrate and ferric chloride, which were obtained from Fisher Scientific. Silver nitrate was purchased from Spectrum Chemical Manufacturing Corporation, and potassium bromide was obtained from Mallinckrodt Chemical Company. Sodium nitroprusside was obtained from Merck and Company, while sodium ferrocyanide was obtained from J.T. Baker Chemical Company. These salts were used without additional purification.

## 4.4: Preparation of Compounds

### 4.4.1: Silicon Tetraisothiocyanate

A procedure modified from that outlined by Neville and McGee<sup>54</sup> was employed to prepare silicon tetraisothiocyanate. After refluxing silicon tetrachloride and ammonium thiocyanate for three hours, a white crystalline solid precipitated out of the benzene, but was not isolated due to the hygroscopic nature of the benzene-soluble product. The solution was then used as the stock silicon tetraisothiocyanate.

### 4.4.2: Silver Thiocyanate

Silver thiocyanate was prepared by following the procedure outlined by Neville and McGee.<sup>52</sup> A light grey precipitate was collected in almost quantitative yield: mp ~250 °C with decomposition; IR 3000b, 2100s, 1400w, and 510bw cm<sup>-1</sup>. The product was protected from light by wrapping it in foil.

#### 4.4.3: Ethylene-1,2-bis(thiourea)

Ethylene-1,2-bis(thiourea) was synthesized using a modification of the procedure reported by Wolfe, Loo, and Arnold.<sup>19</sup> Instead of using a dilute hydrochloric acid solution as the solvent, water or acetone was chosen as an alternate solvent. The reaction that was carried out in water afforded a yellow crystalline solid in 25% yield: mp 124-126 °C with decomposition; IR 3000b, 2020s, 1500w, 1400w, 3000b, 2020s, 1500w, 1400w, and 1050m cm<sup>-1</sup>; TLC R<sub>f1</sub> = 0.17 R<sub>f2</sub> = 0.79; % thiocyanate by mass 57.75%, as determined by the Vollhard titration. The sample was recrystallized twice from methanol and found to be 12.8% thiocyanate by mass. The reaction performed in acetone also yielded a similar mixture of products: mp 130-131°C; IR 2980b, 2020s 1480m, 1050m, 790w, and 470w cm<sup>-1</sup>.

An attempt was also made to synthesize the ethylene-1,2-bis(thiourea) following the procedure outlined by Neville and McGee<sup>25</sup>, with the exception of the addition of soluble silicon tetraisothiocyanate (See 4.4.1: Silicon Tetraisothiocyanate.). This process yielded a yellow product: mp 200-202 °C [lit.<sup>25</sup> 202 °C]; IR 3000b, 2010s, 1400s, 1020s, 700m, 490m cm<sup>-1</sup>.

#### 4.4.4: Synthesis of Hexane-1,6-bis(thiourea)

The synthesis of hexane-1,6-bis(thiourea) was attempted using the method of Neville and McGee<sup>25</sup>, except for the addition of silicon tetraisothiocyanate dissolved in benzene (see 4.4.2: Silicon Tetraisothiocyanate). A yellow residue, which gelled upon exposure to air, was collected: mp ~300 °C with decomposition; IR 3000b, 2010s,

1600m, 1450m, and 1100b  $\text{cm}^{-1}$ . This gummy solid was insoluble in methanol, ethanol, ethyl acetate, toluene, acetone, petroleum ether, and hexanes.

An attempt was made to synthesize 1,6-hexanebis(thiourea) from 0.0015 moles of silver thiocyanate and 0.0077 moles of 1,6-hexanediamine using the diamine as the solvent. The reaction solution was refluxed for three hours, and then allowed to cool to room temperature. A heterogeneous black and white solid, which smelled of the diamine, was collected: mp 31-36 °C; IR 3200bm, 2850bm, 2060m, 1600mb, and 950wb  $\text{cm}^{-1}$ . The above reaction was repeated, except that concentrated ammonium hydroxide was used as the solvent. A white crystalline solid was collected, and was subsequently recrystallized from isopropyl alcohol in 40 % yield: mp 104-109 °C; IR 3500bm, 2100s, and 1070bm.

Finally, an attempt was made to synthesize 1,6-hexanebis(thiourea) from 0.0026 moles of thiourea, 0.0013 moles of silver thiocyanate, and .0014 moles of 1,6-hexanediamine in ammonium hydroxide. Upon addition of all the starting materials, it was observed that silver precipitated out of solution. The reaction mixture was then stirred for 20 minutes, and was subsequently filtered to yield a grey solution. Upon acidification of the solution, the color dissipated. The volume was reduced to about half *in vacuo*, and the resulting white crystalline precipitate was collected via suction filtration: mp sublimes at 229 °C; IR 3100b, 2840b, 200w, 1700m, 1540m, 1400b, and 720w  $\text{cm}^{-1}$ . Then the filtrate was evaporated to dryness, and a second white crystalline solid was collected: mp sublimes at 230 °C; IR 3000b, 2000wb, 1700mb, 1400sb, and 700bw  $\text{cm}^{-1}$ .

#### 4.4.5: Quantitative Determination of Thiocyanate

The amount of thiocyanate ion present in the reaction mixture was quantitatively determined using a Vollhard titration.<sup>49</sup> The product obtained



from using ethylenediamine in aqueous solution, was found to contain 57.75% (s.d.=.05) thiocyanate ion, by mass. After recrystallization of the ethylene-1,2-bis(thiourea)reaction mixture carried out in water, the sample was determined to contain only 12.8% thiocyanate ion by mass. The product from the reaction reaction of 1,6-hexanediamine and silicon tetraisothiocyanate contained 40.3% (s.d.=2.07) thiocyanate ion, by mass.

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