Synthesis of 2-Amino-4-imino-4,5-dihydrothiazoles from *N*-Sulfonyl-α-chloroamidines and Thiourea [1]

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A number of new and interesting 2-amino-4-(*N*-substituted)imino-4,5-dihydrothiazoles were synthesized by reacting thiourea (or thiourea hydrochloride) with *N*-alkyl- or *N,N*-dialkyl-*N'*-*p*-toluenesulfonyl-α-chloroacetamidines, where the *N*-alkyl groups were ethyl, cyclohexyl, benzyl, β-phenethyl, (3,5-dimethyl-1-adamantyl)methyl, as well as *N,N*-dimethyl- and *N,N*-pentamethylene. Reactions of *N*-alkyl-*N'*-*p*-toluenesulfonyl-2-chloroacetamidines (substituents being *N*-ethyl, *N*-benzyl and *N,N*-dimethyl) with thiourea hydrochloride in hot 2-propanol furnished 2-amino-4-(*p*-toluenesulfonyl)imino-4,5-dihydrothiazole (in 51, 60 and 65% yields, respectively) and the corresponding amine hydrochloride. In hot acetone or butanone, the reactions of these *N*-sulfonyl-2-chloroacetamidines with excess thiourea provided 2-amino-4-*N*-(alkyl or *N,N*-dialkyl)imminium-4,5-dihydrothiazole chlorides in 25-80% yield. The by-product from these reactions was *p*-toluenesulfonamide. The structures of the products were established by chemical transformations and spectral methods (nmr and mass spectra).

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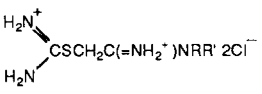
Synthesis of *N*-alkyl- and *N,N*-dialkyl-2-mercaptoacetamidines **1** as potential radioprotective agents have received considerable attention in this Laboratory [2,3]. An unexplored approach was to react 2-chloroacetamidine hydrochlorides **2** first with thiourea to form isothiuronium salts **3**, which could be hydrolyzed [4] under mild alkaline conditions to furnish **1**. However, the reactions of **2** with thiourea yielded a complex mixture of products. For example, the major product from the reaction of *N*-benzyl-2-chloroacetamidine hydrochloride (**2a**) with thiourea was 2-amino-4-imino-4,5-dihydrothiazole (and/or its tautomer, 2,4-diiminothiazolidine) hydrochloride, which are best represented by the tautomeric resonance-stabilized structures, **4** [5-7].

$HSCH_2C(=NH)NRR'$

1

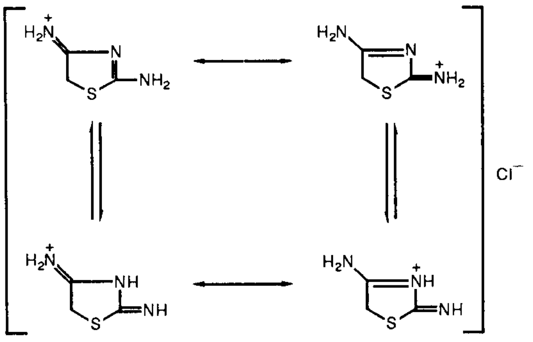
$ClCH_2C(=NH_2^+)NRR'\ Cl^-$

2



$(H_2N)_2C^+SCH_2C(=NH_2^+)NRR'\ 2Cl^-$

3



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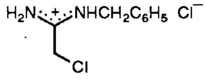
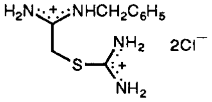
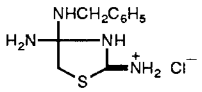


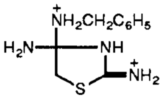
2a



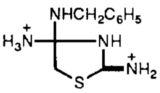
3a



5



6a



6b

$$2 + ArSO_2Cl \xrightarrow{Na_2CO_3} ClCH_2C(=NSO_2Ar)NRR'$$

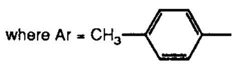
7

$$ClCH_2C(=NSO_2Ar)NHR \rightleftharpoons ClCH_2C(=NR)NHSO_2Ar$$

7a 7b

$ClCH_2C(=NH)N(R)SO_2Ar$

8

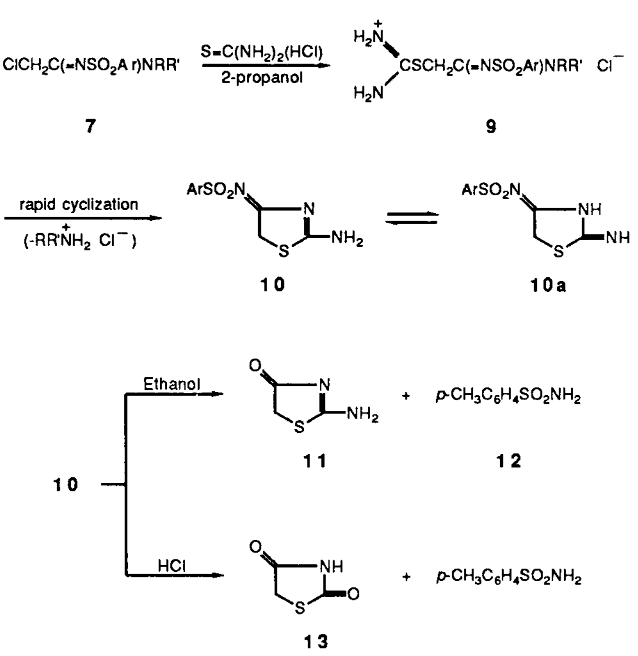


The synthesis of **4** had been reported before. The reaction of chloroacetonitrile with thiourea in cold acetone (2-4 days) provided the isothiuronium salt **3** (R = R' = H) in 80% yield [8] which changed upon warming to **4** [9,10]. A number of 5-substituted-2-amino-4-imino-4,5-dihydrothiazoles have been synthesized through the reaction of a number of α-halo and α-sulfonyloxynitriles and thiourea [10,11]. It was claimed that 2-chloroacetamidine reacts with thiourea to form **4** [12]. Apparently, the intermediate isothiuronium salt **3** (R = R' = H) cyclizes spontaneously with the elimination of ammonia. In the light of the last report, the reaction of *N*-benzyl-2-chloroacetamidine hydrochloride (**2a**) with thiourea should give two products, namely **4** and the 4-*N*-benzyl analog **14b**. But, close examination of the products revealed that **4** and benzylamine hydrochloride were the major products. Examination of many fractions (nmr, ms) indicated that some **14b** was present, but did not appear to be the major product. Change of solvents or acid catalysis by using thiourea hydrochloride instead of thiourea, still gave **4** as the major product.

In the first step thiourea converts **2a** to **3a**, which cyclizes quickly. During the cyclization, one of the amino groups of the isothiuronium moiety of **3a** attacks the amidine carbon to form a tetrahedral intermediate **5**. Protonation of either of the two exocyclic amino groups provides either **6a** and **6b**, from which either benzylamine or ammonia can be eliminated to furnish either **4** or **14b**, respectively.

One can cautiously relate this preferential elimination in our system to the somewhat analogous behavior reported for the hydrolysis of unsymmetrical amidines. In a recent and extensive study on base-catalyzed hydrolyses of unsymmetrical amidines to amides and amines, certain patterns evolved regarding preferential cleavage of amines from the amidines [13]. The base-catalyzed hydrolysis of an amidine is expected to proceed *via* a tetrahedral intermediate, which can be considered to be a hemiorthoamide. As one of the amines departs, this hemiorthoamide collapses to form the amide. Barring untoward steric and electronic effects, the investigators found that the more basic amine departed preferentially from the hemiorthoamide and concluded that "basicity governs cleavage because a nitrogen anion is so poor a leaving group that (except for some extreme cases [14]), it must require a proton [15] either prior to cleavage or concerted with it" [13]. Hence, a primary amine may be a better leaving group, "because a primary amine is more basic than ammonia". On such a premise, one could argue that in our system the more basic amine, namely benzylamine would be expected to be eliminated in preference from intermediates **6a** or **6b**.

Our inability to isolate isothiuronium salts **3**, due to their rapid cyclization, prompted us to examine the reactions of *N*-sulfonyl-α-chloroamidines **7** with thiourea in order to obtain isothiuronium salts of type **9**. Such structural modification of **2** to **7**, should change the course of the reactions with thiourea. *N*-Sulfonylamidines have been prepared by Schotten Baumann acylations of amidines with sulfonyl halides [16], or by the reaction of amines with *N*-sulfonylbenzimidoyl chlorides [17]. A novel synthesis of tertiary sulfonyl amidines resulted from a 1,3-dipolar cycloaddition of sulfonyl azides to enamines, followed by the rearrangement of the resultant unstable triazoline with the loss of nitrogen [18]. More esoteric methods involved the reactions of *N*-sulfonyl imidates with amines [19], or imidates with sulfonamides [20]. A few *N*-sulfonyl-α-chloroamidines had been synthesized from *N*-sulfonyl-α-diazoacetamidines with hydrogen chloride [21].



In general, amidines are quite stable in anhydrous media and can even be distilled as free bases [22], but are best handled as amidinium salts in aqueous solutions to minimize hydrolysis. While pure 2-chloroacetamidinium chlorides **2** can be handled and stored without decomposition, the free bases were quite unstable. They darkened and decomposed (nmr) already at room temperature after several hours. However, the free bases were sufficiently stable at room temperature to react with *p*-toluenesulfonyl chloride under mild Schotten-Baumann conditions to form a series of *N*-alkyl- and *N,N*-dialkyl-*N'*-(*p*-toluenesulfonyl)-2-chloroacetamidines **7** in respectable yields.

Mono-*N*-alkylsulfonylamidines could exist as tautomers **7a** and **7b**, or as the isomers **8**. Proton magnetic resonance spectra (pmr) were clear, did not show rotamers, and established conclusively that their structures were **7a** by showing couplings between adjacent methylene (or methine) to NH protons. Only the *N,N*-dimethyl derivative **7** (R = R' = methyl) showed rotamers due to restricted rotation about the C-N bond in the pmr spectrum in deuteriodimethyl sulfoxide [23].

The reactions of **7** with thiourea were fast and produced a number of interesting products. The solvent and acid-catalysis appeared to play an important role in determining the course of the major reaction. However, even in cold solvents, it became abundantly clear that the reaction of **7** with thiourea could not be stopped at the isothiuronium salt stage **9**. The reaction of a number of *N*-alkyl-*N'*-sulfonyl-2-chloroacetamidines **7** with thiourea in boiling

2-propanol for a relatively short time furnished 2-amino-4-(p-toluenesulfonyl)imino-4,5-dihydrothiazole (**10**) or its tautomer, 2-imino-4-(p-toluenesulfonyl)iminothiazolidine (**10a**) in relatively good yield. The by-product was the amine hydrochloride corresponding to the *N*-alkylamino group in **7**. When thiourea was replaced by thiourea hydrochloride, **10** was isolated in better yield. This point becomes important when discussing the mechanisms of these reactions, below.

The structure of **10** was established through its relatively simple pmr spectrum in deuteriodimethyl sulfoxide. The spectrum consisted of signals associated with a p-toluenesulfonyl group, a singlet (2 protons) at δ 4.42 indicative of a methylene group, and two broad singlets, at δ 9.48 and 9.80 (representing 1 proton, each). The last three signals disappeared almost instantly upon addition of deuterium oxide. While one would have anticipated that the amino proton exchanged instantly, it was surprising that the methylene protons also exchanged so fast.

Hydrolysis of **10** in boiling ethanol yielded 2-amino-2-thiazolin-4-one (**11**) and p-toluenesulfonamide (**12**). More drastic acid-catalyzed hydrolysis of **10** led to 2,4-thiazolidinedione, (**13**). The structure of **10** is based on the 4,5-dihydrothiazole system. This conclusion was reached after comparing its nmr spectrum with those of a number of model compounds which are listed in Table I. There are a number of characteristic features associated with these 2-amino-4-imino-4,5-dihydrothiazoles. In their pmr spectra, the 5-methylene ring protons give rise to a singlet between 4 and 5 ppm, and their cmr spectra show a signal between 35 and 40 ppm (downfield from internal tetramethylsilane, in deuteriodimethyl sulfoxide) [5-7,24], Table I. Furthermore, the methylene protons exchanged rapidly with deuterium when deuterium oxide was added to the nmr sample.

Had **10** been a derivative of the aromatic tautomer [2-amino-4-(p-toluenesulfonamido)thiazole] then the H-5 aromatic proton signal of the thiazole ring would be expected around 6.5-7.0 ppm [25], and that of C-5, around 90-100 ppm. For example, the C-5 carbon signal of 2-aminothiazole appears at 107 ppm [26]. Examples are the H-5 and C-5 signal for 2,4-di(acetamido)thiazole at 6.60 (7.03[5]) and 92 ppm, respectively, in deuteriodimethyl sulfoxide [7]. Furthermore, **10** could not exist as 2-imino-4-(p-toluenesulfonylamino)thiazoline since H-5 and C-5 would be more deshielded. For example, 2-imino-3-methylthiazoline shows H-5 and C-5 at 5.72 and 97.1 ppm, respectively (in deuteriochloroform) [26].

Reactions of *N*-alkyl- (and *N,N*-dialkyl)-*N'*-p-toluenesulfonyl-α-chloroacetamidines **7** with preferably an excess of thiourea in either hot or cold acetone (or butanone) furnished as major products, 2-amino-4-alkylimino-4,5-dihy-

TABLE I

^{1}H and ^{13}C NMR Chemical Shifts at Position 5 of some 2-Amino-4,5-dihydrothiazoles

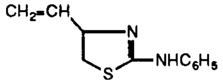
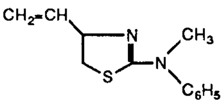
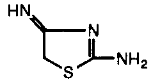
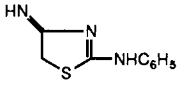
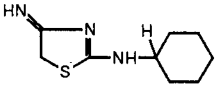
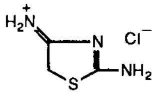
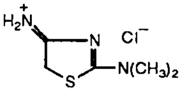
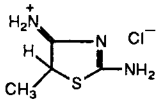
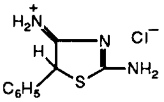
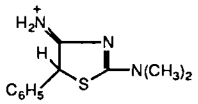
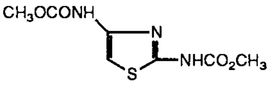
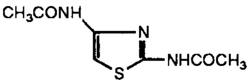
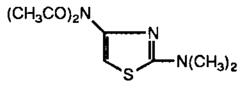
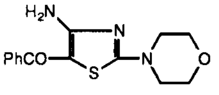
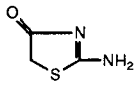
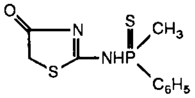
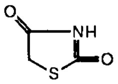
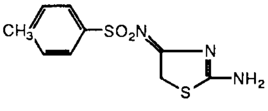
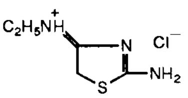
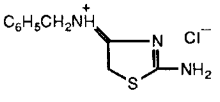
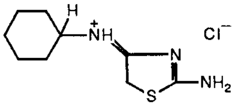
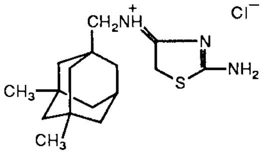
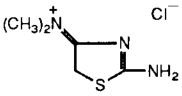
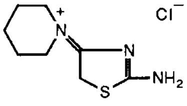
Structure	H-5 [a]	C-5 [a]	Reference
	2.98, 3.30 (2H, ABq) [b]	35.59 [b]	[24a]
	3.05, 3.37 (2H, ABq) [b]	39.69 [b]	[24a]
	4.10 (2H, s) 4.10 (2H, s) 4.43 (2H, s)	--- --- 39.50	[5] [6] [7]
	4.05 (2H, s)	---	[24b]
	4.05 (2H, s)	---	[24b]
	4.58 (2H, 2) 4.85 (2H, s) 4.53 (2H, s) 4.58 (2H, s)	-- --- 39.70 ---	[5] [6] [7] This work
	4.97 (2H, s)		[6]
	5.13 (1H, q)	---	[5]
	6.39 (1H, s) 6.35 (1H, s)	--- ---	[5] [6]
	6.60 (1H, s)	---	[6]
	6.60 (1H, s)	92.00	[7]
	7.03 (1H, s)	---	[5]
	6.82 (1H, s)	---	[6]
	---	94.80 [b]	Hirai *et al.*, 1980

TABLE I
(Continued)

Structure	H-5 [a]	C-5 [a]	Reference
	3.80 (2H, s)	40.00	[7]
	---	35.49	[24c]
	4.04 (2H, s)	36.00	[7]
	4.42 (2H, s)	43.31	This work
	4.59 (2H, s)	41.08	This work
	4.69 (2H, s)	47.60	This work
	4.58 (2H, s)	---	This work
	4.66 (2H, s)	---	This work
	4.75 (2H, s)	---	This work
	4.80 (2H, s)	---	This work

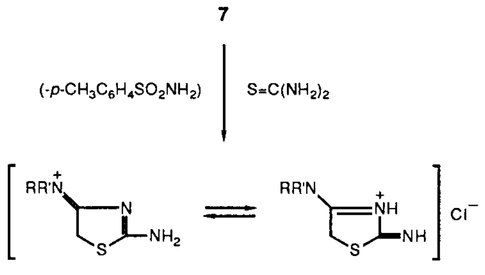
[a] Chemical shifts are reported downfield from internal tetramethylsilane in deuteriodimethyl sulfoxide. [b] Determined in deuteriochloroform.

drothiazole hydrochlorides **14** and *p*-toluenesulfonamide (**12**). The pmr spectra of these salts **14** differed from the one of **10** by the conspicuous absence of signals attributable to the *p*-toluenesulfonyl group. Furthermore, the hallmark proton and carbon resonances of the 5-methylene group so characteristic of 4,5-dihydrothiazoles were present in **14** (Table I). Furthermore, the proton signals (between 4.5 and 4.8 ppm) also readily exchanged upon addition of deuterium oxide.

These new salts **14** were very soluble in water and ethanol, but practically insoluble in acetone or butanone. The best purification procedure called for repeated extraction with hot acetone or butanone. Attempts to crystallize these salts from alcohols or mixed solvents frequently gave poor recovery and/or caused extensive decomposition. Attempts to isolate the corresponding free bases proved to be quite disappointing. Although a number a papers claim that the isolation of dihydrothiazoles of this type is plausible [5-7], the free bases associated with **14** decomposed too fast in attempts to extract them into methylene chloride from ice-cold alkaline solutions. Even immediate acidification of such methylene chloride solutions did not regenerate the salts.

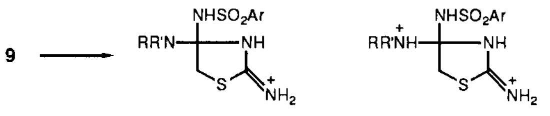
The mother liquors from the reactions producing **14** were scanned for identifiable byproducts. In their pmr spectra, the presence of **7** and **10** could be detected by readily exchangeable singlets in the 4-5 ppm region. While **7** can be chromatographed, any of the 4,5-dihydrothiazoles, **10**, **14** could not be separated either by column chromatography or high-pressure liquid chromatographic separations due to extensive decomposition.

The most successful syntheses of **14** were those in which the alkyl groups were benzyl, cyclohexyl and (3,5-dimethyl-1-adamantyl)methyl. It could just be that the relatively bulky alkyl substituent renders these salt least susceptible to hydrolysis (at C-4). When the alkyl substituent was *β*-phenethyl, the reaction failed to produce a salt of type **14**, but rather produced **10** in excellent yield. No obvious explanation for this deviation can be rendered at present.



14

where a, $R = H, R' = C_2H_5$
b, $R = H, R' = CH_2C_6H_5$
c, $R = H, R' = (CH_2)_2C_6H_5$
d, $R = H, R' = cycloC_6H_{11}$
e, $R = H, R' = [3,5\text{-}(CH_3)_6\text{-}1\text{-adamantyl}]CH_2$
f, $R = R' = CH_3$
g, $R = R' = (CH_2)_5$



15 16

Some unexpected problems were encountered for the products from the reactions of thiourea with the *N*-ethyl, *N,N*-dimethyl and *N,N*-pentamethylene (piperidino) analogs **14a**, **14f** and **14g**. These salts crystallized from boiling acetone or butanone, the solvents for the reactions. Subsequently repeated extraction with large volumes of boiling butanone (in which thiourea is very soluble), did not remove tightly held thiourea. Nor did the melting points or the nmr spectra change and the presence of thiourea could be demonstrated in the pmr, cmr as well as in their mass spectra. The molar ratios or thiourea was confirmed by integration of the broad signal around 7.1 ppm (in deuteriodimethyl sulfoxide). Apparently, salts of type **14** in which the 4-(*N*-alkyl) substituents were relatively small tended to co-crystallize, or formed some type of strong complex, or even a type of inclusion compound with thiourea. The presence of bound thiourea was also confirmed in their cmr spectra, with a signal at 184 ppm (in deuteriodimethyl sulfoxide) attributable to thiourea. The mass spectra of **14** showed molecular ions of the corresponding base (M - HCl) as the highest ion, but the mass spectra of **14a**,**f** and **g** contained distinct ions (m/z 76, 60, 43) expected from thiourea.

This study suggests that the reaction begins with the displacement of the halo group of the *N*-sulfonyl-α-chloroacetamidines **7** by thiourea to form isothiuronium salts **9**. We had not been able to detect **9** in either the pmr or mass spectra of impure mixtures, even after very short reaction times. Then **9** commences to cyclize to form the tetrahedral intermediate **15**, from which two distinctly different eliminations lead to either type of 4,5-dihydrothiazole, **10** or **14**. If indeed the departure of the more basic amine is preferred, the elimination of the amine is preferred, as its hydrochloride. Since the reaction proceeds best when thiourea hydrochloride is added, it is reasonable to assume that the protonation of the amino group in **15** to form **16** takes place followed by the elimination of the amine hydrochloride to form **10**.

It was felt that basic catalysis might encourage the elimination of the acidic and electron-withdrawing sulfonamide, particularly since the sulfonamide can be stabilized as the anion (once it commences to depart). Attempts to conduct the reaction in acetone or butanone in the presence of catalytic quantitities of either triethylamine or pyridine led to intractable mixtures. It was found however that a large excess of thiourea promoted the formation of **14**. It is conceivable that in anhydrous ketonic solvents, thiourea can act as a weak base and in that capacity aids the elimination of the sulfonamide from **15** to form **14**. It was also shown that **10** and **14** could not be interconverted, that is, *p*-toluenesulfonamide did not displace the amino group in **14**, nor did amine hydrochlorides displace the sulfonamido group in **10**. Free amines could not be used in attempts to displace the sulfonamide group of **10**, since both **10**, and the potential product, **14**, decomposed in alkaline media.

EXPERIMENTAL

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Elemental analyses (C, H, N) were determined by Micro-Tech Laboratories, Skokie, Illinois. Mass spectra (EI, 70 eV, direct insertion) were obtained by Mr. Richard Dvorak using a Finnigan mass spectrometer, Model MAT 112S. Usually, only the more intense ions (10% or more) are reported unless otherwise deemed important) and relative intensities are shown in parentheses. Proton magnetic resonance spectra were recorded in deuteriodimethyl sulfoxide unless specified otherwise, on a T60A Varian spectrometer fitted with a Nicolet TT-7 Fourier transform accessory or on a Varian XL-300 spectrometer. Carbon magnetic resonance spectra were determined at 75.4 MHz on the Varian XL-300 spectrometer. Chemical shifts are reported in ppm (δ) downfield from internal tetramethylsilane and signals are described as s, singlet, d, doublet, t, triplet, q, quartet and m, multiplet. The abbreviation br is used to describe broad signals. When complex spins systems of the AA'XX' type are described, the two reported chemical shifts are the ones which are at the center of the two sets of multiplets. All NH signals were broad and exchanged readily when deuterium oxide was added.

All research chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI. Reagent grade acetone was purchased from Mallinckrodt and was stored over anhydrous magnesium sulfate. Butanone was stored over anhydrous calcium sulfate for 24 hours prior to distillation. Chloroacetonitrile was distilled prior to its use. Solvents for the reactions were distilled before use. Evaporation, *in vacuo*, implies that solvents were removed by means of a rotary flash evaporator at the water pump (20-30 Torr) at about 40°, unless otherwise specified. All analytical samples were dried at room temperature in a vacuum desiccator.

Preparation of *N*-Substituted-2-chloroacetamidine Hydrochlorides.

The general method [2,27-30] consists of generating methyl α-chloroacetimidate, *in situ*, [31] which is reacted with an amine hydrochloride to form an α-chloroamidine hydrochloride. One of the modifications introduced here is in the neutralization step by using concentrated hydrochloric acid instead of anhydrous hydrogen chloride in a suitable alcohol. One typical preparation is presented, as well as nmr data not published previously.

N-(Cyclohexyl)-2-chloroacetamidine Hydrochloride.

Chloroacetonitrile (7.55 g, 0.1 mole) was added dropwise to a cold stirred solution of sodium (0.23 g, 0.01 g-atom) in absolute methanol (100 ml). The temperature was kept below 10°. After 1 hour, cyclohexylamine hydrochloride (14.85 g, 0.11 mole) was added and the mixture was stirred at 0-10° for 1 hour. Solids were filtered off and the filtrate was rendered strongly acidic by the addition of concentrated hydrochloric acid (0.1 ml), and the solution was then evaporated to dryness *in vacuo*. The light purple resin was triturated with acetone (2 × 10 ml), then with dry ether (2 × 10 ml) and the solid was dried *in vacuo* at 25° (18 hours). Recrystallization from 2-propanol-anhydrous ether gave colorless crystals (11.3 g, 54%), mp 180-184°, lit mp 181-182.5° [30]; ^{1}H nmr: δ 1.25-1.75 (m, C_6H^{11}), 3.60 (m, CHN), 4.46 (s, CH_2Cl), 8.14, 9.25 (br s, NH's).

The following 2-chloroacetamidine hydrochlorides were prepared (0.1 molar scale) and were usually recrystallized from isobutyl alcohol.

N-Ethyl-2-chloroacetamidine Hydrochloride.

This compound was obtained in 74% yield, mp 115-117°, lit mp 114-117° [27]; ^{1}H nmr: δ 1.15 (t, J = 7.2 Hz, CH_3), 3.32 (quintet, NCH_2, $J_{CH_2\text{-}CH_3} = J_{CH_2\text{-}NH} = 7.2$ Hz), 4.49 (s, CH_2Cl), 9.53 (br s, 3NH's).

N-Benzyl-2-chloroacetamidine Hydrochloride.

This compound was obtained in 76% yield, mp 143°, lit mp 141-142° [27]; ^{1}H nmr: δ 4.57 (s, CH_2Cl), 4.62 (s, CH_2N), 7.57 (br s, ArH), 9.67, 9.98 (br s, NH's). To isolate the free base, the following procedure was adopted: the hydrochloride was added a mixture of equal volumes of methylene chloride and ice-cold 10% aqueous sodium carbonate. The mixture was shaken for 3 minutes, the lower layer drawn off and evaporated to dryness *in vacuo*, at room temperature; ^{1}H nmr (on the colorless solid obtained directly after evaporation): δ 4.08 (s, CH_2N), 4.19 (s, CH_2Cl), 5.77 (br s, 2NH's), 7.28 (m, ArH). The residue, although stored in a tightly closed vessel, changed gradually to a black tar.

N,N-Dimethyl-2-chloroacetamidine Hydrochloride.

This compound was obtained in 62% yield, mp 177-179°, lit mp 176-179° [27]; ^{1}H nmr: δ 3.16, 3.25 (2s, NCH_3's, due to restricted rotation about the C-N bond, [23,28]), 4.77 (s, CH_2Cl), 9.32, 10.12 (br, s, 2NH).

N,N-(Pentamethylene)-2-chloroacetamidine Hydrochloride.

This compound was obtained in 50% yield, mp 181-183°, lit mp 182-184° [27]; ^{1}H nmr: δ 1.58-1.64 [m, C-(CH_2($_3$-C], 3.62 [m, $N(CH_2)_2$], 4.68 (s, CH_2Cl), 9.16 (br s, 2NH's).

N-β-Phenethyl-2-chloroacetamidine Hydrochloride.

This compound was made by the general method in 34% yield. The crude gum solidified with difficulty upon trituration with acetone, then with ether, was dried *in vacuo* at 25° (18 hours), mp 100-104°; ^{1}H nmr: δ 2.88 (t, J = 6.6 Hz, $CH_2C_6H_5$), 3.55 (t, J = 6.6 Hz, CH_2N), 4.49 (s, CH_2Cl), 7.27 (narrow m, ArH), 9.7 (br s, 3NH's). No lit mp has been recorded but this salt had been converted by sodium thiosulfate to a crystalline Bunte salt [28] but could not be recrystallized satisfactorily from either isobutyl alcohol, isopropyl alcohol or ethanol-ether. In this work this product was converted to a crystalline *N*-sulfonyl derivative (below).

N-[(3,5-Dimethyl-1-adamantyl)methyl)]-2-chloroacetamidine Hydrochloride.

This compound was obtained as a resin which was triturated with cold water (30 ml), then with benzene to furnish an amorphous solid (60% yield) which was dried *in vacuo* at 25° (18 hours), mp 178-179°, lit mp 176-178° [2]; ^{1}H nmr: δ 0.80 [s, $(CH_3)_2$], 1.10-1.39 (m, adamantane H's), 3.10 (d, J = 7.2 Hz, CH_2N), 4.54 (s, CH_2Cl), 9.60 (br s, 3NH's).

Synthesis of *N*-Substituted-*N'*-(*p*-toluenesulfonyl)-2-chloroacetamidines.

The general procedure is illustrated for the synthesis of *N*-(cyclohexyl)-*N'*-(*p*-toluenesulfonyl)-2-chloroacetamidine. *N*-(Cyclohexyl)-2-chloroacetamidine hydrochloride (2.1 g, 0.01 mole) was added to a stirred solution of *p*-toluenesulfonyl chloride (1.90 g, 0.01 mole) in acetone (30 ml) at 25°, followed by a 10% sodium carbonate solution (25 ml). The mixture was stirred at room temperature for 10-15 minutes, then diluted with water (150 ml), and continued to be stirred at room temperature to permit crystallization (30 minutes). The solid was filtered, washed with water (2 × 30 ml) and was dried, *in vacuo*, at 25° (18 hours). Recrystallization from ethanol gave colorless prisms (1.70 g, 52%), mp 110-113°; ^{1}H nmr: δ 1.15-1.69 [m, C-(CH_2)5-C], 3.63 (m, CHN), 4.56 (s, CH_2Cl), 7.31 and 7.70 (centers of 2 multiplets of an AA'XX' system), 8.85 (br d, $J_{NH\text{-}CH}$ = 6.6 Hz); ms: m/z (relative intensity) 330 (7), 329 (3), 328 (M^+, 18), 249 (38), 247 (100), 175 (10), 173 (35), 155 (62), 98 (23), 91 (79).

Anal. Calcd. for $C_{15}H_{21}ClN_2O_2S$: C, 54.78; H, 6.43; N, 8.51. Found: C, 54.82; H, 6.57; N, 8.44.

The other preparations were carried out on a 0.10 molar scale, and the products recrystallized from ethanol.

N-Ethyl-*N'*- (*p*-toluenesulfonyl)-2-chloroacetamidine.

This compound was obtained in 40% yield, mp 105-108°; ^{1}H nmr: δ 1.04 (t, J = 7.2 Hz, C*H*$_3$CH$_2$), 2.37 (s, CH_3), 3.20 (q, J = 7.2 Hz, C*H*$_2$CH$_3$), 4.62 (s, CH_2Cl), 7.33 and 7.73 (centers of 2 multiplets of an AA'XX" system, ArH), 9.97 (br s, NH); ms: m/z (relative intensity) 275 (11), 274 (M^+, 26), 245 (9), 175 (10), 155 (20), 120 (18), 119 (49), 91 (52), 44 (65), 32 (100).

Anal. Calcd. for $C_{11}H_{15}ClN_2O_2S$: C, 48.08; H, 5.50; N, 10.19. Found: C, 48.17; H, 5.54; N, 10.17.

N-Benzyl-*N'*-(*p*-toluenesulfonyl)-2-chloroacetamidine.

This compound was obtained in 65% yield, mp 110-115°; ^{1}H nmr: δ 2.35 (s, CH_3), 4.40 (d, J = 6.0 Hz, CH_2Ph), 4.69 (s, CH_2Cl), 7.26-7.7 (m, AA'XX', ArH), 9.35 (br s, NH); ms: m/z (relative intensity) 336 (M^+, 1), 300 (1), 183 (20), 181 (60), 155 (6), 106 (100), 91 (50).

Anal. Calcd. for $C_{16}H_{17}ClN_2O_2S$: C, 57.05; H, 5.09; N, 8.31. Found: C, 57.28; H, 5.10; N, 8.22.

This product was made also by an alternate method: *N*-Benzyl-2-chloroacetamidine hydrochloride (2.20 g) was added to a solution of *p*-toluenesulfonyl chloride (1.90 g, 0.01 mole) in methylene chloride (30 ml) and 10% aqueous sodium carbonate (25 ml). The mixture was shaken at room temperature for 10 minutes and was then separated. The organic phase was washed with water (10 ml) and solvents were evaporated, *in vacuo*. Recrystallization from ethanol afforded the pure product (1.8 g, 55%).

N-[(3,5-Dimethyl-1-adamantyl)methyl]-*N'*-(*p*-toluenesulfonyl)-2-chloroacetamidine.

This compound was obtained in 81% yield, mp 143-146°; ^{1}H nmr: δ 0.71 [s, 2 (Adm CH_3's)], 1.00-1.23 (m, Adm), 2.35 (s, CH_3), 2.95 (d, J = 6.0 Hz, NCH_2Adm), 4.63 (s, CH_2Cl), 7.31-7.74 (m, AA'XX', ArH), 8.84 (br s, NH); ms: m/z (relative intensity) 424 (4), 4.22 (M^+, 10), 373 (11), 323 (4), 269 (24), 268 (12), 267 (71), 192 (40), 163 (100), 155 (11), 107 (56).

Anal. Calcd. for $C_{22}H_{31}ClN_2O_2S$: C, 62.46; H, 7.38; N, 6.62. Found: C, 62.47; H, 7.52; N, 6.58.

This product was produced also when the amidinium salt (1.5 g, 0.005 mole) was added to a stirred solution of *p*-toluenesulfonyl chloride (0.95 g, 0.005 mole) in 35 ml of triethylamine at 25°. After 15 minutes, the solution was poured into a mixture of hydrochloric acid and ice. The reddish-brown gum was extracted into methylene chloride. Upon workup of the organic layer, the pure product (0.85 g, 40%) was obtained.

N-(β-Phenethyl)-*N'*-*p*-toluenesulfonyl-2-chloroacetamidine.

This compound was obtained in 34% yield, mp 100-104°; ^{1}H nmr: 2.36 (s, CH_3), 2.75 (t, J = 7.2 Hz, CH_2Ph), 3.39 (q, J = 7.5 Hz, NCH_2), 4.62 (s, CH_2Cl), 7.11-7.70 (m, AA'XX', ArH), 9.17 (br s, NH); ms: m/z (relative intensity) 354 (2), 352 (2), 350 (M^+, 4), 249 (6), 247 (18), 155 (42), 105 (21), 104 (100), 91 (87).

Anal. Calcd. for $C_{17}H_{19}ClN_2O_2S$: C, 58.19; H, 5.45; N, 7.98. Found: C, 58.19; H, 5.57; N, 7.52.

N,N-Dimethyl-*N'*-(*p*-toluenesulfonyl)-2-chloroacetamidine.

This compound was initially obtained as a gum (24%), which was extracted into methylene chloride. The organic layer was washed, the solvent removed and the residue suspended in ether when it gradually solidified at 5°, mp 100-101°. Recrystallization from ethanol furnished the analytical sample, mp 104-106°; ^{1}H nmr: δ 2.36 (s, CH_3), 3.19, 3.30 (2s, 2NCH_3, restricted rotation [23,28]), 4.85 (s, CH_2Cl), 7.32-7.71 (m, AA'XX', ArH); ms: m/z (relative intensity) 276 (2.5), 274 (M^+, 6), 238 (2), 199 (41), 155 (42), 119 (58), 91 (100), 65 (29), 44 (100).

Anal. Calcd. for $C_{11}H_{15}ClN_2O_2S$: C, 48.08; H, 5.50; N, 10.19. Found: C, 47.98; H, 5.57; N, 10.11.

N,N-(Pentamethylene)-*N'*-(*p*-toluenesulfonyl)-2-chloroacetamidine.

This compound tended to be isolated as an oil (30%) which slowly crystallized, mp 80-83°. Recrystallization from ethanol afforded the analytical sample, mp 85-88°; ^{1}H nmr: δ 1.49-1.63 [m, $(CH_2)_3$], 2.37 (s, CH_3), 3.57-3.67 [m, $N(CH_2)_2$], 4.90 (s, CH_2Cl), 7.34-7.69 (m, AA'XX', ArH); ms: m/z (relative intensity) 279 (M^+-Cl, 2), 238 (5), 161 (12), 159 (100), 155 (18), 124 (6), 123 (6), 91 (25), 84 (100).

Anal. Calcd. for $C_{14}H_{19}ClN_2O_2S$: C, 53.41; H, 6.08; N, 8.89. Found: C, 53.30; H, 6.21; N, 9.10.

Reactions of *N*-Benzyl-2-chloroacetamidine Hydrochloride with Thiourea Hydrochloride.

Thiourea (30.4 g, 0.4 mole) was dissolved in concentrated hydrochloric acid (50 ml) and the solution evaporated to dryness, *in vacuo*, to provide thiourea hydrochloride (43.7 g, 98%), mp 131-135°, lit mp 130° [32].

A solution of *N*-benzyl-2-chloroacetamidine hydrochloride (1.10 g, 0.005 mole) and thiourea hydrochloride (0.056 g, 0.005 mole) was refluxed in 2-propanol (30 ml) for 30 minutes during which time a copious colorless precipitate was formed. The solid was filtered hot, washed with 2-propanol (4 ml) and dried *in vacuo* at 25° (18 hours) and weighed 0.67 g (89%). The product was identified by means of pmr and mass spectroscopy to be 2-amino-4-imino-4,5-dihydrothiazole hydrochloride (**4**), mp >360°, identical to a sample produced from chloroacetonitrile and thiourea by the lit method, lit mp >360° [10]; ^{1}H nmr: δ 4.58 (s, CH_2S), 9.96, 10.02, 10.28, 10.33 (4 br s, due to restricted rotation, or due to tautomers, NH's); ms: identical to lit ms [7].

Evaporation of the 2-propanol filtrate gave a white resin which was shown to be a mixture of **4** and **14b** by pmr and mass spectra.

When thiourea was used instead of its hydrochloride, the yield of **4** was only 67%.

Reactions of *N*-Sulfonylamidines with Thiourea and Thiourea Hydrochloride. 2-Amino-4-(*p*-toluenesulfonylimino)-4,5-dihydrothiazole, **10**.

N-Benzyl-*N'*-(*p*-toluenesulfonyl)-2-chloroacetamidine (1.00 g, 0.003 mole) and thiourea hydrochloride (0.34 g, 0.003 mole) were dissolved in boiling 2-propanol (20 ml). The mixture was refluxed for 1 hour, during which time a yellowish-white precipitate appeared. The hot mixture was filtered, the solid washed with 2-propanol [(2 × 2 ml), mother liquor *A*] then with water [(2 × 2 ml), mother liquor **B**] and was dried *in vacuo* at 25° (18 hours).

The 2-propanol mother liquor **A** was cooled to 5° to provide a relatively small amount of additional product, which was filtered, washed as before and after drying proved to be identical to the first product. Since both fractions had similar mp's and ^{1}H nmr spectra, they were combined (0.48 g, 59%). Recrystallization from 2-propanol produced the analytical sample of **10**, mp 199-200°; ^{1}H nmr: δ 2.37 (s, CH_3), 4.42 (s, CH_2S), 7.30, 7.75 (m, AA'XX', ArH), 9.48, 9.80 (br s, 2 NH's); ^{13}C nmr: δ 22.24, (CH_3), 43.31 (CH_2S), 128.2 (C-3, C-5'), 130.2 (C-2', C-6'), 140.3 (C-4'), 143.3 (C-1'), 178.8 (C-2), 182.1 (C-4); ms: m/z (relative intensity) 271 (3), 270 (4), 269 (M^+, 34), 171 (43), 155 (48), 133 (15), 114 (30), 91 (100), 43 (30).

Anal. Calcd. for $C_{10}H_{11}N_3O_2S_2$: C, 44.59; H, 4.11; N, 15.60. Found: C, 44.44; H, 3.94; N, 15.53.

The aqueous mother liquor **B** was evaporated *in vacuo* and the colorless solid isolated, mp 256-258°, was identified as benzylamine hydrochloride by comparison with an authentic sample (mp 256°); ^{1}H nmr: δ 4.01 (d, CH_2N, J = 7.0 Hz), 7.25 (m, ArH), 8.57 (br s, NH).

This reaction was repeated (on a 0.003 molar scale) using the *N*-ethyl- **7a**, and *N,N*-dimethyl- **7f**, sulfonylamidines with thiourea hydrochloride. There was obtained **10** in 51 and 65% yields, respectively. This compound **10** was also the major product when *N*-(β-phenethyl)-*N'*-*p*-toluenesulfonyl-2-chloroacetamidine was reacted with thiourea in boiling acetone (30 minutes) or in butanone at 25° (18 hours), 25 and 54% yield, respectively.

In an attempt to crystallize **10** from hot ethanol, a dark solution was produced. Upon cooling, colorless crystals separated, mp 245-249°; ^{1}H nmr: δ 4.07 (s, CH_2S), 10.25 (br s, NH); ms: (relative intensity) 118 (5), 117 (5), 116 (M^+, 100), 74 (7), 70 (90), 69 (9), 46 (74), 45 (29), 43. This solid was identified as 2-amino-4-thiazolidinone, lit mp 230-240° [10], 255-258° [33].

Upon boiling **10** with concentrated hydrochloric acid for 5 hours, then evaporated to dryness, yielded a white solid which was identified as a mixture of *p*-toluenesulfonamide [^{1}H nmr: δ 2.37 (s, CH_3), 7.29 (br s, NH_2), 7.36 and 7.71 (centers of 2 multiplets of an AA'XX' system)] and thiazolidine-2,4-dione [^{1}H nmr: δ 4.14 (s, CH_2S), 8.10 (br s, NH)] as compared to authentic samples, prepared by the lit method [10].

Synthesis of 2-Amino-4-alkylimino-4,5-dihydrothiazole Hydrochlorides.

2-Amino-4-[(3,5-dimethyl-1-adamantyl)methyl]imino-4,5-dihydrothiazole Hydrochloride.

N-[(3,5-Dimethyl-1-adamantyl)methyl]-*N'*-(*p*-toluenesulfonyl)-2-chloroacetamidine (1.26 g, 0.003 mole) and thiourea (0.23 g, 0.003 mole) were dissolved in acetone (15 ml) and the solution refluxed (30 minutes). The yellow solution was cooled at 0-5° (36 hours) when white flakes were deposited. The product (0.81 g, 83%) was filtered, washed with acetone (2 × 2 ml) and dried *in vacuo* at 25° (18 hours), mp 199-201°, whose nmr spectrum did not change when recrystallized by suspending in boiling acetone, and adding ethanol dropwise to that hot mixture until a solution was affected, mp 202-205°; ^{1}H nmr: δ 0.81 (s, $2CH_3$), 1.05-1.36 (m, Adm), 3.23 (s, CH_2N), 4.66 (s, CH_2S), 10.20 (br s, NH_2); ms: m/z (relative intensity) 293 (6), 292 (19), 291 (M^+, 100), 258 (13), 128 (3), 45 (2), 36 (2), 32 (13).

Anal. Calcd. for $C_{16}H_{26}ClN_3S{\cdot}0.75H_2O$: C, 56.28; H, 8.12; N, 12.31. 12.14. Found: C, 56.15; H, 8.00; N, 12.24.

Evaporation of the mother liquor gave a gummy residue which contained some starting *N*-sulfonylamidine and *p*-toluenesulfonamide.

2-Amino-4-benzylimino-4,5-dihydrothiazole Hydrochloride.

N-Benzyl-*N'*-(*p*-toluenesulfonyl)-2-chloroacetamidine (0.60 g, 0.002 mole) and thiourea (0.076 g, 0.001 mole) were warmed to 60° in 10 ml of butanone for 30 minutes when some gummy material separated from the hot mixture. The liquid was decanted from the gum and was stirred at 25° for 20 hours. During that time a heavy white solid was formed. The solid was filtered, washed with butanone (2 × 2 ml) and was dried *in vacuo* at 25° (18 hours) to give a white solid, (0.095 g, 39%), mp 160-164°; ^{1}H nmr: δ 4.67 (s, CH_2N), 4.69 (s, CH_2S), 7.30-7.39 (m, ArH), 10.5 (br s, NH); ^{13}C nmr: δ 39.82 (CH_2N), 47.60 (CH_2S), 127.4 (C-3', C-5'), 128.2 (C-4'), 128.3 (C-2', C-6'), 136.0 (C-1'), 179.9 (C-2), 185.9 (C-4); ms: m/z (relative intensity) 207 (5), 206 (11), 205 (M^+, 86), 204 (17), 106 (42), 91 (100), 36 (51).

Anal. Calcd. for $C_{10}H_{12}ClN_3S{\cdot}0.25H_2O$: C, 48.77; H, 5.12; N, 17.06. Found: C, 48.83; H, 5.15; N, 17.51.

2-Amino-4-cyclohexylimino-4,5-dihydrothiazole Hydrochloride.

A stirred solution of *N*-cyclohexyl-*N'*-(*p*-toluenesulfonyl)-2-chloroacetamidine (0.98 g, 0.003 mole) and thiourea (0.68 g, 0.009 mole) was refluxed in butanone (30 ml) for 30 minutes. During this time, a colorless solid precipitated which was filtered hot, washed with butanone, (2 × 4 ml) and dried, *in vacuo*, at 25° (18 hours). It weighed 0.57 g (81% yield), mp 256-258°; ^{1}H nmr: δ 1.06-1.97 (m, C_6H_{11}), 3.75 (m, CHN), 4.58 (s, CH_2S), 9.03 (br s, NH); ms: m/z (relative intensity) 199 (4), 198 (9), 197 (M^+, 77), 196 (4), 168 (13), 154 (33), 116 (100), 117 (61), 36 (16).

Anal. Calcd. for $C_9H_{16}ClN_3S$: C, 46.24; H, 6.90; N, 17.90. Found: C, 45.75; H, 6.88; N, 17.90.

2-Amino-4-ethylimino-4,5-dihydrothiazole Hydrochloride.

A solution of *N*-ethyl-*N'*-(*p*-toluenesulfonyl)-2-chloroacetamidine (0.55 g, 0.002 mole) and thiourea (0.46 g, 0.006 mole) was stirred and refluxed in butanone (20 ml) for 30 minutes. The colorless solid which formed during reflux was filtered hot, and washed twice with hot butanone (2 × 10 ml) and was dried (25°) *in vacuo* (18 hours), and weighed 0.239 g, (54%), mp 150-151°; ^{1}H nmr, δ 1.18 (t, J = 7.2 Hz, CH_3N), 3.49 (q, J = 7.2 Hz, CH_2N), 4.59 (s, CH_2s), 10.11 (br s, NH); ^{13}C nmr: δ 14.71 (CH_3), 40.91 (CH_2N), 41.08 (CH_2S), 180.6 (C-2), 184.0 (thiourea), 187.2 (C-4); ms: m/z (relative intensity) 145 (5), 144 (7), 143 (M^+, 79), 142 (4), 128 (29), 76 (8), 36 (100).

Anal. Calcd. for $C_5H_{10}ClN_3O{\cdot}0.5CH_4N_2S$: C, 30.36; H, 5.55; N, 25.73. Found: C, 30.21; H, 5.60; N, 25.06.

All attempts to extract thiourea from the sample, by repeated boiling with butanone (in which thiourea is very soluble in the hot) provided the same sample, with same mp and nmr spectrum. A more satisfactory analysis for nitrogen was not obtained.

2-Amino-4-(*N,N*-dimethyl)imminium-4,5-dihydrothiazole Chloride.

A stirred solution of *N,N*-dimethyl-*N'*-(*p*-toluenesulfonyl)-2-chloroacetamidine (0.904 g, 0.0033 mole) and thiourea (0.228 g, 0.003 mole) was refluxed in butanone (20 ml) for 30 minutes. At that time a solid commenced to precipitate, which was filtered while hot after an additional 6 minutes of reflux, and washed with hot butanone (2 × 25 ml). After drying, *in vacuo* at 25° (18 hours) there was obtained 0.295 g, mp 177-180.

The mother liquors deposited another 0.075 g (with the same mp) after 24 hours at 25°. Both crops of this pinkish-white solid had the same ^{1}H nmr spectrum: δ 3.23, 3.31 (2s, NCH_3, due to restricted rotation), 4.75 (s, CH_2S), 7.10 (br s, NH_2 of thiourea) 10.16 (NH); ms: m/z (relative intensity) 145 (1), 144 (2), 143 (M^+, 15), 128 (15), 100 (27), 86 (18), 76 (37), 60 (42), 43 (100), 36 (10).

Anal. Calcd. for $C_5H_{10}ClN_3S\cdot CH_4N_2S\cdot 0.25\ H_2O$: C, 27.68; H, 6.19; H, 26.90. Found: C, 27.38; H, 5.71; N, 26.83.

2-Amino-4-(*N,N*-pentamethylene)imminium-4,5-dihydrothiazole Chloride.

N,N-(Pentamethylene)-*N'*-(*p*-toluenesulfonyl)-2-chloroacetamidine (0.949 g, 0.003 mole) and thiourea (0.68 g, 0.009 mole) were refluxed in butanone (30 ml) for 30 minutes. The solid (0.22 g, 24%) was filtered from the hot solution, and washed with boiling butanone (2 × 10 ml), mp 165-167°; ^{1}H nmr: δ 1.65-1.72 [m, $-(CH_2)_3$], 3.57, 3.88 (m's, 2 signals due to restricted rotation, CH_2N), 4.80 (s, CH_2S), 7.18 (br s, thiourea NH's), 10.12 (br s, NH); ms: m/z (relative intensity) 184 (7), 183 (M^+-1, 60), 182 (22), 168 (26), 150 (30), 128 (15), 127 (18), 126 (10), 115 (17), 100 (27), 84 (58), 76 (63), 43 (85), 41 (100), 36 (66).

Anal. Calcd. for $C_8H_{14}ClN_3S\cdot CH_4N_2S\cdot 0.5H_2O$: C, 35.52; H, 6.25; N, 23.02. Found: C, 35.43; H, 6.18; N, 22.82.

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